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Phone: (+48 58) 320 94 94, fax: (+48 58) 320 94 60
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Editorial Address

Klinika Nowotworów Płuca i Klatki Piersiowej
Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie — Państwowy Instytut Badawczy
ul. Roentgena 5, 02–781 Warszawa, Poland
Phone: (+48 22) 546 21 69
e-mail: sekretariat4@pib-nio.pl

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ORIGINAL ARTICLE

Ireneusz Raczyński[1], Barbara Radecka[2, 3], Maciej Krzakowski[4]

[1]General Medical Practic, Warsaw, Poland
[2]Clinical Department of Oncology, Institute of Medical Sciences, University of Opole, Poland
[3]Tadeusz Koszarowski Cancer Centre in Opole, Opole, Poland
[4]Department of Lung Cancer and Thoracic Tumors, The Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Survival of pancreatic cancer patients treated with nab-paclitaxel (nab-P) in clinical practice: analysis of National Health Fund data

Address for correspondence:
Ireneusz Raczyński, MD
General Medical Practice
ul. Cylichowska 23 B, 04–769 Warsaw, Poland
tel.: +48 734 466 224
e-mail: ireneusz.raczynski@wp.pl

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ABSTRACT

Introduction. Despite advances in the last few decades, pancreatic cancer is still characterized by systematically increasing morbidity and high mortality with a low survival rate. The introduction of nab-paclitaxel (nab-P) to the first-line treatment of patients with metastatic pancreatic adenocarcinoma in combination with gemcitabine resulted in improvements in overall survival (OS), progression-free survival (PFS) and objective response rate (ORR).

Material and methods. This study analyzes OS and PFS in pancreatic cancer patients treated with nab-P in the real world setting in Poland, based on data from the National Health Fund (NFZ) database.

Results. Data from 873 patients were found (2014–2019). PFS in the entire population was 169 days (95% CI 147–189) without difference between men and women, but significantly better in younger patients (29–50 years). OS in the entire population was 379 days (95% CI 337–non-assessable), with no difference between men and women. A statistically significant longer PFS and OS was demonstrated in the group of patients diagnosed in 2014–2016.

Conclusion. Nab-paclitaxel, when used in clinical practice, provides treatment results similar to those in clinical trials. Collecting and periodically analyzing demographic and clinical data could help to assess the place of nab-P in the treatment of patients with pancreatic cancer more accurately.

Keywords: advanced pancreatic cancer, nab-paclitaxel, overall survival, progression-free survival
Oncol Clin Pract 2023; 19, 6: 391–397

Introduction

Adenocarcinoma accounts for over 90% of all primary pancreatic neoplasms, and its incidence systematically and significantly increases [1]. Pancreatic cancer is one of the leading causes of cancer-related mortality [2]. Based on data from 2017–2019, it has been estimated that approximately 1.7% of men and women will be diagnosed with pancreatic cancer at some point in their lives [3]. Currently, pancreatic cancer is the 12th most common cancer and the 7th leading cancer death worldwide [4, 5].

During the period from 1990 to 2017, the number of pancreatic cancers doubled worldwide (196 000 *vs.* 441 000). It is believed that the significantly increased incidence results from age structure changes in the world population (the risk of pancreatic cancer increases with age) and the improvement in diagnosis and detection of this disease in developed countries [2].

Europe is ranked second in terms of the incidence of pancreatic cancer after the Western Pacific region (9.3 per 100 000 men and 6.3 per 100 000 women). The highest number of cases is recorded in Germany, France,

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and Italy. Pancreatic cancer is the fourth leading cause of cancer death in Europe (8.8 deaths per 100 000 men and 5.7 per 100 000 women) after lung, colon, and breast cancer [6].

In Poland, 3852 cases were recorded in 2019 (incidence rate of 10.3%), and the number of deaths was 5068 (mortality rate of 13.2%) [7].

The survival rate of patients with pancreatic cancer is still very low, median overall survival (OS) in locally advanced stages does not exceed a year while it is 3–6 months in metastatic disease [8]. Although there has been an increase in the 5-year survival rate in the USA and Europe from less than 5% in the 1990s to 9% in 2019, the global mean rate is only about 3% [2, 9]. Unfavorable results are mainly related to late diagnosis. In most cases, the disease is diagnosed at either a locally advanced or metastatic stage, and only 15–20% of cases are diagnosed at early stages when radical surgery is possible [2].

Chemotherapy is used to treat patients with advanced pancreatic cancer, either as monotherapy or multidrug regimens with gemcitabine, fluoropyrimidine, nab-paclitaxel (nab-P), or irinotecan. The choice of the first-line treatment regimen should be adapted to the patient's general condition. Multidrug regimens (e.g. FOLFIRINOX — oxaliplatin, irinotecan, leucovorin, and fluorouracil) in the first line, and regimens with nanoliposomal irinotecan in the second line are more effective than monotherapy but should only be used in patients with good and very good performance status [10–13].

Nab-paclitaxel (nab-P) is a nanoparticle albumin-bound paclitaxel, showing pharmacological properties different from the conventional form of the drug. It is approved — among other indications — for the first-line treatment of adult patients with metastatic pancreatic adenocarcinoma in combination with gemcitabine [14]. The MPACT study showed that the combination of both drugs compared with gemcitabine alone improves OS, with a median of 8.5 *vs.* 6.7 months, progression-free survival (PFS), with a median of 5.5 *vs.* 3.7 months and objective response rate (23% *vs.* 7%) [13, 15].

The therapeutic value of nab-P in combination with gemcitabine was confirmed by real-world data (RWD), for example, the data from the German pancreatic cancer registry TPK collected prospectively in 104 centers between 2014 and 2017 [16].

Aim of study

This study aims to analyze the results of treatment with nab-P in daily clinical practice in Poland in terms of OS and PFS based on data from the National Health Fund (NHF) database.

Material and methods

The data of pancreatic adenocarcinoma patients treated with nab-paclitaxel (Abraxane®, Bristol-Myers Squibb Pharma EEIG, Ireland) from the NHF database were reviewed. The NHF data were collected after obtaining appropriate approval.

The analyzed data included the demographic characteristics of the patients and the results in terms of OS and PFS.

Overall survival was defined as the time to the last record in the database confirming that the patient was still alive. Progression-free survival was defined as the time to the last record in the database confirming the lack of disease progression in imaging tests and that the patient is still alive.

Statistical analysis

Statistical analysis was performed using survival assesement metods. Overall survival was calculated as the number of days from initiation of treatment to completion of observation or death. Progression-free survival was calculated as the number of days from initiation of treatment to completion of follow-up, disease progression, or death.

The significance of factors influencing OS and PFS was assessed using the log-rank test. The analysis was conducted using the R 4.0.5 software [17].

Results

Data from a total of 873 patients — 447 women (51.2%) and 426 men (48.8%) — treated between 2014 and 2019 were analyzed. The median age was 66 years [range 29–87 years; interquartile range (IQR) 61–70 years] with a predominance of patients over 60 years of age (80.0%).

Most patients were diagnosed in 2018 (n = 373; 42.7%) and 2019 (n = 198; 22.7%), and only 5.2% of patients were diagnosed in 2016 or earlier (n = 45).

Most patients were treated in centers located in the Masovian Provincial Department of the National Health Fund (n = 193; 22.1%), and the least in the Opole Provincial Department of the National Health Fund (n = 13; 1,5%),

The most common causes of treatment discontinuation were disease progression (n = 254; 43.4%) and death (n = 121; 20.7%). In 3 (0.5%) patients, treatment was discontinued due to a change of service provider. Detailed data on the analyzed group available in the NHF database are presented in Table 1.

Progression-free survival in the entire study group was 169 days (95% CI 147–189) (Fig. 1). There was

Table 1. Characteristics of pancreatic adenocarcinoma patients treated with nab-paclitaxel based on data from the National Health Fund database

Feature	Number of pts. n (%)
Sex	
Female	447 (51.2)
Male	426 (48.8)
Median age (years), (range) (IQR)	
66 (29–87) (61–70)	65.3 (8.2)
Age group	
29–50	39 (4.5)
50–60	135 (15.5)
60–70	429 (49.1)
70–87	270 (30.9)
Reason for treatment discontinuation	
Disease progression	254 (43.4)
Change of treatment	22 (3.8)
Patient withdrawal	38 (6.5)
Unacceptable side effects	56 (9.6)
Hypersensitivity to the active substance or excipient	18 (3.1)
Death	121 (20.7)
Another cause	73 (12.5)
Change of service provider	3 (0.5)
Year of diagnosis	
2014–2016	45 (5.2)
2017	257 (29.4)
2018	373 (42.7)
2019	198 (22.7)
Accounting Department of the National Health Fund	
Lower Silesia	40 (4.6)
Kuyavian-Pomeranian	24 (2.7)
Lublin	67 (7.7)
Lubuski	18 (2.1)
Lodzki	19 (2.2)
Lesser Poland	40 (4.6)
Masovian	193 (22.1)
Opole	13 (1.5)
Subcarpathian	49 (5.6)
Podlaski	31 (3.6)
Pomeranian	93 (10.7)
Silesian	107 (12.3)
Świętokrzyski	41 (4.7)
Warmia–Masuria	15 (1.7)
Greater Poland	61 (7.0)
West Pomeranian	62 (7.1)

IQR — interquartile range

no difference in survival between men and women ($p = 0.95$; Fig. 2). On the other side, a statistically significantly longer PFS was demonstrated in younger patients in the 29–50 age group ($p = 0.41$) (Fig. 3). A statistically significant difference ($p < 0.0001$) was demonstrated depending on the year of diagnosis with the highest median in the group patients diagnosed between 2014–2016 (Fig. 4).

Overall survival in the entire study group was 379 days (95% CI 337–not assessable) (Fig. 5). There were no statistically significant differences regarding sex ($p = 0.76$; Fig. 6) and age ($p = 0.65$; Fig. 7). On the other hand, a statistically significant difference ($p = 0.18$) was shown depending on the year of diagnosis with the highest median in the group of patients diagnosed between 2014–2016 (Fig. 8).

Discussion

Pancreatic cancer is still one of the major cancer-related threats to life and health. High mortality is primarily a consequence of the diagnosis at advanced disease stages. There has been some progress in the treatment of advanced disease in recent years, mainly with the introduction of multidrug regimens, but PFS and OS outcomes are still disappointing.

In the phase III PRODIGE 4 study, a statistically significant improvement in median PFS (6.4 *vs.* 3.3 months, $p < 0.001$) and OS (11.1 *vs.* 6.8 months, $p < 0.001$) with the FOLFIRINOX regimen (oxaliplatin, irinotecan, leucovorin, and fluorouracil) use was shown as compared to gemcitabine monotherapy, but the toxicity of the multidrug regimen was significantly greater [12]. In the MPACT study mentioned above, an increase in OS was achieved in patients with metastatic pancreatic cancer with a 28% reduction in the relative risk of death after adding nab-P to gemcitabine compared to gemcitabine alone. Multidrug regimens were moderately toxic with manageable side effects. The combination of nab-P with gemcitabine has become a new standard of systemic therapy in patients with advanced or metastatic pancreatic cancers [13].

In Poland, nab-P in the first-line treatment of patients with metastatic pancreatic adenocarcinoma has been used in combination with gemcitabine since 2017 as part of the Ministry of Health drug program only in patients non-eligible for more intensive chemotherapy according to the FOLFIRINOX regimen. The decision to use nab-P with gemcitabine was in line with the 2014 Polish Society of Clinical Oncology guidelines and the 2015 European Society of Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) guidelines. No study has ever been conducted to directly compare the results

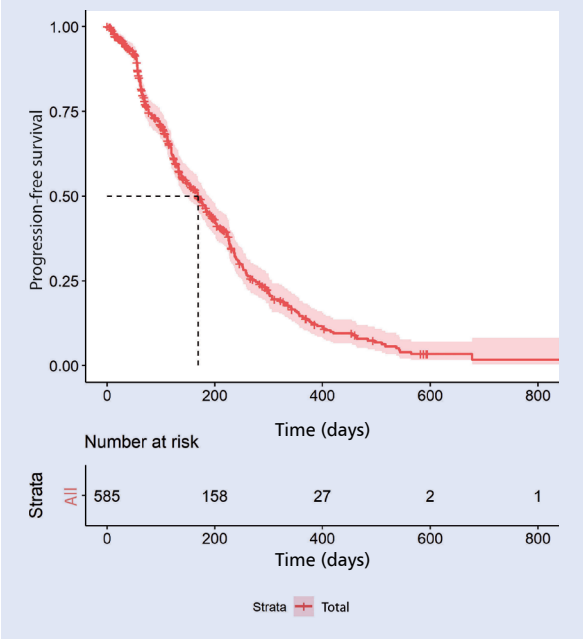

Figure 1. Progression-free survival in the entire group of patients

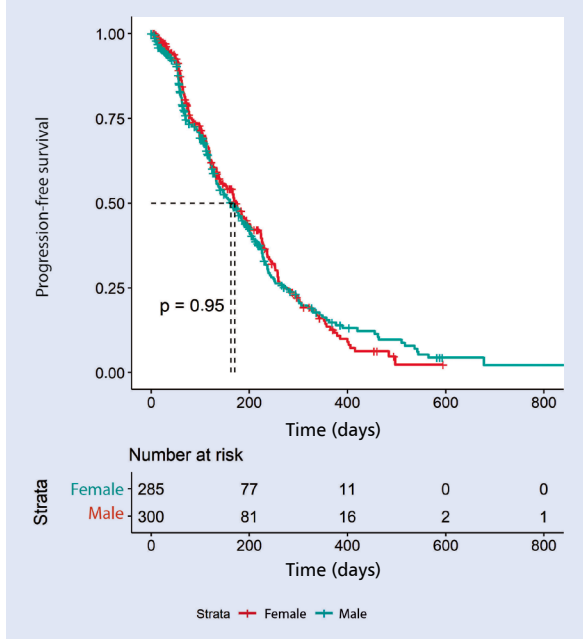

Figure 2. Progression-free survival depending on sex

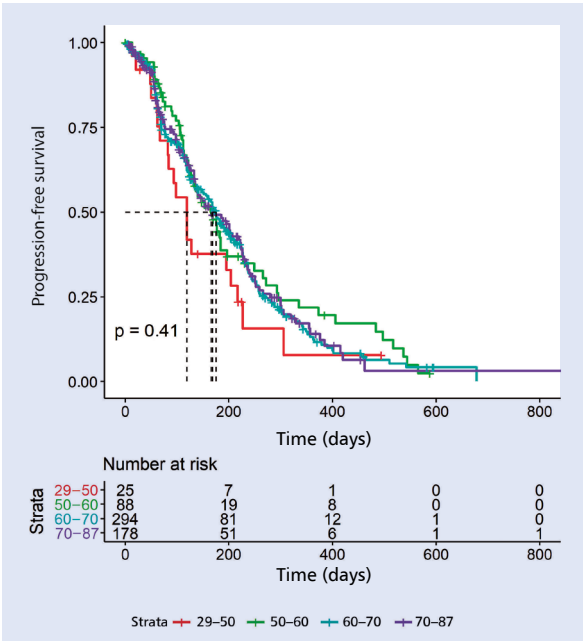

Figure 3. Progression-free survival depending on age

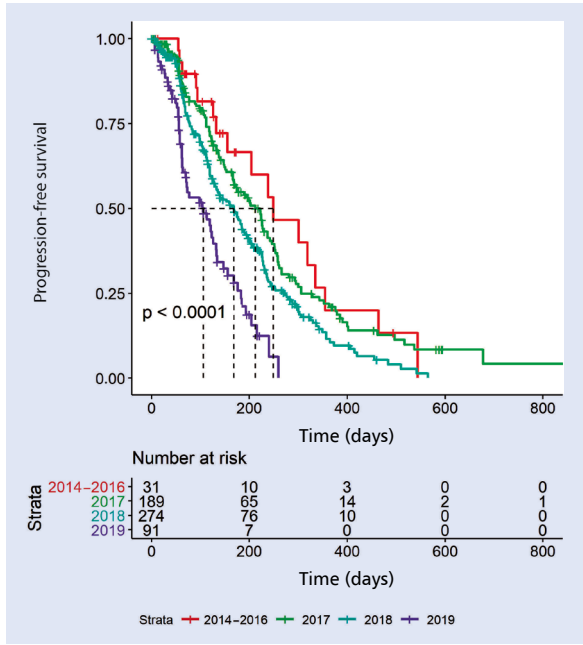

Figure 4. Progression-free survival depending on the year of diagnosis

of chemotherapy with the FOLFIRINOX regimen and the combination of nab-P with gemcitabine, which could help decide on the optimal treatment. However, when analyzing the studies comparing these two regimens with gemcitabine monotherapy (ACCORD 11 with FOLFIRINOX chemotherapy and MPACT with nab-P and gemcitabine) in first-line treatment, it can be noted that both studies included similar patient populations. This is evidenced not only by patient characteristics but also by almost identical results obtained in the control groups. The percentage of patients who received second-line treatment was similar (48% in

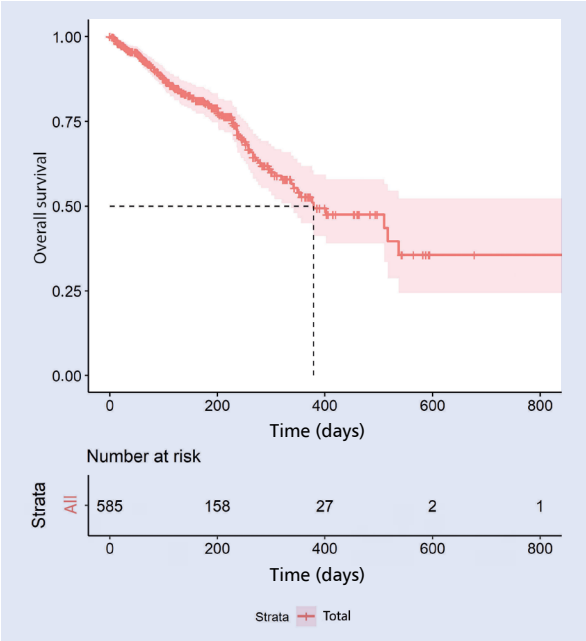

Figure 5. Overall survival in the entire group of patients

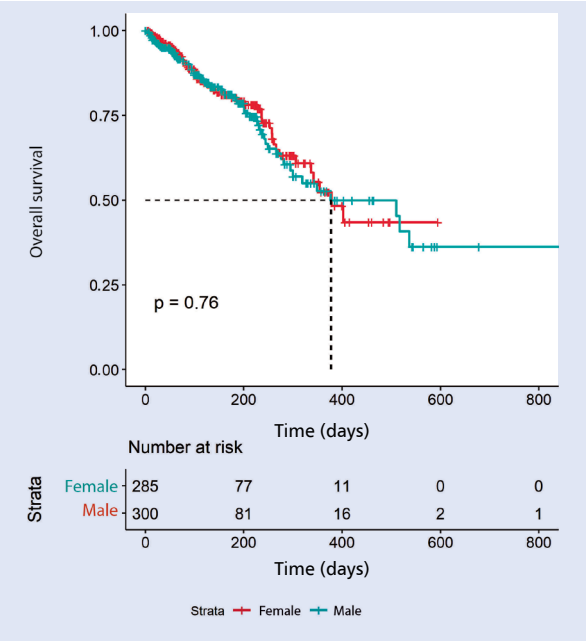

Figure 6. Overall survival depending on sex

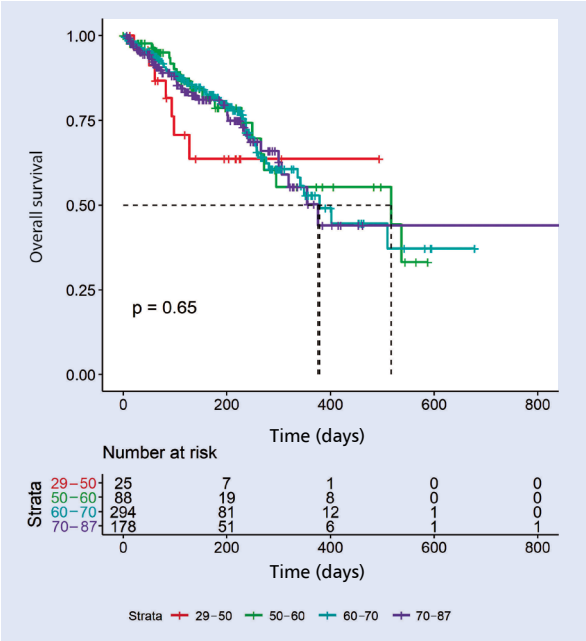

Figure 7. Overall survival depending on age

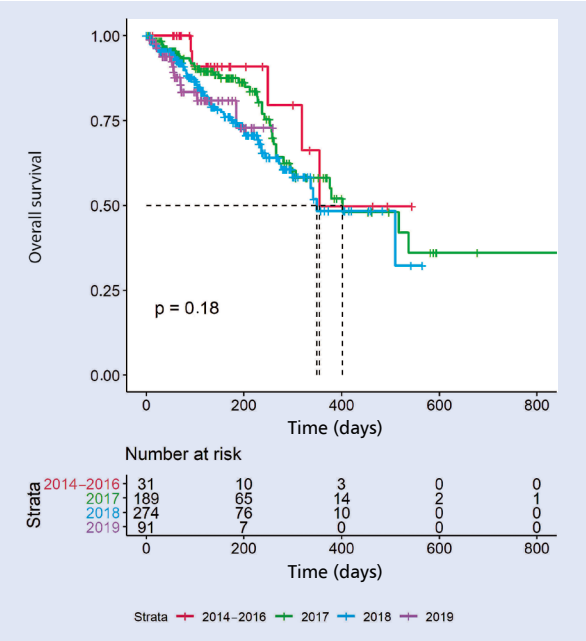

Figure 8. Overall survival depending on the year of diagnosis

ACCORD 11 and 40% in MPACT). Median OS, PFS, and objective response rates (ORR) were numerically better in ACCORD 11 than in the MPACT study (11.1 months, 6.4 months, and 32% *vs.* 8.5 months, 5.5 months, and 23%, respectively) [18]. An indirect comparison of the toxicity of both multidrug regimens indicates a higher incidence of adverse reactions during the FOLFIRINOX regimen, which could favor nab-P with gemcitabine, especially in patients with a worse performance status [19].

The European Society of Medical Oncology (ESMO) recommends the use of multidrug regimens (FOLFIRINOX and nab-P with gemcitabine) in patients with good or very good performance status, which means

scores 1 or 0 according to the Eastern Cooperative Oncology Group (ECOG) classification. Patients with reduced performance status (ECOG 2) should receive gemcitabine monotherapy. ECOG performance status 3-4 and the presence of comorbidities is an indication for the best supportive care [19]. The National Comprehensive Cancer Network (NCCN) guidelines distinguish between patient populations with good and poor performance status. According to the guidelines, combination therapy is recommended in the first group (FOLFIRINOX, nab-P with gemcitabine, and other regimens, e.g. gemcitabine with erlotinib) while monotherapy is recommended in the second group (gemcitabine, capecitabine or fluorouracil) [20].

This article presents the results of treatment with nab-P in the Polish population in daily clinical practice. In terms of sex and age, this population corresponds to patients treated in clinical trials. Unfortunately, the NHF databases do not include complete and detailed information on performance status or other clinical parameters and laboratory test results. This makes it impossible to compare the obtained results to the data from the subgroup analyses presented in individual prospective clinical trials and the current recommendations, taking into account patient performance status in the treatment eligibility criteria.

In the entire analyzed group of 873 patients, PFS was 169 days, and OS was 379 days. In both analyzes, no statistically significant differences were found depending on sex, and in the case of OS, also age. However, in both analyzes, a statistically significant difference was found depending on the year of diagnosis with the greatest benefit in the group of patients diagnosed in 2014–2016. On the one hand, this situation may be the result of the small (lowest!) size of this group, and, on the other hand, the lack of complete data on PFS and OS in the NHF database. The statistically significant improvement in PFS in patients in the youngest age group may be due to similar reasons. Nevertheless, even such a limited analysis shows that the use of nab-P in combination with gemcitabine in the systemic treatment of patients with pancreatic adenocarcinoma allows us to obtain PFS and OS similar to the results of clinical trials.

In 2019, an analysis of data from the pancreatic cancer registry collected prospectively in 104 centers between 2014 and 2017 was conducted in Germany, including a total of 1174 patients with locally advanced, inoperable, or metastatic pancreatic ductal adenocarcinoma. The median age of patients receiving nab-P with gemcitabine was 71 years, and in 64% of patients, ECOG performance status was ≥ 1. The corresponding values for patients receiving gemcitabine monotherapy or the FOLFIRINOX regimen were 78 years and 60 years, and 73% and 52%, respectively. Median PFS after first-line nab-P plus gemcitabine was 5.6 months (95% CI: 5.0–6.2) [for gemcitabine monotherapy and FOLFIRINOX: 4.6 months (95% CI: 3.7–5.2) and 6.3 months (95% CI: 5.5–6.9), respectively], and median OS was 9.1 (95% CI: 8.2–10.1) [for gemcitabine monotherapy and FOLFIRINOX: 6.8 (95% CI: 6.1–9.0) and 11.3 months (95% CI: 10.5–12.5), respectively]. The authors of the study concluded that the 3 most frequently chosen treatment regimens (gemcitabine, nab-P with gemcitabine, and FOLFIRINOX) were used in different patient populations, which confirms that all of them are applicable depending on the clinical situation [16].

In turn, according to the 2018 French guidelines for the diagnosis and treatment of patients with pancreatic cancer, both FOLFIRINOX and gemcitabine in combination with nab-P are the standard for first-line treatment in patients with good performance status [21].

Apart from clinical trials and research conducted in daily clinical practice, registers and databases are valuable sources of knowledge about the actual effectiveness and safety of various technologies. The prerequisite to such usefulness is a systematic, preferably prospective, supply of registers with complete, readable, and reliable data. Only then can the analyzes allow for correct conclusions useful in making therapeutic decisions.

When analyzing the data collected in the National Health Fund, it seems that their poor quality and quantitative value may result from the fact that these registers are used for evaluation, drawing inferences, and decision-making in the area of administration and management of resources rather than for purposes related to clinical practice. The above conditions were the greatest limitation of the presented analysis.

Conclusions

The results of treatment with nab-paclitaxel in daily clinical practice in patients with advanced pancreatic cancer are similar to those known from clinical trials. The drug has an established place in the therapeutic algorithm in the first-line of treatment. Collecting and periodically analyzing demographic and clinical data could further determine the role of nab-P in this still-difficult-to-treat population.

Article Information and Declarations

Conflict of interest

B.R.: advisory/consulting role & travel and accommodation support — Servier, Roche, AstraZeneca, BMS, MSD, Lilly, Pierre Fabre, Novartis.
M.K.: advisory/consulting role & travel and accommodation support — Servier, Roche, AstraZeneca, BMS.
I.R. declares no conflict of interest.

