VIA MEDICA

CONFERENCE REPORT

Dawid Sigorski[1–3], Małgorzata Osmola[3, 4], Bartosz Spławski[5], Sylwia Tabor[3, 6], Mirosława Püsküllüoğlu[7], Renata Pacholczak-Madej[8–10], Edyta Hunia-Prejsnar[3, 11], Michał Gola[2,12], Michał Wilk[3, 13], Agnieszka Markiewicz[14], Joanna Kiszka[3, 11]

[1]Department of Oncology, University of Warmia and Mazury in Olsztyn, Poland
[2]Department of Oncology and Immuno-Oncology, Clinical Hospital of the Ministry of Internal Affairs and Administration with the Warmia-Mazury Oncology Centre, Olsztyn, Poland
[3]Section of Young Oncologists at the Polish Society of Clinical Oncology
[4]Maria Sklodowska-Curie Medical Academy in Warsaw, Warsaw, Poland
[5]Head and Neck Cancer Department, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland.
[6]Department of Lung Cancer and Thoracic Tumors, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[7]Department of Clinical Oncology, Maria Sklodowska-Curie National Research Institute of Oncology Kraków Branch, Kraków, Poland
[8]Department of Anatomy, Jagiellonian University Medical College, Krakow, Poland
[9]Department of Gynecological Oncology, Maria Sklodowska-Curie National Research Institute of Oncology, Krakow Branch, Krakow, Poland
[10]Department of Chemotherapy, The District Hospital, Sucha Beskidzka, Poland
[11]Department of Clinical Oncology, Subcarpathian Cancer Center, Brzozów, Poland
[12]Department of Human Histology and Embryology, School of Medicine, University of Warmia and Mazury in Olsztyn, Poland
[13]Department of Oncology, Centre of Postgraduate Medical Education, European Health Centre, Otwock, Poland
[14]Department and Clinic of Dermatology, Sexually Transmitted Diseases and Clinical Immunology, University of Warmia and Mazury, Olsztyn, Poland

Advances in oncology after the 2024 European Society for Medical Oncology (ESMO) congress

Address for correspondence:
Dawid Sigorski, MD PhD
Department of Oncology,
University of Warmia and Mazury
in Olsztyn
ul. Wojska Polskiego 37,
10–228 Olsztyn, Poland
tel.: +48 895 398 511
e-mail: dawid.sigorski@uwm.edu.pl

Oncology in Clinical Practice
DOI: 10.5603/ocp.103719

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

The European Society of Medical Oncology (ESMO) Congress is the most important and clinically relevant oncological conference in Europe. It provides a forum to share the latest advances in cancer research, diagnostics, and treatment. In this review, we present the most significant new data on cancer treatment, which may change future oncological and patient outcomes.

Keywords: ESMO, head and neck cancers, lung cancer, breast cancer, gastric cancer, colorectal cancer, pancreatic cancer, kidney cancer, prostate cancer, bladder cancer, melanoma

Oncol Clin Pract

Introduction

The annual congress of the European Society for Medical Oncology (ESMO) is a key event for the oncology community, spotlighting cutting-edge advancements in cancer research, treatment, and patient care. In this review, we aim to present this year's highlights that contribute to improving cancer care in Poland and globally. We have described the advancements in the treatments of head and neck, lung, breast, gastrointestinal cancers, urological cancers, and melanoma.

Received: 24.11.2024 Accepted: 25.11.2024 Early publication: 17.01.2025

Head and neck cancers

The most significant study presented at ESMO 2024 was the GORTEC 2017-01 REACH trial, a phase III randomized study comparing avelumab + cetuximab + radiotherapy (RT) to standard-of-care treatments in patients with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN). The trial enrolled 707 patients with Stage III, IVa, and IVb head and neck squamous cell carcinoma (HNSCC) who were not candidates for surgery. The study allocated patients to two cohorts based on their eligibility for receiving cisplatin. In the cisplatin cohort, comprising 430 patients, participants were randomized to receive either RT with cisplatin, standard treatment, or RT with avelumab and cetuximab. In the cohort without cisplatin, which included 277 patients, participants were randomized to receive RT with cetuximab as the standard of care or RT with avelumab and cetuximab.

In the cisplatin cohort with a median follow-up of 50.8 months [interquartile range (IQR) 45.8; 57.4], progression-free survival (PFS), the primary endpoint, was evaluated over four years. The 4-year PFS rate was 54.7% (95% CI 47.8–61.4%) in the RT + cisplatin group, compared to 42.3% (95% CI 35.7–49.2%) in the RT + avelumab + cetuximab group. The hazard ratio (HR) was 1.40 [95% confidence interval (CI) 1.07–1.82], with a p-value of 0.013. For the secondary endpoint of overall survival (OS) in this cohort, the 4-year OS rate was 67.1% (95% CI 60.4–73.2%) in the RT + cisplatin group, compared to 55.1% (95% CI 48.3–61.8%) in the RT + avelumab + cetuximab group. The HR for death was 1.43 (95% CI 1.05–1.93), with a p-value of 0.021. These results indicate a statistically significant disadvantage for the combination of RT, avelumab, and cetuximab compared to the standard RT + cisplatin treatment.

In the cohort without cisplatin, with a median follow-up of 47.7 months (IQR 40.7; 56.4), the primary endpoint of PFS showed 4-year PFS of 33.7% (95% CI 26.2–42.2%) in the RT + avelumab + cetuximab group, compared to 18.4% (95% CI 12.5–26.1%) in the RT + cetuximab group. The adjusted HR was 0.80 (95% CI 0.60–1.06; p = 0.059), indicating a trend toward improvement but without statistical significance. The crude HR was 0.75 (95% CI 0.57–0.99; p = 0.022), reaching significance in the unadjusted analysis.

For the secondary endpoint of OS, the 4-year OS rate was 42.6% (95% CI 34.3–51.3%) in the avelumab + cetuximab group *vs.* 39.4% (95% CI 30.8–48.7%) in the cetuximab-only group, with an HR for death of 1.05 (95% CI 0.76–1.43; p = 0.77), indicating no significant difference in OS between the two groups.

In conclusion, replacing cisplatin with avelumab and cetuximab was detrimental in patients eligible for cisplatin. In ineligible patients, adding avelumab to cetuximab led to a favorable and clinically meaningful trend in PFS, with an HR of 0.80 and significantly reduced distant metastases, evidenced by a sub-hazard ratio of 0.24. Despite these positive effects on disease progression and metastasis, no OS benefit was observed in this group [1].

The TACTI-003 trial, a randomized phase IIb study, presented its primary results at ESMO 2024, focusing on the combination of eftilagimod alpha (efti, a soluble LAG-3 protein) with pembrolizumab *vs.* pembrolizumab alone, in the treatment of first-line recurrent or metastatic HNSCC with a combined positive score (CPS) ≥ 1.

This study aimed to assess whether adding efti to pembrolizumab could enhance the immune response and improve outcomes compared to pembrolizumab monotherapy. The LAG-3 pathway is known to play a key role in immune evasion in cancers, and combining LAG-3 inhibition with anti-programmed cell death protein 1 (anti-PD-1) therapy, such as pembrolizumab, could potentially boost antitumor activity.

The TACTI-003 trial demonstrated encouraging results, particularly in patients with higher CPS values, reinforcing the potential benefit of combining Efti with pembrolizumab in the treatment of recurrent or metastatic HNSCC. In patients with CPS ≥ 1, the combination therapy showed a numerically higher overall response rate (ORR) of 32.8% compared to 26.7% with pembrolizumab alone. The benefit was most pronounced in patients with CPS ≥ 20, where the combination led to a 1.7-fold increase in the ORR (31.0% for efti + pembrolizumab *vs.* 18.5% for pembrolizumab alone). Notably, no difference was observed in the CPS 1–19 subgroup, with an unexpectedly high ORR of 33.3% for pembrolizumab alone. Regarding overall response across both cohorts (A&B), regardless of CPS expression, the ORR for efti + pembrolizumab was 34.8%. This included patients with CPS < 1, suggesting broader efficacy. A key finding of the trial was the durability of response, with the median duration exceeding 17 months in both groups. These results are favorable compared to historical data from pembrolizumab therapy combined with chemotherapy. Safety profiles were consistent, with no new safety signals detected, confirming that the combination of left + pembrolizumab is safe and well tolerated. These findings highlight the potential of eftilagimod alpha in enhancing immune responses and improving outcomes in HNSCC, particularly in high-CPS patients, and support the need for further investigation. OS data will be provided in future updates [2].

The MYTHOS trial, a phase II study, evaluated the efficacy and safety of trastuzumab deruxtecan (T-DXd) in patients with human epidermal growth factor receptor 2 (HER2)-positive recurrent or metastatic salivary gland cancer (SGC). While HER2 overexpression is well-studied in breast cancer, it is relatively rare

in salivary gland tumors, making this trial particularly significant in exploring new treatment options for this patient group.

The MYTHOS trial focused on a specific patient population with recurrent or metastatic salivary gland cancer, characterized by HER2 expression [immunohistochemistry (IHC) 1+ to 3+], as confirmed by central assessment. Patients included in the study had varying levels of HER2 expression, reflecting the diversity of HER2 status in this rare cancer type. Importantly, prior anti-HER2 treatment was allowed. To ensure safety, the trial excluded patients with a history of interstitial lung disease (ILD) or pneumonitis, given the known risk of lung-related side effects with T-DXd.

The MYTHOS trial demonstrated the promising efficacy of T-DXd in patients with HER2-positive SGC, specifically those with IHC 3+ or IHC 2+ with *in situ* hybridization (ISH) + HER2 expression. The ORR was 68.4% (13 of 19 patients; 95% CI 43.4–87.4), indicating strong antitumor activity in this population. The disease control rate (DCR) was 100% (19/19; 95% CI 82.4–100), with all patients experiencing some degree of disease control. The median PFS rate was 15.9 months [95% CI 5.8–not estimated (NE)], suggesting a durable benefit from the treatment.

The safety data were consistent with the known profile of T-DXd. Still, there was a higher incidence of ILD/pneumonitis in this population — 31.6% of patients experienced grade 1–2 ILD/pneumonitis, and 5.3% had grade 3. Low-grade gastrointestinal and hematologic adverse events (AEs) were the most common, aligning with the drug's established safety profile. The results from the MYTHOS trial suggest that T-DXd is a highly effective treatment option for patients with HER2-positive SGC, including those who have received prior HER2-targeted therapies. However, the increased risk of side effects requires vigilant monitoring. The trial is ongoing, and further assessments of OS and PFS will be reported [3].

In another study presented at ESMO 2024, researchers evaluated the efficacy and safety of androgen deprivation therapy (ADT) compared to chemotherapy in patients with recurrent and/or metastatic androgen receptor (AR)-expressing SGCs.

Salivary gland cancers account for fewer than 5% of head and neck cancers and are characterized by a complex histopathological classification comprising over 20 distinct epithelial cancer types. This diversity results in heterogeneous behavior and varying prognoses among different SGC subtypes [4].

One notable subtype is salivary duct carcinoma (SDC), recognized for its AR expression. This aggressive histotype is primarily associated with AR positivity. In rare instances, AR expression can also be found in adenocarcinoma not otherwise specified, occurring in approximately 30% of cases [5].

Currently, platinum-based chemotherapy remains the standard of care for patients with recurrent and/or metastatic SGCs [4]. However, recent findings indicate that ADT has shown efficacy in advanced AR-expressing SGCs, highlighting its potential as a therapeutic strategy. Despite this, there is currently no data supporting the use of ADT over chemotherapy in treatment-naïve AR-expressing SGC patients. This underscores the need for further clinical research to determine the optimal treatment approach for this population.

