ORAL PRESENTATIONS

S1 – ANTIBODY-DRUG CONJUGATES FOR BREAST CANCER TREATMENT

ANUŠKA BUDISAVLJEVIĆ[1]

[1]*Department of Internal Medicine, General Hospital Pula, Pula, Croatia*

Antibody–drug conjugates (ADCs) represent a new generation of therapeutics whose characteristics and clinical efficacy are determined by several key components: the monoclonal antibody, the cytotoxic payload, the linker connecting the antibody to the payload, and a bystander effect, which enables ADC activity in neighboring tumor cells lacking target antigen expression.

In breast cancer, four ADCs are currently in clinical use: trastuzumab emtansine (T-DM1), trastuzumab deruxtecan (T-DXd), datopotamab deruxtecan (Dato-DXd), and sacituzumab deruxtecan.

In early breast cancer, a future highly relevant clinical question will be the selection between T-DM1 and T-DXd in the adjuvant setting following neoadjuvant therapy for high-risk HER2-positive disease. Traditionally, T-DM1 has been administered in cases of residual disease after neoadjuvant chemotherapy (NACT). However, this approach is likely to change in the near future based on the results of the DESTINY-Breast05 trial, which compared T-DM1 and T-DXd in high-risk patients with early HER2-positive breast cancer who did not achieve a pathological complete response (pCR) in patients with cT4 or cN2–3 or cT1–3/N0–1 + yN+). T-DXd achieved an invasive disease-free survival (IDFS) rate of 92.4% versus 83.7% with T-DM1 (HR 0.47; 95% CI 0.34–0.66; $p<0.001$), and is therefore likely to become the new standard of adjuvant treatment in this setting(1).

Multiple ongoing trials are evaluating ADCs in high-risk early triple-negative breast cancer (TNBC), which is currently treated with neoadjuvant chemoimmunotherapy followed by adjuvant immunotherapy according to the KEYNOTE-522 regimen. Several important studies are investigating ADCs in escalation strategies, particularly in patients who fail to achieve pCR after neoadjuvant therapy. The ASCENT-05/OptimICE-RD trial is assessing sacituzumab govitecan plus pembrolizumab versus pembrolizumab with or without capecitabine in patients with TNBC and residual disease after neoadjuvant chemoimmunotherapy. TROPION-Breast03 is comparing datopotamab deruxtecan plus durvalumab versus standard therapy in TNBC patients with residual disease. TROPION-Breast04 is evaluating neoadjuvant datopotamab deruxtecan plus durvalumab followed by adjuvant durvalumab versus standard of care. The results of these trials may support the integration of ADCs into the treatment of high-risk early TNBC(2,3).

In metastatic breast cancer (mBC), T-DXd has established role in the management of HR-positive/HER2-low and HER2-ultralow disease. The DESTINY-Breast04 trial positioned T-DXd in HR-positive/HER2-low mBC after two lines of endocrine therapy and one line of chemotherapy, demonstrating a median progression-free survival (mPFS) of 10.1 months versus 5.4 months with standard of care (HR 0.51; 95% CI 0.40–0.64). DESTINY-Breast06 further demonstrated efficacy in the HR-positive/HER2-ultralow population after two lines of endocrine therapy and prior to chemotherapy, with a mPFS of 13.2 months versus 5.1 months with standard therapy (HR 0.62; 95% CI 0.52–0.75)(4).

The therapeutic landscape of HER2-positive mBC has been substantially reshaped by the introduction of T-DXd, which is now standard of care in the second-line setting based on the DESTINY-Breast03 trial. In this study, T-DXd achieved a mPFS of 29 months compared with 7.2 months for T-DM1 (HR 0.30; 95% CI 0.24–0.38)(5).

Recently reported results from DESTINY-Breast09 may further shift T-DXd into the first-line setting for HER2-positive mBC, with a mPFS of 40 months compared with 28 months for the traditional first-line THP regimen established in the CLEOPATRA trial. Long-term follow-up from CLEOPATRA demonstrated that 16% of patients treated with THP remained progression-free at 8 years, and 36% were alive at 8 years. Additional analyses identified long-term responders as patients with the following characteristics: long disease-free interval (DFI), non-visceral disease, PR-positive tumors, HER2 3+ expression, high HER2 mRNA levels, and PIK3CA wild-type status. A key clinical question remains whether all patients with HER2-positive mBC should receive T-DXd in the first line, given the favorable tolerability of THP, limited chemotherapy exposure (6–8 cycles of docetaxel), and the potential for prolonged disease control with excellent quality of life on dual HER2 blockade maintenance therapy. Clinical and molecular characteristics of potential long-term responders may help identify patients who could continue to benefit from THP in the first-line setting(6,7).