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REVIEW ARTICLE

Teodoro J. Oscanoa[1–3], Xavier Vidal[4], Brady E. Beltran[2, 5], Roman Romero-Ortuno[6, 7]

[1]Universidad Nacional Mayor de San Marcos, Facultad de Medicina, Lima, Perú
[2]Universidad de San Martín de Porres, Facultad de Medicina Humana, Lima, Perú
[3]Geriatric Department, Almenara Hospital, ESSALUD, Lima, Perú
[4]Clinical Pharmacology, Vall d'Hebron University Hospital, Barcelona, Spain
[5]Department of Oncology and Radiotherapy, Hospital Nacional Edgardo Rebagliati Martins, ESSALUD, Lima, Perú
[6]Discipline of Medical Gerontology, School of Medicine, Trinity College Dublin, Dublin, Ireland
[7]Global Brain Health Institute, Trinity College Dublin, Ireland

Comprehensive geriatric assessment and clinical outcomes of frail older adults with diffuse large B-cell lymphoma: a meta-analysis

Address for correspondence:
Teodoro J. Oscanoa PhD
Universidad de San Martín de Porres,
Facultad de Medicina Humana, Drug Safety Research Center
Av. Alameda del Corregidor 1502,
La Molina 15024. Lima, Perú
e-mail: tjoscanoae@gmail.com; toscanoae@usmp.pe

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ABSTRACT

Introduction. Comprehensive geriatric assessment (CGA) is used to personalize cancer treatments in frail older adults. However, its utility to guide treatments in frail older patients with diffuse large B-cell lymphoma (DLBCL) is not well known. We performed a meta-analysis of evidence published in this area.

Material and methods. We searched PubMed and Google Scholar for studies published between January 2000 and January 2023 that included patients aged ≥ 65 years with a diagnosis of DLBCL who underwent CGA before treatment (CGA-modulated studies) and who did not (non-CGA-modulated studies). We evaluated clinical outcomes in frail/unfit patients in terms of complete response (CR), incidence of grade ≥ 3 toxicity, and 2-year overall survival (OS) in both types of studies.

Results. Fifteen studies [8 CGA-modulated (n = 733, median age 76, 54% male, 52% frail/unfit) and 7 non-CGA-modulated (n = 2447, median age 76, 52% male, 32% frail/unfit)] were included. In the CGA-modulated studies, the CR proportion of frail/unfit patients was 34% (95% CI 23–46%) *vs*. 28% (95% CI 19–38%) in the non-CGA-modulated studies (p = 0.436). Grade 3–4 hematological toxicity in frail/unfit patients was 26% (95% CI 5–55%) *vs*. 36% (95% CI 13–63%) (p = 0.583), respectively. Two-year OS of frail/unfit patients was 52% (95% CI 38–66%) *vs*. 27% (95% CI 19–36%) (p = 0.003), respectively.

Conclusions. Although the proportion of frail/unfit patients was lower in non-CGA-modulated studies, CGA-modulated studies reported higher OS. CGA could be useful to guide the treatment plan in older patients with DLBCL. Randomized clinical trials with standardized CGA instruments are necessary to confirm these findings.

Keywords: comprehensive geriatric assessment, diffuse large B-cell lymphoma, frailty, meta-analysis, older adults, outcomes

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most frequent type of malignant lymphoma and constitutes about 40% of non-Hodgkin lymphoma (NHL) cases. The mean age at onset is 65 years, and its incidence increases with age [1]. The standard therapeutic regimen is 6 courses of combined therapy with rituximab and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone). The 5-year overall survival (OS) rate is 50–60%, and complete response (CR) and 5-year OS decrease with age [2].

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Prognostic scores such as the International Prognostic Index (IPI) have been adopted in DLBCL patients. Among other criteria such as disease stage, the IPI considers older chronological age (> 60 years) and worse performance status [Eastern Cooperative Oncology Group (ECOG) Performance Status > 2] as markers of higher risk [3–5]. Rituximab-CHOP (R-CHOP) is standard first-line therapy. However, about 40% of older patients do not tolerate the standard dose of R-CHOP due to such causes as comorbidities, malnutrition, and the presence of other geriatric syndromes [6]. Frailty is defined as physiological vulnerability to stressors, is more related to biological than chronological age [7], and encapsulates many of the systemic dysregulations that are associated with poorer outcomes in geriatric oncology [8].

In frail older adults, the application of comprehensive geriatric assessment (CGA) has been shown to improve outcomes in the acute general hospital setting [9]. This is because CGA is a multidisciplinary diagnostic and treatment process that identifies medical, psychosocial, and functional capabilities of older adults to develop a coordinated plan to maximize overall health with aging [2]. Therefore, by performing a CGA, the frailty status of an older adult can be improved, conferring more resilience before he/she experiences a planned stressor. This has been exemplified in prehabilitation of frail older adults undergoing elective surgery [10]. Some abbreviated CGA tools have been made available for implementation in research studies [11].

Comprehensive geriatric assessment is used to personalize cancer treatments in frail older adults. However, its utility to guide treatments in frail older DLBCL patients is not well known [12]. We performed a meta-analysis of evidence published in this area, with a specific aim to compare the outcomes of non-CGA-modulated studies versus CGA-modulated studies, in terms of CR, incidence of grade ≥ 3 toxicity, and 2-year OS.

Material and methods

We searched PubMed, Google Scholar, and the Cochrane Database of Systematic Reviews for studies including DLBCL patients aged above 64 years. The research period ranged from January 2000 to January 2023. Case reports, editorials, comments, and reviews were excluded. Our study followed the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [13] (Tab. S1 in supplementary file).

Search strategy

The search terms were "Comprehensive geriatric assessment", "diffuse large B-cell lymphoma", "chemotherapy", "immunochemotherapy", "Humanized anti-CD19 CART", and "frailty".

Inclusion criteria

Studies that met the following criteria were included a) patients equal to or older than 65 years and diagnosed with DLBCL; b) CGA was used to categorize patients into fit or unfit/frail, prospectively or retrospectively. "CGA-modulated studies" were those in which CGA was used to select patients (frail/unfit or fit) for a specific chemotherapy scheme. Those in whom this criterion was not used to qualify them for specific chemotherapy or was done retrospectively were called "non-CGA-modulated studies"; c) Studies reported clinical outcome data such as overall survival (OS), complete response (CR), and the incidence of at least grade 3 hematological toxicity [14].

Quality assessment

The quality of the studies was appraised according to the Reporting of Observational Studies in Epidemiology (STROBE) [15].

Statistical analyses

Outcomes of CGA-modulated studies were compared to those of non-CGA-modulated studies in frail/unfit patients. The statistical comparison of proportions was carried out with the Chi-square statistic.

When possible, overall estimates in the pooled analysis were obtained using Stata 13 software (Stata Corp LP, College Station, TX) and the Meta XL (www.epigear.com) add-in for Microsoft Excel [12]. A pooled prevalence was calculated with 95% confidence interval (CI) by combining estimates from selected studies based on a random-effects model [13]; this is a variant of the inverse of the variance method, and it incorporates intra- and inter-variability of studies. Heterogeneity between estimates was assessed using the I^2 statistic, which describes the percentage of variation across studies not caused by sampling error [16]. To perform the meta-analysis of two-year OS of frail/unfit patients in the studies, only those studies that reported such outcomes were selected.

Results

After screening 814 citations, 15 studies (8 cohort and 7 non-randomized clinical trials) were included (Fig. 1). The total number of patients was 3180, mean age 76.4 ± 4.1 years, and 53.2% were male. Eight studies were carried out in Italy [17–24], 3 in China [25–27], 1 in Australia [28], 1 in Japan [29], 1 in Mexico [30], and 1 in Norway [31] (Tab. 1).

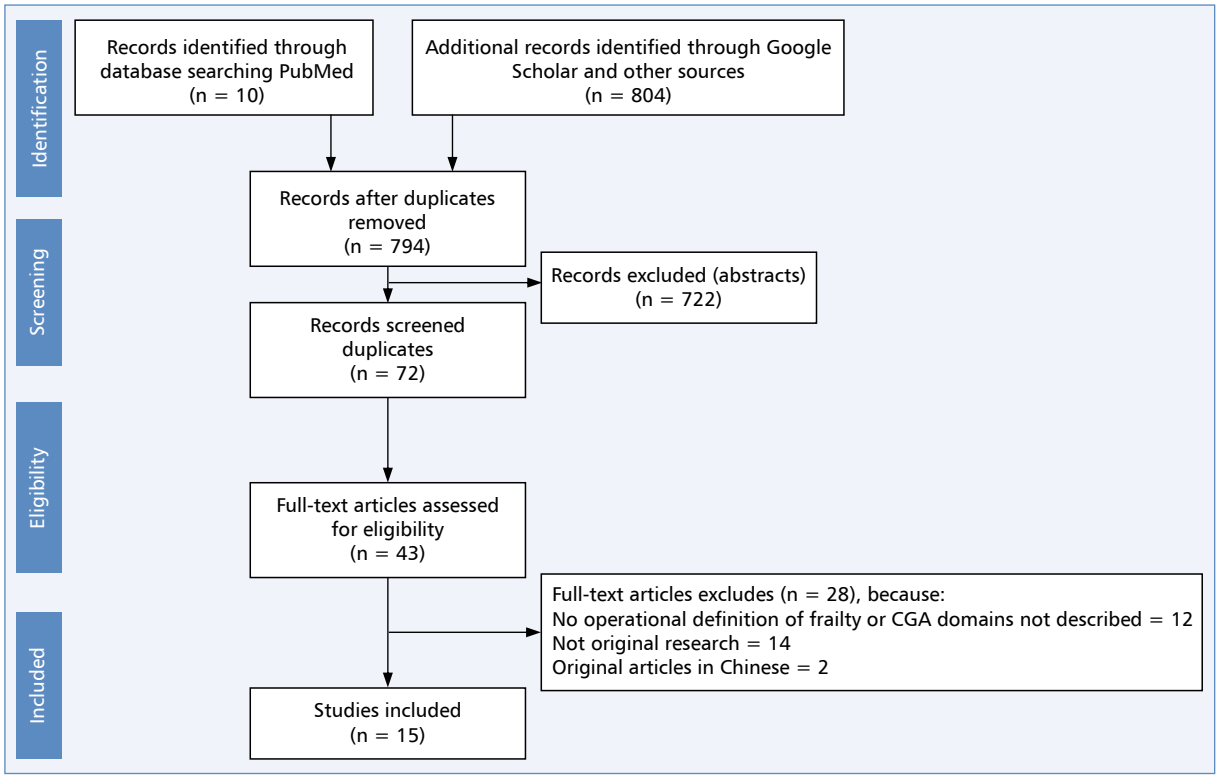

Figure 1. Study flowchart; CGA — comprehensive geriatric assessment

For the categorization of patients according to CGA, simplified CGA (sCGA) was used in 80% of the studies [17–28], full CGA [29, 31] in 13.3%, and the frailty phenotype model [30] in 6.7%. The instruments used for CGA and operational criteria for the identification of frail/unfit and fit patients are in Table S1 in the supplementary file. One study only included frail patients [20] (Tab. 1).

The prevalence of frail, unfit, and fit patients was 32% (95% CI 25–40), 27% (95% CI 21–32), and 47% (95% CI 38–58), respectively.

Eight studies were CGA-modulated (n = 733, median age 76, 54% male, 52% frail/unfit) and 7 non-CGA-modulated (n = 2447, median age 76, 52% male, 32% frail/unfit) (Tab. 2).

In five-eighths of CGA-modulated treatment studies *vs*. three-eighths of non-CGA-modulated treatment studies, two-year OS of frail/unfit patients was 52% (95% CI 38–66) and 27% (95% CI 19–36) (p = 0.003), respectively (Fig. 2). A meta-analysis of three-year or five-year OS was not performed because there were not enough studies reporting it (minimum 2 studies).

In six-ninths of CGA-modulated treatment studies *vs.* three-ninths of non-modulated treatment studies, the CR of frail/unfit patients was 34% (95% CI 23–46) and 28% (95% CI 19–38) (p = 0.436), respectively (Fig. 3).

In four-sixths of CGA-modulated treatment studies with *vs*. two-sixths of non-modulated treatment studies, grade 3–4 hematological toxicity in frail/unfit patients was 26% (95% CI 5–55%) and 36% (95% CI 13–63%) (p = 0.583), respectively (Fig. 4). While in two-fourths of CGA-modulated treatment studies *vs.* two-fourths of non-modulated treatment studies, grade 3–4 non-hematological toxicity in frail/unfit patients was 22% (95% CI 11–36%) and 31% (95% CI 25–37%) (p = 0.106), respectively (Fig. 5).

Discussion

We performed a metanalysis to compare the outcomes of non-CGA-modulated versus CGA-modulated studies in the treatment of frail/unfit older adults with DLBCL, in terms of CR, incidence of grade ≥ 3 toxicity, and 2-year OS. Although the proportion of frail patients was lower in non-CGA-modulated studies and the studies had no significant differences in CR or grade 3–4 hematological/non-hematological toxicity, CGA-modulated studies reported higher two-year OS.

Two systematic studies with similar findings have previously been published, with studies covering the period up to 2016 [32] and 2020 [33]. Regarding the usefulness of CGA as a guide for selecting a thera-

Table 1. Characteristics of included studies

Study	Country	Type of study	Age [median]	Sex [male %]	Number of patients	Prevalence of frailty [%]	Frailty criteria	Categories	Quality assessment: STROBE [%]
CGA-modulated studies									
Xu et al. (2022)	China	Non-randomized clinical trial	80	77	30	80	sCGA	Fit, unfit, frail	96.7
Bocci et al. (2022)	Italy	Non-randomized clinical trial	84	64	22	99	sCGA	Unfit, frail, "superfrail"	93.3
Bai et al. (2020)	China	Non-randomized clinical trial	69	57.7	78	36	sCGA	Fit, unfit, frail	76.6
Storti et al. (2018)	Italy	Non-randomized clinical trial	81	58	45	99	sCGA	Frail	90
Lastra-German et al. (2018)	Mexico	Cohort	70	42.9	49	41	Phenotype	Fit, unfit, frail	83.3
Merli et al. (2013)	Italy	Non-randomized clinical trial	78	43	318	29.6	sCGA	Fit, Frail	90
Spina et al. (2012)	Italy	Non-randomized clinical trial	75	41	100	13	sCGA	Fit, unfit, frail	90
Olivieri et al. (2012)	Italy	Cohort	74	50.5	91	16	sCGA	Fit, patients with comorbidities, frail	83.3
non-CGA-modulated studies									
Tanaka et al. (2022)	Japan	Cohort	79	52.6	78	53	Full CGA	Independent, dependent	80
Zhang et al. (2022)	China	Non-randomized clinical trial	73	52	31	13	sCGA	Fit, unfit, frail	83.3
Merli et al. (2021)	Italy	Cohort	76	50	1207	18	sCGA	Fit, unfit, frail	90
Isaksen et al. (2021)	Norway	Cohort	79	52	747	34	full CGA	Fit, unfit, frail	90
Ong et al. (2019)	Australia	Cohort	73	55.8	138	38	sCGA	Fit, unfit, frail	96.7
Tucci et al. (2015)	Italy	Cohort	77	52.6	173	38	sCGA	Fit, unfit, frail	90
Marchesi et al. (2013)	Italy	Cohort	78	49.32	73	28.77	sCGA	Fit, intermediate, frail	90

CGA — comprehensive geriatric assessment

Table 2. Treatment, comprehensive geriatric assessment, and outcomes for frail older adults with diffuse large B-cell lymphoma

Studies	Treatment	Complete response (CR)	Overall survival (OS)	Event-free survival (EFS)/progression--free survival (PFS)	Treatment-related mortality (TRM)	Adverse drug reaction (ADR)
CGA-modulated studies						
Xu et al. (2022)	Unfit or frail: ibrutinib, rituximab, lenalidomide	Complete response rate: Unfit/frail: 56.7% (95% CI 37.4–74.5), overall response: 66.7% (95% CI 47.2–82.7)	2 years: Unfit/Frail (66.7%; 95% CI 46.9–80.5)	PFS: 2 years: 53.3% (95% CI 34.3-69.1)	Missing	Hematological grade 3–4 toxicity: neutropenia (23%) thrombocytopenia (10%), and anemia (7%)
Bocci et al. (2022)	Metronomic all-oral DEVEC [prednisolone/deltacortene, vinorelbine (VNR), etoposide (ETO), cyclophosphamide] combined with i.v. rituximab (R)	Overall response (ORR) and complete remission rate (CRR): 64%	2 years: frail: 54% (95% CI 32–72)	EFS: 54% (95% CI = 32––72)	Missing	Treatment-related serious adverse events (27%)
Bai et al. (2020)	Fit: R-CHOP, unfit + frail: R-CHOP with reduced dose of anthracycline, R-CVP, or R-miniCHOP	Fit (84.4%), unfit + frail (51.5%) (p = 0.002)	2 years: fit (98%), unfit + frail (69%) (p = 0.0013). 3 years: fit (91%), unfit + frail (69%) (p = 0.021)	2 years PFS: fit (72%), unfit + frail (69%) (p = 0.77). 3 years PFS: fit (72%), unfit + frail (35%) (p = 0.0013)	0%	Hematological grade 3–4 toxicity: fit (51.1%), unfit + frail (54.5%) (p > 0.05).
Storti et al. (2018)	Frail: bendamustine and rituximab	Frail: 53%	2 years: Frail (51%)	The median progression-free survival: 10 months	Missing	Total grade 3–4 toxicity (51.1%). Hematological grade 3–4 toxicity 46.7%). Non-hematologicalal grade 3–4 toxicity (15.6%)
Lastra-German et al. (2018)	Fit: R-CHOP, unfit: R-CHOP, frail: R-COP	Fit (66.6%), unfit (78.3%), frail (40.0%) (p = 0.121)	2 years: fit (87%, unfit (82%), frail (59%) (p = 0.159)	Mean 2-year disease-free survival (DFS): frail (87%), fit (100%) (p = 0.287).	Missing	Grade 3–4 hematological toxicity: fit (83.3%), unfit (65.2%), frail (45%) (p = 0.192). Nonhematological toxicity: fit (33%), unfit (65%), frail = 70%. (p = 0.445)
Merli et al. (2013)	Treatment of frail patients: polychemotherapy with anthracyclines (includes CHOP, mini-CEOP, CNOP, P-VEBEC); polychemotherapy without anthracyclines (includes CVP); mono-chemotherapy, radiotherapy, palliation	NR	Worse OS, hazard ratio: frail *vs.* fit: 3.09 (95% CI 2.2––4.33; p < 0.001)	NR	NR	Treatment-related complications/toxicity (22% of deaths, 18% of treated patients)

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Table 2 cont. Treatment, comprehensive geriatric assessment, and outcomes for frail older adults with diffuse large B-cell lymphoma

Studies	Treatment	Complete response (CR)	Overall survival (OS)	Event-free survival (EFS)/progression--free survival (PFS)	Treatment-related mortality (TRM)	Adverse drug reaction (ADR)
Spina et al. (2012)	A. No comorbidities: rituximab ± CHOP; Mild cardiopathy (NYHA class II or CIRS-G grade 2): R ± CEOP; Severe cardiopathy (NYHA class III/IV or CIRS-G grade ≥ 3): R ± CVP B. 100%, if ADL 6 or IADL 7–8; 75%, if ADL 5 or IADL 6; % (p = 0.11) 50%, if ADL < 5 or IADL < 5	Fit (85%), unfit (72%), frail (85%) (p = 0.34); > 80 y (83%); all (70.6%)	5 years: fit (76%), unfit (53%;), frail (29%) (p = 0.001)	5y EFS: 80% (> 80 y: 67%, p = 0.96); 5 y EFS: 52% (> 80 y: 46%, p = 0.06)	4%	Total grade 3–4 toxicity: fit (31%), unfit (48%), frail (58%) (p = 0.11). Toxic deaths (5%, 9%, and 11%, respectively) (p > 0.05)
Olivieri et al. (2012)	Fit: R-CHOP, intermediate: R-CDOP, frail: Mini-CHOP	Fit (81.5%), patients with comorbidities (64%), Frail (60%). Fit *vs.* frail + patients with comorbidities (p = 0.0408)	37 months. Fit (34%), patients with comorbidities (9.5%), frail (7.1%). Fit *vs.* frail + patients with comorbidities (p = 0.0044)	5 y EFS: fit (18.9%) patients with comorbidities (9.5%), frail (7.1%)	Early toxic deaths: fit (1.9%), patients with comorbidities (9.2%), frail (6.7%). Fit *vs.* frail + patients with comorbidities (p < 0.05	Hematological grade 3–4 toxicity: fit (7%), patients with comorbidities (0%), frail (7%). Fit *vs.* patients with comorbidities + frail (p > 0.05)
Non-CGA-modulated studies						
Tanaka et al. (2022)	CHOP-like (R-CHOP, R-CHOP + RTx; R-THPCOP; R-EPOCH; R-ECOP; R-CHOEP, CHOP) = 72 (92.3); low toxicity regimen (R-mini-CHP, = 6 (7.7); R-oral sobuzoxane and etoposide)	Dependent (70.7%); independent (78.4%)	4-year survival rate: independent (72.7%); dependent (56.9%).	Missing	Missing	Non-hematological toxicity: dependent (53.7%), independent (16.2%);
Zhang et al. (2022)	Anti-CD19 chimeric antigen receptor (CAR) T-cell therapy	ORR, CR, and PR rates in the fit group were 88.2%, 58.8%, and 29.4%, respectively, while the ORR, CR, and PR rates in the unfit/frail group were 64.3%, 42.9%, and 21.4%, respectively	Median OS in the fit group (not reached) was better	The fit group had a higher median PFS rate than the unfit/frail group (11.4 months *vs.* 7.0 months; p = 0.037)	Missing	Hematological grade 3–4 toxicity: fit (23.5%), unfit/frail (50%)
Merli et al. (2021)	Full dose: R-CHOP, R-COMP, R-VNCOPB, R-DAEPOCH, R-CNOP, R-CEOP Reduced dose: R-mini-CHOP and similar Palliative therapy: R-Bendamustine, R-CVP, R-other (without anthracycline), rituximab only RT, cyclophosphamide, surgery, etoposide, prednisone, metronomic chemotherapy	NR	3 years: fit (87%), unfit (69%), frail (42%) (p < 0.001)	NR	NR	NR

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Table 2 cont. Treatment, comprehensive geriatric assessment, and outcomes for frail older adults with diffuse large B-cell lymphoma

Studies	Treatment	Complete response (CR)	Overall survival (OS)	Event-free survival (EFS)/progression--free survival (PFS)	Treatment-related mortality (TRM)	Adverse drug reaction (ADR)
Isaksen et al. (2021)	Treatment intensity was divided into 4 categories: full-dose R-CHOP, attenuated R-CHOP, anthracycline-free regimen, and no chemotherapy	Missing	2 years: fit (82%); unfit (47%); frail (14%); $p < 0.001$).	Missing	Missing	NR
Ong et al. (2019)	Fit: R-CHOP (55/57), R-CHEP (1/57), R-PACEBOM (1/57), unfit: R-CHOP (16/29), R-miniCHOP (8/20), R-CEOP (3/29), R-CHEP (1/57), frail: R-CHOP (34/52), R-miniCHOP (11/52), R-CEOP (6/52), R-CNOP (1/52)	Missing	2 years: fit (90%), unfit (71%), frail (56%). 3-year: fit (82%), unfit (60%), frail (53%)	PFS: 2-year fit (79%); unfit (64%), frail (65%). 3-year fit (66%), unfit (58%), frail (46%)	Fit (4%), unfit (10%), frail (10%)	Any grade ≥ 3 toxicity: fit = 72%, unfit = 62%, frail = 79%
Tucci et al. (2015)	Unfit and frail: full-dose therapy (CHOP or CHOP-like regimens with rituximab). Remaining patients received palliation [low-dose chemotherapy without anthracyclines, and prednisone (COP), low-dose COP], rituximab as a single agent, corticosteroids alone, oral mono chemotherapy or anthracycline-based cycles at a relative dose intensity less than 70%)	ORR, overall response rate (complete remission + partial remission): curative unfit = 14 (82%), frail 13 (72%), palliative: unfit = 7 (64%), frail = 25 (52%)	2 years: fit (84%), non-fit (frail + unfit) (47%) $p < 0.0001$	Missing	Missing	Nonhematological toxicity of grade 3–4: curative or palliative intent (45% *vs.* 38%; $p = 0.3$)
Marchesi et al. (2013)	Curative anthracycline-based treatment, Full-intensity R-CHOP, attenuated R-CHOP, conservative without anthracyclines (R-CVP)	Irrespective of the type of treatment, the overall response (OR), the complete response (CR), and the failure rates were 80.5%, 55.2%, and 19.5%, respectively	Irrespective of the type of treatment, "fit" and "intermediate" patients had similar outcomes, whereas "frail" patients showed a significantly worse 2-year OS rate than the other two patient categories ($p < 0.001$)	2-year OS and PFS rates were 39.7%	Missing	Curative *vs.* conservative treatments and the CGA stratification did not significantly affect the occurrence of grades 3–4 toxicities and toxic death incidence

ADLs — activities of daily living; CEOP — cyclophosphamide, epirubicin, vinblastine, prednisone; CHOEP — addition of etoposide to CHOP mini-CHP subtraction of vincristine from 50% dose CHOP; CIRS-G — Cumulative Illness Rating Scale-Geriatric; CNOP — cyclophosphamide, mitoxantrone, vincristine, prednisone; COP — cyclophosphamide, vincristine, prednisolone; CVP — cyclophosphamide, vincristine, prednisone; DA-R-EPOCH (o R-DAELPOCH) — rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; DEVEC — prednisolone–etoposide–vinorelbine–cyclophosphamide; ECOP — addition of etoposide to COP; EPOCH — consists of continuously infused etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, IADLs — instrumental activities of daily living; NYHA — New York Heart Association; PACEBOM — prednisolone, doxorubicin, cyclophosphamide, etoposide, bleomycin, vincristine, and methotrexate; P-VEBEC — prednisone, vinblastine, epirubicin, bleomycin, etoposide, cyclophosphamide; R — rituximab; R-CHOP — rituximab + CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone); R-COMP — rituximab, cyclophosphamide, vincristine, myocet, prednisone; R-COP — rituximab + cyclophosphamide, vincristine, and prednisolone; RTx — radiotherapy; R-VNCOP-B — rituximab, etoposide, mitoxantrone, cyclophosphamide, vincristine, prednisolone, bleomycin; THPCOP — addition of pirarubicin to COP

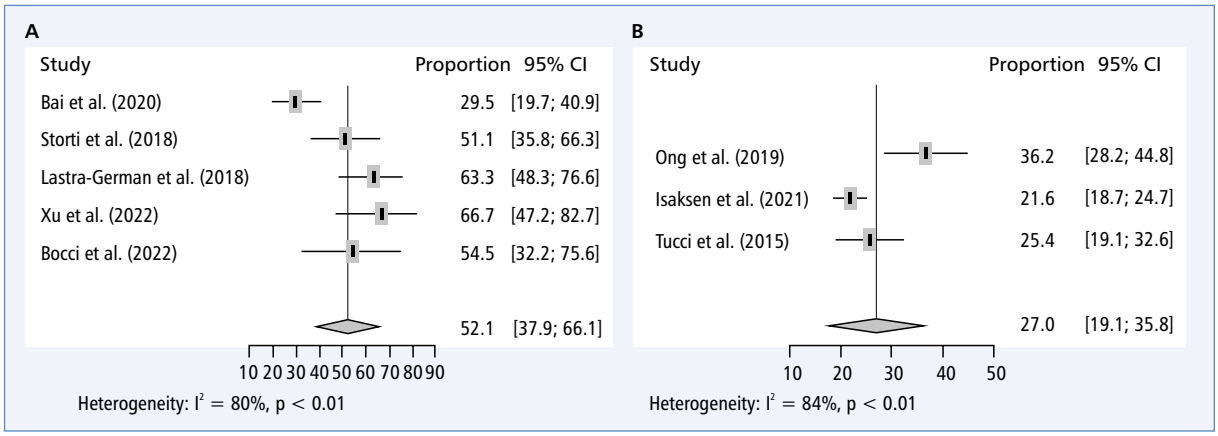

Figure 2. Forest plot of frequencies of two-year overall survival (OS) of frail/unfit patients; **A.** OS2: comprehensive geriatric assessment (CGA)-modulated studies; **B.** OS2: Non CGA-modulated studies; CI — confidence interval