The primary endpoint in treatment-naïve patients was PFS. Median PFS in the ADT group was 4 months (95% CI 3.6–8.7), and in the chemotherapy group, 6.5 months [95% CI 5.3–8.6; HR = 1.12 (80% CI 0.77–1.63); p = 0.6]. Median OS in the ADT group was 22.4 months (95% CI 14.3–27.7), and in the chemotherapy group, 29.4 months [95% CI 16.6–NE; HR = 1.91 (80% CI 1.18–3.09); p = 0.9].

This trial represents the first-ever randomized study completed in AR-expressing SGCs. The results indicated that ADT did not demonstrate superiority or inferiority compared to chemotherapy in AR-expressing SGC treatment-naïve patients [6].

Another noteworthy presentation at ESMO 2024 was KEYNOTE-122, a phase II open-label randomized study evaluating the efficacy and safety of pembrolizumab with or without bevacizumab in patients with platinum-resistant recurrent/metastatic nasopharyngeal carcinoma (NPC).

No significant advances have been made in the treatment of NPC since standard first-line platinum-based chemotherapy failed. Results from KEYNOTE-122 demonstrated that pembrolizumab was not superior to chemotherapy in this setting, highlighting the need for more effective treatment strategies.

In NPC, vascular endothelial growth factor is overexpressed, driving angiogenesis and suppressing immune cell infiltration. Previous research showed that administering bevacizumab (7.5 mg/kg) one week before chemotherapy led to blood vessel maturation within the tumor, which is thought to improve immune cell infiltration. This resulted in increased infiltration of CD4+ and CD8+ T cells into the NPC tumor microenvironment, potentially enhancing the effectiveness of pembrolizumab [7].

The primary endpoint ORR was 12.5% for pembrolizumab monotherapy (arm A) *vs.* 58.3% for the combination therapy (arm B), with a 95% CI 22.1–69.6%, p = 0.001, indicating a statistically significant result. Significant improvements were observed in both secondary endpoints, PFS and OS, with the combination therapy. With a median follow-up of 28.3, the median PFS rate was 1.6 months for pembrolizumab alone compared to 13.8 months for the combination of pembrolizumab and bevacizumab. Similarly, median OS was 11.7 months in the pembrolizumab group *vs.* 18.5 months

in the combination group. These results suggest that adding bevacizumab to pembrolizumab significantly prolongs both PFS and OS in patients with platinum-resistant NPC, offering a promising treatment option for this challenging disease [8].

Lung cancer

Non-small cell lung cancer, non-metastatic

In recent years, we have observed a paradigm shift in the perioperative treatment of patients diagnosed with non-small cell lung cancer (NSCLC) through the use of immunotherapy and targeted molecular therapies. Data from successive randomized phase III clinical trials confirm the rationale behind this type of treatment, given the high risk of NSCLC recurrence, even among patients with a low initial stage of the disease.

At this year's ESMO Congress, an update on the results of the CheckMate 77T study was presented, comparing neoadjuvant nivolumab (NIVO) plus chemotherapy and adjuvant NIVO *vs.* neoadjuvant chemotherapy plus placebo in patients with a diagnosis of NSCLC at stages IIA to IIIB according to the 8th edition of the American Joint Committee on Cancer (AJCC) classification. The event-free survival (EFS) rate at 24 months of treatment was 65% in the experimental arm compared to 44% in the control arm; the medians were 40.1 and 17.0 months, respectively (HR = 0.59, 95% CI 0.45–0.79). The clearance rate of circulating tumor DNA (ctDNA) after the first cycle of neoadjuvant treatment was 66% in the NIVO/chemotherapy arm *vs.* 38% in the placebo/chemotherapy arm. This result correlated with the percentage of pathological complete response (pCR) in 50% of patients with ctDNA clearance in the studied arm. In contrast, pCR was not observed in any of the patients without ctDNA clearance in the NIVO/chemotherapy arm. Additionally, among patients in whom ctDNA clearance was not observed, the 2-year EFS rate was 50% in the NIVO/chemotherapy arm compared to 81% in the presence of ctDNA clearance. The use of NIVO was associated with lower risk of ctDNA recurrence, measured from the first cycle of adjuvant therapy, which was 8% compared to 20% in the placebo arm. This could potentially be linked to lower risk of lung cancer relapse in the future [9].

A similar analysis was conducted in the AEGEAN study, where durvalumab was compared to placebo in the perioperative treatment of patients with resectable NSCLC [10]. Patients from both study arms who achieved pCR 89.6% or a major pathological response (MPR, > 93%) belonged to the group where ctDNA clearance was confirmed on day 1 of cycle 4 of the neoadjuvant therapy. Among all patients with ctDNA clearance on day 1 of cycle 2, pCR was more frequent in the arm receiving durvalumab compared to the placebo arm (49% and 11%, respectively). ctDNA clearance in the experimental arm correlated with an improvement in EFS, both when compared to the group without ctDNA clearance, HR = 0,30 (95% CI 0.12–0.71) and to the control arm, HR = 0.31 (95% CI 0.11––0.85) [11]. Similar results were seen for OS, suggesting that ctDNA clearance may serve in the future as a surrogate marker for response to neoadjuvant immunochemotherapy, predicting prolonged EFS and OS.

The results of an exploratory biomarker analysis from the phase III ALINA study were presented in molecularly targeted therapy. This study evaluated the benefit of adjuvant alectinib [second-generation anaplastic lymphoma kinase (ALK) inhibitor] treatment compared to chemotherapy in patients with ALK-rearranged NSCLC of stage Ib (≥ 4 cm) to IIIA according to the 7th edition of the AJCC classification, who had undergone radical lung resection [12]. Based on the results of this study, alectinib has become the standard of care for this indication. During the presentation, it was shown that alectinib remained effective regardless of the echinoderm microtubule-associated protein-like 4 (EML4)-ALK fusion variant. For the analyzed mutations, the co-mutation in the *TP53* gene was associated with shortened disease-free survival (DFS) in the alectinib arm, with an HR of 2.73 (95% CI 0.89–8.39), which was not observed in the chemotherapy arm [13]. The study results strengthen the rationale for using alectinib for this indication and identifying a group of patients with a poorer prognosis. However, this does not currently alter the established standard of care.

During the conference, an analysis from the phase III LAURA trial was presented. The study compared maintenance treatment with osimertinib [third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor] *vs.* placebo in patients with locally advanced stage III NSCLC with EGFR-activating mutations who had undergone concurrent chemoradiotherapy (CRT). It confirmed clinically significant prolongation of median PFS in the experimental arm compared to the control arm [39.1 months *vs.* 5.6 months, respectively, HR = 0.23 (95% CI 0.13–0.38)] [14]. An additional analysis showed that the administration of osimertinib significantly prolonged the median time to distant metastases or death compared to placebo, with an HR of 0.21 (95% CI 0.11–0.38; $p < 0.001$). Similarly, an 83% reduction in the risk of central nervous system recurrence was demonstrated with active treatment, HR = 0.17 (95% CI 0.09–0.32; $p < 0.001$)[15]. The results of the LAURA trial suggest osimertinib may change the standard of care.

Non-small cell lung cancer, metastatic

In the context of metastatic NSCLC, several congress reports appeared significant for the future treatment of cancers with molecular abnormalities.

Currently, the standard of care after lorlatinib (third-generation generation ALK tyrosine kinase inhibitor) administration in patients with ALK-rearranged NSCLC is chemotherapy. During the congress, results were presented from the phase I/II clinical trial ALKOVE-1, which tested a new molecularly targeted drug, NVL-655. The study included patients who had undergone at least one line of tyrosine kinase inhibitors treatment and up to two lines of chemotherapy and/or immunotherapy. The ORR was 38% in the whole group and 64% in patients with compound mutations. Central nervous system penetration was confirmed in lorlatinib-naïve patients, with the intracranial ORR reaching 50%. The drug has been shown to have good safety, with no neurotoxicity-related AEs reported [16]. A phase II study with the NVL-655 is now underway.

Another drug worth mentioning is zipalertinib, a drug targeting the insertion in exon 20 of the *EGFR* gene. Currently, the only molecularly targeted drug with confirmed efficacy and registered for this indication is amivantamab [17, 18]. Treatment with amivantamab is not available in Poland. A phase I/II study of zipalertinib recruited patients who experienced disease progression during or after treatment with amivantamab. A total of 45 patients were enrolled, with an ORR of 40% and median PFS of 9.7 months [19]. These results seem promising, given the extremely aggressive course of the disease, but they require confirmation in later-phase clinical trials.

The latest report that appears to be significant in NSCLC treatment is an update on the phase II trial PHAROS, in which encorafenib was combined with binimetinib. In this study, patients with NSCLC and BRAF V600E mutation were included. One arm consisted of 59 patients who had not previously received treatment for metastatic disease, while the other included 39 patients who had undergone one line of systemic therapy. The ORR in the first group was 75% (95% CI 62–85), and in the second group, it was 46% (95% CI 30–63). The median duration of response was 40 months (95% CI 23.1–NE) in the first group and 16.7 months (95% CI 7.4––NE) in the second. The median PFS rate for treatment-naïve patients was 30.2 months (95% CI 15.7–NE), while median OS had not yet been reached (95% CI 31.3–NE). In the previously treated patients, median PFS was 9.3 months (95% CI 6.2–24.8), and median OS was 22.7 months (95% CI 14.1–32.2) [20]. The combination of encorafenib with binimetinib received a positive opinion from the European Medicines Agency (EMA) in September 2024, providing a second therapeutic option, alongside dabrafenib with trametinib, for patients with metastatic NSCLC with the V600E mutation in the *BRAF* gene. At the moment, none of these drug combinations are available for lung cancer treatment in Poland.

Breast cancer

HR+/HER2-negative breast cancer

During the 2024 ESMO Congress, 4-year outcomes on invasive DFS, distant disease-free survival (DDFS), and OS were presented for the NATALEE trial. In this study, patients were randomized to receive adjuvant ribociclib (400 mg/day, 3 weeks on, 1 week off for 3 years), a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor, plus a non-steroidal aromatase inhibitor (AI) (letrozole or anastrozole) or AI alone. Men and premenopausal women also received goserelin. Eligible patients had stage IIA [N0 with risk factors or N1 (1–3 nodes)], IIB, or III breast cancer (BC) per AJCC 8th edition. For the cut-off date, all patients in the ribociclib arm had discontinued the treatment, with 62.8% completing the entire 3-year course and 20% stopping early due to AEs. Ribociclib-AI treatment significantly improved invasive DFS compared to hormonal treatment alone (HR = 0.715; 95% CI 0.609–0.840; $p < 0.0001$), with 3- and 4-year DFS rates of 90.8% *vs.* 88.1% and 88.5% *vs.* 83.6%, respectively. The benefit was consistent across nodal and stage subgroups and extended to DDFS (HR = 0.715; 95% CI 0.604–00.847). OS data remain immature but show a favorable trend for ribociclib (HR = 0.827; 95% CI 0.636–1.074). Safety outcomes were consistent with prior analyses, confirming the benefit of adding ribociclib to adjuvant AI in hormone receptor-positive (HR+)/HER2-negative early BC. Using these data, the US Food and Drug Administration (FDA) approved ribociclib in this setting. As per previously published data from the phase III MonarchE trial, in patients with high-risk hormone receptor-positive HR+/HER2-negative BC abemaciclib (another CDK4/6 inhibitor) improved invasive DFS and distant relapse-free survival. However, the populations from NATALEE and MonarchE trials were not overlapping [21]. Currently, no CDK4/6 inhibitor is reimbursed in Poland in the adjuvant setting of the BC treatment.