In metastatic TNBC, first-line treatment is determined by PD-L1 status. In PD-L1–positive disease, immunotherapy is combined with chemotherapy. Recently published results from the ASCENT-04/KEYNOTE-D19 study in PD-L1–positive patients demonstrated superiority of sacituzumab deruxtecan plus pembrolizumab over chemotherapy plus pembrolizumab, with an mPFS of 11.2 versus 7.8 months (HR 0.65; 95% CI 0.51–0.84). Regulatory approval of this combination is anticipated(8).

In PD-L1–negative metastatic TNBC, first-line efficacy of sacituzumab deruxtecan was demonstrated in the ASCENT-03 trial (mPFS 9.7 vs 6.7 months; HR 0.62; 95% CI 0.50–0.77), while datopotamab deruxtecan showed benefit in TROPION-Breast02 (mPFS 10.6 vs 5.6 months; HR 0.57; 95% CI 0.47–0.69). In the second-line setting, sacituzumab govitecan is established based on the ASCENT trial, with an mPFS of 5.6 months versus 1.7 months for standard therapy (HR 0.41; 95% CI 0.32–0.52)(9).

In conclusion, ADCs are reshaping the therapeutic landscape of early breast cancer, particularly in escalation strategies for high-risk disease. In the metastatic setting, improvements in efficacy are increasingly driven by combinations of ADCs with immunotherapy and monoclonal antibodies. However, longer follow-up and overall survival data are needed to fully define their clinical impact. Careful consideration is also required regarding the distinct toxicity profiles of different ADCs, their incidence, and optimal management strategies.

REFERENCES:

1. Loibl S, Park YH, Shao Z, Huang CS, Barrios C, Abraham J, et al. Trastuzumab deruxtecan in residual HER2-positive early breast cancer. N Engl J Med. 2025 Dec 10. doi:10.1056/NEJMoa2514661.
2. Bardia A, Pusztai L, Albain K, Ciruelos EM, Im SA, Hershman D, et al. TROPION-Breast03: a randomized phase III global trial of datopotamab deruxtecan ± durvalumab in patients with triple-negative breast cancer and residual invasive disease at surgical resection after neoadjuvant therapy. Ther Adv Med Oncol. 2024 Jan 1;16. doi:10.1177/17588359241248336.
3. McArthur HL, Tolaney SM, Dent R, Schmid P, Asselah J, Liu Q, et al. TROPION-Breast04: a randomized phase III study of neoadjuvant datopotamab deruxtecan (Dato-DXd) plus durvalumab followed by adjuvant durvalumab versus standard of care in patients with treatment-naïve early-stage triple negative or HR-low/HER2− breast cancer. Ther Adv Med Oncol. 2025 Jan 1;17. doi:10.1177/17588359251316176.
4. Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, Tokunaga E, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. N Engl J Med. 2022 Jul 7;387(1):9–20. doi:10.1056/nejmoa2203690.
5. Cortés J, Hurvitz SA, Im SA, Iwata H, Curigliano G, Kim SB, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in HER2-positive metastatic breast cancer: long-term survival analysis of the DESTINY-Breast03 trial. Nat Med. 2024 Aug 1;30(8):2208–15. doi:10.1038/s41591-024-03021-7.

6. Tolaney SM, Jiang Z, Zhang Q, Barroso-Sousa R, Park YH, Rimawi MF, et al. Trastuzumab deruxtecan plus pertuzumab for HER2-positive metastatic breast cancer. N Engl J Med. 2026;394:551-562. doi:10.1056/nejmoa2508668.
7. Swain SM, Miles D, Kim SB, Im YH, Im SA, Semiglazov V, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. Lancet Oncol. 2020 Apr 1;21(4):519–30. doi:10.1016/S1470-2045(19)30863-0.
8. Tolaney SM, de Azambuja E, Kalinsky K, Loi S, Kim SB, Yam C, et al. Sacituzumab Govitecan plus Pembrolizumab for Advanced Triple-Negative Breast Cancer. N Engl J Med. 2026 Jan 22;394(4):354–66. doi:10.1056/NEJMoa2508959.
9. Cortés J, Bardia A, Punie K, Barrios C, Hurvitz S, Schneeweiss A, et al. Primary Results From ASCENT-03: A Randomized Phase 3 Study of Sacituzumab Govitecan vs Chemotherapy in Patients With Previously Untreated Metastatic Triple-Negative Breast Cancer Who Are Unable to Receive PD-(L)1 Inhibitors Declaration of Interests [Internet]. Report. Available from: https://www.esmo.org/guidelines/living-guidelines/esmo-living-guideline-metastatic-breast-cancer.