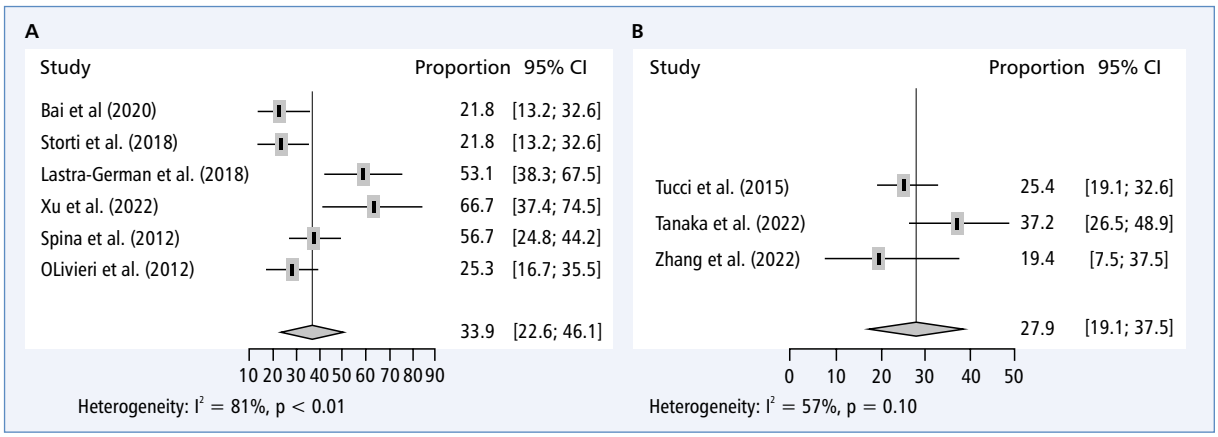

Figure 3. Forest plot of frequencies of complete response (CR) of frail/unfit patients; **A.** CR: comprehensive geriatric assessment (CGA)-modulated studies; **B.** CR: Non CGA-modulated studies; CI — confidence interval

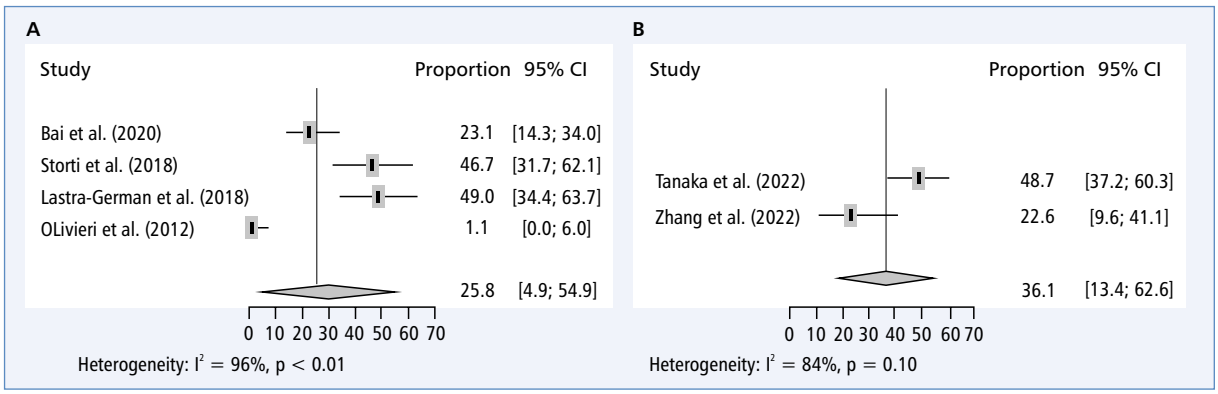

Figure 4. Forest plot of frequencies of grade 3–4 hematological toxicity in frail/unfit patients; **A.** Grade 3–4 hematologic toxicity in frail/unfit patients [comprehensive geriatric assessment (CGA)-modulated studies]; **B.** Grade 3–4 hematologic toxicity in frail/unfit patients (Non CGA-modulated studies); CI — confidence interval

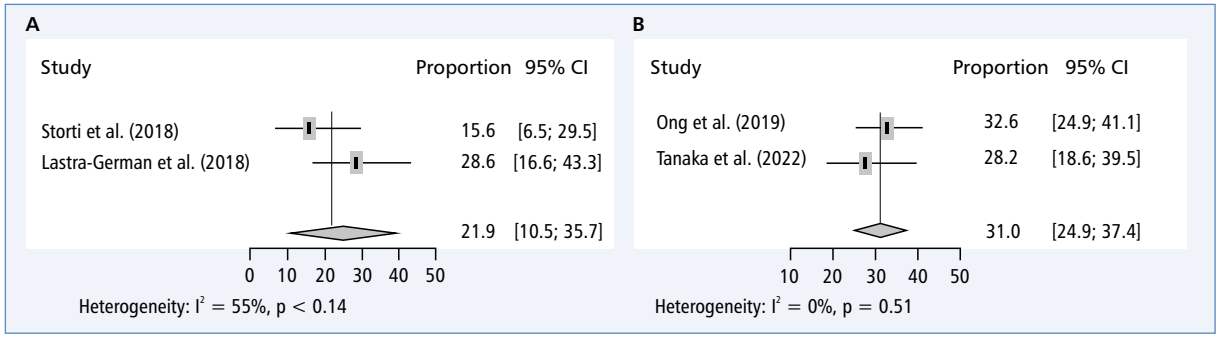

Figure 5. Forest plot of frequencies of grade 3–4 non-hematological toxicity in frail/unfit patients; **A.** Grade 3–4 hematologic toxicity in frail/unfit patients [comprehensive geriatric assessment (CGA)-modulated studies]; **B.** Grade 3–4 hematologic toxicity in frail/unfit patients (non CGA-modulated studies); CI — confidence interval

peutic scheme in older DLBCL patients, there are currently two approaches. The first supports the performance of CGA as a guide in the selection of a therapeutic scheme based on risk stratification [34]. The other approach, based on a 2019 consensus, does not recommend using CGA in determining the chemotherapy regimen for older DLBCL patients. However, it concedes that CGA is useful in identifying issues that may have been overlooked and clarifies that using CGA is not ruled out in cancer patients [35].

There may be mechanisms by which categorization of patients with CGA could improve outcomes, especially in frail DLBCL patients. This strategy could reduce overtreatment in frail and undertreatment in fit patients. Frail patients have been reported to have high treatment-related mortality, especially if treated with full-dose regimens [19, 29, 36]. Frail patients have high rates of treatment discontinuation due to adverse reactions, which leads to disease progression that affects their survival, and the low tolerance to chemotherapy can be partly explained by other comorbidities [29]. The severity of these comorbidities is detected during a CGA, in which instruments such as the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) can identify frailty when grade 3–4 comorbidities are present [37]. Modifying the dose of chemotherapy (R-CHOP) has been shown to decrease adverse reactions to chemotherapy in frail patients, without impairing the efficacy of treatment [18, 30]. In this regard, it has been postulated that the explanation for the reduced doses of anthracycline in frail patients having the same therapeutic results is that the half-life of this medication is prolonged due to the aging process and patients' comorbidities [12, 38, 39].

Comprehensive geriatric assessment is potentially one of the strategies to predict chemotherapy tolerability, that is, it could have prognostic capacity with regard to the severity of adverse reactions associated with chemotherapy. In our study, no significant differences were found in grade ≥ 3 hematological and non-hematological toxicity. The latter may be due to only 2 studies on each side of the comparison. Regarding instruments to predict adverse reactions in DLBCL patients, two strategies have been described, among which are the Elderly Prognostic Index (EPI) [22] and the Norwegian score [31]. However, it should be noted that the last two proposals contain data from CGA (e.g. activities of daily living and CIRS-G).

This study has some limitations. For example, the frail/unfit were compared as if they were a single group because most of the studies reported their data in this way. The analysis was not performed only with frail patients due to a small number of studies with such data. For the same reason, the meta-analysis was performed only with two-year OS because few studies reported data for three or five-year OS. Similarly, only a few studies reported the frequency of CR and grade 3–4 hematological and non-hematological toxicity. Carrying out a joint analysis of CGA as if it were a standard or homogeneous instrument might also be debatable, given that the different studies used different models for the CGA (sCGA, full CGA, and the phenotype model), which use different criteria (Tab. S2 in supplementary file). Another limitation of this study is that it only evaluated the usefulness of CGA in the reduction of the incidence of grade ≥ 3 toxicity and not in relation to specific types of adverse drug reactions (ADR). It is known that toxicities for chemo or non-chemo protocols may be different; for example, the ADR called "immune effector cell-associated neurotoxicity syndrome (ICANS)" occurs only with chimeric antigen receptor (CAR) T-cell therapy [40].

Conclusions

In conclusion, our metanalysis suggests that CGA could serve as a guide for the treatment plan in older DLBCL patients and lead to better patient survival. Randomized clinical trials are necessary to confirm these findings as well as the standardization and homogenization of the instruments used in CGA.

Article Information and Declarations

Author contributions

T.J.O.: concept and design, acquisition, analysis, and interpretation of the data, drafting of the manuscript, critical revision of the manuscript; X.V.: analysis, and interpretation of the data, critical revision of the manuscript; B.E.B.: acquisition, analysis, and interpretation of the data, drafting of the manuscript, critical revision of the manuscript; R.R.-O.: acquisition, analysis, and interpretation of the data, drafting of the manuscript, critical revision of the manuscript, supervision.

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Conflict of interest

None.

Supplementary material

Tables S1 and S2.

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Supplementary material

Table S1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist (from [13])

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	3
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies)	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12)	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot	6

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Table S1 cont. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist (from [13])

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression (see item 16)]	
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers)	7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias)	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	8
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review	1

Table S2. Frailty classification in older patients with diffuse large B-cell lymphoma

Study	Operational definition		
	Frail	Unfit	Fit
CGA-modulated studies			
Xu et al (2022)	Frail: ADL < 5; IADL < 6; CIRS-G: ≥ 1 grade 3–4 comorbidities or > 8 comorbidities grade 2 score; age ≥ 80 o morbidities), age ≥ 80 unfit	Unfit: ADL6-5; IADL ≤ 6–7; CIRS-G: no comorbidities score 3–4 and 5–8 comorbidities score 2, age ≥ 80 fit	Fit: ADL6-6; IADL = 8; CIRS-G: no comorbidities score 3–4 and < 5 comorbidities score 2
Bocci et al. (2022)	Frail: age ≥ 80 years and CIRS-G: ≥ 1 score = 3–4; ≥ 5 score 5 = 2; ADL < 6; and IADL < 8 scores	Unfit: < 80: CIRS-G: ≥ 1 score = 3–4; > 8 score = 2; ADL < 5; and IADL < 6; unfit: ≥ 80: CIRS-G: ≥ 0 score = 3–4; < score = 2; ADL = 6; and IADL = 8	
Bai et al. (2020)	Frail: ADL < 5 or IADL < 6; or MCIRS-G: ≥ 1 comorbidity score 3–4 (or > 8 comorbidity score 2) or age ≥ 80 yr unfit	Unfit: ADL = 5 or IADL = 6–7 or MCIRS-G = no comorbidity score 3–4 (and 5–8 comorbidity score 2) or; age ≥ 80 yr fit	Fit: ADL = 6 and IADL = 8 and MCIRS no comorbidity score 3–4 (and < 5 comorbidity score 2); and; age = And < 80 yr
Storti et al. (2018)	Frail: inpatients aged between 70 and 80 years, ADL < 4 or IADL < 5 or 1 grade 3 comorbidity or > 8 grade 2 comorbidities (CIRS-G) were required; in patients older than 80 years, ADL > 5 or IADL > 6 or 5–8 grade 2 comorbidities were required		

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Table S2 cont. Frailty classification in older patients with diffuse large B-cell lymphoma

Study	Operational definition		
	Frail	**Unfit**	**Fit**
Lastra-German et al. (2018)	≥ 3 points: frail 1. Unintentional loss of ≥ 5 kg during the past year 2. Physical exhaustion: The previous week… a) "Did you feel that everything required a lot of effort?"; b) „Did you feel that you could not go on?"; "Moderate amount" or "most of the time" in any circumstance scores as positive; 3. Low physical activity: Lowest quintile adjusted for gender; 4. Slowness: 4-meter gait speed below the lowest quintile adjusted for height*; 5. Weakness: grip strength below the lowest quintile adjusted for BMI	1–2 points: unfit	0 points: fit
Merli et al. (2013)	Frail: ≥ 80 years; or frail: < 80 years who were not fit according to one or more of the previous features were also considered as frail	Missing	Fit: < 80 years and had an ADL = 6, < 3 grade 3 CIRS-G comorbidities and no grade 4 comorbidities (hematological comorbidities were not investigated), and none of the criteria defining the presence of geriatric syndrome
Spina et al. (2012)	Frail: ADL < 5, or IADL < 5. CIRS-G: ≥ 1 grade 3 comorbidities (or > 5 grade 2 comorbidities)	Unfit: an ADL = 5, and/or an IADL = 5 or 6; CIRS-G: no grade 3 comorbidities (or 3–5 grade 2 comorbidities)	Fit: ADL = 6, and/or an IADL = 7 or 8; CIRS-G: no grade 3 comorbidities (or < 3 grade 2 comorbidities)
Olivieri et al. (2012)	Frail: age ≥ 85 years and dependence ≥ 1 ADLs and geriatric syndromes: ≥ 1. Frail: CIRS-G score ≥ 3	Patients with comorbidities: CIRS-G score 0–2	Fit (no frail, no patientes with comorbidities)
non-CGA-modulated studies			
Study	**Frail**	**Prefrail**	**Fit**
Tanaka et al. (2022)	Dependent: ≥ 1 problems in 6 CGA domains; a) ADL Barthel Index < 100; b) IADL (Lawton and Brody) < 5; c) Psychological status GDS-15 > 10; d) Cognitive function Hasegawa's dementia scale (HDS-R) ≤ 20; e) Nutritional status MNA < 17; g) Comorbidities Charlson comorbidity index ≥ 5 MNA < 17; comorbidities Charlson comorbidity index ≥ 5	Missing	Independent = remaining cases were definedas „independent"
Zhang et al. (2022)	Frail: > 80 y or ≤ 80 y with CIRS-G: any grade 3 or 4 comorbidities or > 8 grade 2 comorbidities or with higher scores on the ADLs/IADLs scales	Unfit ≥ 80y with an ADL = 5, an IADL = 6–7, CIRS-G: no grade 3 or 4 comorbidities, and 5–8 grade 2 comorbidities	Fit ≤ 80 y with normal ADLs and IADLs scores, CIRS-G: no grade 3 or 4 comorbidities, and < 5 grade 2 comorbidities

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Table S2 cont. Frailty classification in older patients with diffuse large B-cell lymphoma

Study	Operational definition		
	Frail	**Unfit**	**Fit**
Merli et al. (2021)	Frail: age ≥ 80 years and CIRS-G: ≥ 1 score = 3–4; ≥ 5 score 5 = 2; ADL < 6; and IADL < 8 scores	Unfit: < 80: CIRS-G: ≥ 1 score = 3–4; > 8 score = 2;ADL < 5; and IADL < 6 unfit: ≥ 80: CIRS-G: ≥ 0 score = 3–4; < score = 2; AD = 6; and IADL = 8	Fit: ≤ 80: CIRS-G: ≥ 0 score = 3–4; ≤ 8 score = 0; ADL ≥ 5; and IADL ≥ 6
Isaksen et al. (2021)	Frail: Katz Activities of Daily Living (ADL): independent = 1, dependent = 2; Charlson Comorbidity Index (CCI): score 0–1 = 1; score 2 = 1.5; score ≥ 3 = 2; Geriatric Nutritional Risk Index (GNRI): absent/low = 1; moderate = 2; severe = 2.5; age: < 85 = 1; ≥ 85 = 2; total score: multiply obtained scores (rank: 1–20) (example: ADL = 2, CCI = 2; GNRI = 2; age: 2. Total Score = 2 × 2 × 2 × 2 = 16). Frail: total score > 3	Unfit: score: 1.5–3	Fit score = 1
Ong et al. (2019)	Frail: those not meeting CGA-fit or unfit criteria were classified CGA-frail	Unfit: aged ≥ 80 years, with ADL = 5, IADL = 7, no CIRS-G grade 3–4 comorbidities and up to 5–8 grade 2 comorbidities	Fit: aged < 80 years, with no limitations in ADL (score 6/6) and IADL (score 8/8), CIRS-G no severe comorbidities grade 3–4/4 (excluding haematological comorbidities) and < 5 grade 2–4 comorbidities
Tucci et al. (2015)	Frail: ADL ≤ 4, IADL ≤ 5, CIRS-G ≥ 1 comorbidity score 3–4 or > 8 comorbidity score 2, age ≥ 80	Unfit: ADL ≤ 5, IADL ≤ 7–6, CIRS-G no comorbidity score 3–4 and 5–8 score 2, age ≥ 80	Fit: ADL ≤ 6, IAL ≤ 8, CIRS-G no comorbidity score 3–4 and < 5 score 2
Marchesi et al. (2013)	Frail (CGA 3): ≥ 1 of the following parameters: age > 85 years, presence of a geriatric syndrome, ADL score < 6) and ≥ 3 moderate morbidities or one or more severe morbidities	Intermediate (CGA 2) < 85 years old, ADL = 6; and at least one moderate morbidity but no geriatric syndromes	Fit: < 85 years, ADL = 6 and no moderate morbidities and geriatric syndromes

ADL — Activities of Daily Living; CIRS-G — Cumulative Illness Rating Scale-Geriatric; IADL — Instrumental Activities of Daily Living Scale

VIA MEDICA

REVIEW ARTICLE

Martyna Tyszka, Rafał Stec

Medical University of Warsaw, Warsaw, Poland

Niraparib maintenance in newly diagnosed advanced ovarian cancer — review and case series

Address for correspondence:
Martyna Tyszka, MD
Medical University of Warsaw,
Warsaw, Poland
e-mail: mtyszka@wum.edu.pl

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ABSTRACT

Introducing PARP inhibitors maintenance therapy into clinical practice significantly improved treatment outcomes in patients with high-grade platinum-sensitive advanced ovarian cancer, the most lethal gynecological malignancy. Niraparib is a potent PARP inhibitor whose safety and efficacy were assessed in the placebo-controlled, randomized clinical trial PRIMA. Niraparib significantly prolonged progression-free survival in the overall population of high-grade advanced ovarian cancer regardless of *BRCA1* and *BRCA2* mutation and homologous deficiency status compared to placebo. However, the most significant benefit was observed in *BRCA* mutated and homologous recombination deficient subgroups. Niraparib has a manageable toxicity profile and is well-tolerated by patients. Most common toxicities are hematological and can be managed with drug interruption and/or dose reduction that do not decrease efficacy. Niraparib is recommended for patients who responded to the first-line chemotherapy with platinum compound regardless of homologous recombination status. This review will discuss the use of niraparib in newly diagnosed advanced ovarian cancer patients focusing on its efficacy and tolerability. Additionally, a case series will be presented to further discuss this drug use in clinical practice in Poland.

Keywords: ovarian cancer, maintenance therapy, niraparib, PARP inhibitors, synthetic lethality

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Introduction

Epithelial ovarian cancer is the fifth most common type of cancer in women and the fourth most common cause of cancer death. The estimated number of new ovarian cancer cases worldwide in 2020 was 313 959, with 207 252 deaths. Approximately 30% of cases are diagnosed in Europe [1]. The incidence of ovarian cancer in Poland is about 15% higher than in other European Union countries, with 3 734 cases and 2 829 deaths in 2018 [2]. In most cases, diagnosis is made at an advanced stage. High-grade serous ovarian cancer (HGSOC), the most common ovarian cancer subtype, is conventionally treated with surgery and paclitaxel/carboplatin combination chemotherapy [3]. Initial response rates are 60–80%, but eventually, the majority of patients relapse. The addition of a third agent to the adjuvant chemotherapy or the use of high-dose sequential therapies increased the toxicity and did not benefit patients. Second and other lines of chemotherapy consisting of a platinum compound in the case of platinum sensitivity or pegylated liposomal doxorubicin, weekly paclitaxel, gemcitabine, etoposide or topotecan in the case of platinum-refractory or resistant relapse are used in clinical practice but usually with poor outcomes. In this landscape, the innovative maintenance treatment with poly (ADP-ribose) polymerase (PARP) inhibitors demonstrated an outstanding activity in ovarian cancer and changed clinical practice. Niraparib is an orally active small-molecule PARP inhibitor.

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Among 733 patients with newly diagnosed advanced ovarian cancer who had a response to platinum-based chemotherapy, those who received niraparib via participation in the PRIMA trial had significantly longer progression-free survival (PFS) than those who received placebo, regardless of the presence or absence of homologous-recombination deficiency (HRD) although the benefit was more significant in the HRD subgroup [4]. This review will discuss the use of niraparib in newly diagnosed advanced ovarian cancer patients focusing on its efficacy and tolerability. Additionally, a case series will be presented to further discuss this drug use in clinical practice in Poland.

Homologous recombination and PARP inhibitors

Homologous recombination (HR) is one of six main ways in which cells can repair DNA damage and one of two pathways for repairing double-strand DNA breaks (DSBs) [5]. Cells with homologous recombination deficiency (HRD) rely only on the second mechanism, Non-Homologous End Joining (NHEJ), a pathway that is less exact and more mistake prone, which predisposes for tumorigenesis [6]. In approximately 50% of all ovarian cancers, HRD is present due to mutations or epigenetic changes in HR pathway genes. The most common changes responsible for HRD are *BRCA1* and *BRCA2* germline and somatic mutations that can be found in up to 25% of ovarian cancer patients [7, 8]. Additional changes responsible for HRD are alterations in other genes like *PALB2, FANCA, FANCI, FANCL, FANCC, RAD50, RAD51, RAD51C, RAD54L, ATM, ATR, CHEK1*, and *CHEK2* [5]. *BRCA1* and *BRCA2* are the most widely studied genes which, when mutated, increase the risk of developing various cancers, mainly breast cancer (lifetime risk up to 60–85%) but also ovarian, pancreatic and prostate cancer [9]. Ovarian cancer patients with *BRCA1* and *BRCA2* mutations often present at an advanced stage and younger age. In this subgroup of patients, good responses to platinum and generally better outcomes are often observed. PARPs are a family of proteins that allow the transfer of ADP-ribose to various target proteins essential for vital cellular processes like proliferation and apoptosis, but not only. PARP-1 and PARP-2 isoforms are best known because of their role in DNA repair by base excision repair (BER) of the single-stranded DNA breaks (SSBs) and nucleotide excision repair (NER) [10–12]. Originally it was believed that PARP inhibition causes accumulation of SSBs which are converted to DSBs that cannot be repaired in the case of HRD and lead to the process called synthetic lethality resulting in cell death [13]. Recently novel models explaining synthetic lethality between PARPis and HRD focusing on PARP1 trapping at DNA damage sites have been proposed [5]. Regardless of an exact mechanism of synthetic lethality relying on PARP inhibition, it is still the only case when this concept was successfully translated into clinical practice.

Clinical efficacy of niraparib

Niraparib is a potent PARP-1 and PARP-2 inhibitor whose efficacy was first observed in *BRCA* mutated cell lines and in-vivo models [14]. Finally, the effectiveness in newly diagnosed ovarian cancer was confirmed in the pivotal double-blind, placebo-controlled, multicenter phase III trial PRIMA [4]. Patients aged 18 years and older with histologically confirmed advanced ovarian cancer of high-grade serous or endometrioid histology were offered participation in the study. The advanced disease was classified as the International Federation of Gynecology and Obstetrics (FIGO) stage III with visible residual tumor after primary debulking surgery, inoperable stage III disease or any stage IV disease. Patients who received neoadjuvant chemotherapy were not excluded.

All the patients had to receive six to nine cycles of first-line chemotherapy that included platinum compound and resulted in partial (PR) or complete response (CR). Tumor samples were evaluated for HRD defined as a deleterious *BRCA* mutation, 42 out of 100 points on the "Myriad MyChoice" test [calculated by the presence of the loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale state transitions (LST)] or both.

The trial was conducted in 20 countries at 181 clinical sites. Within 12 weeks after receiving the last cycle of the platinum-based chemotherapy, the patients were randomly assigned in a 2:1 ratio to receive oral niraparib or placebo. Randomization included stratification according to clinical response after first-line platinum-based chemotherapy, receipt of neoadjuvant chemotherapy, and status regarding tumor homologous recombination. Initially, patients were scheduled to receive a fixed dose of 300 mg once daily for 28-day cycles until disease progression or up to 36 months. However, the dose reduction rate due to a treatment-emergent adverse event (TEAE) was 68.9%, and the discontinuation rate due to TEAE was 14.7%, including 3.3% due to thrombocytopenia. Therefore, after analysis of factors predicting the risk of TEAE development, an amendment in the protocol was made to include an individualized starting dose of 200 mg once daily for patients with a baseline body weight of less than 77 kg, a baseline platelet count of less than 150 000/μL, or both. Importantly PFS in patients with dose reductions was consistent with those who remained on the dose of 300 mg [15]. During the trial, computed tomography (CT) or magnetic resonance (MR) imaging was per-

formed to assess progressive disease according to RECIST 1.1 every 12 weeks until treatment discontinuation.

The primary endpoint was PFS in patients who had tumors with HRD and in those in the overall population. Progression-free survival was defined as the time from randomization to the earliest date of objective disease progression on imaging or death from any cause. Overall survival was a key secondary endpoint. In total, 733 patients underwent randomization, and 728 received treatment.

Patient characteristics at baseline were well-balanced between the two trial groups. Of the 733 patients, 373 (50.9%) had tumors with HRD based on myChoice testing, including 223 tumors with *BRCA* mutations.

In the overall population, niraparib treatment significantly prolonged the median duration of PFS to 13.8 months compared to 8.2 months with placebo ($p < 0.001$). Niraparib significantly prolonged the median duration of PFS in the HRD group [21.9 months with niraparib and 10.4 months with placebo ($p < 0.001$)]. Within this population, the median duration of PFS for $BRCA_{mut}$ patients was slightly more prominent compared to patients with HRD but not $BRCA_{mut}$ (Tab. 1). The overall survival data are not mature yet, but the interim analysis showed that niraparib significantly increased the chance for survival of 24 months in the overall population and the HRD group.

Niraparib efficacy was recently confirmed in PRIME trial comparing niraparib maintenance therapy with placebo in a larger population of patients with advanced serous or endometroid high grade ovarian cancer patients that responded to the chemotherapy with platinum. In this study niraparib maintenance significantly prolonged the PFS for the whole population regardless of *BRCA* status or cytoreductive surgery outcome (24.8 months with niraparib *vs.* 8.3 months with placebo; $p < 0.001$) [16].