HER2-positive breast cancer

T-DXd showed efficacy in HER2-positive BC in a few clinical trials [22, 23]. According to the Polish reimbursement program, T-DXd is administered to HER2-positive metastatic BC patients in the 2nd to 4th palliative treatment line. During the 2024 ESMO

Congress, data from the DESTINY Breast12 trial were presented. In this study, adults with HER2-positive metastatic BC who had progressed on up to two prior lines of therapy were treated with T-DXd 5.4 mg/kg every 3 weeks. Patients were assigned to two cohorts: those with brain metastases (BM) and those without. At the final data cutoff, with a median follow-up of 15.4 months (BM cohort) and 16.1 months (non-BM cohort), T-DXd demonstrated significant efficacy. In the BM cohort, 12-month PFS was 61.6%, and CNS-specific PFS was 58.9%, with CNS ORR of 79.2% in stable BM and 62.3% in active BM. In the non-BM cohort, the ORR was 62.7%. The ILD/pneumonitis occurred in 16% of patients in the BM cohort and 12.9% in the non-BM cohort, with some cases coinciding with opportunistic infections. T-DXd showed substantial intracranial and overall activity with no new safety flags, which supports its use in HER2-positive metastatic BC, including BM patients [22, 24].

Triple-negative breast cancer

For patients with stage II or III triple-negative breast cancer (TNBC) undergoing neoadjuvant chemotherapy (NACT) and without contraindications, such as autoimmune conditions, pembrolizumab is recommended alongside NACT and continuation post-surgery. This recommendation is supported by the KEYNOTE-522 trial, which demonstrated higher rates of pCR (63% *vs.* 56%) and improved 36-month event-free survival (85% *vs.* 77%) when pembrolizumab was added to NACT [25]. These results were consistent across programmed death-ligand 1 (PD-L1)-positive and -negative tumors and in patients with or without nodal involvement. Other immune checkpoint inhibitors, such as atezolizumab, have been evaluated with NACT in this setting [26]. However, pembrolizumab is the only one that has shown significant enhancements in both pCR rates and long-term outcomes. In Poland, the reimbursement program allows the treatment of patients with cT1-4 and N1-2 or cT2-T4 N0 disease.

During the 2024 ESMO Congress, updated KEYNOTE-522 trial results showed that pembrolizumab contributed to an increase in OS rates. After 60 months, the survival estimate was 87% for those treated with pembrolizumab, compared to 82% for the placebo group, resulting in an absolute difference of 4.9% (95% CI 0.3–9.4) [25]. The outcomes confirm applying pembrolizumab for patients with stage II and III TNBC, making this treatment the current standard of care. However, the data do not identify which patients benefit from the addition of pembrolizumab, highlighting the need for further research into biomarkers. Additionally, the necessity of continuing pembrolizumab in the adjuvant setting, as well as the benefit of combining this immune checkpoint inhibitor (ICI) with olaparib or capecitabine, remains uncertain.

Radiotherapy in breast cancer

Hypofractionated RT has become the standard approach for whole breast irradiation; however, in many countries, the normofractionated regimen, delivering 50 Gy across 25 fractions, remains the standard treatment of locoregional early BC. The HypoG-01 trial, a UNICANCER, phase III study (NCT03127995), aimed to evaluate the non-inferiority of hypofractionated RT, administering 40 Gy in 15 fractions (2.67 Gy per fraction), compared to the normofractionated regimen of 50 Gy in 25 fractions (2.0 Gy per fraction). This open-label, multicenter, randomized trial assessed the efficacy and safety of the two approaches. A total of 1265 patients were randomized between 2016 and 2020. The surgeries performed included mastectomies (45%) and axillary clearances (82.8%). After a median follow-up of 4.8 years, 275 cases of lymphedema were reported. The hypofractionated regimen was shown to be non-inferior to normofractionated RT regarding the arm lymphedema risk (HR = 1.02; 90% CI 0.83–1.26; non-inferiority p-value < 0.001). There were no significant safety concerns or differences in locoregional recurrence-free survival or OS. These results support the adoption of the 40 Gy/15 fraction regimen for loco-regional radiation therapy in early BC [27].

Advances in digestive cancers

Gastric cancer and gastroesophageal junction cancer

The management of gastric cancer has seen significant advancements, as demonstrated by several pivotal clinical trials presented at the 2024 ESMO Congress. These trials provide important insights into treatment strategies, including perioperative chemotherapy and CRT.

The TopGear Phase III trial randomized patients with resectable gastric cancer to two treatment arms: arm A, which received perioperative chemotherapy (ECF or FLOT), and arm B, which was treated with chemotherapy (2 cycles of ECF or 3 cycles of FLOT), followed by CRT (45 Gy + 5-FU), surgery, and adjuvant chemotherapy (3 cycles of ECF or 4 cycles of FLOT).

The study demonstrated that preoperative CRT significantly improved pathological complete response (pCR) rates (16.7% *vs.* 8.0%) and major pathological response (49.5% *vs.* 29.3%) compared to chemotherapy alone. However, after median follow-up of 66.7 months, there were no significant differences in PFS or OS between the two groups. Importantly, preoperative CRT did not result in higher treatment-related toxicities or an increased rate of surgical complications [28].

The Space-FLOT study, an international cohort analysis, focused on the role of pathological response following neoadjuvant FLOT chemotherapy in patients with non-metastatic gastroesophageal junction (GEJ) or gastric adenocarcinoma. Patients were categorized based on their pathological response after surgery into three cohorts: minimal pathological response (n = 459), partial pathological response (n = 1207), and pCR (n = 221). These cohorts were further randomized to receive or not adjuvant FLOT chemotherapy. The results indicated that pathological response to neoadjuvant FLOT chemotherapy could predict the benefit of adjuvant therapy. Notably, patients with complete or minimal pathological response did not derive significant survival benefits from adjuvant FLOT, suggesting that adjuvant therapy may not be warranted in these groups [29].

In the DESTINY-Gastric 03 Phase Ib/II trial, T-DXd was evaluated in combination with fluoropyrimidine and/or pembrolizumab in patients with HER2-positive metastatic gastric or gastroesophageal junction adenocarcinoma (GC/GEJA). The study showed promising anti-tumor activity with T-DXd (6.4 mg/kg), achieving an ORR of 49%, median PFS of 9 months, and median OS of 18 months as first-line therapy. When combined with fluoropyrimidine, the confirmed ORR increased to 78%, with median PFS of 20 months and median OS of 23 months. The addition of pembrolizumab in combination with T-DXd and full-dose fluoropyrimidine resulted in enhanced anti-tumor activity, especially in tumors with a CPS ≥ 1; however, it was associated with increased toxicity, leading to treatment discontinuations. Reducing the dose of fluoropyrimidine in combination with T-DXd and pembrolizumab offered a manageable safety profile with promising early efficacy [30].

Overall, T-DXd combinations showed significant anti-tumor activity in HER2-positive GC/GEJA, establishing this regimen as a promising option in the first-line setting.

The KEYNOTE-811 study evaluated the addition of pembrolizumab to trastuzumab and chemotherapy in the first-line treatment of unresectable or metastatic HER2-positive gastric or GC/GEJA. With a median follow-up of 50.2 months, the addition of pembrolizumab resulted in a median OS rate of 20 months, compared to 16.8 months with placebo.

In the subgroup of patients with a PD-L1 CPS ≥1, median OS was 20.1 months in the pembrolizumab arm *vs.* 15.7 months in the control arm. Additionally, median PFS was significantly improved with pembrolizumab, showing 10 months *vs.* 7.3 months in the overall population and 10.0 months *vs.* 7.7 months in the PD-L1 CPS ≥ 1 subgroup [31].

These findings underscore the potential of combining pembrolizumab with trastuzumab and chemotherapy as an effective first-line treatment option for HER2-positive gastric cancer.

The NCT04950322 Phase III study assessed the efficacy of SHR-1701, a monoclonal antibody, in combination with chemotherapy (CAPOX) *vs.* placebo in the first-line treatment of HER2-negative GC/GEJA [32]. Adding SHR-1701 showed a trend towards improved PFS and ORR, with median PFS of 7.6 months *vs.* 5.5 months in the placebo group. In the PD-L1 CPS ≥ 5 subgroup, the ORR was 56.5% *vs.* 32.7%, and median OS was 16.8 months *vs.* 10.4 months in the SHR-1701 and placebo arms, respectively. These results indicate that SHR-1701, in combination with CAPOX, offers superior efficacy compared to placebo with an acceptable safety profile, making it a viable treatment option for patients with previously untreated, unresectable, or metastatic HER2-negative gastric cancer [32].

The IKF-AIO-Moonlight study is an investigator-initiated phase II trial evaluating the efficacy of combining modified FOLFOX (mFOLFOX) with NIVO and ipilimumab (IPI) *vs.* FLOT with NIVO in patients with previously untreated advanced or metastatic GC/GEJA.

The trial included four arms: arm A1 (mFOLFOX + + NIVO + IPI), arm A2 (sequential mFOLFOX + NIVO + IPI), arm B (mFOLFOX alone), and arm C (FLOT + NIVO). The results demonstrated that the combination of mFOLFOX with NIVO and IPI (arm A1) was associated with the highest rate of treatment-related adverse events (TRAEs), leading to treatment discontinuation.

The longest median PFS rate was observed in arm C (FLOT + NIVO) at 7 months, with arm B (mFOLFOX alone) showing median PFS of 6.6 months, and arm A1 demonstrating 5.8 months. The median OS rate was also the longest in arm C (14.6 months), followed by arm B (12.5 months) and arm A1 (10.1 months) [33].

These findings suggest that the combination of FLOT and NIVO may provide superior efficacy compared to mFOLFOX regimens. However, the limited sample size may limit the generalization of these results.

Hepatocellular carcinoma

A pivotal study presented at ESMO 2024 was the LEAP-012 trial, a multicenter, randomized, double-blind phase III investigation involving individuals diagnosed with unresectable, intermediate-stage hepatocellular carcinoma (HCC). The study evaluated the efficacy of combining lenvatinib and pembrolizumab with transarterial chemoembolization (TACE) *vs.* TACE.

The trial enrolled patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. In the experimental arm, patients received lenvatinib (12 mg for those ≥ 60 kg or 8 mg for those < 60 kg, orally) and pembrolizumab (400 mg intravenously every six weeks) for up to two years, in addition to TACE. The control arm received TACE with placebo.

The combination therapy group demonstrated median PFS of 14.6 months compared to 10.0 months in the TACE alone group. This reflects a 34% reduction in the risk of progression or death (HR = 0.66; 95% CI 0.51–0.84; p = 0.0002). While there was a trend toward improved OS in the combination group, the data were not mature enough for definitive conclusions.

Grade 3–5 AEs were significantly higher in the combination group, occurring in 73% of patients *vs.* 31.5% in the TACE alone group. These findings suggest that while adding lenvatinib and pembrolizumab to TACE may enhance efficacy, it also increases toxicity, necessitating careful patient selection. The LEAP-012 trial suggests that combining lenvatinib and pembrolizumab with TACE may improve PFS in unresectable, non-metastatic HCC, though increased toxicity is a concern [34].

Pancreatic cancer

Another significant study was the PANDAS/PRODIGE 44 trial, a Phase II randomized study assessing the role of CRT in patients with borderline resectable pancreatic cancer.

Participants with ECOG performance status 0–1 received four cycles of neoadjuvant-modified FOLFIRINOX (mFOLFIRINOX). Those with controlled disease were randomized into two arms: arm A received two additional cycles of mFOLFIRINOX and arm B — two cycles of mFOLFIRINOX followed by CRT with 50.4 Gy in 28 fractions and concurrent capecitabine administration (825 mg/m^2, five days per week). All patients underwent surgery, if feasible, followed by three months of adjuvant chemotherapy.