S2 – BLADDER PRESERVATION STRATEGY IN MUSCLE INVASIVE DISEASE

MIRELA ŠAMBIĆ PENC[1], Maja Kovač Barić[1], Maja Drežnjak Madunić[1,2], Zdravka Krivdić Dupan[1,3], Luka Perić[1,2], Tara Cvijić Perić[1,2], Dino Belić[1,2], Sebastijan Spajić[1,2], Dominik Seletković[1], Dora Muršić[1,2], Vedrana Pavlović[1], Laura Zahirović[1], Ivana Canjko[1]

[1]*Department of Oncology, University Hospital Center Osijek, Osijek, Croatia*
[2]*Faculty of Medicine, University of J.J.Strossmayer Osijek, Osijek, Croatia*
[3]*Clinical Department of Diagnostic and Interventional Radiology, University Hospital Center Osijek, Osijek, Croatia*

Urothelial carcinoma of the bladder is one of the most prevalent cancers worldwide, diagnosed as muscle invasive in 25% of cases.Muscle-invasive bladder cancer (MIBC) is a highly aggressive chemosensitive disease with nearly 50% of patients developing metastatic disease, likely owing to the presence of micrometastases at diagnosis and is characterized by an overall poor prognosis with a 5-year overall survival (OS) of ~50%. Radical cystectomy (RC) with cisplatin-based neoadjuvant chemotherapy (NAC) has demonstrated improved survival in eligible patients and is the current guideline-recommended treatment. But however muscle-invasive bladder cancer (MIBC) still remains a therapeutic challenge. Despite improvements in systemic therapy, the morbidity associated with radical surgery and urinary diversion significantly impacts quality of life. Over the past decade, bladder preservation strategies have evolved rapidly, moving beyond conventional therapy (NAC followed with RC) or, in selected patients trimodal therapy (TMT) to biomarker-guided, response-adapted paradigms that aim to optimize oncologic outcomes while maintaining organ function.

Current guidelines strongly support the integration of multidisciplinary evaluation when considering bladder-sparing alternatives to radical cystectomy, especially in patients with cT2–cT3 N0 disease without extensive carcinoma in situ or hydronephrosis. Traditional TMT, which include maximal transurethral resection of bladder tumor (TURBT) followed by concurrent chemoradiotherapy, has demonstrated survival benefit in selected cohorts that approach those of radical cystectomy, particularly when strict patient selection and rigorous follow-up protocols are employed. These observations are supported by systematic reviews showing comparable five-year overall survival rates between TMT and cystectomy in well-selected MIBC populations, although prospective randomized comparisons are lacking.

In the last few years, there has been significant progress in oncology, and numerous studies have been conducted that have focused on bladder preservation and personalization of patient treatment. One

of them is RETAIN trial. RETAIN-1, a phase II trial of risk-enabled therapy after neoadjuvant chemotherapy, evaluated a cohort of MIBC patients treated with accelerated methotrexate, vinblastine, doxorubicin, and cisplatin (AMVAC), selecting those with favorable biomarker profiles and clinical downstaging for active surveillance without immediate cystectomy. Although the predefined primary endpoint of 2-year metastasis-free survival (MFS) narrowly missed formal noninferiority thresholds, a substantial proportion of patients avoided cystectomy without metastatic progression, and overall survival remained robust across study arms.

Building on RETAIN-1, RETAIN-2, presented at ASCO Genitourinary Cancer Symposium 2026, further refined a response-adapted framework by integrating chemo-immunotherapy (dose-dense MVAC plus nivolumab) followed by active surveillance in patients achieving clinical regression of tumor. Interim data demonstrate that approximately two-thirds of patients under active surveillance remain metastasis-free with an intact bladder, with ctDNA clearance emerging as a strong predictor of systemic control. Persistent ctDNA positivity was associated with significantly inferior MFS, irrespective of local treatment modality, and ctDNA dynamics provided prognostic information beyond pathological staging. These findings highlight the potential for ctDNA to guide individualized decisions about the safety of avoiding radical cystectomy and stratifying systemic risk.

The other important trial of potential bladder-sparing approach is SURE-2. The SURE-02 study is a Phase 2 study of neoadjuvant Sacituzumab Govitecan + Pembrolizumab, followed by response-adapted bladder sparing and adjuvant Pembrolizumab in patients with MIBC presented on the 2025 ASCO annual meeting reported a clinically meaningful complete response (cCR) rate (~44%) among evaluable patients, with a high rate of subsequent bladder preservation and encouraging 12-month event-free survival. These data, although interim, suggest that antibody-drug conjugate and immune checkpoint inhibitor combinations may extend bladder-sparing options, particularly for patients ineligible for cisplatin-based therapy.