Regarding the combination maintenance therapy of niraparib with bevacizumab, its safety in newly diagnosed advanced ovarian cancer was assessed in the OVARIO study which was a phase II, single-arm, open-label trial that showed promising results and safety profiles consistent with those known from bevacizumab and niraparib monotherapy [17]. The phase III trial, which aims to compare the efficacy of the niraparib monotherapy maintenance with combined niraparib and bevacizumab maintenance therapy in patients with FIGO III/IV (except FIGO stage IIIA2 without nodal involvement) ovarian cancer regardless of *BRCA* status and debulking surgery outcome, is about to start recruitment (NCT05009082).

Safety and tolerability

In the PRIMA trial, TEAEs, especially of grades 3 and 4 according to Common Terminology Criteria for Adverse Events (CTCAE), were more frequently reported in the niraparib group compared to placebo, which was consistent with the class effects of PARP inhibitors (Tab. 2).

The most common complaints from the patients were slight nausea, constipation, and fatigue. The most frequent adverse effects of grade 3 and higher were hematological: anemia in 31% of patients, neutropenia in 12.8%, and thrombocytopenia in 28.7%. Dose reduction due to the TEAEs occurred in 70.9% of patients receiving niraparib, and 12% discontinued the treatment. In the PRIMA trial, there were no treatment-related deaths reported.

Recommendations on ovarian cancer and the use of niraparib in ovarian cancer treatment in Poland

Several guidelines recommend niraparib as a maintenance treatment option for newly diagnosed ovarian cancer. According to National Comprehensive Cancer Network (NCCN), niraparib is a recommended post-primary treatment option in patients with FIGO II–IV ovarian cancer with CR or PR according to RECIST

Table 1. Efficacy of niraparib in the PRIMA trial

	PFS (months)		HR
	Niraparib (n)	Placebo (n)	
Overall population	13.8 (487)	8.2 (246)	0.62 95% CI, 0.50 to 0.76
HRD	21.9 (247)	10.4 (126)	0.43 95% CI, 0.31 to 0.59
$BRCA_{mut}$	22.1 (152)	10.9 (71)	0.40 95% CI, 0.27 to 0.62
HRD but not $BRCA_{mut}$	19.6 (95)	8.2 (55)	0.50 95% CI, 0.31 to 0.83
HRp	8.1 (169)	5.4 (80)	0.68 95% CI, 0.49 to 0.94

CI — confidence interval; HRD — homologous recombination deficiency; $BRCA_{mut}$ — *BRCA mutated*; HR — hazard ratio; HRp — homologous recombination proficiency; N — number of patients; PFS — progression-free survival

Table 2. Treatment-related adverse events of special interest in the PRIMA trial

Adverse Events	Niraparib (n = 484)	Placebo (n = 244)
	n (%)	
Any	478 (98.8)	224 (91.8)
Grade ≥ 3	341 (70.5)	46 (18.9)
Leading to dose reduction	343 (70.9)	20 (8.2)
Leading to discontinuation	58 (12)	6 (2.5)
Adverse events of special interest		
Anemia		
Any grade	307 (63.4)	43 (17.6)
Grade ≥ 3	150 (31.0)	4 (1.6)
Nausea		
Any grade	278 (57.4)	67 (27.5)
Grade ≥ 3	6 (1.2)	2 (0.8)
Thrombocytopenia		
Any grade	222 (45.9)	9 (3.7)
Grade ≥ 3	139 (28.7)	1 (0.4)
Neutropenia		
Any grade	128 (27.5)	16 (6.6)
Grade ≥ 3	62 (12.8)	3 (1.2)

1.1 after chemotherapy with a platinum compound who did not receive bevacizumab regardless of *BRCA* and HRD status. In patients with *BRCA* mutation, after treatment with bevacizumab, niraparib is an option if a combination of bevacizumab and olaparib is not available [18]. According to European Society for Medical Oncology (ESMO), niraparib for 36 months is recommended for FIGO III and IV HRD population with CR or PR after primary chemotherapy without bevacizumab. In the case of negative or unknown HRD status, a decision on niraparib treatment should be made individually as long-term outcome data in this setting are not available [19]. American Society of Clinical Oncology (ASCO) guidelines state that all patients with newly diagnosed stage III–IV high-grade serous or endometrioid epithelial ovarian cancer with CR or PR after first-line platinum-based chemotherapy should be offered maintenance therapy with niraparib while the subgroup of patients with *BRCA1/2* mutations should be treated with olaparib [20].

Since the 1st of January 2022, niraparib has been available in Poland for the patients with advanced (FIGO III and IV) high-grade ovarian or fallopian tube and primary peritoneal cancer irrespective of *BRCA* or HRD status who responded to platinum-based chemotherapy. Detailed inclusion and exclusion criteria are listed in Table 3. Treatment in a maximal dose of 300 mg daily must be initiated within 12 weeks after the last dose of chemotherapy and can last up to 36 months.

Table 3. Inclusion and exclusion criteria for the niraparib prescription program in Poland

Inclusion criteria	Exclusion criteria
High grade ovarian, fallopian tube or primary peritoneal cancer of stage: — FIGO III with *BRCA1/2* mutation regardless of the status of primary debulking surgery or — FIGO III after primary debulking surgery or — FIGO III or IV after neoadjuvant chemotherapy or — FIGO IV	Hypersensitivity to the active substance or to any of the excipients Breast feeding Progresive disease Persistent grade 3 adverse events Any medical condition making the treatment unfeasible as per physician decision
PR or CR according to RECIST 1.1 after 1st line chemotherapy with platinum PS 0–1 > 18 years old Hemoglobin level ≥ 10 g/dL WBC ≥ 3000/μL ANC ≥ 1500/μL Platelets ≥ 100 000/uL Bilirubin level < 1.5 × UNL (excluding patients with Gilbert syndrome) ALT and AST < 2.5 × UNL (< 5 when liver metastasis present) Creatinine level < 1.5 × UNL Patient is not pregnant	

ANC — absolute neutrophile count; AST — aspartate transaminase; ALT — alanine transaminase; CR — complete response; FIGO — The International Federation of Gynecology and Obstetrics staging system; PR — partial response; WBC — white blood cells; UNL — upper normal limit

Case series

Before the year 2022, our department was participating in an expanded access program (EAP) offering niraparib to patients with advanced platinum-sensitive ovarian cancer. Inclusion criteria were age 18 and older, diagnosis of advanced high-grade ovarian, fallopian tube or primary peritoneal cancer, PR or CR after first-line platinum-based chemotherapy, ANC ≥ 1500/μL, platelets ≥ 100.000/μL, hemoglobin level ≥ 9 g/dL, sufficient liver and renal function. Exclusion criteria were severe, uncontrolled medical condition, hematological toxicity of grade ≥ 3 lasting for more than four weeks, uncontrolled hypertension, hypersensitivity to the active substance or any of the excipients, diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), qualification or participation in a clinical trial involving niraparib, pregnancy and breastfeeding.

Between January and April 2021, four patients were enrolled in the program. All patients were diagnosed with advanced high-grade serous ovarian cancer (FIGO IIIA to FIGO IVB), one was *BRCA1* mutated, and one was

diagnosed with HRD on the basis of LOH. All patients underwent primary cytoreductive surgery and 6 to 8 cycles of adjuvant carboplatin-paclitaxel chemotherapy that resulted in PR or CR according to RECIST 1.1. All the patients initiated the niraparib treatment with an individualized starting dose of 200 mg once daily. To avoid nausea, they were instructed to take the medication at bedtime. Two patients underwent dose reduction, one due to grade 2 thrombocytopenia according to CTCAE during the first cycle and one due to grade 3 anemia according to CTCAE that required blood transfusion after completing the ninth cycle. The last patient also complained of double vision and moderate headaches lasting for a few days. Similar symptoms occurred twice in the past years. The patient underwent a detailed ophthalmologist evaluation that did not reveal the underlying cause. The consulting neurologist ordered a brain MR that did not show any signs of metastasis, bleeding or posterior reversible encephalopathy syndrome (PRES). Double vision resolved without causative treatment during one week break from niraparib. The patient was rechallenged with a reduced dose of 100 mg, and we did not observe the symptoms' recurrence. Our patients were monitored weekly during the first cycle with complete blood count and later on monthly with complete blood count, liver and kidney function and Ca-125 blood tests. CT was performed every 3–6 months. At the time of publication, all of the patients were stable on niraparib treatment (treatment time 16–18 months).

Details on patient characteristics and treatment are listed in Table 4.

Discussion

Along with other PARPi, niraparib has shown a great benefit in patients with advanced ovarian cancer in the first-line maintenance treatment and should be considered in every patient that responded to first-line platinum-based chemotherapy. Niraparib shows a good tolerability profile with patient-reported outcomes. In PRIMA trial there were no decrease in health-related quality-of-life scores, including Functional Assessment of Cancer Therapy — Ovarian Symptom Index (FOSI), EuroQol-5 Dimensions (EQ-5D), and European Organisation for Research and Treatment of Cancer quality of life questionnaire for ovarian cancer patients EORTC-QLQ-C30/OV28 questionnaires [4]. Our experience with niraparib shows excellent tolerability, and our patients did not complain of drug-related symptoms.

The biggest concern during niraparib treatment is hematological toxicity leading to dose reduction. Post-hoc analysis from the preceding NOVA trial assessing the niraparib efficacy in recurrent ovarian cancer showed lower body weight and platelet count as predictive factors for hematologic toxicities and dose reductions. Based on these findings, the PRIMA trial protocol was amended to include individualization of the starting dose. Furthermore, the efficacy was not decreased in the group with an individualized starting dose [21].

Since the introduction of niraprab into the clinical practice, some concerns regarding an increased risk of developing secondary MDS and AML have been discussed but with scarce data. In the PRIMA trial, one patient was diagnosed with MDS in the niraparib group [4]. Beyond the PRIMA trial, cases of AML and MDS were seen in patients receiving niraparib in monotherapy or combined therapy from 0.5 months to more than 4.9 years (in total, 15 cases in 1785 patients). All cases were secondary MDS/AML in patients receiving chemotherapy, including platinum compounds and others resulting in DNA changes [22]. The latest meta-analysis of 28 randomized clinical trials from 2021 showed that PARPi treatment significantly increased the risk of developing MDS and AML with an incidence of 0.73%

Table 4. Niraparib EAP patients and treatment characteristics

Age	48	44	64	57
HRD	Yes	No	Yes	No
$BRCA_{mut}$	Yes	No	No	No
FIGO stage	IVA	IIIA	IIIC	IIIC
Surgical intervention	Primary debulking surgery — R1	Primary debulking surgery — R0	Primary debulking surgery — R1	Primary debulking surgery — R1
Chemotherapy	6 cycles of CBDCA + PXL	6 cycles of CBDCA + PXL	8 cycles of CBDCA + PXL	6 cycles of CBDCA + PXL
Starting dose	200 mg	200 mg	200 mg	200 mg
Serious adverse events	Thrombocytopenia G3	No	Anemia G3	No
Dose reduction	Yes	No	Yes	No
Treatment time (months)	19	17	17	16

HRD — homologous recombination deficiency; $BRCA_{mut}$ — *BRCA mutation;* CBDCA — carboplatin; PXL — paclitaxel

compared to 0.47% in the placebo group [23]. Another concern voiced by the European Medicine Agency (EMA) is the risk of hypertension, as grade 3 or 4 hypertension was reported in 6% of the niraparib group in the PRIMA trial. Therefore, weekly blood pressure monitoring is recommended for the first two months and later monthly for the first year [22].

In our patient, symptoms of double vision raised concerns about PRES syndrome, a rare reversible neurological disorder presenting with rapidly evolving symptoms including headache, seizures, visual disturbance or cortical blindness, with or without hypertension. Its etiology is complex, but it was observed after treatment with many oncological agents like bevacizumab, kinase inhibitors, gemcitabine and cisplatin. When clinically suspected, diagnosis is confirmed by MR. PRES during niraparib treatment was reported in clinical trials and post-marketing sources as early as within the first month. However, the total incidence is expected to be lower than 0.1%, and no patient was diagnosed with PRES in the PRIMA trial [22].

Article Information and Declarations

Conflict of interest

Authors declare no conflict of interest.

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VIA MEDICA

REVIEW ARTICLE

Adam Płużański[1], Andrzej Tysarowski[2], Maciej Kawecki[3], Jakub Kucharz[4], Kinga Winiarczyk[1], Maciej Krzakowski[1]

[1]Department of Lung and Chest Cancer, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[2]Department of Genetic and Molecular Diagnostics of Cancer, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[3]Department of Oncology and Radiotherapy, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[4]Department of Urogenital Cancer, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Use of next-generation sequencing in daily routine practice

Address for correspondence:
Adam Płużański, MD PhD
Department of Lung and Chest Cancer,
Maria Sklodowska-Curie National Research Institute of Oncology
ul. Roentgena 5, 02–781 Warsaw, Poland
e-mail: Adam.Pluzanski@pib-nio.pl

Translation: dr n. med. Dariusz Stencel
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ABSTRACT

Developments in molecular diagnosis and implementation of mutation-driven targeted therapy marked a milestone in cancer treatment. Next-generation sequencing allows sequencing of a high number of nucleotides in a short time and from a limited quantity of pathology or cytology specimens. This is a review of actual indications, utility of next-generation sequencing, and availability of targeted therapies in different neoplasms. We present the European Society for Medical Oncology Precision Medicine Working Group recommendations for tumor multigene sequencing use with the Scale for Clinical Actionability of molecular Targets ranking determined for each alteration.

Keywords: next-generation sequencing, targeted therapy, experts recomendations

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Introduction

Next-generation sequencing (NGS) is currently the most advanced method of molecular biology used in genetic diagnostics. The main advantage of NGS is its ability to evaluate many genetic markers and classes of mutations during one test and from one tissue or cell sample. A growing understanding of the underlying molecular biology of cancer accelerates the development of targeted therapy. However, the availability of drugs targeting these genetic abnormalities varies between solid tumors. We present a review of current indications for NGS in daily clinical practice, taking into account the recommendations of the European Society of Medical Oncology (ESMO) Precision Medicine Working Group.

Methodology of next-generation sequencing

Biological material for genetic testing should be collected after obtaining patients' written consent for diagnostic genetic testing and sent directly for pathological evaluation. Based on qualitative and quantitative assessment of tissue samples and tumor cell percentages, the pathologist evaluates if the sample is suitable for molecular testing and selects the most representative specimen. The diagnostic material is usually paraffin-embedded tissue and, alternatively, cytological preparations (cytoblocks or smears) or, in selected situations, circulating tumor DNA (ctDNA). Before the molecular analysis, a histological preparation is made from the paraffin block, which enables morpho-

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logical verification in terms of the content and location of cancer cells in the preparation. Evaluated preparations should contain not less than 20% of tumor tissue. The amount of nucleic acids necessary for NGS analysis, depending on the test manufacturer, is on average about 200 ng of DNA/RNA. The quality of the isolated nucleic acids is crucial. Quantification should be based on measurement using a fluorometer, a device based on the fluorescence intensity of fluorescent dye binding to DNA/RNA. Quality assessment (integrity and presence of enzyme reaction inhibitors) is measured by dedicated quality tests using the polymerase chain reaction (qPCR).

Genetic abnormalities can be assessed at the RNA- and DNA-level. It should be emphasized that in the case of identifying gene fusions, NGS is currently the gold standard, evaluating genetic variations at the RNA level. The main advantages of this method for identification of gene fusions are: high sensitivity and specificity, the ability to identify many gene fusions during one test, the ability to identify fusion partners and the exact locations of breakpoints in the identified fusion partners, the ability to assess whether the identified fusion is contained in the reading frame (pathogenic variant, functional or non-functional, with no clinical relevance). In addition to pointing at mutations, small deletions/insertions, and gene fusions, it is also possible to test for microsatellite instability (MSI) and tumor mutation burden (TMB, number of mutations per 1 million base pairs of the cancer genome), as well as the homologous recombination deficiency (HRD).

In cases of identifying a rare mutation variant or fusion variant not yet reported, the results of NGS should be confirmed by another method. Sanger sequencing, a method of DNA sequencing, which can verify variants or fusion junctions in DNA is typically used to confirm changes.

The genetic test report should contain the result, its precise interpretation understandable to the clinical oncologist and pathologist, as well as the description and scope of the method used. The laboratory issuing the result should have a confirmation of the current certification of the European external quality control program for a given test. NGS results should be available within 20 working days from sample delivery.

Genetic tests must be performed using equipment with full documentation of repairs, validations, and annual inspections (Ministry of Health regulation of March 21, 2006 [1]). The laboratory must meet the requirements described in the Ministry of Health Regulation on standards for medical diagnostic and microbiology laboratories [2].

Determining the value of NGS tests in clinical practice

The indications and value of NGS tests in individual cancers were the subject of recommendations of ESMO Precision Medicine Working Group experts [3]. The indications for performing NGS in daily clinical practice were evaluated in comparison to molecular diagnostics methods currently used. Based on the analyzes performed, individual genetic disorders were classified according to the ESMO Scale for Clinical Actionability (ESCAT), depending on the availability of the appropriate drug in daily clinical practice (Tab. 1 and 2). It should be highlighted, that the cost of NGS tests is higher than the cost of simpler molecular diagnostics methods. This is especially true for indications where the availability of drugs targeting particular molecular pathways is limited.

Non-small cell lung cancer

Activating mutations in the *EGFR* gene were the first to be investigated and constituted the basis for advances in the treatment of patients with advanced non-small cell lung cancer (NSCLC) of non-squamous type [4]. For the most common activating mutations, such as deletion in exon 19 and point mutation in exon 21 (L858R), all 3 generations of tyrosine kinase inhibitors (TKI) (erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib) are active. Many randomized studies have demonstrated the effectiveness of these drugs in EGFR-positive NSCLC [5–7]. Rare mutations involving exons 18–21 of the *EGFR* gene (G719X exon 18, L861Q exon 21, S768I exon 20) have been shown in several non-randomized studies to be associated with prolongation of progression-free survival (PFS) in patients

Table 1. Scale for clinical actionability of the observed genetic disorders

ESCAT Level	Definition
I	Drug has clinically proven activity in a given molecular disorder and is used in clinical practice
II	Drug activity was demonstrated in phase I and II clinical trials or retrospective analyzes of randomized controlled trials
III	Drug activity is observed in genetic disorders in another indication
IV	Potentially treatable genetic disorders observed in preclinical studies

ESCAT — ESMO Scale for Clinical Actionability

Table 2. ESMO Scale for Clinical Actionability (ESCAT) levels for selected molecular abnormalities in various cancers

Diagnosis	Genetic disorder	ESCAT level
NSCLC	*EGFR* — del19, L858R, acquired T790M exon 20, other (G719X ex18, L861Q exon 21, S768I exon 20)	I
	ALK, *MET* exon 14, *BRAF* V600E, *ROS1*, *NTRK*, *RET*	
	EGFR — exon 20 insertions	II
	MET amplification, *KRAS* G12C, *HER2*	
Prostate cancer	*BRCA 1 and 2*, MSI-H	I
	PTEN, *ATM*, *PALB2*	II
Cholangiocarcinoma	*FGFR2*, *IDH1*, *NTRK*	I
	BRAF V600E	II

NSCLC — non-small cell lung cancer

receiving afatinib and Osimertinib [8, 9]. In the group of patients with an *EGFR* gene exon 20 insertion, mobocertinib was shown to be effective in terms of PFS [10]. The drug received Food and Drug Administration (FDA) approval for the treatment of NSCLC patients with exon 20 insertion after failure of platinum-based chemotherapy. Amivantamab was granted European marketing authorization for this indication. In a phase II study, 40% objective responses and a median time to disease progression of 8.3 months were observed among patients treated with amivantamab after chemotherapy failure [11].

In patients with disease progression on first- or second-generation tyrosine kinase inhibitors, the presence of the T790M resistance mutation in exon 20 should always be assessed. Confirmation of the presence of this disorder is an indication for osimertinib treatment [12].

Another molecular disorder assessed during diagnostics of advanced non-squamous NSCLC is rearrangement in the *ALK* gene. Many randomized studies have confirmed the effectiveness of ALK tyrosine kinase inhibitors in patients with confirmed *ALK* gene rearrangement [13–16]. Three generations of ALK pathway inhibitors are currently used in clinical practice — crizotinib, alectinib, brigatinib, ceritinib, and lorlatinib.

In patients with advanced NSCLC with *MET* gene exon 14 skipping mutation (METex14), the efficacy of tepotinib and capmatinib was confirmed based on a significantly increased objective response rate (ORR) [17, 18]. Both drugs have received European registration for use in patients with METex14 after failure of previous immunotherapy and/or platinum-based chemotherapy.

The V600E mutation in the *BRAF* gene occurs in 2% of patients with non-squamous NSCLC. The combination of dabrafenib and trametinib has been shown to be effective in patients with this disorder [19].

In patients with *NTRK* gene fusion, the efficacy of entrectinib was confirmed in phase I and II studies (STARTRK-1, STARTRK-2), and the drug was registered by the European Medicine Agency (EMA) [20]. Entrectinib is also active in patients with *ROS1* gene fusion.

The G12C mutation in the *KRAS* gene occurs in approximately 12% of patients with non-squamous NSCLC. The effectiveness of sotorasib in the treatment of patients with NSCLC with the G12C mutation of the *KRAS* gene after failure of chemotherapy and immunotherapy was evaluated in the CodeBreaK100 [21] and Code-Break200 studies, which compared the efficacy of the drug with docetaxel. The approximately 18-month follow-up confirmed improvement in PFS (HR = 0.66; 95% CI 0.51–0.86; p = 0.002) and ORR (28.1 *vs.* 13.2%) after sotorasib treatment compared to docetaxel [22]. Another drug active in this group of patients is adagrasib, which was evaluated in the phase I/II KRYSTAL study in the population of patients with the *KRAS* gene mutation after failure of chemotherapy and immunotherapy. The primary endpoint was the objective response rate, which was 42.9%; the median time to disease progression was 6.5 months, and overall survival was 11.7 months [23]. Selpercatinib, a small-molecule RET kinase inhibitor showed efficacy in a phase I/II study, in the form of an increased objective response rate (ORR) in patients with NSCLC with *RET* gene fusions [24]. Mutations in the human epidermal growth factor receptor 2 (HER2), which is a member of the ErbB family of receptor tyrosine kinases, occur in about 3% of patients with NSCLC. In patients with HER2-positive NSCLC after chemotherapy failure, the efficacy of the immunoconjugate trastuzumab derukstecan was confirmed. The objective response rate, which was the primary endpoint in a phase II study, was 55%, and the mean time to disease progression was 8.2 months [25].

Taking into account the increasing number of molecular disorders assessed when qualifying patients with advanced non-squamous NSCLC for treatment and the possibility of using appropriate molecularly targeted therapy in daily clinical practice, it seems reasonable to use NGS, which is in line with the ESMO recommendations for NGS testing in patients with non-squamous lung cancer to detect treatable ESCAT Level I molecular changes. If appropriate drugs are available, NGS should also capture a broader gene profile.

Urogenital neoplasms

Undoubtedly advances in the treatment of patients with urinary tract neoplasms result, among others, from the introduction of more and more accurate diagnostic methods and several new therapeutic strategies into clinical practice. The latter include application of the so-called modern hormonal drugs at various stages of treatment in patients with metastatic prostate cancer [26], targeted therapies and immunocompetent drugs in patients with renal cell carcinoma (RCC) [27], as well as immunotherapy, antibody-cytostatic conjugates, and targeted therapies in patients with urothelial cancer [28]. However, it should be remembered that not all patients benefit from treatment, which may additionally be associated with significant toxicity, therefore, it is extremely important to search for biomarkers that allow for treatment personalization.

Castration-resistant prostate cancer

Molecular tests indicate that approximately 30% of patients with castration-resistant prostate cancer (CRPC) have abnormalities in DNA repair genes. Germline mutations are present in about 12% of patients, and the frequency of somatic mutations increases with disease progression [29]. Therefore, the efficacy of poly (ADP-ribose) polymerase (PARP) inhibitors in this indication was assessed. Based on the PROfound study, olaparib was approved [26]. It should be emphasized that the EMA indication [treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) with confirmed germline or somatic mutation in *BRCA1* or *BRCA2* genes] and the FDA-registered indication [mCRPC with the presence of germinal or somatic mutations in homologous recombination repair (HRR) genes] are different. Another PARP inhibitor, rucaparib, received FDA accelerated approval in patients with mCRPC with a mutation in the *BRCA1/2* gene after previous use of new hormonal drugs and docetaxel [27]. The drug is not registered in this indication by the EMA.

Combinations of PARP inhibitors with new hormone therapy (e.g. abiraterone or enzalutamide) may also be a therapeutic option in patients with mCRPC. The PROpel study evaluated the combination of abiraterone acetate with olaparib compared to abiraterone acetate with placebo — in the general population, median radiographic PFS (rPFS) was longer by more than 8 months (HR = 0.66; 95% CI 0.54–0.81) [30]. In a subgroup analysis, a greater benefit was found in patients with mutations in HRR genes. OS data is immature. In the MAGNITUDE study, the benefit of combining niraparib with abiraterone acetate was evaluated in patients with mutations in HRR genes, and it was greater in patients with mutations in *BRCA1* and *BRCA2* genes [31]. In countries where PARP inhibitors can be used in this indication, NGS is recommended in patients with advanced prostate cancer (recommendation I).

Urothelial carcinoma

Patients with metastatic urothelial carcinoma (mUC) continue to have a poor prognosis. Platinum-based chemotherapy (preferably cisplatin) is the primary treatment, which allows for obtaining short-term disease control in the majority of patients (about 20% of patients show primary resistance to treatment) [32]. Prolongation of OS is possible after use of maintenance immunotherapy [33].

Erdafitinib, a fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor, is a targeted therapy registered by the FDA for the treatment of patients with mUC. The FGF pathway is associated with the proliferation, migration, and invasiveness of cancer cells. Mutations or rearrangements are found in about 20% of patients with mUC, and significantly more often in urothelial carcinoma of the upper urinary tract. In a pivotal study, the use of erdafitinib in patients with the aforementioned disorders previously receiving systemic treatment resulted in an objective response rate of approximately 40% [34]. RT-PCR is the recommended test for routine diagnostics.

Renal cell carcinoma

Systemic treatment of patients with renal cell carcinoma (RCC) has progressed with the use of targeted drugs (multikinase inhibitors) and immune checkpoint inhibitors (ICIs) (alone or in combination) as well as sequential treatment. Molecular predictors for these therapies have not yet been determined. It is worth noting, however, that approximately 13% of patients with papillary carcinoma have overexpression of MET kinase. Based on the results of the SWOG1500 (PAPMET) study, in the treatment of RCC patients with this disorder, cabozantinib is preferred due to its activity against the HGF/MET pathway [35]. It is worth noting that in the SAVOIR study savolitinib, an MET inhibitor, was not significantly more effective compared to sunitinib and is not registered in the treatment of patients with RCC [36]. There are no ESCAT recommendations regarding genetic diagnostics in RCC patients.

Breast cancer

Due to the availability of routine diagnostic methods (RT-PCR, immunohistochemistry), which enable qualification for targeted therapy, NGS with the use of tumor sample is not recommended in routine clinical practice in breast cancer patients [3]. On the other hand,

assessment of germline mutations in *BRCA1/2* genes using the NGS method is already a common diagnostic standard, aimed at qualifying patients for targeted therapies or modifying standard treatment regimens.