The R0 resection rates were similar between the two arms — 54.1% in arm A and 58.1% in arm B. The median OS rate for all patients was 32.8 months in arm A and 30 months in arm B. Notably, in patients who underwent pancreatectomy, median OS was longer in the CRT group (47.9 months in arm B *vs.* 35.7 months in arm A), indicating a potential benefit in this subgroup.

These findings suggest that adding conventional CRT to mFOLFIRINOX does not significantly improve outcomes in the overall population but may offer advantages for patients who proceed to surgery. The PANDAS/PRODIGE 44 trial indicates that adding CRT to mFOLFIRINOX may benefit patients who undergo surgery, but it does not significantly enhance outcomes in the overall population [35].

Biliary tract cancer

The TOPAZ-1 study, a phase III trial, evaluated the addition of durvalumab, an anti-PD-L1 immunotherapy, to the standard chemotherapy regimen of gemcitabine and cisplatin (GC) in patients with advanced biliary tract cancer (BTC).

After a three-year follow-up, the study reported a sustained OS benefit. The HR for OS was 0.74 (95% CI 0.63–0.87). Median OS was longer in the durvalumab arm, confirming the durability of the survival advantage.

Approximately 55% of patients in both arms received subsequent anticancer therapy after disease progression. The use of further immunotherapy was higher in the chemotherapy alone group (7.8% *vs.* 3.2%). Despite this, the OS benefit of durvalumab remained consistent, regardless of subsequent therapy. No new safety concerns emerged during extended follow-up. The AE rates were comparable between the two groups, and durvalumab did not exacerbate chemotherapy-related toxicity. The TOPAZ-1 study confirms that adding durvalumab to standard chemotherapy significantly improves OS in advanced BTC, setting a new treatment benchmark [36].

Colorectal cancer

For colorectal cancer (CRC), surgery remains the mainstay for early-stage disease, with adjuvant chemotherapy recommended in stage III and high-risk stage II patients. In metastatic settings, combinations of chemotherapy with targeted agents like bevacizumab or anti-EGFR therapies are standard, while immunotherapy is used for microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) tumors. While MSI-H/dMMR status is found in 15–20% of localized CRC cases, it appears in only about 5% of metastatic cases [37]. For anal cancer, CRT is the standard for localized disease, and cisplatin-based regimens are used in metastatic cases. PD-1 inhibitors offer options for refractory or recurrent disease [38].

The NICHE-2 trial demonstrated remarkable results in patients with locally advanced dMMR CRC. At a median of 36.5 months of follow-up after surgery, a three-year DFS rate of 100% was achieved in 111 patients (64% had cT4 tumors) treated with a neoadjuvant regimen of a single dose of IPI and two doses of NIVO followed by surgery within six weeks. Importantly, 45% of patients showed ctDNA clearance after just 15 days of treatment (pre-surgery), and all patients were ctDNA-negative three weeks post-surgery. Therefore, two co-primary endpoints of this trial, safety (reported previously) and 3-year DFS, have already been met. These results highlight the potential of short-course immunotherapy to dramatically improve outcomes in this subset of patients, suggesting it may become a standard treatment option after confirming its efficacy in phase III trials [39].

Building on the success of NICHE-2, the NICHE-3 study explored a combination of NIVO and relatlimab (anti-LAG-3) in locally advanced, resectable dMMR CRC. A pathologic response was seen in 54/56 (96%) of patients, with 68% achieving a pCR. Although

the treatment was well-tolerated, long-term endocrine issues (such as hypothyroidism and adrenal insufficiency) were noted in some patients. NICHE-3 adds to the growing evidence of the benefits of immune checkpoint inhibitors in dMMR CRC, with potential implications for organ-sparing strategies in future clinical practice [40].

The phase III POD1UM-303 trial tested the addition of retifanlimab, a PD-1 inhibitor, to standard chemotherapy for patients with previously untreated locally recurrent or metastatic squamous cell carcinoma of the anal canal. The trial met its primary endpoint, showing a significant improvement in median PFS (9.30 *vs.* 7.39 months; p = 0.0006) with retifanlimab compared to chemotherapy alone. Moreover, a significant trend toward improved OS was observed, even though the data remains immature. This study highlights retifanlimab + chemotherapy as a potential new standard of care for advanced SCAC, offering a well-tolerated and effective first-line treatment option [41].

In the CIRCULATE-Japan GALAXY study — the largest ctDNA observational cohort of patients with clinical stage II-IV CRC undergoing planned curative surgical resection — ctDNA-based molecular residual disease (MRD) detection proved to be a key tool in stratifying patients with resected colorectal liver metastases or adjuvant chemotherapy [42]. Molecular residual disease -positive patients showed a significant improvement in DFS from adjuvant chemotherapy, while MRD-negative patients did not. This study supports the use of ctDNA as a biomarker to personalize treatment plans, ensuring that only those likely to benefit receive adjuvant chemotherapy; it paves the way for precision oncology in CRC management. Therefore, future clinical trials should focus on confirming ctDNA's predictive value and optimizing its use in guiding treatment decisions across different CRC stages [42].

Urological cancers

Muscular invasive bladder cancer — perioperative setting

Cisplatin-based neoadjuvant chemotherapy followed by cystectomy is the standard of care for MIBC patients [43]. Several trials showed the activity of immunotherapy, especially in metastatic muscular invasive bladder cancer (MIBC) [44]. In addition, immunotherapy improves DFS in the adjuvant setting. The NIAGARA trial is the first phase III trial, which showed the activity of immunotherapy in a perioperative setting. The study population included cisplatin-eligible patients with MIBC (cT2-T4N0/1M0) with creatinine clearance of ≥ 40ml/min. In the study arm, patients were treated with durvalumab + chemotherapy (GC). After 4 cycles of systemic therapy, patients underwent radical cystectomy followed by 8 cycles of durwalumab every 4 weeks. In the control arm, patients received chemotherapy only, followed by cystectomy. The primary endpoints were EFS and pCR. The secondary endpoint was OS. The median of EFS rate in the durwalumab arm was not reached (NR), whereas in the comparator arm, it was 46.1 months [95% CI 32.2–NR), HR = 0.68 (0.56–0.82; p < 0.0001). The pCR rate was 37.3% (95% CI 33.2–41.6) *vs.* 27.5% (23.8–31.6), p = 0.0005. The probability of survival after 24 months was 82.2% in the immunotherapy arm and 75.2% in the control arm. The HR for OS was 0.75 (0.59–0.93), p = 0.0106. The most common AEs, grade 3 or 4, in the study arm, were anemia (13.8%), urinary tract infection (14.2%), and neutropenia (14.3%). The most common AEs, grade 3 or 4, were anemia (15%), urinary tract infection (13.3%), and neutropenia (16.9%) in the control arm. The AEs led to the discontinuation of adjuvant durvalumab in 8% of patients. The results of NIAGARA showed that durwalumab combined with chemotherapy improves EFS and OS. The safety profile was consistent between chemotherapy and immunotherapy. EFS and OS with tolerable safety profiles indicate that perioperative durvalumab can be a new standard of care in MIBC [45].

The SunRISe-4 is the phase IIb study, which asses neoadjuvant TAR-200 (gemcitabine intravesical targeted releasing system) + checkpoint inhibitor — cetrelimab in patients with predominant urothelial histology MIBC (cT2-T4aN0M0), who are ineligible for neoadjuvant chemotherapy and qualified for cystectomy. Patients were stratified into cohort 1 (n =79) TAR-200 (225 mg gemcitabine Q3W indewelling 12 weeks) + cetrelimab (anti–PD-1) for 12 weeks. Cohort 2 (n =41) received cetrelimab for 12 weeks. After 4 cycles of treatment, patients underwent cystectomy. The primary endpoint was pCR. The secondary endpoints were recurrence-free survival and safety. The pCR rate was 42% (95% CI 28–56) in cohort 1 and 23% (95% CI 10–41) in cohort 2. The pathologic objective response (pOR) defined as ≤ ypT1N0 was 60% (95% CI 46–74) in cohort 1 and 36% (95% CI 19–55) in cohort 2. The tolerance of treatment was good, and only 13% of TRAEs led to treatment discontinuation. The SunRISe-4 trial was the first to demonstrate that adding TAR-200 to checkpoint inhibitors provides a benefit as neoadjuvant therapy for MIBC patients [46].

The TOMBOLA trial was a national, non-randomized ctDNA-based intervention study in which patients underwent regular ctDNA testing after cystectomy. If ctDNA was detected, they were recommended to receive atezolizumab therapy for one year. The primary objective was complete response, defined as both the absence of detectable ctDNA and no visible metastases on computed tomography (CT) imaging, following the initiation of treatment based on ctDNA-positive status after radical cystectomy.

The secondary objectives included the duration of freedom from clinical relapse, OS, and cancer-specific survival. The inclusion criteria were cT2-4a N0-1M0, cisplatin-fit, and eligibility to receive immunotherapy MIBC. Patients underwent transurethral resection of bladder tumors (TURBT), neoadjuvant therapy followed by cystectomy. Upon the ctDNA detection, patients were treated with 18 cycles of atezolizumab. One hundred sixty-six patients underwent radical cystectomy (RC), and 56% were ctDNA positive post cystectomy. Seventy-five percent of relapses were detected < 4 months post-RC. Only 2% of ctDNA-negative patients developed metastases during follow-up. The ctDNA measure is a sensitive tool for identifying patients who may benefit from immunotherapy in the adjuvant setting [47].

During ESMO 2023, results of the EV-302 study confirmed that pembrolizumab + enfortumab vedotin should be the standard of care in patients with metastatic bladder cancer, significantly prolonging survival [44, 48]. Enfortumab vedotin (EV) is the antibody-drug-conjugate (ADC) directed against nectin-4. The H-score of nectin-4 expression in the primary tumor (median 267, IQR: 215–295) and metastasis (median 287, IQR: 235–300) is high. The analysis of EV-302 study subgroups regarding the nectin-4 H-score in tumors favors EV + pembrolizumab independently of H-score expression, which rules out nectine-4 expression as a prognostic biomarker in selection of patients who may benefit from EV treatment [49].

NCT04601857 was the two-cohort, noncomparative phase II study that assessed the confirmed ORR (primary endpoint) and DCR, DOR, PFS, OS, and safety profile (secondary endpoints) in patients with metastatic bladder cancer who were unfit for or declined platinum-based chemotherapy. Patients were treated with an inhibitor of fibroblast growth factor receptor 1-4 (FGFR1–4), futibatinib (20 mg p.o.), plus pembrolizumab 200mg i.v. until disease progression or unacceptable toxicity. Patients were assigned to cohort A (FGFR mutations/rearrangements/fusions) and cohort B (wild-type or other FGFR, non-FGFR-aberrant tumors not included in cohort A). In cohort A (= 17), the ORR was 47.1% (95% CI 23–72.2), mPFS: 8.3 months (95% CI 3.5–8.5), and mOS not estimable (NE). In cohort B, the ORR was 26.9%, mPFS: 4.1 months (95% CI 2.1––8.3), and mOS 18.3 (95% CI 6.2–NE). The combination of futibatinib and pembrolizumab was well tolerated, with no unexpected safety concerns identified. The most common TRAEs were hyperphosphatemia (64.7%), diarrhea (41.2%), and dry mouth (47.1%) [50].

Renal cell carcinoma

The final analysis of the phase III LITESPARK-005 study of belzutifan *vs.* everolimus in participants with previously treated advanced clear cell renal cell carcinoma (ccRCC) was presented during ESMO 2024. Belzutifan is an oral hypoxia-inducible factor 2α (HIF-2α) inhibitor that works by blocking heterodimerization with HIF-1β and inhibiting downstream oncogenic pathways by increasing c-Myc, mTOR, and β-catenin activity and decreasing p53 activity [51].

Eligible patients were adults with advanced ccRCC who had received 1 to 3 prior systemic therapies, including at least one ICI and one vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR--TKI). Participants were randomized to receive either belzutifan at 120 mg or everolimus at 10 mg once daily until disease progression or occurrence of unacceptable toxicity. The primary endpoints were PFS and OS. A key secondary endpoint was the ORR. A total of 746 patients were randomized to receive either belzutifan (n = 374) or everolimus (n = 372). The median follow-up was 35.8 months (range: 26.9–49.2 months), with 14.5% of patients continuing treatment with belzutifan, compared to 1.4% of patients remaining on everolimus. Belzutifan demonstrated a sustained PFS benefit compared to everolimus, with median PFS of 5.6 months for both groups (HR = 0.75; 95% CI 0.63–0.88). The estimated progression-free rates at 12 months (33.7% *vs.* 17.6%) and at 24 months (17.5% *vs.* 4.1%) favored belzutifan. The ORR was 22.7% for belzutifan *vs.* 3.5% for everolimus. Median OS was 21.4 months for belzutifan and 18.2 months for everolimus (HR = 0.92; 95% CI 0.77–1.10; p = 0.18). The estimated OS rates at 12 months were 67.9% for belzutifan *vs.* 65.8% for everolimus, and at 24 months, 45.2% *vs.* 41.2%, respectively. Fewer patients discontinued belzutifan due to AEs of any cause (6.2%) compared to those on everolimus (15.3%). The incidence of grade ≥ 3 TRAEs was comparable between the two groups, at 39.5% for belzutifan and 40.0% for everolimus. The final analysis of the phase III LITESPARK-005 study demonstrated that belzutifan continued to provide benefits in PFS and ORR over everolimus, with a durable response extending beyond two years. It must be noted that there was no statistically significant OS difference between these two drugs. These final results support belzutifan as a treatment option in advanced clear cell RCC in subsequent treatment lines [52].

TiNivo-2 study evaluated the combination of the PD-1 inhibitor NIVO with tivozanib *vs.* tivozanib monotherapy in patients with advanced ccRCC following progression on prior ICI-based therapy.

Eligible patients with advanced ccRCC and 1–2 previous lines of therapy, including an ICI, were randomized to receive either tivozanib (0.89 mg) with NIVO or tivozanib monotherapy (1.34 mg). The primary endpoint was PFS. Key secondary endpoints included OS, PFS, ORR, DOR, and safety. Median PFS was 5.7 months for tivozanib + NIVO and 7.4 months for tivozanib alone (HR = 1.10, 95% CI 0.82–1.43), indicating that

the primary endpoint was not met. There was no observed benefit in either the second or third-line treatment settings. The median OS rate was 17.7 months (95% CI 15.1–NR) with tivozanib + NIVO and 22.1 months (95% CI 15.2–NR; HR = 1.00, 95% CI 0.68–1.46) with tivozanib monotherapy. The TiNivo-2 trial, the first phase III study to assess a PD-1 inhibitor combination therapy in metastatic ccRCC, showed no clinical benefit from adding NIVO to tivozanib compared to tivozanib alone. Findings suggest that rechallenging with ICI is generally ineffective regardless of treatment order. In addition, tivozanib monotherapy at 1.34 mg demonstrated meaningful efficacy as a second-line therapy following prior immunotherapy [53].

Among 4–23% of cases of newly diagnosed RCC, intravascular tumor extension located in the inferior vena cava (IVC) can be found [54]. Surgical resection remains the primary treatment for this type of cancer with venous tumor thrombus (TT) extension. However, radical nephrectomy combined with thrombectomy has been linked to significant surgical morbidity and mortality. The shrinkage of the TT before surgery could potentially offer better outcomes and higher patient safety [55]. The phase II NEOTAX trial evaluated a combination of toripalimab (PD-1 inhibitor) and axitinib (VEGF inhibitor) as neoadjuvant therapy for ccRCC with IVC-TT. The primary endpoint was the downstaging rate of the TT level. Secondary endpoints included surgical approach and IVC-TT length changes, PFS response rate, surgical morbidity, and biomarker analysis. Among 25 patients treated, 44% experienced a reduction in IVC-TT level, and 96% achieved a decrease in thrombus length, with a median reduction of 2.3 cm. As a result, surgical strategies were altered in 62% of patients, with many requiring less extensive procedures. The 1-year and 2-year PFS rates were 89.1% and 54.8%, respectively. The NEOTAX study provides evidence that combining toripalimab with axitinib significantly reduces the level and length of IVC, which allows for a reduced surgical extent and altered surgical strategy in up to 62% of cases. These results highlight the potential of this combination therapy to improve surgical outcomes for IVC-TT patients [56].

The CheckMate 9ER trial, with NIVO + cabozantinib, demonstrated superior PFS, OS, and ORR compared to sunitinib, with a median follow-up of 55.6 months and introduced this combination as a standard of care for metastatic RCC [57]. Despite these advances, predictive biomarkers in this group remain scarce. The subject of the presentation was a post-hoc exploratory analysis that examined the role of serum glycopeptides as potential biomarkers for treatment response using glycoproteomics via the InterVenn GlycoVision™ platform. Among 24 identified glycopeptides, higher levels of fucosylated and sialylated glycans were linked to poorer PFS and OS with both treatments, indicating that altered glycosylation patterns may influence resistance to NIVO + Cabozantinib therapy. Elevated serum complement protein 3 (CO3) glycopeptide and reduced complement factor H (CFAH) glycopeptide were associated with better outcomes in the NIVO + Cabozantinib group, suggesting these glycopeptides as potential predictive biomarkers [58].

Data from the SUNNIFORECAST study, which included patients with non-clear cell RCC and randomized them in a 1:1 ratio to receive either NIVO 3 mg/kg intravenously (i.v.) combined with IPI 1 mg/kg i.v. every 3 weeks for four doses, followed by a flat dose of NIVO at 240 mg i.v. every two weeks or 480 mg every four weeks. That therapy was compared with the investigator's choice of the standard of care until disease progression or unacceptable toxicity. Patients were stratified by papillary *vs.* non-papillary RCC subtype and by the International Metastatic RCC Database Consortium (IMDC) risk score.

The study randomized 309 patients (70.9% males, 29.1% females). One hundred fifty-seven were assigned to the NIVO plus IPI group and 152 to the standard of care group (124 received a TKI, 17 TKI/ICI, two other regimens, while nine patients did not start treatment). Subtype distribution included 57.6% with papillary RCC, 19.4% with chromophobe, 3.9% with MiT family translocation, 2.9% with collecting duct carcinoma, and 50 patients with other non-clear cell RCC subtypes. According to the IMDC risk stratification, 23.9% were low-risk, 51.8% intermediate-risk, and 24.3% high-risk. The 12-month OS rate was 82.5% across all participants, with the NIVO + IPI arm showing a statistically significant OS advantage (86.9%, 95% CI 80.2–91.5%) over the standard of care (76.8%, 95% CI 68.6–83.1%; p = 0.014). Median PFS was similar between the groups, at 5.52 months (95% CI 4.30–8.23) for the NIVO + IPI arm and 5.65 months (95% CI 5.49–8.46) for the standard of care arm. Median OS reached 42.4 months with NIVO + IPI *vs.* 33.9 months with standard care. Patients with PD-L1 positivity (≥ 1%) benefited from NIVO + IPI (HR = 0.56, 95% CI 0.33–0.95), as did those with lymph node metastases (HR = 0.62, 95% CI 0.39–0.98). The ORR was 32.8% for NIVO + IPI *vs.* 19.6% for standard of care in the non-clear cell RCC population. This trial is the first prospective, randomized study comparing dual checkpoint inhibition with the standard of care in non-clear cell RCC, showing a significant 12-month OS benefit for IPI + NIVO *vs.* predominantly TKI monotherapy. While PFS did not differ significantly between the groups, OS and ORRs suggest a clear advantage for the combination therapy across both papillary and non-papillary RCC [59].

Prostate cancer (PCa)

Treatment with radiopharmaceuticals

The first results from two phase III studies of Radium-223 dichloride (223Ra) and 177Lu-PNT2002 may help to elucidate the role of radiopharmaceuticals in the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC). 223Ra is an alpha particle-emitting calcium mimetic that selectively targets bone metastases and induces double-stranded DNA breaks. Its role in the treatment of patients with mCRPC and bone metastases was confirmed in the ALSYMPCA trial [60]. However, as shown in the ERA-223 trial, combining 223Ra with ARPI-abiraterone acetate did not bring benefits in OS and led to an increased frequency of bone fractures compared with placebo [61].

The PEACE-3 trial showed the efficacy of the combination of the androgen receptor pathways inhibitor (ARPI), enzalutamide, with bone-targeting 223Ra, compared with enzalutamide alone in patients with mCRPC and bone metastases.

The inclusion criteria were patients with mCRPC and bone metastases, asymptomatic or mildly symptomatic, ECOG performance status of 0 or 1, no prior treatment with enzalutamide or 223Ra (abiraterone in the hormone-sensitive setting was allowed), no known visceral metastases, ongoing ADT. Co-administration of zoledronic acid or denosumab was obligatory.

At a median follow-up of 42.2 months, the study was positive for the primary endpoint of radiological PFS of 19.4 months (95% CI 17.1–25.3) in the enzalutamide plus 223Ra arm and 16.4 months (95% CI 13.8–19.2; HR = 0.69; p = 0.0009) in the enzalutamide-only arm. OS was also considered superior in the treatment arm in the pre-planned interim analysis (HR = 0.69; p = 0.0031), but the final results are still awaited. Regarding safety, grade 3 or more TRAEs were more common in the 223Ra plus enzalutamide arm (65.6% *vs.* 55.8%, respectively).

In conclusion, the PEACE-3 showed an improvement in rPFS and OS in the 223Ra treatment arm in combination with enzalutamide *vs.* enzalutamide alone in mCPRC patients, with acceptable toxicity. We think that data from that study are useful in practice depending on what the patient receives in the castration-sensitive setting [chemotherapy or androgen receptor pathway inhibitor (ARPI)]. The PEACE-3 trial shows that ARPI could be combined with 223Ra to improve patient outcomes in the mCRPC setting [62].

The second study, the phase III SPLASH trial, involved radiopharmaceuticals used in prostate-specific membrane antigen (PSMA)-based therapy. PSMA is an enzyme that belongs to the class II membrane glycoprotein. It exhibits high expression in mCRPC. Lutetium-177 is a radioligand therapy that delivers beta-particle radiation to PSMA-expressing cells and their microenvironment. Its effectiveness was confirmed in the VISION study, which evaluated the effectiveness of LuPSMA after taxane-based chemotherapy and ARPI and has confirmed improved OS (median OS of 15.3 months *vs.* 11.3 months for the standard of care). The treatment is currently included in the Polish guidelines in this setting but is unavailable.

In the SPLASH trial, inclusion criteria were progressive mCRPC that progressed on previous ARPI treatment, disease with PSMA-avid positron emission tomography (PET), ECOG 0 to 1; notably, taxane-based chemotherapy for castration-sensitive prostate cancer (CSPC) > 1 year before enrolment was allowed (unlike in the PSMAfore study). The study enrolled men with PSMA-positive mCRPC who were randomized to receive either a beta-emitting radioisotope chelated to 177Lu-PNT2002 or an alternative ARPI. At the first interim analysis, the primary endpoint, rPFS, was improved with 177Lu-PNT2002 compared with the alternative ARPI (9.5 months *vs.* 6.0 months; HR = 0.71; p = 0.008). The final results, including OS, are awaited. Interestingly, 85% of patients crossed over between the arms. TRAE of grade ≥ 3 occurred in 30.1% of patients in the Lutetium arm and 36.9% in the alternate ARPI arm. The most commonly reported side effect was fatigue. The hematological side effects characteristic of Lutetium occurred in around 5% of patients [63].