Ovarian cancer

Due to the greater sensitivity to PARP inhibitors in patients with ovarian cancer with the *BRCA1/2* gene mutation, the ESCAT recommendations allow for the routine use of multi-gene NGS panels to identify this population [3]. The NGS study plays an important role in this case because it allows not only for determination of the status of *BRCA1/2* genes but also the so-called HRD genomic signature. In addition, it should be highlighted that the benefit of PARP inhibitors in patients with ovarian cancer is probably independent of the *BRCA1/2* genes status, which reduces the practical advantages of using NGS [37].

Gastrointestinal (GI) neoplasms

For almost two decades, targeted therapies have been an important element in the treatment of some GI malignancies [38]. Initially, it concerned selected cancers (colorectal cancer or hepatocellular carcinoma), but emerging new molecular targets expanded the range of indications. The need to detect appropriate biomarkers, necessary to benefit from the use of some drugs, has led to spreading of comprehensive molecular diagnostics (including NGS). At the same time, the routine use of polygenic panels in clinical practice is limited to some patients with gastrointestinal cancers.

Colon cancer

Modern treatment of patients with metastatic colorectal (CRC) or rectal cancer is based on the use of biomarkers. Detection of *hotspot* mutations in *KRAS*/*NRAS* genes determines resistance to anti-EGFR antibodies, preventing their use in this patient population [39]. In turn, the detection of the $BRAF^{V600E}$ mutation, which is an important prognostic factor, makes it possible to use the combination of encorafenib with cetuximab in the second line of systemic treatment [40]. Diagnostics of *KRAS*/*NRAS* and *BRAF* genes status are based on the PCR method and are usually performed sequentially due to the extremely rare coexistence of *KRAS*/*NRAS* and $BRAF^{V600E}$ mutations. The high-level microsatellite instability (MSI-H) is a biomarker playing an increasingly important role as a selection factor for immunotherapy in the first and subsequent treatment lines [41]. Microsatellite instability status is routinely assessed by immunohistochemistry (ICH) or PCR. The last of the unambiguously recognized biomarkers in this population are *NTRK* fusions although it should be emphasized that the frequency of their occurrence in patients with metastatic colorectal cancer is very low (about 0.5%). There is currently no clear consensus on how to detect *NTRK* fusions. It is often suggested to use immunohistochemistry as a screening method and to use molecular biology methods only in patients with a positive IHC result [42].

Another biomarker of potentially significant importance are disorders in the *HER2* gene (mainly amplifications), as there are more and more data on the effectiveness of HER2 receptor blockade [43]. The primary diagnostic method, in this case, is IHC with the possible use of fluorescent in situ hybridization (FISH) in ambiguous situations. Further biomarkers may be used in the future (e.g. *PIK3CA* mutation, *RET* and *ALK* fusions, or *MET* amplifications), but given the lack of consensus regarding treatment when such disorders are detected, they should be considered the domain of clinical trials.

The presence of numerous potential biomarkers of practical clinical significance would support the routine use of NGS in patients with metastatic colorectal or rectal cancer. An additional benefit could be the acceleration of the diagnostic process, which is already multi-stage and includes at least the determination of the status of *KRAS*/*NRAS* genes with a possible sequential assessment of the *BRAF* gene, and an independent MSI assessment. Nevertheless, the current recommendations do not suggest a routine replacement of standard PCR with the NGS method in colorectal cancer patients (note — NGS may be considered unless it is associated with significantly higher costs). The potential benefit of using multi-gene NGS panels would mainly concern the identification of patients with *HER2* gene amplification and routine assessment of NTRK fusion [3].

Bile duct cancer

Bile duct cancers, also called cholangiocarcinomas, are a diverse group of cancers that are characterized by significant molecular differences. The difference depends on the level of the bile ducts from which the cancer originates. Targeted therapies are currently most useful in intrahepatic cholangiocarcinomas, where *FGFR2* gene fusions (10–15% of patients) and *IDH1* gene mutations (up to 20% of patients) are detected more often than in other cholangiocarcinomas. In the presence of *FGFR2* fusions, the use of FGFR inhibitors (e.g. pemigatinib or infigratinib) allows for high response rates, exceeding the values obtained with standard chemotherapy [44]. From the perspective of molecular biology, the detection of *FGFR2* gene fusions, especially with rare or novel partners, is difficult and requires the use of NGS or modified PCR [45].

In terms of the clinical significance of the *IDH1* gene mutation, there is evidence of the effectiveness of ivosidenib, whose use improved PFS and OS [46]. There is currently no consensus on the optimal method for detecting *IDH1* mutations, and possible strategies include the screening use of IHC or the baseline use of PCR or NGS [47]. These molecular abnormalities concern almost exclusively intrahepatic cholangiocarcinomas, but other subtypes of cholangiocarcinoma are also characterized by the possibility of the presence of significant biomarkers. The emerging reports on the effectiveness of targeted therapies in patients with the $BRAF^{V600E}$ mutation or *HER2* gene amplification are noteworthy [48, 49]. As in the case of other gastrointestinal cancers, the possibility of detecting MSI-H and *NTRK* fusion should be considered [42, 50]. Other regularly occurring molecular disorders (e.g. *BRCA1/2* and *PIK3CA* mutations or *MET gene* amplifications) do not currently translate into additional treatment options and are only relevant in clinical trials.

Due to the nature of the detected molecular disorders, the use of NGS is an option for routine diagnostics in patients with cholangiocarcinoma, which results from the specific nature of the most common biomarkers (*FGFR2* fusions and *IDH1* mutations), for which NGS is considered one of the reference methods [3]. However, attention should be paid to the high costs associated with the routine use of multi-gene NGS panels and the alternative possibility of using dedicated NGS panels, covering only selected biomarkers.

Pancreatic cancer

The possibilities of targeted therapy in patients diagnosed with advanced pancreatic adenocarcinoma remain scarce and concern mainly patients with confirmed germline *BRCA1/2* mutations in whom maintenance treatment with PARP inhibitors may be considered after initial platinum-based chemotherapy [51]. Possible detection of the *BRCA1/2* mutation in multi-gene NGS panels requires confirmation of the germinal nature of the mutation before the possible use of PARP inhibitors. Taking into account the relatively rare occurrence of other genetic disorders qualifying for targeted therapy (high TMB, *KRAS G12C* mutation, *NTRK* fusions), the routine use of multi-gene NGS panels in patients with pancreatic cancer is not recommended [3].

Other GI malignancies

Despite the widespread use of targeted therapies in advanced cancers originating in the gastrointestinal system, we do not have predictive biomarkers for most of the therapies used. Therapies that are agnostic to the origin of cancer (e.g. immunotherapy in the case of MSI-H or NTRK inhibitors in the case of *NTRK* fusions) have brought some change in recent years [42, 50]. The list of such agnostic therapies is likely to get longer. Unfortunately, some biomarkers will elude unambiguous assessment, for example TMB, whose determination in gastrointestinal cancers is currently recommended only in the case of neuroendocrine tumors [3]. Therefore, taking into account alternative methods of MSI-H and *NTRK* fusion assessment, routine NGS in GI malignancies, other than those described above, is not recommended. However, it should be emphasized that NGS may be indicated as a screening method in centers conducting scientific research when qualifying patients for appropriate clinical trials.

Other neoplasms

Diagnostics using NGS may be considered in the absence of other diagnostic methods and access to treatment for patients with specific genetic disorders. An example is tropomyosin inhibitors in patients with *NTRK* rearrangements (found in patients with secretory carcinomas of the salivary glands and breasts, thyroid cancers, and sarcomas) [3].

Conclusions

The advantage of NGS is its ability to evaluate multiple genetic markers from one tissue or cell sample. In indications where it is possible to use specific groups of targeted therapies depending on the present genetic disorder, the NGS test is the recommended diagnostic option. Taking into account the available therapeutic methods, the highest value in clinical practice is to perform NGS in advanced NSCLC, prostate cancers, and biliary tract cancers. The discussion concerns the size of the gene panel covered by NGS. In centers conducting scientific research, including basic research and phase I/II clinical trials, the NGS method covering a wide panel of gene disorders is indicated as a screening method during qualification of patients for appropriate clinical trials.

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REVIEW ARTICLE

Agnieszka Chmielewska[1], Tomasz Kubiatowski[1, 2]

[1]"Rafal Masztak, MD PhD" Grochowski Hospital in Warsaw [sp. z o.o.], Poland
[2]Department of Oncology, University of Warmia Mazury in Olsztyn, Poland

Role of TROP 2 overexpression in selected solid tumors

Address for correspondence:
Agnieszka Chmielewska, MD
"Rafal Masztak, MD PhD" Grochowski Hospital in Warsaw [sp. z o.o.]
ul. Grenadierów 51/59,
04–073 Warsaw, Poland
e-mail: achmielewska@grochowski.waw.pl

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ABSTRACT

Cancer cell research development has led to the identification of many cell-surface proteins and signaling pathways that are required for cancer cell proliferation. TROP2 is one of the cell-surface proteins expressed in normal tissues. However, its overexpression is present in many types of malignant tumors. TROP2 overexpression may be a prognostic factor and a foothold for targeted therapies. Treatment with antibody-drug conjugates is applied in systemic cancer therapy. Currently, clinical trials are underway to evaluate the efficacy and safety of TROP2-targeted therapies.

Keywords: TROP 2 protein, targeted therapy, antibody-drug conjugate

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Introduction

Trophoblast-cell surface antigen 2 (TROP2) receptor protein — also referred to as GA733-1 (gastrointestinal antigen 733-1), EGP-1 (epithelial glycoprotein-1), TACSTD2 (tumor-associated calcium signal transducer- 2) — is a transmembrane glycoprotein with a molecular weight of 36 kDa, which was initially discovered on both normal and neoplastic trophoblast cells [1, 2]. TROP2 is a protein product of the TACSTD2 gene located on chromosome 1p32, which acts as a cellular proto-oncogene. Its mutation leads to the acquisition of an oncogenic function, which determines the transformation process of the primary cancer cells and their ability to metastasize. The TROP2 protein is synthesized in the endoplasmic reticulum, and then it is transported to the Golgi apparatus, where its glycosylation takes place. Its expression is found on the surface of the cell membrane and within the cytoplasm, with the presence of membrane expression associated with — unlike the cytoplasmic location — worse clinical prognosis manifested by an increased percentage of disease recurrences [3].

The question of causes of TROP2 protein overexpression in cancer cells remains open. It is thought that some transcription factors [e.g. Wilm's tumor 1 (WT1)] involved in progression of cancer are also factors regulating TROP2 transcription [4].

TROP2 overexpression in cancer cells, having prognostic significance, makes the protein a potential candidate for targeted therapies. The meta-analysis by Zeng et al. [5], published in 2016, showed, in a group of over 2500 patients with solid tumors, a relationship between TROP2 protein overexpression and shortened overall survival (OS) and disease-free survival (DFS).

The following article summarizes the data in the literature on changes in the expression of the TROP2 protein on the surface of cells of selected cancers and discusses its clinical implications and possible directions for the development of targeted therapies.

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Cervical cancer

Analyzing the expression of the TROP2 protein in cervical cells, Liu et al. [6] showed a relationship between its expression found immunohistochemically in 89% of the examined preparations and the stage of the neoplastic process according to the The International Federation of Gynecology and Obstetrics (FIGO) classification, the degree of histological differentiation, depth infiltration, the presence of metastases in the lymph nodes, and the expression of Ki67. The authors showed that patients with TROP2 overexpression were characterized by shorter progression-free survival (PFS) and OS. Overexpression of the TROP2 protein significantly stimulated the proliferation of cervical cancer cells and was closely related to the activation of stromal cell infiltration in the tumor. Reduced expression of TROP2 increased the sensitivity of tumor cells to the effects of platinum derivatives.

Endometrial cancer

In patients diagnosed with endometrial cancer, TROP2 overexpression in conjunction with FIGO staging is an independent factor of poor prognosis. In the study by Bignotti et al. [7], overexpression of TROP2 correlated with a lower grade of tumor differentiation ($p = 0.02$), shortened DFS ($p = 0.01$), PFS ($p = 0.05$), and OS ($p = 0.06$).

Ovarian cancer

High expression of TROP2 was demonstrated in 83% of ovarian cancer cell lines based on quantitative real-time polymerase chain reaction (qRT-PCR) and flow cytometry [8]. Overexpression of TROP2 correlates with a more aggressive clinical course of ovarian cancer and resistance to chemotherapy. In studies evaluating the importance of TROP2 in ovarian cancer, it was confirmed that the reduction of TROP2 expression inhibits the proliferation of cancer cells and reduces their metastatic capacity [9].

Central nervous system tumors

Central nervous system (CNS) glial tumors clearly overexpress the TROP2 protein, which is not found in normal tissues. The lower the tumor grade (WHO III and WHO IV gliomas), the greater the degree of TROP2 expression. The relationship between TROP2 expression and sex or age of patients has not been determined [10].

Colorectal cancer

TROP2 expression in colorectal cancer cells is clearly higher than in normal cells and is associated with worse prognosis, increased risk of recurrence, and metastases in the liver [11]. TROP2 overexpression is found more frequently in tumors involving the left side of the intestine (67.5% *vs.* 32.5%; $p = 0.002$). Mortality associated with colorectal cancer is four times higher in patients with high TROP2 expression (40% *vs.* 10%; $p = 0.002$). Patients with left-sided colorectal cancer and high expression of TROP2 have shorter median OS (45.9 *vs.* 63.1 months, $p = 0.032$) compared to those with low expression. In the case of cancers of the right half of the large intestine, TROP2 expression has no clear effect on survival ($p = 0.235$).

Gastric cancer

TROP2 expression is an independent risk factor for disease recurrence, which is particularly true for intestinal gastric cancer, regardless of the degree of regional lymph node involvement caused by the neoplastic process [12]. Finding overexpression of TROP2 is associated with shorter DFS ($p = 0.03$). In a study by Farivar et al. [13], it was shown that the TROP2 protein is a potential candidate for targeted therapy. The use of modified liposomes, which are a "transporter" for apoptosis activator 2, and then their introduction into gastric adenocarcinoma cell lines with overexpression of TROP2, allowed determining the activation of the apoptosis process in a greater percentage of the analyzed cells.

Esophageal cancer

In a study by Nakashima et al. [14], the presence of antibodies against TROP2 in the serum of patients diagnosed with squamous cell carcinoma of the esophagus was analyzed. The presence of anti-TROP2 antibodies found in 31% of patients correlated with the size of the primary tumor. The association of anti-TROP2 antibody presence with other clinical features has not been confirmed. The analysis of pathomorphological features showed a significantly higher expression of the TROP2 protein on the surface of cancer cells compared to hyperplastic lesions of the esophageal mucosa.

Cholangiocarcinoma

In the case of cholangiocarcinoma (CCA), the expression of TROP2 on cancer cells is significantly higher than that shown in normal tissue ($p = 0.001$). The

analysis of data from the study by Ning et al. [15] showed a relationship between the expression of TROP2, the degree of histological differentiation of the tumor ($p = 0.016$), and the size of the tumor (T feature $p = 0.031$). Patients diagnosed with cholangiocarcinoma with high expression of TROP2 are characterized by shorter OS compared to those with low expression of the TROP2 receptor protein. TROP2 expression in CCA is considered to be an independent prognostic factor.

Pancreatic cancer

TROP2 expression is clearly higher in pancreatic cancer cells compared to peritumoral tissues (87.1% *vs.* 9.7%) [16]. High expression of TROP2 is associated with a low degree of tumor differentiation and is not dependent on sex or age of the patient.

Oral cavity cancer

TROP2 overexpression in the study by Fong et al. [17] in patients diagnosed with squamous cell carcinoma of the oral cavity was associated with shortened OS ($p < 0.01$), with the relationship being inversely proportional to the degree of overexpression of the receptor protein. Therefore, similar to other cancers, finding TROP2 overexpression in oral cavity squamous cell carcinoma cells is considered an independent prognostic factor associated with poor prognosis.

Lung cancer

TROP2 overexpression is more common in squamous cell lung cancer than in adenocarcinoma ($p < 0.01$) and is related to the degree of histological differentiation [18]. It seems that the role of TROP2 varies depending on the histological type of lung cancer. In the study by Inamura et al. [19], overexpression of TROP2 on adenocarcinoma cells was associated with shortened OS, while no similar relationship was observed in squamous cell carcinoma. Also, in the case of patients diagnosed with small cell lung cancer, high TROP2 expression did not affect survival time.

The effect of using an antibody combined with a cytotoxic drug (sacituzumab govitecan) in subsequent lines of treatment in patients with advanced non-small cell lung cancer (NSCLC) was assessed in a single-arm phase II study [20]. The study included 54 patients who received from two to seven lines of systemic therapy in the earlier stages of treatment. The objective response rate (ORR) was 19%, and the mean duration of response to treatment was 6 months (range 4.8–8.3 months). The clinical benefit rate (sum of complete and partial responses plus disease stabilization for more than 4 months) was 43%. Median PFS and OS were 5.2 months (range 3.2–7.1 months) and 9.5 months, respectively. Treatment was well tolerated, grade 3 and higher toxicities included neutropenia (28%), diarrhea (7%), nausea (7%), fatigue (6%), and febrile neutropenia (4%). Based on the conducted analyses, it can be concluded that the use of sacituzumab govitecan in this group of patients led to obtaining, with acceptable toxicity, long-term responses in patients with metastatic NSCLC in subsequent lines of treatment.

The clinical effect and toxicity resulting from the use of sacituzumab govitecan in patients with advanced small cell lung cancer (SCLC) was evaluated in a phase II study [21]. Clinical benefit from treatment, defined similar to that of the previous study, was reported by 34% of the subjects. Median OS was 7.5 months and median PFS was 3.7 months. Treatment was well tolerated, grade 3 and higher toxicities included anemia (6%), diarrhea (9%), and fatigue (13%), with the most commonly observed being neutropenia (34%). In the study, no significant differences were observed in the response to treatment with sacituzumab govitecan in the groups of patients sensitive and resistant to first-line treatment.

Work on anti-TROP2 antibodies and conjugates of antibodies with cytotoxic drugs allowed the creation of another molecule, which is datopotamab deruxtecan (Dato-Dxd; DS-1062), which is a conjugate of a humanized monoclonal anti-TROP2 class IgG1 with topoisomerase type inhibitor I. Preclinical studies confirmed the in vitro activity of the drug in cells expressing TROP2 [22]. In the TROPION-PanTumor01 study [23], 133 patients diagnosed with relapsed NSCLC received at least 1 cycle of treatment (81% — prior immunotherapy, 90% — prior platinum-based chemotherapy). According to the results of the preliminary analysis, the ORR was 79% at a dose of 4 mg/kg and 75% and 79% in patients receiving the study drug at a dose of 6 mg/kg and 8 mg/kg, respectively. Most of the patients experienced adverse effects of treatment of varying severity (96%), with nausea (50%), stomatitis (44%), alopecia (40%), and increased fatigue (48%) being the most common.

Breast cancer

The expression of the TROP2 receptor protein on ductal breast cancer cells is significantly higher than in normal tissues and correlates with the degree of histological differentiation ($p = 0.023$) and the presence of metastases in regional lymph nodes ($p < 0.01$) and distant metastases ($p = 0.04$) [24]. High expression of TROP2 and the presence of metastases in lymph nodes

are independent prognostic factors and are associated with worse prognosis in the case of ductal breast cancer. The level of TROP2 expression is closely related to the cancer subtype and is higher in triple-negative breast cancer (TNBC) and luminal HER2-negative breast cancer cells compared to HER2-positive breast cancer cells [25, 26].

In studies of breast cancer conducted on mouse models, it was found that fragments binding the TROP2 antigen (TROP2-Fab, TROP2 antigen-binding fragment) have an inhibitory effect on tumor cell proliferation and activation of the apoptosis process as a result of stimulating the expression of caspase 3 and inhibiting the function of the bcl2 protein [27]. The findings led to the creation of an anti-TROP2 antibody conjugate with a cytotoxic drug. Sacituzumab govitecan is a combination of anti-TROP2 antibody with SN-38, which is the active metabolite of irinotecan. Goldenber et al. [28] confirmed in their studies that the use of govitecan sacituzumab allows for a much higher concentration of irinotecan in mouse breast cancer cells with lower toxicity of the treatment. In the phase I-II basket study, involving 25 patients with confirmed malignant disease with varying primary tumor locations, the use of sacituzumab govitecan allowed 3 out of 4 patients with metastatic TNBC to achieve a partial response to treatment — with a duration of 10.4 months, 6.9 months, and 3.1 months, respectively [29].

In another single-arm phase I–II study, the efficacy of govitecan sacituzumab was assessed in a group of 108 patients with disseminated TNBC who progressed despite the use of subsequent lines of chemotherapy [30]. The ORR rate was 33.3% (including complete remission in 3 patients). The median duration of response was 8.9 months (range 6.1–11.3 months). The treatment was well tolerated, and the most common grade 3 and higher adverse events were mainly hematological complications (neutropenia — 26%, anemia — 11%, and diarrhea — 8%). Diarrhea in lower toxicity grades affected 62% of patients. The results of the study confirmed that treatment with sacituzumab govitecan leads to a rapid and durable response in patients with TNBC previously having undergone systemic treatment of subsequent lines.

The results of the presented analyses made it possible to plan the first phase III study — ASCENT study [31]. It included 468 patients diagnosed with metastatic TNBC following at least two systemic treatments. The efficacy of treatment with sacituzumab govitecan was compared to what was observed in the chemotherapy arm of the study (eribulin, vinorelbine, capecitabine, or gemcitabine). The use of anti-TROP2 conjugated to the active metabolite of irinotecan led to an improvement in median PFS of 3.9 months compared to chemotherapy alone (5.6 *vs.* 1.7 months, risk reduction of 59%, $p < 0.001$), median OS of 5.4 months (12.1 *vs.* 6.7 months, 52% risk reduction, $p < 0.001$). The duration of response with sacituzumab govitecan and chemotherapy alone was 6.3 months and 3.6 months, respectively (61% risk reduction). Treatment with sacituzumab govitecan was fairly well tolerated, and only 5% of patients in the experimental arm discontinued treatment due to intolerable toxicity.

The clinical effect and safety of sacituzumab govitecan were also assessed in a group of 50 patients with early TNBC (NeoSTAR study) [32]. According to the study protocol, the patients received 4 cycles of treatment, followed by a biopsy of the lesion and, if the presence of neoplastic cells was found, chemotherapy treatment was continued. Pathologic complete response (pCR) was achieved in 30% of patients.

There are currently many studies evaluating the clinical effect of combining sacituzumab govitecan with other drugs in patients with TNBC (e.g. phase II randomized study Saci-IO = NCT04468061 — in combination with pembrolizumab in the first-line treatment of metastatic TNBC).

Clinical trials are also conducted using anti-TROP2 antibody conjugates with cytotoxic drugs in breast cancer subtypes other than TNBC. In a study by Kalinsky et al. [33], the efficacy of treatment with sacituzumab govitecan was assessed in a group of 54 patients with metastatic hormone-sensitive and HER2-negative breast cancer who experienced disease progression during hormonal treatment and received at least one line of chemotherapy treatment. With a median follow-up of 11.5 months, the ORR was 31.5%, and median PFS and OS were 5.5 and 12 months, respectively.

The preliminary results of the studies were confirmed in the phase III study TROPICS-02, which assessed the efficacy of treatment with sacituzumab govitecan [34]. The study included 543 patients diagnosed with disseminated luminal B carcinoma with HER2(–) feature, who had previously received two to four lines of treatment, including hormone therapy, CDK4/6 inhibitor, and taxane-based chemotherapy. Patients were randomized 1:1 to either the experimental arm (sacituzumab govitecan) or the control arm (chemotherapy of investigator's choice — eribulin, vinorelbine, capecitabine, or gemcitabine). The results of the interim analysis showed that the use of sacituzumab govitecan led to a statistically significant prolongation of PFS compared to patients undergoing chemotherapy (5.5 *vs.* 4.0 months — risk reduction by 44%, $p = 0.0003$). A subsequent analysis (median follow-up 12.5 months) showed prolonged OS compared to chemotherapy (median 14.4 *vs.* 11.2 months, risk reduction of 21%, $p = 0.020$).

Data on the use of Dato-Dxd in treatment of patients with disseminated TNBC following failure of previous therapies were presented in the form of congress reports presented during the SABCS (San

Antonio Breast Cancer Symposium) [35]. The study involved 44 patients with disseminated TNBC after an average of three lines of treatment for advanced disease. CNS metastases were found in 11% of patients. The ORR was 32% and the median duration of response to presentation time was not reached. Grade 3 or higher treatment-related adverse events were observed in 45% of patients included in the treatment, with nausea (66%) and stomatitis (55%) being the most common. Neutropenia, anemia, and diarrhea have been observed less frequently than with sacituzumab govitecan.

Further studies are aimed at evaluating the clinical efficacy and safety of using Dato-Dxd in previous lines of treatment or in combination with other drugs. To date, the preliminary results of the BEGONIA study evaluating the therapeutic effect of the combination of Dato-Dxd with durvalumab in the first-line treatment of patients with generalized TNBC have been presented [36]. In the group of 27 patients evaluated thus far, a 74% ORR was obtained, regardless of PD-L1 expression.

Urothelial cancers

TROP2 protein is overexpressed on the surface of cancer cells in 80% of patients with urothelial carcinoma. The prognostic significance of TROP2 overexpression in this tumor has not been confirmed, however, the presence of TROP2 protein may be a candidate for targeted therapies. In a phase I-II study by Faltas et al. [37], the efficacy of sacituzumab govitecan was assessed in a group of 6 patients diagnosed with advanced urothelial carcinoma following an average of three lines of previous treatment. In 3 patients, response to treatment was achieved, PFS was between 6.7 and 8.2 months, depending on the patient, and OS was between 7.5 and 11.4 months. The treatment was well tolerated.

Prostate cancer

Research conducted in prostate cancer confirmed the role of TROP2 protein in regulating the function of integrin b1, which affects the ability of cancer cells to form metastases. TROP2 also affects the activity of GTPase Rac1 and consequently the induction of the activity of the PAK4 protein, which increases the ability of prostate cancer cells to migrate and form distant metastases. The study by Trerotola et al. [38] demonstrated the regulatory effect of TROP2 on the adhesion of prostate cancer cells to fibronectin through the signaling pathway mediated by integrin b1, -RACK1, -Src- and FAK proteins, which is essential for the ability of cancer cells to migrate and metastasize.

Conclusions

TROP2 expression is present in normal and neoplastic cells. Overexpression of the TROP2 protein is a prognostic factor in many cancers and a candidate for targeted therapies. Therapy using anti-TROP2 antibody conjugates with a cytotoxic drug is applicable in the treatment of patients with multiple solid tumors. The presence of the TROP2 protein in normal cells does not lead to a significant increase in the toxicity of the treatment, which is most likely due to the stronger relationship between the toxicity and the cytotoxic drug contained in the conjugations. The results of many studies that confirm the efficacy of anti-TROP2 treatment are already available. The results of further studies evaluating the clinical effect and safety of anti-TROP2 antibody conjugates with a cytotoxic drug in monotherapy and in combination with other molecules are awaited with great interest.