This study suggests the potential benefit of using 177Lu-PNT2002 in the treatment of mCRPC. However, we still await data from complete rPFS and OS, which may provide a more comprehensive picture of the effectiveness of this therapy.

Tyrosine kinase inhibitors combined with immunotherapy in metastatic castration-resistant prostate cancer

Immunotherapy with PD-1/PD-L1 ICIs plays a limited role in prostate cancer. Based on a prospective study, immunotherapy can be considered in mCRPC patients with MSI-H/dMMR, and in this indication, it is recommended by the current Polish guidelines for metastatic prostate cancer. Immunotherapy has not been shown to be effective outside MSI-H/dMMR tumors, a rare condition in mCRPC (~1% of patients). Studies regarding the efficacy of combining immunotherapy with other agents are lacking.

The phase III CONTACT-02 trial results, which evaluated the combination of an immune checkpoint inhibitor with a tyrosine kinase inhibitor (TKI) cabozantinib or a second-line ARPI in patients with mCRPC who progressed on a first-line ARPI, are negative regarding patient OS. No OS advantage from the experimental treatment was noted in the intention-to-treat population at a median follow-up of 24 months (14.8 months for the treatment arm *vs.* 15 months for the control

arm; HR = 0.89; 95% CI 0.72–1.10; p = 0.3). The study showed only prolonged PFS for the treatment arm (HR = 0.65; 95% CI 0.50–0.84; p = 0.0007). Additionally, the treatment with combination was associated with significant side effects; grade 3 or 4 = TRAEs were reported in 40% of patients from the study arm, compared with 8% in the ARPI arm [64].

In conclusion, ICIs, in combination with TKI, did not significantly improve OS in an unselected population of mCRPC patients.

Melanoma

Neoadjuvant therapies in melanoma

Neoadjuvant treatment of patients with at least stage IIIB melanoma has recently become a subject of intense research. In 2021, the International Neoadjuvant Melanoma Consortium published a pooled analysis of 196 melanoma patients who received neoadjuvant immunotherapy or *BRAF*/*MEK* targeted therapy. At ESMO 2024, an updated long-term survival analysis was presented, highlighting the significance and modalities of neoadjuvant therapies even further. The analyzed cohort comprised 818 patients. The patients received various neoadjuvant treatments, including ICIs, BRAF/MEK inhibitors, or a combination of ICI and targeted therapy (TargT). The major pathological response (MPR) rate in the ICI group was 58%, compared to 51% in the BRAF/MEK group and 46% in the ICI + TargT group. In the ICI cohort, MPR rates varied: 46% for PD-1 alone, 62% for PD-1 + CTLA-4, and 67% (95% CI 70–95) for PD-1 + LAG-3. The three-year EFS rates were 64% (95% CI 55–73) for PD-1 alone, 76% (95% CI 72–81) for PD-1 + CTLA-4, and 82% (95% CI 70–95) for PD-1 + LAG-3. The EFS rate for BRAF/MEK was notably lower (37%), indicating that this treatment is inferior to checkpoint inhibitors. These findings confirm again the long-term benefits of neoadjuvant immunotherapy, demonstrating improved EFS and MPR with combination immunotherapies.

Another significant presentation and milestone in neoadjuvant therapy was an update on the NADINA trial. This study was designed to randomize patients with resectable, macroscopic stage III melanoma into two treatment groups: one receiving neoadjuvant IPI at 80 mg plus NIVO at 240 mg (administered twice every three weeks) followed by therapeutic lymph node dissection (TLND) and the other undergoing upfront TLND followed by adjuvant NIVO at 480 mg (administered twelve times every four weeks). In the neoadjuvant arm, subsequent adjuvant treatment was not given if a major pathological response (MPR; ≤ 10% viable tumor) was achieved. The first interim analysis, with a median follow-up of 10 months, showed significantly improved EFS for the neoadjuvant IPI + NIVO group compared to the adjuvant NIVO group in patients with resectable, macroscopic stage III melanoma [1-year EFS: 83.7% *vs.* 57.2%; HR = 0.32 (99.9% CI 0.15–0.66; p < 0.0001)] [65].

The phase I/II KEYMAKER-U02 trial (NCT-04303169) is investigating neoadjuvant pembrolizumab, both with and without investigational agents, followed by adjuvant pembrolizumab for patients with stage IIIB-D melanoma. The investigational agents added to pembrolizumab in the trial were MK-4830 (anti-ILT4), favezelimab (anti-LAG-3), vibostolimab (anit TIGIT), gebasexturev (oncolytic Coxackievirus A21).

The primary endpoints were safety and pCR. The study had promising results, particularly regarding MPR: 50% for arm 1 (pembrolizumab + vibostolimab, an anti-TIGIT antibody), 40% for arm 2 [pembrolizumab + gebasaxturev (coxsackievirus A21)], 47% for arm 3 (pembrolizumab alone), 32% for arm 4 (pembrolizumab and MK-4830, an anti-ILT4), and 58% for arm 5 (pembrolizumab 200 mg Q3W and favezelimab 800 mg). Notably, the arm with favezelimab combined with pembrolizumab demonstrated the most favorable outcomes, showing better MPR than arm 3 (pembrolizumab alone) while maintaining acceptable toxicity levels [66].

Advanced melanoma

The KEYNOTE-006 phase III study showed that pembrolizumab exhibited superior efficacy compared to ipilimumab in patients with ipilimumab-naïve advanced melanoma. These findings laid the groundwork for treatment recommendations for advanced melanoma [67]. At ESMO 2024, prolonged follow-up results were presented. Patients eligible for KEYNOTE-006 had unresectable stage III or IV melanoma and had received no more than one prior line of therapy, excluding cytotoxic T-lymphocyte associated protein 4 (CTLA-4) or PD-(L)1 inhibitors. They were randomly assigned to receive pembrolizumab every two or three weeks for up to two years or IPI every three weeks for four cycles. Following the completion of KEYNOTE-006, patients could opt to participate in the KEYNOTE-587 extension study. Eligible patients could receive a second course of pembrolizumab for up to one year in either KEYNOTE-006 or KEYNOTE-587.

A total of 834 patients were randomly assigned to receive pembrolizumab (n = 556) or IPI (n = 278) in KEYNOTE-006, with 211 patients transitioning to KEYNOTE-587 (pembrolizumab, n =159; IPI, n =52). The median OS rate was 32.7 months (95% CI 24.5––41.6) for pembrolizumab compared to 15.9 months (95% CI 13.3-22.0) for IPI (HR = 0.71; 95% CI 0.60–0.85)], with 10-year OS rates of 34.0% and 23.6%,

respectively. Among patients who completed at least 94 weeks of pembrolizumab (n = 103), median OS was not reached (95% CI NR–NR), and the 8-year OS rate was 80.8%. The median modified PFS rate was 9.4 months (95% CI 6.7–11.6) for pembrolizumab *vs.* 3.8 months (95% CI 2.9–4.3) for IPI (HR = 0.64; 95% CI 0.54–0.75). The median modified PFS rate from the start of the second course for patients receiving second-course pembrolizumab (n = 16) was 51.8 months (95% CI 11.0–NR), with a 6-year modified PFS rate of 49.2%.

In the CheckMate 067 trial, better survival rates were noted with the combination of NIVO and IPI or with nivolumab alone, in comparison to IPI for patients with advanced melanoma. At ESMO 2024, the authors presented the results from a 10-year follow-up. Patients in the study received either NIVO (1 mg/kg) plus IPI (3 mg/kg) four doses, followed by NIVO (3 mg/kg) every two weeks; NIVO (3 mg/kg) every two weeks plus placebo; or IPI (3 mg/kg) every three weeks for four doses plus placebo, until disease progression or intolerable toxicity occurred. The primary endpoints included OS and PFS. The results of the trial confirmed the superiority of treatment with a combination of IPI + niwolumab, as did the conclusions from an earlier, shorter follow-up. After 10 years, median OS was recorded at 71.9 months for the combination of NIVO and IPI, compared to 36.9 months for NIVO alone and 19.9 months for IPI alone. The HR was 0.53 (95% CI 0.44–0.65) when comparing NIVO + IPI to IPI, and 0.63 (95% CI 0.52–0.76) for NIVO compared to IPI, indicating consistent benefits across various subgroups, including those based on PD-L1 expression and BRAF mutation status. The median melanoma-specific survival (MSS) rate was NR for the NIVO + IPI group (exceeding 120 months), while it was 49.4 months for NIVO and 21.9 months for IPI. Among patients who maintained PFS for three years or more, the 10-year MSS rates were 96% for NIVO + IPI, 97% for NIVO, and 88% for IPI. Notably, only 8 patients experienced progression beyond 60 months of follow-up, and they were evenly split between the NIVO + IPI and NIVO arms. For those in the NIVO + IPI arm who discontinued treatment during the induction phase due to AEs, the 10-year OS rates remained consistent with the intention-to-treat group at 43%, and MSS rates were similar (50% *vs.* 52%) [68].

The interesting fact coming from the trial is that in the cohort of patients who had serious grade 3–4 AEs, the treatment with only niwolumab turned out to be more effective than NIVO+ IPI in the general group. This may be connected to IPI toxicities treatment with glicocorticosteroids, which may reduce the efficacy of melanoma treatment.

The modalities that proved to be the most effective in advanced melanoma, according to the above-mentioned trials (IPI+NIVO, PEMBRO), are now considered the standard of care and are available in Poland

Conclusions

The recent ESMO 2024 conference presented significant advancements in oncology, showcasing promising new therapies across various cancer types. Key highlights included the ongoing success of immunotherapy in improving long-term outcomes for melanoma and breast cancer patients. For instance, the CheckMate-067 study demonstrated the durable survival benefits of combining NIVO and IPI for advanced melanoma [68]. In triple-negative breast cancer, the KEYNOTE-522 trial highlighted pembrolizumab's potential to significantly extend OS [25]. Additionally, the NIAGARA trial showcased promising outcomes for muscle-invasive bladder cancer, where combining durvalumab with chemotherapy before surgery extended event-free and OS compared to chemotherapy alone [45].

Article Information and Declarations

Author contributions

D.S.: conception, writing (bladder cancer), supervision; M.O.: writing (prostate cancer), language editing; B.S.: writing (head and neck cancers); S.T.: writing (lung cancer); M.P., R.P-M: writing (breast cancer); E-H-P., M.G., J.K.: writing (digestive system cancers), M.W.: writing (kidney cancer), editing; A.M.: writing (melanoma).

Funding

None.

Acknowledgements

None.

Conflict of interest

D.S.: received honoraria for lectures from Astellas, MSD, AstraZeneca, Ipsen, and a travel grant from Ipsen.
M.O.: received travel grants from Angelini Pharma, Accord, and honoraria for lectures from Bayer, Astellas, Sandoz,
B.S., E.H-P., M.G., A.M., J.K.: have no conflict of interest.
S.T.: received travel grants and lecture fees: AstraZeneca, MSD, Takeda, BMS, Roche; Advisory Board: Accord.
M.P.: declares receiving travel grants and lecture fees from Gilead, AstraZeneca, Novartis, Roche, Amgen, Pierre Fabre Médicament, Eli Lilly, Accord, and Janssen.
R.P-M.: reports travel grants from Accord, BMS, MSD, and lecture fees from AstraZeneca, BMS, GSK, Novartis, Roche, and MSD.
M.W.: received travel grants from Pfizer, Novartis, and Bayer, and honoraria for lectures from Pfizer and Sandoz.