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REVIEW ARTICLE

Katarzyna Pogoda, Agnieszka Jagiełło-Gruszfeld, Michał Kunkiel, Anna Niwińska, Zbigniew Nowecki

Department of Breast Cancer and Reconstructive Surgery, The Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Recent advances in the treatment of triple-negative breast cancer

Address for correspondence:
Katarzyna Pogoda, MD PhD
Department of Breast Cancer and Reconstructive Surgery,
The Maria Sklodowska-Curie National Research Institute of Oncology
ul. Roentgena 5, 02–781 Warsaw, Poland
e-mail: katarzyna.pogoda@pib-nio.pl

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ABSTRACT

Triple-negative is the rarest breast cancer biological subtype of breast cancer, but has the most aggressive course. The resuls of chemotherapy, especially in advanced disease, are unsatisfactory. Numerous clinical trials have been conducted, that resulted in registrations of new drugs decreasing the risk of recurrence and improving the outcome of patients with metastatic disease. The article summarizes the data on modern therapies registered in recent years. The role of pembrolizumab in perioperative treatment in the early stage was indicated, as well as the importance of olaparib in *BRCA* mutation carriers. Additionally, in patients with metastatic the indication for immunotherapy (pembrolizumab and atezolizumab), sacituzumab govitecan and PARP inhibitors (olaparib and talazoparib) in *BRCA* mutation carriers were highlighted.

Keywords: triple-negative breast cancer, immunotherapy, olaparib, talazoparib, atezolizumab, pembrolizumab, sacituzumab govitecan

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Introduction

Triple-negative breast cancer (TNBC) has been difficult to treat for many years. This biological subtype is diagnosed in approximately 10–15% of all breast cancer patients [1]. Young women are more frequently affected, and in up to 20–25% of patients *BRCA* gene mutations are detected (especially *BRCA1*), which has therapeutic implications [2–4].

Triple-negative breast cancer is an aggressive subtype of breast cancer with a high risk of recurrence (especially in the first 3–5 years after diagnosis), regardless of sensitivity to neoadjuvant chemotherapy [5]. Optimization of perioperative chemotherapy (use of regimens with shorter intervals between cycles, preoperative addition of carboplatin or capecitabine in the case of residual disease) reduces the risk of disease relapse [6–8]. However, 20–30% of patients still experience disease recurrence (sometimes very quickly and with high tumor burden, usually involving the lungs) [5]. In such cases standard chemotherapy usually shows limited effectiveness. The overall survival (OS) rate of patients with metastatic TNBC is low, with the median not exceeding 2 years [4, 9].

In recent years, numerous clinical trials have been conducted with new drugs in patients with early and advanced TNBC. This article summarizes the results of studies with drugs registered in the last few years which improve treatment outcomes and are included in the management algorithms for patients with TNBC.

Systemic treatment of early triple-negative breast cancer

Pembrolizumab

The results of the phase-III clinical trial KEYNOTE-522 led to the registration of pembrolizumab. Pembrolizumab is the first immunotherapy in patients with early TNBC, regardless of the expression of the programmed death

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receptor 1 (PD-L1) [10, 11]. The study involved patients with previously untreated stage II or III TNBC, who were randomized to preoperative treatment consisting of 12 cycles of paclitaxel (weekly) with carboplatin (every 1 or 3 weeks), followed by 4 cycles of doxorubicin or epirubicin plus cyclophosphamide (every 3 weeks). In the experimental arm, pembrolizumab was additionally used in both preoperative (8 doses every 3 weeks) and postoperative therapy (9 subsequent doses). No treatment was used for the residual disease. The primary endpoints of the study were pathological complete response (pCR) and event-free survival (EFS) in the entire study population [12].

In the first interim analysis, which involved the first 602 randomized patients of all 1174 patients enrolled in the study, the pCR rate was 64.8% [95% confidence interval (CI) 59.9–69.5] in the pembrolizumab group compared to 51.2% (95% CI 44.1 58.3) in the placebo group (pCR difference 13.6%; 95% CI 5.4–21.8; $p < 0.001$). A benefit of pembrolizumab treatment was demonstrated after 39 months of follow-up (median). The 3-year EFS rate was 84.5% (95% CI: 81.7–86.9) in the pembrolizumab arm versus 76.8% (95% CI 72.2—80.7) in the placebo arm [hazard ratio (HR) = 0.63; 95% CI 0.48–0.82; $p < 0.001$]. The most commonly reported events were distant recurrences (7.7% *vs.* 13.1%, respectively). Reassessment of the pCR in the entire study population indicated the advantage of immunotherapy, but the numerical difference was smaller (7.4%) [10]. Patients are still being monitored.

A pooled analysis of preoperative and postoperative adverse events revealed that grade ≥ 3 complications considered by the investigator to be related to study treatment were found in 77.1% of 783 patients in the pembrolizumab arm and 73.3% of 389 patients in the placebo group. The most common events were nausea, alopecia, and anemia. Discontinuation of study treatment due to adverse events (AEs) was 27.7% in the immunotherapy group and 14.1% in the placebo group. Serious treatment-related AEs occurred in 34.1% of patients in the pembrolizumab group and 20.1% in the placebo group. Deaths resulting from treatment-related adverse events occurred in 4 patients (0.5%) in the pembrolizumab group and 1 patient (0.3%) in the placebo group. The majority of treatment-related complications occurred during preoperative treatment. Adverse events with an incidence of at least 5% higher in the pembrolizumab group than in the placebo group were fever (28.2% *vs.* 18.5%), hypothyroidism (15.1% *vs.* 5.7%), diarrhea (40.6% *vs.* 34.2%), rash (29.9% *vs.* 23.7%), decreased appetite (22.7% *vs.* 16.7%), and hypokalemia (11.2% *vs.* 6.2%) %). It should be emphasized that most adverse events occurred during preoperative chemotherapy [10].

Quality of life (QoL) data were assessed using the European Organization for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30) and EORTC QLQ-BR23 questionnaires, which were collected from over 80% of patients at week 21 of preoperative treatment and after 24 weeks of postoperative treatment. There were no significant differences between the study groups according to quality-of-life outcomes (global health status, emotional functioning, physical functioning, and breast symptoms, including skin problems) [13].

Taking into account the data showing statistically significant pCR improvement and reducing the risk of recurrence (improvement of the 3-year EFS rate) as well as maintaining the quality of life, pembrolizumab was recommended for perioperative treatment in patients with early TNBC [14, 15].

Olaparib

Patients diagnosed with TNBC are more often carriers of *BRCA* gene mutations compared to other breast cancer subtypes. Considering the unsatisfactory results of treatment in patients with a high risk of recurrence, the OlympiA clinical trial was designed to evaluate the benefits of additional targeted therapy after standard chemotherapy in *BRCA* mutation carriers. The OlympiA study compared patients treated for one year with olaparib {PARP, poly[adenosine diphosphate(ADO)-ribose] polymerase} inhibitor with the placebo group. The study included 1836 randomly assigned patients [including 1509 (82%) patients with TNBC] with residual disease after preoperative chemotherapy or patients who had undergone initial surgery and had lymph node involvement (pN+ disease) or advanced pT2-4N0 disease. In 94% of patients, chemotherapy based on anthracyclines and taxanes was used, and 26% of patients additionally received platinum derivatives [16]. The primary endpoint of the OlympiA study was invasive disease-free survival (IDFS). The secondary endpoints included distant disease-free survival (DDFS) and overall survival (OS).

After a median follow-up of 3.5 years, there was a significant improvement in OS in the olaparib group compared to placebo (HR = 0.68; 98.5% CI 0.47–0.97; $p = 0.009$). After 4 years of follow-up, the difference in OS between treated (olaparib) and untreated (placebo) patients was 3.4% (89.8% *vs.* 86.4%). Similarly, a significant reduction in the risk of relapse was demonstrated (HR for IDFS = 0.63; 95% CI 0.50–0.78) — IDFS after 4 years was 82.7% in the olaparib group and 75.4% in the placebo group as well as a reduction in the risk of distant metastases (HR for DDFS = 0.61; 95% CI 0.48–0.77) — DDFS after 4 years was 86.5% *vs.* 79.1%, respectively. An analysis of the effectiveness of treatment depending on the subtype of breast cancer

was also performed, confirming the benefit of olaparib treatment in patients with TNBC (HR for IDFS = 0.62; HR for DDFS = 0.59; HR for OS = 0.64).

More than 11 months of treatment — out of the planned 12 months — were completed by 76% of patients in the olaparib group versus 82% of patients in the placebo group, and 25% of patients in the olaparib group required a dose reduction versus 5% of patients in the placebo group. Adverse events were more frequent in the experimental arm. The most common AEs were nausea (57% *vs.* 24%), asthenia (40% *vs.* 27%), anemia (24% *vs.* 4%), vomiting (23% *vs.* 8%), headache (20% *vs.* 17%), diarrhea (18% *vs.* 14%), neutropenia (16% *vs.* 6%). AEs leading to drug discontinuation occurred in 11% of patients in the olaparib group and 5% of patients in the placebo group. The most common AEs leading to discontinuation of olaparib were nausea (2%), anemia (2%), fatigue (2%), and neutropenia (1%). Grade ≥ 3 AEs in the olaparib group included anemia (9%), neutropenia (5%), leucopenia (3%), fatigue (2%), and lymphopenia (1%). There was 1 death from cardiac arrest in an olaparib-treated patient and 2 deaths from other cancer in the placebo group (acute myeloid leukemia and ovarian cancer). There were patients requiring blood transfusion during the study (6% in the olaparib group and 1% in the placebo group). There were 5 cases of myelodysplastic syndrome or acute myeloid leukemia (2 in the olaparib group and 3 in the placebo group).

Preliminary data on the quality of life of patients in the OlympiA study indicate that olaparib was well tolerated. A slightly higher incidence of complications did not affect the patients' well-being — no significant difference in fatigue and quality of life was noted. Treatment with olaparib led to a mild increase in nausea and vomiting during treatment, but symptoms resolved after treatment discontinuation. A gradual improvement in physical and emotional functioning, as well as general health, was observed over 24 months after adjuvant chemotherapy [17]. Longer follow-up of patients is planned.

Based on presented results, olaparib was approved for adjuvant treatment in *BRCA* mutation carriers with HER2-negative breast cancer at high risk of recurrence [18], which is also recommended by international expert panels [3, 14, 15].

It should be emphasized that there have been no studies comparing the efficacy of olaparib with capecitabine in patients with early TNBC with residual disease after preoperative chemotherapy. Data on mutation status in *BRCA* genes in patients treated with capecitabine in the CREATE-X study were also not presented [8]. The results of studies in patients with advanced breast cancer, in whom PARP inhibitor therapy was more effective than chemotherapy (including capecitabine) in *BRCA* mutation carriers, can provide hints while deciding on the choice of treatment in the case of residual disease [19, 20].

The results of studies with new drugs are summarized in Table 1. The introduction of pembrolizumab and olaparib to the treatment of patients with early TNBC will reduce the risk of recurrence of a very aggressive breast cancer subtype. Adding both therapies to the currently used treatment regimen results in longer therapy time. The need to determine the *BRCA* mutation status in patients with TNBC should be emphasized [21]. The use of immunotherapy prompts consideration of specific complications that may be different from the side effects of chemotherapy that clinicians may anticipate in patients with TNBC.

Systemic treatment in metastatic triple-negative breast cancer

Studies conducted in recent years in patients with metastatic TNBC led to the development of a new management algorithm. The key role is played by PD-L1 expression tests (with a specific test depending on the type of planned immunotherapy) and *BRCA* gene status assessment, which should be ordered in the case of TNBC recurrence. The results of these tests are of key

Table 1. Results of clinical trials with new therapies in patients with early triple-negative breast cancer

Study	Randomization	Number of patients	Inclusion criteria	Treatment regimen	DFS	OS	Remarks
KEYNOTE-522	2:1	1174	Stage II–III	Chemotherapy ± pembrolizumab	ESF: HR = 0.63	Data still collected	pCR: 64.8% *vs.* 51.2%
OlympiaA	1:1	1836 (TNBC 1509)	*BRCA* mutation, residual disease, or ≥ pT2 or pN+	± olaparib	iDFS: HR = 0.62	HR = 0.64	

Chemotherapy: paclitaxel + carboplatin followed by doxorubicin/epirubicin + cyclophosphamide; DFS — disease-free survival; iDFS — invasive disease-free survival; EFS — event-free survival; OS — overall survival; pCR — pathological complete response; TNBC — triple-negative breast cancer; HR — hazard ratio

importance in determining the therapeutic path for patients. In the first-line treatment of patients with TNBC with PD-L1 expression, immunotherapy (atezolizumab or pembrolizumab) in combination with chemotherapy is preferred. PARP inhibitors (olaparib or talazoparib) should be considered in *BRCA* mutation carriers. In the second-line treatment, sacituzumab govitecan is preferred. In the remaining patients, standard chemotherapy should be used. This management requires determination of predictive factors [4].

Atezolizumab

Atezolizumab was the first immunotherapy registered for patients with advanced breast cancer [22]. The pivotal study IMpassion130 involved 902 patients with metastatic or unresectable locally advanced TNBC. Patients who had previously undergone perioperative chemotherapy (including taxane-based chemotherapy) were eligible for the study, provided that their treatment had been completed ≥ 12 months before randomization. Screening tests included PD-L1 expression determination using the Ventana SP142 test, which was found in 41% of TNBC patients. In first-line treatment, nab-paclitaxel was used either in monotherapy or in combination with atezolizumab. The primary endpoints of the study were progression-free survival (PFS) and OS assessed in the entire population and the group of patients with PD-L1 expression. The results of the study showed a significant improvement in PFS in the entire group of patients receiving immunotherapy (7.2 versus 5.5 months, HR = 0.80; 95% CI 0.69–0.92; p = 0.0025) and, above all, in the group with PD-L1 expression (7.5 *vs.* 5.0 months, HR = 0.62; 95% CI 0.49–0.78; p < 0.0001). The first and final OS analysis showed no improvement after immunotherapy in the entire study population (21 *vs.* 18.7 months, HR = 0.86; 95% CI 0.75–1.02; p = 0.077), which resulted in abandoning the determination of the OS benefit in patients with PD-L1 expression. Additional analysis indicated a clinically significant benefit of atezolizumab in the PD-L1 positive group (OS: 25.4 *vs.* 17.9 months, HR = 0.67; 95% CI 0.53–0.86). The overall response rate (ORR) was also higher in the immunotherapy group (59% *vs.* 43%; HR = 1.96; p = 0.002) [23].

The most common AEs in patients treated in the IMpassion130 study were alopecia, asthenia, nausea, and diarrhea. Complications (grades 3–4) were reported in 51% of patients in the immunotherapy group and 43% of patients in the control group. Among patients with grade ≥ 3 AEs, the most common were neutropenia (8% in both groups), peripheral neuropathy (6% in the atezolizumab group *vs.* 3% in the control group), and asthenia (4% in the atezolizumab group *vs.* 3% in the placebo group). As a result of adverse events, treatment with at least one drug was discontinued in 19% of patients receiving combination therapy and in 8% of patients receiving chemotherapy alone (neuropathy was the most common cause). Typical immunotherapy side effects occurred in the experimental arm: rash (36% *vs.* 26% in the control arm), thyroid disorders (hypothyroidism — 18% *vs.* 4% and hyperthyroidism — 5% *vs.* 1%), and pneumonia (4% *vs.* 1%) [23].

The EORTC-C30 and BR23 questionnaires were used to assess the quality of life of patients treated in the IMpassion130 study. Treatment with atezolizumab did not affect the quality of life in the entire population and in patients with TNBC with PD-L1 expression [24].

The results obtained in the IMpassion131 study were a surprise. The design of this study was similar to the IMpassion130 study, while paclitaxel was added to atezolizumab in place of nab-paclitaxel. The primary endpoint of the study was PFS in the entire study population and patients with PD-L1 expression. The secondary endpoint was OS. PD-L1 expression was found in 45% of TNBC patients. There was no improvement in PFS in patients with PDL1 expression (median PFS: 6 *vs.* 5.7 months; p = 0.20) and in the entire study group (median PFS: 5.7 *vs.* 5.6 months; p = 0.86). There was also no difference in OS. Median OS among patients with PD-L1 expression was 22.1 months in the atezolizumab group and 28.3 months in the group treated with paclitaxel (worse result in the group with immunotherapy similar to entire study population — 19.2 and 22.8 months, respectively) [25]. The research is ongoing to explain the reasons for the different outcomes of atezolizumab treatment.

According to the current registration, atezolizumab can be used in combination with nab-paclitaxel in the first-line treatment of patients with metastatic TNBC with PD-L1 expression determined by the SP142 test [22].

Pembrolizumab

Another important study on immunotherapy in patients with metastatic TNBC was the KEYNOTE-355 study. Patients with primary metastatic TNBC and recurrence after at least 6 months from the end of radical treatment (surgery or adjuvant chemotherapy) were eligible for the study. As in the immunotherapy studies discussed above, pembrolizumab was used in combination with chemotherapy in the first-line treatment of advanced TNBC. Chemotherapy included nab-paclitaxel, paclitaxel, or gemcitabine with carboplatin. The study aimed to evaluate the effect of adding pembrolizumab to chemotherapy on treatment outcomes. In total 847 patients were randomly assigned to combination therapy or chemotherapy alone. The study assessed PD-L1 expression status using the Dako 22C3 assay, with a positive combined score (CPS) ≥ 10 in 38%

of tumors. The primary endpoints of the study were PFS and OS in patients with TNBC and CPS ≥ 10 or CPS > 1 in the entire study population. Better treatment results were reported in patients with high PD-L1 expression receiving pembrolizumab with chemotherapy. In patients with TNBC and PD-L1 expression with CPS ≥ 10, median PFS was significantly higher in the group with immunotherapy added to chemotherapy compared to the group receiving chemotherapy alone (median PFS — 9.7 versus 5.6 months; HR = 0.65 95% CI 0.49–0.86; p = 0.0012). The use of immunotherapy in this group also resulted in a significant improvement in OS (median OS — 23.0 versus 16.1 months; HR = 0.93; 95% CI 0.55–0.95; p = 0.0185). However, there was no improvement in treatment outcomes in the subgroup with CPS > 1 and in the entire study population receiving pembrolizumab with chemotherapy [26].

The most common AEs included anemia (49% of patients in the experimental group and 46% of patients in the chemotherapy group), neutropenia (41% and 38%, respectively), and nausea (39% and 41%). Grade ≥ 3 complications occurred in 68% of patients treated with pembrolizumab and 67% of patients treated with chemotherapy; most commonly reported were neutropenia (30% each) and anemia (16% and 15%, respectively). Two deaths were reported in the experimental arm due to acute kidney injury and pneumonia. Immune-related adverse events (irAEs) were reported in 27% of patients in the pembrolizumab group and 6% in the chemotherapy arm; grade ≥ 3 irAEs occurred in 5% of patients receiving immunotherapy [26].

A comparison of the quality of life with the use of the QLQ-30 and BR23 questionnaires after 15 weeks of treatment showed similar results. The addition of pembrolizumab did not affect the quality of life (including global health status, emotional or physical functioning) [27].

In conclusion, significant improvement in PFS and OS and maintenance of quality of life were demonstrated in patients with high PD-L1 expression undergoing combination therapy. Based on the results of the KEYNOTE-355 study, pembrolizumab was registered for use in combination with chemotherapy in the first-line treatment of locally recurrent unresectable or metastatic TNBC in patients with PD-L1 expression with a CPS ≥ 10 [11]. The assessment of PD-L1 expression, when pembrolizumab therapy is considered, should be performed using the 22C3 test.

Olaparib

The first of the studies evaluating the effectiveness of a PARP inhibitor in patients with breast cancer was the OlympiAD study, which compared olaparib with standard chemotherapy in *BRCA* germline mutation carriers suffering from advanced HER2-negative breast cancer. Thus, the study involved two groups of patients diagnosed with TNBC and hormone-dependent breast cancer (almost 50% of patients each). Patients could previously receive no more than 2 lines of chemotherapy due to metastatic disease (33% of patients had not previously used palliative chemotherapy, 40% had received one line of chemotherapy, and further 27% received 2 lines). A small number of patients had previously received platinum derivatives (7% in neoadjuvant treatment and 19% in palliative setting). In the OlympiAD study, 205 patients were randomized to olaparib and 97 to physician's choice chemotherapy (capecitabine, eribulin, or vinorelbine). The primary endpoint of the study was PFS, and the secondary endpoints were OS and safety [28].

There was a statistically significant improvement in PFS in the group of patients treated with olaparib compared to the group treated with physician's choice standard cytotoxic drugs (7.0 months *vs.* 4.2 months; HR = 0.58; 95% CI 0.43–0.80; p < 0.001). The PFS benefit was greater in patients with TNBC compared to other patients (HR for PFS = 0.43). The overall response rate was higher in the PARP inhibitor arm, e.g. 59.9% in the olaparib arm and 28.8% in the standard chemotherapy arm. In contrast, OS results were similar in both arms of the study. The median OS rate was 19.3 months in the olaparib arm and 17.1 months in the chemotherapy arm (HR = 0.90; 95% CI 0.66–1.23; p = 0.513). The OS results did not depend on the biological subtype of breast cancer, but there was a clinical improvement in OS in patients who were treated with olaparib in the first line (OS: 22.6 *vs.* 14.7 months; HR = 0.51; 95% CI 0, 29–0.90) [19].

Adverse events of olaparib were most commonly of grade 1 or 2 and rarely led to discontinuation of treatment. Nausea, anemia, vomiting, fatigue, cough, decreased appetite, back pain, and headache were reported with a slightly higher incidence (≥ 5%) in the olaparib arm compared to the standard arm. Conversely, neutropenia, elevated liver enzymes, alopecia, and hand-foot syndrome were more common (≥ 5%) in the chemotherapy arm compared to olaparib. Grade ≥ 3 AEs were reported in 38% of patients in the olaparib arm and 49% of patients in the chemotherapy arm, with causality suspected in 24.4% and 34.1% of patients, respectively. The most common grade ≥ 3 AE in patients treated with olaparib was anemia, and in patients receiving chemotherapy — neutropenia (three episodes of febrile neutropenia were reported). The treatment discontinuation rate due to AEs was 5% in the olaparib arm and 8% in the chemotherapy arm [19].

Patients assessed olaparib therapy better than chemotherapy (QLQ-C30 questionnaire). A comparison of general health and quality of life between the study

arms indicated a better outcome in patients receiving PARP inhibitors. The median time to deterioration of health status and quality of life was not reached in the olaparib group but was 15.3 months in patients using standard cytotoxic drugs (HR = 0.44; p = 0.004). Among the subscales evaluating symptoms and functioning using the QLQ-C30 questionnaire, only nausea and/or vomiting were more frequently reported during olaparib treatment compared to chemotherapy [29].

Based on the above results of the OlympiAD study (significant improvement in PFS and quality of life), olaparib was approved for use in *BRCA* mutation carriers suffering from advanced HER2-negative breast cancer [18].

Talazoparib

The second study that evaluated the efficacy of a PARP inhibitor versus chemotherapy in *BRCA* germline mutation carriers with HER2-negative advanced breast cancer (44% with TNBC) was the EMBRACA study. Patients who could previously receive no more than 3 lines of palliative treatment were eligible (no previous chemotherapy — 38%, 1 line — 37%, 2 lines — 20%, 3 lines — 5% of patients). The patients were randomly assigned to two groups — 287 received talazoparib and 144 received physician's choice chemotherapy (capecitabine — 44%, eribulin — 40%, gemcitabine — 10%, vinorelbine — 7%). In total 18% of patients had previously received platinum derivatives. The study showed an improvement in PFS in patients using talazoparib with medians of 8.6 and 5.6 months, respectively (HR = 0.54; 95% CI 0.41–0.71; p < 0.001; in a subgroup of TNBC patients HR = 0.60) [30]. The ORR was also higher in the talazoparib group compared to the control arm (62.6% *vs.* 27.2%; odds ratio 5.0; p < 0.001) [30]. However, there was no difference in OS in the whole group, depending on the treatment used — the median OS was 19.3 months in the talazoparib group and 19.5 months in the chemotherapy group (HR = 0.848; 95% CI 0.670–1.073; p = 0.17) [20].

The most common AEs occurring in > 30% of patients were anemia, fatigue, nausea, neutropenia, and headache in the talazoparib group and nausea, fatigue, and neutropenia in the chemotherapy group. Adverse events (grade 3–4) occurred in 70% of patients in the talazoparib group and 64% of patients in the chemotherapy group. Myelotoxicity (grades 3–4) was reported in 57% of patients in the talazoparib arm and 39% of patients in the chemotherapy arm. Blood transfusions were frequent in the PARP inhibitor arm, with 39% of patients receiving at least one blood transfusion in the talazoparib group versus 6% of patients receiving chemotherapy. Adverse events led to discontinuation of treatment in 6% of patients treated with talazoparib and 9% of patients in the chemotherapy group [20].

Important conclusions can be drawn from analyzes of the quality of life assessed using the QLQ-C30 and QLQL-BR23 questionnaires. Significant improvements in general health and quality of life from baseline were observed in the talazoparib group, while there was a significant decrease in quality of life in the chemotherapy group. There was also a significant improvement in breast-related symptoms (BR23) in patients receiving a PARP inhibitor, which was not seen in patients receiving chemotherapy. It should be noted that treatment with talazoparib resulted in a significant delay in the time to clinically significant deterioration of health status and quality of life as well as breast-related symptoms [20, 31].

The results of the EMBRACA study, which showed a statistically significant improvement in PFS and quality of life, contributed to the registration of talazoparib for use in *BRCA* mutation carriers suffering from advanced HER2-negative breast cancer [32].

Sacituzumab govitecan

Sacituzumab govitecan is a conjugate composed of a monoclonal antibody that binds to trophoblast-cell surface antigen 2 (TROP-2) on the surface of tumor cells, the small molecule SN-38 (govitecan, an active metabolite of topoisomerase I), and a linker.