Supplementary material

None.

References

1. Tao Y, Auperin A, Sun X, et al. 854MO Avelumab-cetuximab-radiotherapy (RT) versus standards of care in patients with locally advanced squamous cell carcinoma of head and neck (LA-SCCHN): Final analysis of randomized phase III GORTEC 2017-01 REACH trial. Ann Oncol. 2024; 35: S616, doi: 10.1016/j.annonc.2024.08.915.
2. Kristensen CA, Metcalf R, Braña I, et al. LBA35 Primary results from TACTI-003: A randomized phase IIb trial comparing eftilagimod alpha (soluble LAG-3) plus pembrolizumab versus pembrolizumab alone in first-line recurrent or metastatic head and neck squamous cell carcinoma with CPS ≥1. Ann Oncol. 2024; 35: S1227, doi: 10.1016/j.annonc.2024.08.2274.
3. Kinoshita I, Kano S, Honma Y, et al. 849O Phase II study of trastuzumab deruxtecan in patients with HER2-positive recurrent/metastatic salivary gland cancer: Results from the MYTHOS trial. Ann Oncol. 2024; 35: S613–S614, doi: 10.1016/j.annonc.2024.08.909.
4. Machiels JP, René Leemans C, Golusinski W, et al. EHNS Executive Board. Electronic address: secretariat@ehns.org, ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org, ESTRO Executive Board. Electronic address: info@estro.org. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020; 31(11): 1462–1475, doi: 10.1016/j.annonc.2020.07.011, indexed in Pubmed: 33239190.
5. Yeoh CC, Dabab N, Rigby E, et al. Androgen receptor in salivary gland carcinoma: A review of an old marker as a possible new target. J Oral Pathol Med. 2018; 47(7): 691–695, doi: 10.1111/jop.12741, indexed in Pubmed: 29863801.
6. Licitra L, Locati LD, Digue L, et al. LBA36 A randomised phase II study to evaluate the efficacy and safety of androgen deprivation therapy (ADT) vs chemotherapy (CT) in patients with recurrent and/or metastatic, androgen receptor (AR) expressing, salivary gland cancers. Ann Oncol. 2024; 35: S1227–S1228, doi: 10.1016/j.annonc.2024.08.2275.
7. Elmusrati A, Wang J, Wang CY. Tumor microenvironment and immune evasion in head and neck squamous cell carcinoma. Int J Oral Sci. 2021; 13(1): 24, doi: 10.1038/s41368-021-00131-7, indexed in Pubmed: 34341329.
8. Chong WQ, Low JL, Sooi K, et al. 848MO Phase II open-label randomized study of pembrolizumab with or without bevacizumab in platinum-resistant recurrent/metastatic nasopharyngeal carcinoma (R/M NPC). Ann Oncol. 2024; 35: S614, doi: 10.1016/j.annonc.2024.08.910.
9. Pulla MP, Awad M, Cascone T, et al. LBA50 Perioperative nivolumab (NIVO) v placebo (PBO) in patients (pts) with resectable NSCLC: Clinical update from the phase III CheckMate 77T study. Ann Oncol. 2024; 35: S1239–S1240, doi: 10.1016/j.annonc.2024.08.2291.
10. Heymach JV, Harpole D, Reck M, et al. AEGEAN Investigators. Perioperative Durvalumab for Resectable Non-Small-Cell Lung Cancer. N Engl J Med. 2023; 389(18): 1672–1684, doi: 10.1056/NEJMoa2304875, indexed in Pubmed: 37870974.
11. Reck M, Gale D, Zhu Z, et al. LBA49 Associations of ctDNA clearance (CL) during neoadjuvant Tx with pathological response and event-free survival (EFS) in pts with resectable NSCLC (R-NSCLC): Expanded analyses from AEGEAN. Ann Oncol. 2024; 35: S1239, doi: 10.1016/j.annonc.2024.08.2290.
12. Wu YL, Dziadziuszko R, Ahn JS, et al. ALINA Investigators. Alectinib in Resected -Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2024; 390(14): 1265–1276, doi: 10.1056/NEJMoa2310532, indexed in Pubmed: 38598794.
13. Solomon BJ, Wu YL, Dziadziuszko R, et al. 1206MO ALINA: Exploratory biomarker analyses in patients (pts) with resected ALK+ non-small cell lung cancer (NSCLC) treated with adjuvant alectinib vs chemotherapy (chemo). Ann Oncol. 2024; 35: S775, doi: 10.1016/j.annonc.2024.08.1265.
14. Lu S, Kato T, Dong X, et al. LAURA Trial Investigators. Osimertinib after Chemoradiotherapy in Stage III -Mutated NSCLC. N Engl J Med. 2024; 391(7): 585–597, doi: 10.1056/NEJMoa2402614, indexed in Pubmed: 38828946.
15. Lu S, Ahn MJ, Baisamut TR, et al. 1241MO Osimertinib (osi) after definitive chemoradiotherapy (CRT) in unresectable (UR) stg III EGFRm NSCLC: Analyses of CNS and distant progression from the phase III LAURA study. Ann Oncol. 2024; 35: S794–S795, doi: 10.1016/j.annonc.2024.08.1299.
16. Drilon AE, Lin JJ, Johnson ML, et al. 1253O Phase I/II ALKOVE-1 study of NVL-655 in ALK-positive (ALK+) solid tumours. Ann Oncol. 2024; 35: S802–S803, doi: 10.1016/j.annonc.2024.08.1310.
17. Zhou C, Tang KJ, Cho BC, et al. PAPILLON Investigators. Amivantamab plus Chemotherapy in NSCLC with Exon 20 Insertions. N Engl J Med. 2023; 389(22): 2039–2051, doi: 10.1056/NEJMoa2306441, indexed in Pubmed: 37870976.
18. Park K, Haura EB, Leighl NB, et al. Amivantamab in EGFR Exon 20 Insertion-Mutated Non-Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study. J Clin Oncol. 2021; 39(30): 3391–3402, doi: 10.1200/JCO.21.00662, indexed in Pubmed: 34339292.
19. Passaro A, Yu HA, Nguyen D, et al. 1254MO Safety and anti-tumour activity of zipalertinib in NSCLC patients (pts) with EGFR exon 20 insertion (ex20ins) mutations who received prior amivantamab. Ann Oncol. 2024; 35: S803–S804, doi: 10.1016/j.annonc.2024.08.1311.
20. Riely GJ, Ahn MJ, Clarke J, et al. LBA56 Updated efficacy and safety from the phase II PHAROS study of encorafenib plus binimetinib in patients with BRAF V600E-mutant metastatic NSCLC (mNSCLC). Ann Oncol. 2024; 35: S1246–S1247, doi: 10.1016/j.annonc.2024.08.2298.
21. Hortobagyi G, Stroyakovsky D, Yardley D, et al. Abstract GS03-03: Ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) as adjuvant treatment in patients with HR+/HER2− early breast cancer: final invasive disease–free survival (iDFS) analysis from the NATALEE trial. Cancer Res. 2024; 84(9_Supplement): GS03-03-GS03–03, doi: 10.1158/1538-7445.sabcs23-gs03-03.
22. Harbeck N, Ciruelos E, Jerusalem G, et al. DESTINY-Breast12 study group, DESTINY-Breast12 study group. Trastuzumab deruxtecan in HER2-positive advanced breast cancer with or without brain metastases: a phase 3b/4 trial. Nat Med. 2024; 30(12): 3717–3727, doi: 10.1038/s41591-024-03261-7, indexed in Pubmed: 39271844.
23. Modi S, Saura C, Yamashita T, et al. DESTINY-Breast01 Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. N Engl J Med. 2020; 382(7): 610–621, doi: 10.1056/NEJMoa1914510, indexed in Pubmed: 31825192.
24. Lin N, Ciruelos EM, Jerusalem G, et al. LBA18 Trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2+ advanced/metastatic breast cancer (mBC) with or without brain metastases (BM): DESTINYBreast-12 primary results. Ann Oncol. 2024; 35: S1211–S1212, doi: 10.1016/j.annonc.2024.08.2256.
25. Schmid P, Cortés J, Dent RA, et al. LBA4 Neoadjuvant pembrolizumab or placebo plus chemotherapy followed by adjuvant pembrolizumab or placebo for high-risk early-stage TNBC: Overall survival results from the phase III KEYNOTE-522 study. Ann Oncol. 2024; 35: S1204–S1205, doi: 10.1016/j.annonc.2024.08.2247.
26. Mittendorf EA, Zhang H, Barrios CH, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet. 2020; 396(10257): 1090–1100, doi: 10.1016/S0140-6736(20)31953-X, indexed in Pubmed: 32966830.
27. Rivera S, Ghodssighassemabadi R, Brion T, et al. 231O Locoregional hypo vs normofractionated RT in early breast cancer: 5 years results of the HypoG-01 phase III UNICANCER trial. Ann Oncol. 2024; 35: S309, doi: 10.1016/j.annonc.2024.08.174.
28. Leong T, Smithers BM, Michael M, et al. LBA58 A randomized phase III trial of perioperative chemotherapy (periop CT) with or without preoperative chemoradiotherapy (preop CRT) for resectable gastric cancer (AGITG TOPGEAR): Final results from an intergroup trial of AGITG, TROG, EORTC and CCTG. Ann Oncol. 2024; 35: S1249, doi: 10.1016/j.annonc.2024.08.2300.
29. Liu DS, Hall K, Wong D, et al. 1402MO An international study evaluating pathological response to guide adjuvant FLOT chemotherapy in gastroesophageal cancer. Ann Oncol. 2024; 35: S879, doi: 10.1016/j.annonc.2024.08.1468.
30. Janjigian YY, Laarhoven Hv, Rha SY, et al. 1401O Trastuzumab deruxtecan (T-DXd) monotherapy and combinations in patients (pts) with advanced/metastatic HER2-positive (HER2+) esophageal, gastric or gastroesophageal junction adenocarcinoma (GEJA): DESTINY-Gastric03 (DG-03). Ann Oncol. 2024; 35: S878, doi: 10.1016/j.annonc.2024.08.1467.
31. Janjigian YY, Kawazoe A, Bai Y, et al. 1400O Final overall survival for the phase III, KEYNOTE-811 study of pembrolizumab plus trastuzumab and chemotherapy for HER2+ advanced, unresectable or metastatic G/GEJ adenocarcinoma. Ann Oncol. 2024; 35: S877–S878, doi: 10.1016/j.annonc.2024.08.1466.
32. Peng Z, Wang J, Zhang Y, et al. LBA60 Phase III study of SHR-1701 versus placebo in combination with chemo as first-line (1L) therapy for HER2-negative gastric/gastroesophageal junction adenocarcinoma (G/GEJA). Ann Oncol. 2024; 35: S1250, doi: 10.1016/j.annonc.2024.08.2302.
33. Lorenzen S, Goetze TO, Thuss-Patience PC, et al. LBA59 Modified FOLFOX plus/minus nivolumab and ipilimumab vs FLOT plus nivolumab in patients with previously untreated advanced or metastatic