The ASCENT pivotal study involved 529 patients with metastatic or inoperable locally advanced TNBC. Patients had to have received previously at least 2 lines of chemotherapy (one of them could be neoadjuvant chemotherapy provided that relapse occurred within 12 months of therapy completion). In total 61 patients with stable brain metastases were also recruited. The effectiveness of sacituzumab govitecan was compared with the investigator's choice chemotherapy (eribulin — 54% of patients, vinorelbine — 20%, capecitabine — 13%, or gemcitabine — 12%). The primary endpoint of the study was median PFS in a cohort of 468 patients without brain metastases. The secondary endpoints of the study were OS in patients without brain metastases, PFS and OS in the overall population, ORR, safety, and quality of life. Patients treated in the study had previously received various cytostatics (mean 4 lines) — all patients were treated with taxoids, and the majority also received anthracyclines (82%) and carboplatin (66%). In addition, 7% of patients had previously been treated with PARP inhibitors and 27% had received immunotherapy. The results of the ASCENT study showed a statistically significant benefit from treatment with the new conjugate [33]. The final results of the ASCENT study were recently presented. The median PFS rate was 5.6 months in the conjugate arm and 1.7 months in the chemotherapy arm (HR = 0.39;

Table 2. Results of clinical trials with new therapies in patients with advanced triple-negative breast cancer (TNBC)

Study	Randomization	Number of patients	Inclusion criteria	Treatment regimen	PFS (months)	OS (months)	ORR (%)
IMpassion-130	1:1	902 (369 PD-L1 + 41%)	TNBC first line; DFI > 12 months	Nab-paclitaxel ± atezolizumab	7.5 *vs.* 5.0 (HR = 0.62)*	25.4 *vs.* 17.9*	58.9% *vs.* 42.6%*
IMpassion-131	2:1	651 (292 PD-L1 + 45%)	TNBC first line; DFI > 12 months	Paclitaxel ± atezolizumab	6.0 *vs.* 5.7 (HR = 0.82, NS)*	22.1 *vs.* 28.3 (HR = 1.11; NS)*	63% *vs.* 55%*
KEYNOTE-355	1:1	847 (323 PD-L1 + 38%)	TNBC first line; DFI > 6 months	Chemotherapy ± pembrolizumab	9.7 *vs.* 5.6 (HR = 0.66)*	23 *vs.* 16.1 (HR = 0.73)*	52.7% *vs.* 40.8%*
OlympiaAD	2:1	302	*BRCA* mutation, previously ≤ 2 lines of palliative chemotherapy	Olaparib *vs.* chemotherapy	7.0 *vs.* 4.2 (HR = 0.58)** (TNBC = 0.43)	19.3 *vs.* 17.1 (HR = 0.90)** (TNBC HR = 0.93)	59.9% *vs.* 28.8%**
EMBRACA	2:1	432	*BRCA* mutation, previously ≤ 3 lines of palliative chemotherapy	Talazoparib *vs.* chemotherapy	8.6 *vs.* 5.6 (HR = 0.54)** (TNBC HR = 0.60)	19.3 *vs.* 19.5 (HR = 0.848)** (TNBC HR = 0.899)	62.6% *vs.* 27.2%**
ASCENT	1:1	529	*BRCA* mutation, previously at least 1 line of palliative chemotherapy	Sacituzumab govitecan *vs.* chemotherapy	5.6 *vs.* 1.7 (HR = 0.39)	12.1 *vs.* 6.7 (HR = 0.48)	35% *vs.* 5%

*Results in the population with positive PD-L1 expression; **results in the entire group of patients with HER2-negative breast cancers; DFI — disease-free interval; HR — hazard ratio; NS — not significant; ORR — objective response rate; OS — overall survival; PD-L1+ — positive expression of programmed cell death ligand 1; PFS — progression-free survival; TNBC — triple-negative breast cancer

95% CI 0.31–0.49; $p < 0.0001$). The benefit of therapy with conjugate was observed in all analyzed subgroups. OS results also significantly improved — the median OS rate was 12.1 months in the sacituzumab group and 6.7 months in the chemotherapy group (HR = 0.48; 95% CI 0.39–0.59; $p < 0.0001$). Statistically significant improvement in the ORR (35% *vs.* 5%) and clinical benefit rate (45% *vs.* 9%) was also confirmed [34].

The most common treatment-related AEs of any grade were neutropenia (63% in the conjugate group and 43% in the chemotherapy arm), diarrhea (59% *vs.* 12%), nausea (57% *vs.* 26%), alopecia (46% *vs.* 16%), fatigue (45% *vs.* 30%), and anemia (34% *vs.* 24%). The most common grade ≥ 3 adverse events were neutropenia (51% in the sacituzumab group and 33% in the chemotherapy arm), leukopenia (10% *vs.* 5%), diarrhea (10% *vs.* < 1%), anemia (8% *vs.* 5%), and febrile neutropenia (6% *vs.* 2%) [33].

Recently, the results of the quality-of-life analysis in patients treated in the ASCENT study were published. According to assessment of health and quality of life, physical functioning, severity of fatigue and pain, treatment with sacituzumab govitecan obtained higher scores. Only for nausea, vomiting, and diarrhea, conjugate treatment was more burdensome than chemotherapy. The median time to first clinically significant deterioration in quality of life was greater for sacituzumab govitecan compared to chemotherapy in terms of physical functioning (22.1 *vs.* 12.1 weeks, $p < 0.001$), role (11.4 *vs.* 7.1 weeks, $p < 0.001$), fatigue (7.7 *vs.* 6.0 weeks, $p < 0.05$), and pain (21.6 *vs.* 9.9 weeks, $p < 0.001$) [35].

Based on the results of the ASCENT study, sacituzumab govitecan was registered for the treatment of patients with metastatic TNBC after at least one line of palliative therapy [36].

The results of studies with new drugs in patients with metastatic TNBC are summarized in Table 2.

Discussion

The treatment of patients with TNBC has changed significantly in recent years. Many new drugs have been approved for both early and metastatic TNBC. Registered indications are summarized in Table 3.

Treatment of patients with early TNBC is predominantly based on preoperative chemotherapy consisting of anthracyclines and taxanes, often as part of intensified regimens and with the addition of carboplatin. Intensive chemotherapy translates into achieving pCR in up to half of the treated patients. In the case of residual disease, capecitabine is additionally used.

Table 3. Registered indications of new therapies in triple-negative breast cancer (TNBC) based on the summary of product characteristics

Early TNBC		Dosage
Pembrolizumab	Pembrolizumab in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence	Neoadjuvant pembrolizumab in combination with chemotherapy with 8 doses of 200 mg *i.v.* every 3 weeks followed by adjuvant treatment with pembrolizumab as monotherapy with 9 doses every 3 weeks (or in neoadjuvant with 4 doses of 400 mg *i.v.* every 6 weeks, followed by 5 doses of 400 mg every 6 weeks)
Olaparib	Olaparib in monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline BRCA1/2--mutations who have HER2-negative, high-risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy	300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg for up to 1 year
Advanced TNBC		**Dosage**
Atezolizumab	Atezolizumab in combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease	840 mg *i.v.* every 2 weeks, or 1 200 mg *i.v.* every 3 weeks, or 1 680 mg *i.v.* every 4 weeks in combination with nab-paclitaxel (100 mg/m^2 *i.v.* on days 1, 8, and 15 of each 28-day cycle)
Pembrolizumab	Pembrolizumab in combination with chemotherapy is indicated for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer in adults whose tumors express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease	Pembrolizumab in combination with chemotherapy 200 mg *i.v.* every 3 weeks or 400 mg *i.v.* every 6 weeks
Olaparib	Olaparib in monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have previously been treated with anthracycline and taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments	300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg
Talazoparib	Talazoparib as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should be previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced, or metastatic setting unless patients were not suitable for these treatments	1 mg (one 1 mg capsule) once daily
Sacituzumab govitecan	Sacituzumab govitecan as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, including at least one of them for advanced disease	10 mg/kg body weight *i.v.* on day 1 and day 8 of 21-day treatment cycles

CPS — combined positive score; PD-L1 — programmed cell death ligand 1; PFS — progression-free survival; TNBC — triple-negative breast cancer

The results of recent studies have led to the registration and recommendation of two drugs in patients with early TNBC. The first one is pembrolizumab used in perioperative treatment in patients with disease stages II–III. The drug is used in early TNBC regardless of PD-L1 expression status. The second is olaparib, recommended in a narrower group of patients (carriers of *BRCA* gene mutations) with residual disease or undergoing primary surgery with lymph node metastases or ≥ pT2. Due to the change in management principles, there are now definitely fewer patients starting treatment with surgery. The period when preoperative treatment is used additionally allows for obtaining information about the status of the *BRCA* gene, and thus the test result is known at the time of qualification for surgical treatment and later when making a decision on possible treatment of the residual disease. There are no unequivocal recommendations on the choice of management in residual disease (capecitabine, olaparib) when immunotherapy (pembrolizumab) was used in perioperative treatment. According to the latest recommendations, the treatment of patients with stage II–III TNBC has been extended to 12–18 months, depending on the management plan.

On the other hand, the choice of treatment in the case of recurrence of the disease varies greatly. According to the recommendations, making a decision on palliative treatment requires determination of PD-L1 expression and *BRCA* gene status. The choice of the test to determine PD-L1 expression depends on the planned treatment (two tests are used to qualify for therapy with atezolizumab or pembrolizumab, due to differences between them). The following scenarios are recommended in the first line of TNBC treatment:

— if PD-L1 expression is positive (about 40% of patients) — immunotherapy (pembrolizumab or atezolizumab) + chemotherapy (paclitaxel, nab-paclitaxel or gemcitabine with carboplatin; in the case of atezolizumab therapy, only nab-paclitaxel);
— if a *BRCA* mutation is present (20–25% of patients) — a PARP inhibitor (olaparib or talazoparib; talazoparib has been reimbursed in Poland since November 2022[37]);
— if there is no PD-L1 expression and *BRCA* mutation — chemotherapy.

The choice of chemotherapy is limited by the drugs used in the primary treatment. TNBC recurrences occur in the first years after radical treatment with standard cytotoxic drugs active in TNBC (anthracyclines, taxoids, carboplatin, capecitabine). According to the recommendations, anthracyclines or taxoids (previously used) may be reintroduced if relapse occurred at least one year after completion of chemotherapy with these drugs (taking into account the lifetime cumulative dose of anthracyclines) [4, 15, 21]. Other drugs to be used include vinorelbine, gemcitabine, cyclophosphamide, and eribulin. In turn, in the second and subsequent treatment lines, the recommendations clearly indicate the use of sacituzumab govitecan [4, 15], which has been reimbursed in Poland since November 2022 [37]. In subsequent treatment lines other cytotoxic drugs should be used, taking into account the low treatment response rate. The treatment algorithm for patients with TNBC is shown in Figure 1.

The new drugs discussed above for TNBC patients have positive scores on the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS). Drugs used in early TNBC (pembrolizumab and olaparib) received the highest score A due to a significant reduction of recurrence risk and the absence of a significant increase in toxicity and deterioration of patients' quality of life. On the other hand, in palliative treatment, PARP inhibitors (olaparib and talazoparib) and sacituzumab govitecan scored 4 points on the scale (maximum score — 5). PARP inhibitors significantly prolong PFS and improve patients' quality of life with less treatment toxicity. Sacituzumab govitecan prolongs median PFS and OS with slightly higher toxicity but maintained quality of life. Atezolizumab scored 3 points because the drug improves PFS, but OS analysis was additional. Pembrolizumab scored 3 points, but the score needs to be changed due to the need to take into account the significant OS improvement [38].

The evolution of treatment options for TNBC patients is still highly awaited. Modern drugs significantly improve the prognosis compared to standard chemotherapy. Further studies are needed, especially in patients with metastatic TNBC, to conclude that long-term treatment is also possible for this subtype of metastatic breast cancer.

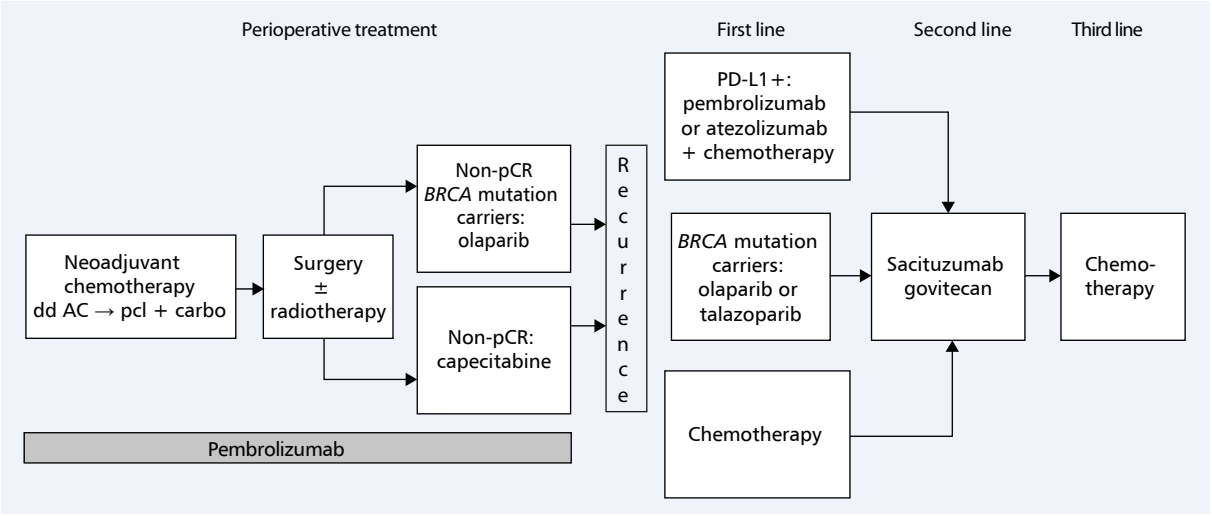

Figure 1. Treatment algorithm for patients diagnosed with triple-negative breast cancer; dose dense (dd) doxorubicin with cyclophosphamide (AC) — AC regimen with shortening of the intervals between cycles; pcl — paclitaxel; carbo — carboplatin; non-pCR — no pathological complete response; PD-L1— programmed cell death ligand 1

Article Information and Declarations

Conflict of interest

KP: honorarium for consultations/lectures/training/clinical trials and compensation for participation in scientific congresses from Roche, Novartis, Eli Lilly, Pfizer, MSD, AstraZeneca, Gilead, Teva, and Egis.
AJ-G.: honorarium for consultations/lectures/training/clinical trials from AstraZeneca, Novartis, Roche, Gilead, Eli Lilly, Amgen, Pfizer, MSD.
MK: honorarium for consultations/lectures/training/clinical trials and compensation for participation in scientific congresses from MSD, Bayer, Novartis, Eli Lilly, Pfizer, Roche, Vipharm, Angelini, AstraZeneca.
AN: no conflict of interest.
ZN: honorarium for lectures/clinical studies from Roche, MSD, Novartis, Eli Lilly, and AstraZeneca.

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Maciej Krzakowski

The Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Commentary

to *Recent advances in the treatment of triple-negative breast cancer*

In about 10–15% of breast cancer patients, the tumor is characterized by the absence of steroid hormone receptors and epidermal growth factor receptor 2 on the cell surface — this biological subtype is classified as triple-negative breast cancer (TNBC). Genetic abnormalities (e.g. *BRCA* gene mutations) are common in TNBC. Triple-negative breast cancer is a difficult-to-treat tumor for several reasons — it is common in younger women and has an aggressive clinical course with a higher stage at diagnosis and early recurrence, resulting in an overall poorer prognosis. The unsatisfactory outcomes in patients with TNBC were related to limited systemic treatment options, which until recently consisted only of cytotoxic drugs. The evolution of knowledge about molecular biology has resulted in a better understanding of many conditions in TNBC and introduction of new treatment options although chemotherapy remains important. New treatment options for patients with TNBC include immune checkpoint inhibitors, inhibitors of poly(ADP-ribose) polymerase (PARP) in patients with *BRCA* genes mutations, and molecularly targeted drugs [e.g. conjugate composed of a monoclonal antibody against trophoblast-cell surface antigen 2 (TROP-2) and cytotoxic drug from topoisomerase I class]. All those options and chemotherapy can be used in the treatment of patients with advanced TNBC. However, depending on the demographic, clinical, and molecular characteristics, it is possible to use different sequences of treatment in the first line and beyond. An example of sequential treatment may be the use of chemotherapy with atezolizumab, then talazoparib (patients with *BRCA* genes mutations) and sacituzumab govitecan, and again chemotherapy. The situation of patients with TNBC indicates the possibility of treatment individualization and, at the same time, is an example of significant benefits obtained as a result of using modern drugs. Side effects of these drugs should be considered, which justifies the ability to manage treatment processes (e.g. immuno-related complications in the case of immune checkpoint inhibitors). The assessment of patients' quality of life — carried out in the trials with all these drugs — confirmed better outcomes in patients receiving immunotherapy, PARP inhibitors, and other new drugs compared to patients in the control groups.

The authors from the Department of Breast Cancer and Reconstructive Surgery of the Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw have prepared a very detailed discussion of all the new options, highlighting the most important benefits resulting from using the presented drugs. The greatest advantage of the report is the presentation of the sequential treatment algorithm for patients with advanced TNBC.

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CASE REPORT

Karolina Pięta[1], Izabela Rudy[1], Maksymilian Kruczała[2]

[1]Student Research Oncology Club at the Department of Oncology, Radiotherapy and Translational Medicine, Institute of Medical Sciences, College of Medical Sciences of the University of Rzeszów, Poland
[2]Department of Oncology, Radiotherapy and Translational Medicine, College of Medical Sciences of the University of Rzeszów, Poland

Metachronous breast cancer in a *BRCA1* mutation carrier

Address for correspondence:
Karolina Pięta
Institute of Medical Sciences, College of Medical Sciences of the University of Rzeszów
ul. Rejtana 16C, 35–310 Rzeszów, Poland
e-mail: karolinapietax@gmail.com

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ABSTRACT

Breast cancer is the most common neoplasm among women in Poland and worldwide. Approximately 8000 women die from breast cancer in Poland each year. It is the second leading cause of cancer-related deaths among Polish women, following lung cancer. This cancer is highly heterogeneous in terms of morphology as well as molecular characteristics, and it requires different therapeutic approaches. Several risk factors for breast cancer have been identified, including genetic, environmental, and individual factors. Mutations in the *BRCA1* and *BRCA2* genes are the best-known genetic factors responsible for approximately 5–10% of breast cancer cases worldwide. The risk of developing bilateral breast cancer in patients with *BRCA1* mutation is significantly higher than in the general population. Furthermore, attention is drawn to the increased risk of metachronous tumors in patients with a *BRCA1* gene mutation who have previously had breast cancer. This article presents a case report on a patient with metachronous breast cancer who has developed bone and liver metastases. Based on the genetic test result showing a *BRCA1* mutation, the patient was qualified for talazoparib treatment.

Keywords: breast cancer, metachronous tumors, *BRCA1* mutation

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Introduction

Breast cancer is the most common malignant tumor among women, and one of the three most prevalent cancers worldwide alongside lung cancer and colorectal cancer [1]. It is estimated that approximately 1.6 million new cases of breast cancer occur worldwide each year, and its incidence continues to increase [2]. In 2020, about 17500 new cases of breast cancer were diagnosed in Poland, and nearly 8 000 patients died of this disease. The highest incidence is observed among women aged 55–65, and the highest number of deaths was recorded in the sixth and seventh decades of life [3]. Mortality from breast cancer may decrease due to early diagnosis, disease detection, and the development of new treatment methods. However, breast cancer remains the leading cause of cancer-related deaths among women in developing countries and the second most common cause of death — after lung cancer — in developed countries [1]. Most breast cancers are invasive tumors that spread to surrounding tissues and lymph nodes. Currently, there are 21 histologically different types of breast cancer and 4 different molecular subtypes [4]. The vast majority of breast cancers are sporadic tumors (approximately 90%), that develop due to somatic mutations in an individual's lifetime [2]. Many known factors may contribute to the development of breast cancer including genetic, hormonal, environmental, dietary, and reproductive factors as well as exposure to ionizing radiation [4]. About 5–10% of breast cancer cases occur in individuals with a known hereditary germline mutation. Among these genetic factors, mutations in the *BRCA1* and *BRCA2* genes, responsible for DNA repair, have been best characterized. The risk of developing breast cancer in carriers of mutated genes is significantly higher than in the general population and ranges from 69% to 72%. There is also a significantly higher risk of developing bilateral breast cancer in this population [5]. Additionally, these individuals are at an increased risk of developing ovarian, pancreatic, and prostate cancer [2].

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Metachronous tumors occurring in *BRCA1* mutation carriers who have previously had breast cancer are more common than in non-carriers, with second breast cancer being most frequently observed [5].

Case report

The patient, aged 35, was diagnosed with left breast cancer (triple-negative subtype, clinical stage pT1cN1) in 2010. The patient underwent breast-conserving surgery and received 6 cycles of adjuvant chemotherapy with doxorubicin and cyclophosphamide as well as adjuvant radiotherapy. In 2021, suspicion of metachronous right breast cancer was raised. Biopsy showed invasive ductal carcinoma grade 3 and luminal B subtype. Immunohistochemical analysis of the tumor cells showed estrogen receptor expression (10%), progesterone receptor expression (5%), negative HER2 status, and a Ki-67 index of 70%. The patient underwent surgery and postoperative examination showed stage pT1cN0. Despite being informed about the risks associated with her decision, the patient declined adjuvant chemotherapy as well as hormonal therapy in the form of goserelin and zoledronic acid. The patient was still menstruating, which is why zoledronic acid was suggested only on the condition of obtaining her consent to goserelin therapy to pharmacologically induce menopause. Treatment with tamoxifen was initiated (as the only form of systemic therapy acceptable for the patient) along with adjuvant radiotherapy.

In May 2022 abdominal computed tomography (CT) raised suspicion of a secondary lesion in the liver. Metastatic disease was confirmed in June on positron emission tomography (PET), which showed skeletal and liver secondary deposits. After a multidisciplinary consultation, a liver biopsy was performed to determine metastasis phenotype. Zoledronic acid therapy was initiated and — after an oncological consultation on radiation – the patient underwent palliative radiotherapy for the Th3–Th5 segment of the spine as well as the left iliac crest and sacrum. The pathology result of the liver biopsy was inconclusive, as only benign tissue was obtained.

Due to the patient's rapidly deteriorating general condition, low expression of steroid receptors in the primary tumor, and impending visceral crisis, palliative chemotherapy with paclitaxel (80 mg/m^2 every week) was initiated, which was completed in October.

In September 2022, remission of liver lesions was observed. A liver biopsy was repeated, and it indicated metastasis of adenocarcinoma. Immunohistochemical analysis of the tumor cells demonstrated the absence of estrogen receptors (ER–), progesterone receptors (PR–) and HER2(–). In January 2023 disease progression was observed, confirming the metastasis of "triple-negative" breast cancer with disease progression after the first-line palliative chemotherapy (paclitaxel). Genetic testing identified the presence of a *BRCA1* mutation (5382 ins. C). Based on this, the patient received talazoparib. After three months of therapy, partial remission (PR) was found according to RECIST 1.1 criteria. The patient continues the treatment.

Discussion

The risk of breast cancer is higher in women with a history of breast cancer and ranges from 10–15% for a 55-year-old woman with a previous breast cancer compared to 2.5% for a healthy 55-year-old woman during a 15-year observation period. From the initial diagnosis, the risk of developing metachronous breast cancer significantly increases over time [5]. The prevalence of *BRCA1* gene mutations in the Polish population is approximately 6% in breast cancer patients diagnosed before the age of 50 [6]. Breast cancers associated with *BRCA1* mutation occur at an early age (42–45 years) and are bilateral in 18–32% of cases [6–9]. The presence of a *BRCA1* mutation increases the risk of developing breast cancer to 50–80% and ovarian cancer to approximately 40%, depending on the type of mutation [10, 11]. In a study by Kruczała et al. [5], the development of metachronous malignancy was observed in 50% of patients with *BRCA1* mutation, with 38% of cases being second breast cancer compared to only 4.8% with metachronous ovarian cancer (possibly because 40% of patients in the studied population underwent prophylactic hysterectomy with bilateral adnexectomy). Due to the high incidence of breast cancer and a significant number of patients undergoing radical treatment as well as the increasingly common and accessible diagnostics for *BRCA1* gene mutations, it is expected that the number of cancer patients with identified mutations will increase in daily clinical practice. With this in mind, it is necessary to raise awareness of the scale of metachronous tumors in patients with *BRCA1* mutations in the medical community, intensify surveillance of *BRCA1* mutation carriers after breast cancer treatment to detect the occurrence of subsequent tumors and consider prophylactic bilateral adnexectomy and mastectomy for *BRCA1* mutation carriers previously treated for breast cancer [5].

A significant prognostic factor in breast cancer patients is the presence of expression of ER and PR as well as HER2 on tumor cells. This is particularly important in the case of tumor metastases, as their presence is one of the most common causes of treatment failure in oncology. The expression status of ER, PR, and HER2 on metastatic tumor cancer cells is crucial for selecting

a therapeutic strategy. However, it should be noted that there is often a significant discordance in the expression of ER and PR receptors between metastatic tumors and the primary tumor focus, while the expression status of HER2 remains relatively stable [12]. In the case of the described patient, the biopsy of liver metastases revealed a discrepancy in the expression of ER and PR receptors compared to the metachronous cancer that occurred later. This suggests the presence of "triple-negative" breast cancer metastases which occurred in the patient in 2010.

Article Information and Declarations

Ethics statement

The patient's consent was obtained for the presentation of a clinical case.

Author contributions

K.P.: responsible for conception, design, execution, writing the paper; I.R.: responsible for conception, design, execution, writing the paper; M.K.: responsible for conception, design, execution, writing the paper. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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Supplementary material

None.

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VIA MEDICA

CASE REPORT

Maria Grodkiewicz, Paweł Kozieł, Izabela Chmielewska, Anna Grenda, Paweł Krawczyk, Janusz Milanowski

Department of Pneumonology, Oncology and Allergology, Medical University of Lublin, Poland

Optimizing treatment strategies for a MET exon 14 skipping mutation in non-small-cell lung cancer: a case report of sequential immunotherapy and targeted therapy and literature review

Address for correspondence:
Izabela Chmielewska, MD, PhD
Department of Pneumonology, Oncology and Allergology, Medical University of Lublin
ul. Jaczewskiego 8, 20–090 Lublin, Poland
e-mail: izabela.chmielewska@umlub.pl

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ABSTRACT

The *MET* exon 14 skipping mutation is found in approximately 3–4% of non-small cell lung cancers (NSCLC). In 2020, the American Food and Drug Administration approved the first drug targeting this mutation. Capmatinib is a selective MET tyrosine kinase inhibitor. In the European Union, capmatinib is used when the patient needs further treatment after receiving immunotherapy or platinum-based chemotherapy, or both. In the described case, due to disease progression during treatment with pembrolizumab and then with platinum-based chemotherapy, next-generation sequencing was performed, which allowed for detection of the *MET* gene exon 14 skipping mutation. Targeted therapy with capmatinib was the only method of treatment resulting in a partial response to the disease and improvement of the patient's quality of life. This case indicates the importance of detailed molecular diagnosis and selection of the optimal method of treatment to prolong survival of the patient with advanced NSCLC. Due to promising results of research conducted so far, in the future, selective MET tyrosine kinase inhibitors — capmatinib and tepotinib — may become the new standard of first-line treatment in NSCLC patients with the *MET* exon 14 skipping mutation.

Keywords: adenocarcinoma, capmatinib, *MET* proto-oncogene, MET exon 14 skipping mutation, non-small-cell lung cancer

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Introduction

Currently, the most common histological type of primary lung cancer (LC) is adenocarcinoma, and in recent years, there has been a steady increase in its incidence (especially in women). A characteristic feature of this type is early spread through the bloodstream; therefore, it is often detected at a metastatic stage, which is associated with poor prognosis [1, 2]. However, by using innovative diagnostic techniques, such as next-generation sequencing (NGS), targetable molecular changes can be found in approximately 50% of tumors, which significantly increases the chances of finding an effective targeted therapy and, consequently, prolonging patients' overall survival [3].

In this article, we will focus on one of the new molecular targets in the treatment of non-small-cell lung cancer (NSCLC) — the abnormal MET protein resulting from the *MET* exon 14 skipping mutation. The *MET* proto-oncogene encodes a receptor tyrosine kinase (RTK) for hepatocyte growth factor (HGF). Activation of this receptor by binding of its ligand stimulates downstream signaling pathways (MAPK, PI3K/AKT, STAT, and NF-κB) [4]. The MET pathway has an es-

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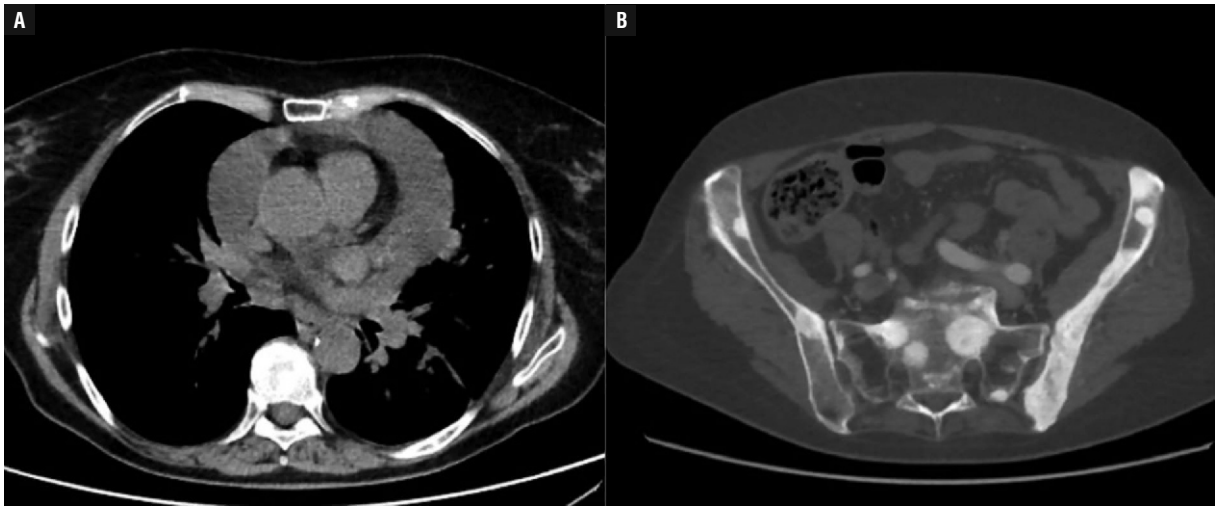

Figure 1A–B. Computed tomography scans presenting pericardial effusion and bone metastasis at the time of diagnosis

sential role during embryogenesis, affecting the development of a diverse set of organs and systems. Beyond embryonic development, MET signaling is important for wound healing and tissue regeneration, especially liver regeneration [5]. However, increased MET RTK activity also causes pleiotropic effects in tumor cells, including survival, proliferation, metastasis, and drug resistance [6]. Furthermore, it has been demonstrated that tumor cells with the *MET* mutation are resistant to apoptosis [7, 8]. Excessive activation of the MET pathway in NSCLC patients results from high expression of this receptor caused by amplification of the *MET* gene, mutations in the tyrosine kinase domain of the *MET* gene, or mutations in the splice site in introns 13–14 or in exon 14 of the *MET* gene. Exon 14 of the *MET* gene encodes CBL tyrosine kinase binding domain and CBL acts as E3 ubiquitin ligase. Therefore, CBL-mediated MET protein degradation is impaired when exon 14 is skipped. No degradation of MET protein leads to the accumulation of MET RTK and activation of MET oncogenic signaling. The exon 14 skipping mutation is found in 3–4% of NSCLC patients (most often with an adenocarcinoma type), who usually have no other target mutation, and the finding is associated with poor prognosis [3, 9, 10].

In 2020, the American Food and Drug Administration (FDA) approved capmatinib, which is a new drug for the treatment of patients with metastatic NSCLC (mNSCLC) with the presence of the *MET* exon 14 skipping mutation. Capmatinib is a MET tyrosine kinase inhibitor (MET-TKI) [11, 12]. In 2022, the drug also gained the European Medicines Agency (EMA) approval. In comparison to other MET inhibitors (e.g. crizotinib), in *in vitro* assays, capmatinib was shown to be more potent and more selective for MET than for other kinases. Similar activity against MET is shown by tepotinib, which has also been registered by the FDA and EMA for the treatment of NSCLC patients with splicing mutations in the *MET* [12–14]. They prevent the activation of downstream effectors in the MET signaling pathway by blocking MET phosphorylation and, as a consequence, restrain tumor cell proliferation and migration [15]. In addition, capmatinib and tepotinib induce apoptosis in MET-dependent tumor cell lines [13].

We present a case report of a patient with mNSCLC and a rare *MET* exon 14 skipping mutation, in whom, after previous immunotherapy and chemotherapy, an innovative capmatinib targeted therapy was started.

Case report

In November 2021, a 70-year-old female patient with atrial fibrillation, hypertension, gout, and without smoking history was referred for diagnostics due to chronic cough. It turned out to be caused by pericardial effusion; therefore, pericardiocentesis was performed. To determine the reason for the accumulation of fluid in a pericardial cavity, computed tomography (CT) was performed. It showed an infiltrative lesion measuring 59 × 42 mm in the lower field of the left lung, lymphadenopathy of the right paratracheal nodes as well as right and left hilar nodes, sclerotic areas corresponding to bone metastases in the spine and left hip bone (Fig. 1). Adenocarcinoma (AC) of the lung was diagnosed in the pathological examination of the material from bronchoscopy with endobronchial ultrasound fine-needle aspiration (EBUS-FNA). Stage IV (T2bN2M1c) was confirmed according to the *Tumor,*

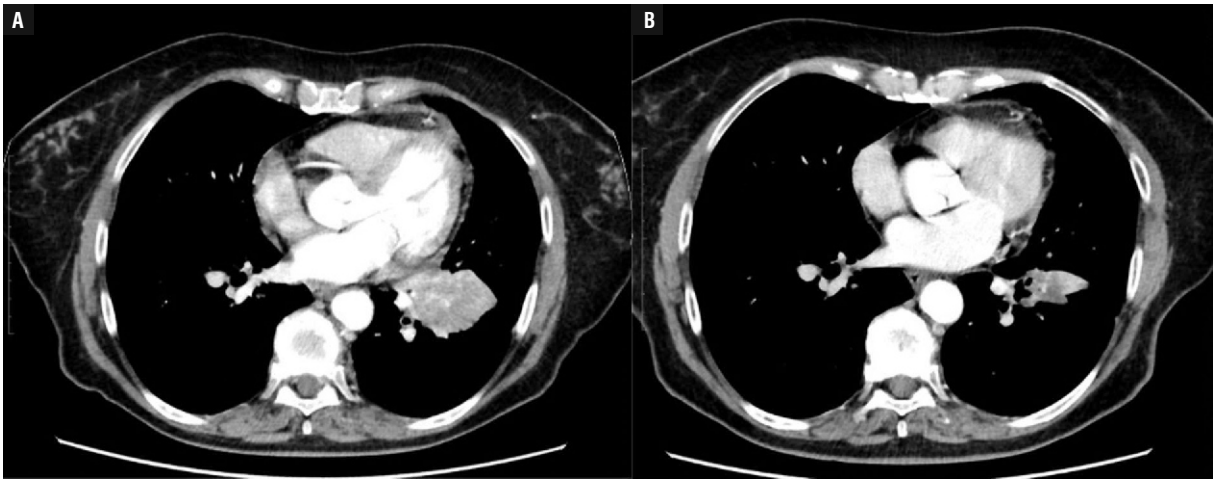

Figure 2A–B. Computed tomography scans presenting partial response after 6 months of effective treatment with capmatinib

Nodes, and Metastases (TNM) classification. Single-gene molecular tests performed at that time did not reveal any driver mutations that would allow administration of reimbursed targeted treatment. Genetic alterations in the *EGFR* (epidermal growth factor receptor) gene and rearrangements of the *ALK* (anaplastic lymphoma kinase) and *ROS1* genes were excluded. Expression of programmed death protein ligand-1 (PD-L1) was present in 80% of the tumor cells; therefore, monotherapy with pembrolizumab was initiated.

Due to tumor adherence to the pericardium, in February 2022, pericardial effusion reappeared, but it was successfully decompressed. Unfortunately, after three cycles of immunotherapy, disease progression was revealed. Computed tomography performed at the end of March, showed, in comparison to the previous examination, enlargement (by 3–5 mm) of the primary lesion that was adjacent to the pericardium with the wider base and connected with the pleura. Some liquid (up to 10 mm) in the left pleural cavity was visible. Moreover, satellite pulmonary nodules were found. An irregular change with a diameter of 24 mm in the liver, suspected metastasis, was also visible. In addition, there was significant progression of osteosclerotic skeletal lesions. Therefore, the treatment was changed to chemotherapy in the form of cisplatin and pemetrexed. As the subsequent cycles of chemotherapy were administered, a slight reduction of the primary lesion and amount of fluid in the pericardium was noticed. Nevertheless, CT performed in August 2022 (after 4 cycles of chemotherapy) showed progression in the number and size of osteosclerotic skeletal lesions, accompanied by severe pain in the affected bones.

Due to the unsatisfactory response to the treatment, the archive tissue sample was diagnosed by next-generation sequencing (NGS) to find targetable molecular changes. The *MET* exon 14 skipping mutation was detected. Treatment with capmatinib was initiated under the expanded access program (EAP). After six months of targeted therapy, CT scans confirmed a partial response (Fig. 2). The patient did not require pericardiocentesis. The skeletal pain diminished completely without local treatment. The patient has continued oral treatment for 9 months with very good tolerance, and no adverse effects have been noted so far.

Discussion

It should be remembered that in the case of metastatic NSCLC, a key influence on the patient's prognosis is not only the patient's health condition or disease stage but also the optimal method of treatment. In AC patients, it is crucial to look for molecular changes that enable targeted therapy. A single test may help to find common genetic alterations. However, only NGS can reveal rare molecular abnormalities. Evaluation of *MET* gene mutations is suggested in NSCLC patients after excluding mutations in the *EGFR* gene and rearrangements in the *ALK* and *ROS1* genes [16].

American Food and Drug Administration approval of two MET tyrosine kinase inhibitors — campatinib in 2020 and tepotinib in 2021 — for the treatment of metastatic NSCLC patients with the *MET* exon 14 skipping mutation opened a completely new chapter in molecularly targeted NSCLC therapy. The evidence of capmatinib efficacy and safety comes from a prospective, multicenter, multiple-cohort, phase II clinical trial — GEOMETRY mono-1. Eligible patients were adults (≥ 18 years of age) with stage IIIB or IV NSCLC with any

Table 1. Comparison of MET-targeting therapies

Drug	Trial and phase	Study group	ORR	DoR	PFS	OS	Most common adverse events
Capmatinib	Phase II GEOMETRY NCT 02414139	97 NSCLC patients with *MET* exon 14 skipping mutation: 69 previously treated and 28 treatment-naïve	41% (95% CI 29–53) in pretreated and 68% (95% CI 48–84) in treatment-naïve	9.7 months (95% CI 5.6–13.0) in pretreated and 12.6 months (95% CI 5.6–NR) in treatment-naïve	5.4 months (95% CI 4.2–7.0) in pretreated and 12.4 months (95% CI 8.2–NR) in treatment-naïve	–	Peripheral edema (41.6% of patients), nausea (33.2%), elevated serum creatinine (19.5%), vomiting (18.9%)
Tepotinib	Phase II VISION NCT 02864992	152 NSCLC patients with *MET* exon 14 skipping mutation	46% (95% CI 36–57)	11.1 months (95% CI 7.2–NR)	8.5 months	17.1 months	Peripheral edema (65.6% of patients), nausea (30.2%), hypoalbuminemia (28.5%), diarrhea (27.8%), elevated serum creatinine (27.1%)

CI — confidence interval; DoR — duration of response; NR — not reported; NSCLC — non-small-cell lung cancer; ORR — overall response rate; OS — overall survival; PFS —progression-free survival

histologic features, without *EGFR* or *ALK* abnormalities, and with at least one measurable lesion, defined according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). A total of 97 NSCLC patients with the *MET* exon 14 skipping mutation were recruited, including 69 previously treated and 28 treatment-naïve patients. They received capmatinib in a 400 mg oral dose twice daily. The primary endpoint was the overall response rate (ORR), and the key secondary endpoint was the duration of response (DoR). Additional secondary endpoints included (1) investigator-assessed response and duration of response, (2) investigator-evaluated and independent review committee-evaluated time to response, disease control, progression-free survival, and (3) the safety profile and pharmacokinetics of capmatinib.

The ORR was observed in 41% [95% confidence interval (CI) from 29 to 53] of previously treated patients and in 68% (95% CI 48–84) of treatment-naïve patients. The median DoR was 9.7 months (95% CI 5.6–13.0) and 12.6 months (95% CI 5.6–not reached), and median progression-free survival was 5.4 months (95% CI 4.2–7.0) and 12.4 months (95% CI 8.2–not reached) in the previously treated and treatment-naïve cohorts, respectively. Responses to therapy were rapid. The majority of patients (82% of the previously treated patients and 68% of treatment-naïve patients) had a response at the first evaluation after the initiation of capmatinib therapy. The most frequently reported adverse events were peripheral edema (41.6% of patients) and nausea (33.2%) These events were mostly of first- or second-grade severity (Tab. 1) [17].

Tepotinib is another MET tyrosine kinase inhibitor, which, by disrupting MET signal transduction pathways, induces apoptosis in tumor cells overexpressing this receptor. The efficacy of tepotinib was demonstrated in the open-label, phase II, multicenter VISION clinical trial that enrolled 152 patients with advanced or metastatic NSCLC with the *MET* exon 14 skipping mutation. Patients received oral tepotinib 500 mg once daily until disease progression or unacceptable toxicity. The primary endpoint was the ORR rate assessed by an independent review committee (IRC) in patients who had undergone at least 9 months of follow-up. The authors reported that tepotinib was associated with a partial response in approximately half of the patients, with an ORR of 46% (95% CI 36–57) according to the IRC review and 56% (95% CI 45–66) by investigator assessment. Median DoR was 11.1 months (95% CI 7.2–not reached). Progression-free survival (PFS) and overall survival (OS) were 8.5 and 17.1 months, respectively. Adverse events of grade 3 or higher were reported in 28% of the patients (Tab. 1) [18].

The favorable results of these trials made capmatinib and tepotinib the first two FDA and EMA-approved targeted therapies for lung cancer with *MET* proto-oncogene mutation. According to the European Society for Medical Oncology (ESMO) guidelines, capmatinib or tepotinib can be recommended following prior treatment with immunotherapy and/or platinum-based chemotherapy in patients with the *MET* exon 14 skipping mutation-positive metastatic NSCLC [19]. Whereas, both agents are preferred as first-line monotherapy options in the same indication according to the Na-

tional Comprehensive Cancer Network (NCCN) [20]. Recommended starting dose of capmatinib is 400 mg twice daily. Tablets can be taken with or without food. Dosing can be modified to manage adverse reactions, but therapy should be discontinued in patients who are unable to tolerate 200 mg twice daily. For tepotinib, the proposed dosing regimen is 450 mg once daily [21].

In addition to the ongoing search for new molecularly targeted therapies, another important issue is to determine the place of immune checkpoint inhibitors (ICIs) in the treatment of NSCLC patients with driver alterations. The efficacy of immunotherapy in patients with *MET* gene mutations remains unknown. Yoshimura et al. assessed the correlation between *MET* amplification, gene copy number gains, and MET expression with the efficacy of nivolumab monotherapy in patients with advanced NSCLC. No significant differences in both PFS and OS were observed between NSCLC patients with and without *MET* gene amplification. The ORR in patients with high and intermediate numbers of *MET* gene copies (50.0% for both) was significantly higher than those without increased *MET* gene copy number (17.6%), yet survival outcomes for both PFS and OS did not improve. This study showed that an increase in the *MET* gene copy number was not associated with greater efficacy of nivolumab in patients with NSCLC [22].

Mazieres et al. [23] conducted a retrospective study in patients receiving ICI monotherapy for advanced NSCLC with at least one oncogenic driver alteration. One of the analyzed subgroups included patients with *MET* amplification or exon 14 skipping mutation (n = 36). Programmed death protein ligand-1 expression was found in 90% of them. In this group, PFS was 3.4 months and the ORR was 16%. Progressive disease (PD) was observed in 51% of patients, which was a relatively low proportion, compared to other driver alterations subgroups [23]. A similar study was conducted by Guisier et al. [24], who obtained the following results: the subgroup of patients with *MET* mutations (n = 30) achieved an ORR of 35.7% and PFS of 4.9 months. These outcomes were better than in other studies, but the authors emphasized the possible impact of high PD-L1 expression status and comparably low number of treatment lines received before immunotherapy in a great percentage of patients [24]. Sabari et al. [25] researched the response to ICIs in a group of 24 NSCLC patients with the *MET* exon 14 skipping mutation. They reported an ORR of 17% and PFS of 1.9 months [25, 26].

A case from our department described by Terlecka et al. [27] indicates that sometimes the PD-1 blockade can be effective in *MET*-altered NSCLC, even despite an advanced stage of the disease. It concerned a patient with metastatic AC with high PD-L1 expression and *MET* exon 14 skipping mutation. Treatment with pembrolizumab was initiated after stereotactic radiotherapy for central nervous system (CNS) metastases. Partial remission was achieved, which was followed by long-term stabilization [27].

To sum up, clinical efficacy of ICIs in NSCLC with *MET* mutation is rather modest. However, it can be effective in some cases and further research is warranted to establish the place of immunotherapy in treatment regimens for patients with *MET*-altered NSCLC.

Conclusions

In conclusion, capmatinib and tepotinib paved the way for personalized molecularly targeted therapy for patients with rare *MET* gene alteration (*MET* exon 14 skipping mutation). Therapeutic management of patients with advanced NSCLC is often based on various methods of treatment. In the case of our patient, due to her resistance to immunotherapy and chemotherapy and lack of targeted alterations in the *EGFR*, *ALK,* and *ROS1* genes, therapeutic possibilities were extremely limited. Performance of the NGS turned out to be crucial. Detection of the uncommon mutation in the *MET* gene made it possible for us to use of capmatinib, which was effective in inhibiting disease progression. The presented case indicates that there is a need for detailed molecular diagnosis in NSCLC (AC in particular). Further research should aim to continue to identify new molecular targets in NSCLC, while clinicians implement targeted treatment as early as possible. Moreover, it is important to determine the place of immunotherapy in the treatment of NSCLC patients with driver alterations. It is needed to demonstrate the efficacy of selective MET tyrosine kinase inhibitors — capmatinib and tepotinib — in the first-line setting in NSCLC, not only in patients who have exhausted other treatment options.

Article Information and Declarations

Ethics statement

Article have been conducted according to the principles stated in the Declaration of Helsinki.

Author contributions

M.G.: conceptualization, investigation, writing — original draft; P.Kozieł: investigation, writing — original draft; I.C.: conceptualization, methodology, investigation, writing — original draft and review and editing; A.G.: methodology, writing — review and editing; P.Krawczyk: conceptualization, methodology, writing — review and editing; J.M.: writing — review and editing

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VIA MEDICA

CLINICAL VIGNETTE

Martyna Ziemińska[1], Aldona Ząber[1], Andrzej Mazurek[2], Bartłomiej Grala[3], Renata Duchnowska[1]

[1]Department of Oncology, Military Institute of Medicine, National Research Institute, Warsaw, Poland
[2]Department of Nuclear Medicine, Military Institute of Medicine, National Research Institute, Warsaw, Poland
[3]Department of Pathology, Military Institute of Medicine, National Research Institute, Warsaw, Poland

Serous cystadenocarcinoma of the pancreas with synchronous breast cancer

Keywords: breast cancer, pancreas, serous cystadenocarcinoma

A 77-year-old female was admitted to an acute surgical service for the management of suspected gastrointestinal bleeding. She was in moderately severe condition (Eastern Cooperative Oncology Group Performance Scale 3) with stable vital signs. Blood tests revealed a hemoglobin level of 5 g/dL (range 11.0–18.0 g/dL), hematocrit of 15% (range 35–55%), red blood cell count of 1.66 × 10^12/L (range 3.5–5.5 × 10^12/L), platelet count of 371 × 10^9/l (range 150–400 × 10^9/L), and white blood cell count of 14.89 × 10^9/L (range 4.0–10.0 × 10^9/L). On physical exam, a tumor in the left breast and a non-moving mass in the epigastrium were palpated. Endoscopy showed moderate erythematous-exudative gastropathy and ulceration in the subcardiac area. Cold saline with adrenaline was locally administered, and red blood cell concentrates were transfused. Additionally, intravenous administration of tranexamic acid, ethamsylate, and pantoprazole was initiated. Mammography showed a tumor size of 28 × 27 mm in the left breast classified as Breast Imaging-Reporting and Data System (BI-RADS) 5. The biopsy revealed an invasive carcinoma, intermediate grade G2 in immunohistochemistry (IHC) staining: estrogen receptor-positive with a strong reaction in more than 90% of the cells (Allred 8), progesterone receptor-negative, human epidermal growth factor type 2 negative (IHC 1+), and Ki67 15%.

Furthermore, contrast-enhanced computed tomography (CT) of the abdominal cavity demonstrated extensive solid-cystic hyperplasia with small calcifications (135 × 92 × 153 mm) originating from the tail of the pancreas. The lesion extended from the fundus of the stomach to the left kidney and infiltrated the surrounding tissues of the spleen and stomach. One suspected lesion in segment 8 of the liver was detected. A biopsy of the lesion in the pancreas was conducted and demonstrated clear cell carcinoma with CKAE1/AE3+, vimentin +, RCC+/–, CD10 (–), CK7 (–), WT1 (–), PR (–), ER (–), mammoglobin (–), GCDFP15 (–), p53 (–). The IHC staining indicated that the origin of the disease is likely to be either the kidney or a reproductive organ.

Considering the advanced stage of the disease and unknown primary origin, the patient was initially qualified for induction chemotherapy with paclitaxel and carboplatin. However, the positron emission tomography (PET-CT) (separately from the breast tumor) showed a lesion with low metabolic activity originating from the pancreas or spleen (Fig. 1A–C). Based on the PET-CT result, the patient was qualified for upper midline laparotomy. A peripheral resection of the pancreas with splenectomy and segmental resection of the colon was performed. The histopathological examination revealed a spongy litho-cystic

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Address for correspondence: Prof. Renata Duchnowska, Department of Oncology, Military Institute of Medicine, National Research Institute, ul. Szaserów 128, 04–141 Warsaw, Poland, e-mail: rdtt@wp.pl

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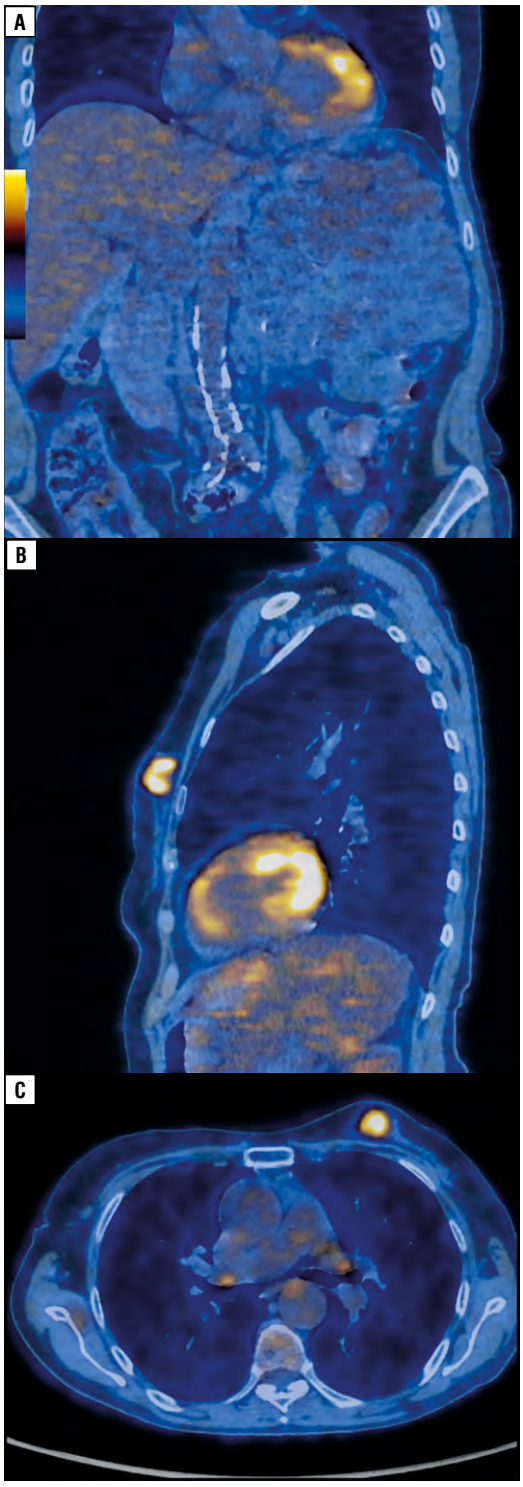

Figure 1. Positron emission tomography with 2-deoxy-2--[fluorine-18]fluoro-D-glucose (^{18}F-FDG PET/CT); nodular lesion 141 × 76 mm; CC 115 mm with mediocre ^{18}F-FDG metabolism; lesion involves the splenic hilum, tail of the pancreas, adjacent to the stomach, the descending colon and the left adrenal gland; focus of increased radiolabel accumulation in the left breast; **A.** Coronal scan; **B.** Sagittal scan; **C.** Axial scan

tumor, size of 128 × 135 × 68 mm, involving a portion of the pancreas, spleen, and subserosal tissues of the large intestine. The morphological characteristics were consistent with a microcystic serous cystadenocarcinoma (SCAC) of the pancreas, with IHC staining: CKAE1/AE3 (+), CK19 (+), CK7 (+) focal, inhibinA (+), vimentin (–), RCC (–), CD10 (–), CK5/6 (–), calretinin (–), WT–1 (–), CD117 (–), MelanA (–), HMB–45 (–), CD4 (–), CD31 (–), CD34 (–), ER (–), PR (–); Ki67 about 5%. Splenic infiltration, angioinvasion, and satellite nodules in the retroperitoneal space were present, while the surgical margin was free of cancer cells (R0 resection).

Approximately eight weeks later, a radical mastectomy with a sentinel node biopsy was performed. The histopathological examination showed invasive breast cancer of no special type, intermediate grade G2, with emboli in blood vessels, TNM staging pT2pN0(sn), L/V1, R0. Considering the patient's age, overall health condition, and preferences, hormone therapy with tamoxifen was started. There were no signs or evidence of disease recurrence during the 4-year follow-up.

Discussion

Synchronous primaries are diagnosed in approximately 20% of cancer patients, mainly in the group over the age of 50. In patients with breast cancer (BC), the common synchronous neoplasms include contralateral BC and gynecologic cancers [1]. SCAC is a very rare tumor and usually occurs in women between the age of 50 and 70. The course of the disease is often asymptomatic. In the case of advanced SCAC, the most common symptoms are abdominal pain, upper gastrointestinal bleeding, weight loss, a palpable tumor or elevated transaminases, and rarely jaundice or pancreatitis [2, 3].

Diagnosis of SCAC by biopsy is difficult because of its similarity to the cells of benign serous cystic neoplasms. Malignant tumors are usually larger, locally invasive, and with distant metastases. Furthermore, they often infiltrate locally adjacent vessels, nerves, spleen, stomach, and duodenum. The differential diagnosis of SCAC should include clear cell carcinomas of the ovary or kidney [2].

The surgery is of crucial importance in SCAC, also in older patients [4]. The excellent prognosis associated with SCAC, even in the case of distant metastases, justifies an aggressive surgical approach. In turn, systemic therapy in SCAC has no proven effect [4]. The occurrence of synchronous primary tumors is always a challenge and often causes dilemmas in clinical practice. The therapeutic regimen should be decided by multidisciplinary teams, considering the patient's general condition, expectations, prognosis, and quality of life.

Article Information and Declarations

Ethics statement

Retrospective description. The patient gave consent. Data anonymized.

Author contributions

M.Z., A.Z., R.D.: conception and design.
All authors: provision of study materials, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript.

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Conflict of interest

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