adenocarcinoma of the stomach or gastroesophageal junction: Final results of the IKF-AIO-Moonlight trial. Ann Oncol. 2024; 35: S1249–S1250, doi: 10.1016/j.annonc.2024.08.2301.
34. Llovet J, Finn RS, Ren Z, et al. LBA3 Transarterial chemoembolization (TACE) with or without lenvatinib (len) + pembrolizumab (pembro) for intermediate-stage hepatocellular carcinoma (HCC): Phase III LEAP-012 study. Ann Oncol. 2024; 35: S1229, doi: 10.1016/j.annonc.2024.08.2277.
35. Lambert A, Bouche O, Ayav A, et al. LBA62 Preoperative modified FOLFIRINOX (mFOLFIRINOX) with or without chemoradiation (CRT) in borderline resectable pancreatic cancer (BRPC): Results from the randomized phase II trial PANDAS/PRODIGE 44. Ann Oncol. 2024; 35: S1252, doi: 10.1016/j.annonc.2024.08.2304.
36. Vogel A, Oh DY, He AR, et al. 55P Subsequent anticancer therapy (SAT) analysis from 3-year follow-up of the phase III TOPAZ-1 study of durvalumab plus gemcitabine and cisplatin in biliary tract cancer (BTC). Ann Oncol. 2024; 35: S233–S234, doi: 10.1016/j.annonc.2024.08.064.
37. Cervantes B, André T, Cohen R. Deficient mismatch repair/microsatellite unstable colorectal cancer: therapeutic advances and questions. Ther Adv Med Oncol. 2024; 16: 17588359231170473, doi: 10.1177/17588359231170473, indexed in Pubmed: 38205076.
38. Rao S, Guren MG, Khan K, et al. ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Anal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021; 32(9): 1087–1100, doi: 10.1016/j.annonc.2021.06.015, indexed in Pubmed: 34175386.
39. Chalabi M, Dungen Lv, Verschoor YL, et al. LBA24 Neoadjuvant immunotherapy in locally advanced MMR-deficient colon cancer: 3-year disease-free survival from NICHE-2. Ann Oncol. 2024; 35: S1217–S1218, doi: 10.1016/j.annonc.2024.08.2263.
40. Gooyer Pde, Verschoor YL, Dungen Lv, et al. 503O Neoadjuvant nivolumab (nivo) plus relatlimab (rela) in MMR-deficient colon cancer: Results of the NICHE-3 study. Ann Oncol. 2024; 35: S428–S429, doi: 10.1016/j.annonc.2024.08.572.
41. Rao S, Samalin-Scalzi E, Evesque L, et al. LBA2 POD1UM-303/InterAACT 2: Phase III study of retifanlimab with carboplatin-paclitaxel (c-p) in patients (Pts) with inoperable locally recurrent or metastatic squamous cell carcinoma of the anal canal (SCAC) not previously treated with systemic chemotherapy (Chemo). Ann Oncol. 2024; 35: S1217, doi: 10.1016/j.annonc.2024.08.2262.
42. Kataoka K, Mori K, Nakamura Y, et al. 558P Survival benefit of adjuvant chemotherapy based on molecular residual disease detection in resected colorectal liver metastases: Subgroup analysis from CIRCULATE-Japan GALAXY. Ann Oncol. 2024; 35: S459–S460, doi: 10.1016/j.annonc.2024.08.627.
43. Wysocki PJ, Chłosta P, Antoniewicz A, et al. Zalecenia postępowania diagnostyczno-terapeutycznego w raku pęcherza moczowego. Onkol Prakt Klin Edu. 2022; 8(4): 229–291.
44. Sigorski D, Osmola M, Wilk M. Advances in genitourinary cancer treatment after the 2023 ESMO congress. Oncol Clin Pract. 2024, doi: 10.5603/ocp.98295.
45. Powles TB, Heijden MSv, Galsky MD, et al. LBA5 A randomized phase III trial of neoadjuvant durvalumab plus chemotherapy followed by radical cystectomy and adjuvant durvalumab in muscle-invasive bladder cancer (NIAGARA). Ann Oncol. 2024; 35: S1271, doi: 10.1016/j.annonc.2024.08.2327.
46. Necchi A, Guerrero-Ramos F, Crispen PL, et al. LBA84 TAR-200 plus cetrelimab (CET) or CET alone as neoadjuvant therapy in patients (pts) with muscle-invasive bladder cancer (MIBC) who are ineligible for or refuse neoadjuvant cisplatin-based chemotherapy (NAC): Interim analysis of SunRISe-4 (SR-4). Ann Oncol. 2024; 35: S1271–S1272, doi: 10.1016/j.annonc.2024.08.2328.
47. Jensen JB, Birkenkamp-Demtröder K, Nordentoft I, et al. 1960O Identification of bladder cancer patients that could benefit from early post-cystectomy immunotherapy based on serial circulating tumour DNA (ctDNA) testing: Preliminary results from the TOMBOLA trial. Ann Oncol. 2024; 35: S1133, doi: 10.1016/j.annonc.2024.08.2045.
48. Powles TB, Valderrama BP, Gupta S, et al. LBA6 EV-302/KEYNOTE-A39: Open-label, randomized phase III study of enfortumab vedotin in combination with pembrolizumab (EV+P) vs chemotherapy (Chemo) in previously untreated locally advanced metastatic urothelial carcinoma (la/mUC). Ann Oncol. 2023; 34: S1340, doi: 10.1016/j.annonc.2023.10.106.
49. Powles TB, Heijden MSv, Gupta S, et al. 1966MO EV-302: Exploratory analysis of nectin-4 expression and response to 1L enfortumab vedotin (EV) + pembrolizumab (P) in previously untreated locally advanced or metastatic urothelial cancer (la/mUC). Ann Oncol. 2024; 35: S1137–S1138, doi: 10.1016/j.annonc.2024.08.2051.
50. Koshkin VS, Barthelemy P, Gravis G, et al. 1965MO Phase II study of futibatinib plus pembrolizumab in patients (pts) with advanced/metastatic urothelial carcinoma (mUC): Final analysis of efficacy and safety. Ann Oncol. 2024; 35: S1136–S1137, doi: 10.1016/j.annonc.2024.08.2050.
51. Zhao J, Du F, Shen G, et al. The role of hypoxia-inducible factor-2 in digestive system cancers. Cell Death Dis. 2015; 6(1): e1600, doi: 10.1038/cddis.2014.565, indexed in Pubmed: 25590810.
52. Rini BI, Rodriguez CS, Albiges L, et al. LBA74 Final analysis of the phase III LITESPARK-005 study of belzutifan versus everolimus in participants (pts) with previously treated advanced clear cell renal cell carcinoma (ccRCC). Ann Oncol. 2024; 35: S1262–S1263, doi: 10.1016/j.annonc.2024.08.2317.
53. Choueiri TK, Motzer RJ, Beckermann K, et al. LBA73 Tivozanib–nivolumab vs tivozanib monotherapy in patients with renal cell carcinoma (RCC) following 1 or 2 prior therapies including an immune checkpoint inhibitor (ICI): Results of the phase III TiNivo-2 study. Ann Oncol. 2024; 35: S1261–S1262, doi: 10.1016/j.annonc.2024.08.2316.
54. Kaptein FHJ, van der Hulle T, Braken SJE, et al. Prevalence, Treatment, and Prognosis of Tumor Thrombi in Renal Cell Carcinoma. JACC CardioOncol. 2022; 4(4): 522–531, doi: 10.1016/j.jaccao.2022.07.011, indexed in Pubmed: 36444235.
55. Toren P, Abouassaly R, Timilshina N, et al. Results of a national population-based study of outcomes of surgery for renal tumors associated with inferior vena cava thrombus. Urology. 2013; 82(3): 572–577, doi: 10.1016/j.urology.2013.04.054, indexed in Pubmed: 23987150.
56. Gu L, Cheng P, Liang Q, et al. 1701P NEOTAX: A phase II trial of neoadjuvant toripalimab plus axitinib for clear cell renal cell carcinoma with inferior vena cava tumor thrombus. Ann Oncol. 2024; 35: S1019, doi: 10.1016/j.annonc.2024.08.1794.
57. Powles T, Burotto M, Escudier B, et al. Nivolumab plus cabozantinib versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended follow-up from the phase III randomised CheckMate 9ER trial. ESMO Open. 2024; 9(5): 102994, doi: 10.1016/j.esmoop.2024.102994, indexed in Pubmed: 38642472.
58. Braun DA, Wang Y, Yu A, et al. 1694MO Novel serum glycoproteomic biomarkers predict response to nivolumab plus cabozantinib (NIVO+CABO) versus sunitinib (SUN) in advanced RCC (aRCC): Analysis from CheckMate 9ER. Ann Oncol. 2024; 35: S1012–S1013, doi: 10.1016/j.annonc.2024.08.1787.
59. Bergmann L, Ahrens M, Albiges L, et al. LBA75 Prospective randomised phase-II trial of ipilimumab/nivolumab versus standard of care in non-clear cell renal cell cancer: Results of the SUNNIFORECAST trial. Ann Oncol. 2024; 35: S1263, doi: 10.1016/j.annonc.2024.08.2318.
60. Parker C, Nilsson S, Heinrich D, et al. ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013; 369(3): 213–223, doi: 10.1056/NEJMoa1213755, indexed in Pubmed: 23863050.
61. Smith M, Parker C, Saad F, et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019; 20(3): 408–419, doi: 10.1016/S1470-2045(18)30860-X, indexed in Pubmed: 30738780.
62. Gillessen S, Choudhury A, Saad F, et al. LBA1 A randomized multicenter open label phase III trial comparing enzalutamide vs a combination of Radium-223 (Ra223) and enzalutamide in asymptomatic or mildly symptomatic patients with bone metastatic castration-resistant prostate cancer (mCRPC): First results of EORTC-GUCG 1333/PEACE-3. Ann Oncol. 2024; 35: S1254, doi: 10.1016/j.annonc.2024.08.2307.
63. Sartor O, Jiang DM, Smoragiewicz M, et al. LBA65 Efficacy of 177Lu-PNT2002 in PSMA-positive mCRPC following progression on an androgen-receptor pathway inhibitor (ARPI) (SPLASH). Ann Oncol. 2024; 35: S1254–S1255, doi: 10.1016/j.annonc.2024.08.2308.
64. Agarwal N, Azad AA, Galceran JC, et al. LBA67 Cabozantinib (C) plus atezolizumab (A) versus 2nd novel hormonal therapy (NHT) in patients (Pts) with metastatic castration-resistant prostate cancer (mCRPC): Final overall survival (OS) results of the phase III, randomized, CONTACT-02 study. Ann Oncol. 2024; 35: S1256–S1257, doi: 10.1016/j.annonc.2024.08.2310.
65. Lucas MW, Menzies AM, Lopez-Yurda M, et al. LBA42 Distant metastasis-free survival of neoadjuvant nivolumab plus ipilimumab versus adjuvant nivolumab in resectable, macroscopic stage III melanoma: The NADINA trial. Ann Oncol. 2024; 35: S1233–S1234, doi: 10.1016/j.annonc.2024.08.2283.
66. Long GV, Robert C, Hill AG, et al. 1082O KEYMAKER-U02 substudy 02C: Neoadjuvant pembrolizumab (pembro) and investigational agents followed by adjuvant pembro for stage IIIB-D melanoma. Ann Oncol. 2024; 35: S712–S713, doi: 10.1016/j.annonc.2024.08.1150.

67. Robert C, Schachter J, Long GV, et al. KEYNOTE-006 investigators. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015; 372(26): 2521–2532, doi: 10.1056/NEJMoa1503093, indexed in Pubmed: 25891173.

68. Larkin J, Sileni VC, Marqueste CG, et al. LBA43 10-y survival outcomes from the phase III CheckMate 067 trial of nivolumab plus ipilimumab in advanced melanoma. Ann Oncol. 2024; 35: S1234–S1235, doi: 10.1016/j.annonc.2024.08.2284.