The HCRN GU16-257 trial, which is also Phase 2 trial, further supports bladder-sparing techniques by sequencing neoadjuvant gemcitabine, cisplatin, and nivolumab followed by maintenance immunotherapy in responders. In this cohort, a substantial subset of patients achieved cCR and was successfully managed with bladder preservation. These findings may help advance a more personalized approach to the management of MIBC leveraging clinical response-based risk stratification underscoring the feasibility of immunotherapy combined with chemotherapy in neoadjuvant setting that may enable safe deferral of radical surgery in select patients.

Incorporating biomarker in treatment of MIBC, particularly molecular residual disease (MRD) assays such as plasma circulating tumor DNA (ctDNA) and urinary tumor DNA (utDNA), is redefining response assessment. Data presented at ASCO GU 2026 highlight the utility of ctDNA for longitudinal monitoring and response adaptation across diverse bladder-sparing trials, where post-therapy ctDNA negativity correlates with improved event-free survival (EFS) and metastasis-free survival. Combined ctDNA and utDNA assessments may improve residual disease detection, with utDNA potentially more sensitive to local recurrence and ctDNA reflecting systemic risk. Despite advances in treatment of MIBC radical cystectomy with cisplatin-based neoadjuvant chemotherapy (NAC) remains the standard of treatment although bladder sparing strategies may be an option in highly selected patients but it is important to balance organ preservation with uncompromised oncologic safety. Rigorous surveillance protocols integrating imaging, cystoscopic evaluation and biomarker monitoring are important and salvage cystectomy remains an option for patients with local recurrence or progression.

The treatment options for bladder preservation in muscle-invasive disease is rapidly evolving. Response-adapted strategies incorporating advanced systemic therapy and biomarker-driven decision,

particularly ctDNA and utDNA, show promise in expanding bladder-sparing opportunities without sacrificing survival outcomes. Continued maturation of these data, together with prospective validation in larger cohorts and randomized settings, will be essential to delineate the patient populations for organ preservation and to establish bladder-sparing treatment as a rigorously evidence-based alternative to radical cystectomy.

Keywords: Muscle-invasive bladder cancer; bladder preservation; radical cystectomy; trimodal therapy; neoadjuvant chemotherapy; immunotherapy; circulating tumor DNA; urinary tumor DNA

REFERENCES

1. Geynisman DM, et al. Phase II RETAIN 1 trial of risk-enabled bladder preservation after neoadjuvant chemotherapy in MIBC. J Clin Oncol. 2025;43(9):1113–1122.
2. Ghatalia P, et al. Integrated ctDNA analysis from RETAIN-1 and RETAIN-2: response-adapted bladder preservation. Presented at ASCO GU 2026 (LBA632).
3. GU16-257 bladder preservation trial summary (ASCO 2025).
4. Signatera MRD data highlighting ctDNA and utDNA in bladder preservation trials (ASCO GU 2026).
5. Roche IMvigor011 ctDNA-guided adjuvant therapy outcomes (ESMO 2025).
6. Parrào D, et al. Bladder preservation alternatives in non-metastatic MIBC: systematic review. Asian J Urol. 2025;12(3):309–319.

S3 – CANCER PREVALENCE IN CROATIA – HOW MANY PEOPLE ARE LIVING WITH A CANCER DIAGNOSIS?

MARIO ŠEKERIJA[1,2], Petra Čukelj[1]

[1]*Divison for Chronic Noncommunicable Disease Epidemiology and Prevention, Croatian Institute of Public Health, Zagreb, Croatia*
[2]*School of Public Health 'Dr Andrija Štampar' and School of Medicine, University of Zagreb, Zagreb, Croatia*

Cancer is one of the leading causes of morbidity and mortality around the world. Number of cases (cancer incidence) is expected to rise, mainly due to the aging population but also due to changes in the distribution of some risk factors. However, earlier detection of the disease and improvements in treatment have led to a significant increase in cancer prevalence – number of people who are currently living with a cancer diagnosis being made sometimes earlier in their lifetime.

International Agency for Research on Cancer estimates that 53 504 187 of people around the world have received a diagnosis of cancer in the last 5 years(1). Most common cancer diagnosis were breast cancer (15.3 % of prevalent cases), colorectal cancer (10.8 %) and prostate cancer (9.4 %). Estimated lifetime prevalence of cancer in the EU27 in 2020 was 22 347 000, with prevalence increasing 3.5 % per year in the 2010-2020 period(2).

Recently published data(3) on lifetime cancer prevalence in Croatia shows that on December 31st, 2023, a total of 187 118 people, (rate 4 845.1 per 100 000) 55.9% of which were women, have had a cancer diagnosis some time in their life. This makes for a total of 4.8 % of the population. Prevalence is the result of cancer incidence and cancer survival; namely, as more people are being diagnosed with cancer, and

a larger proportion of them are surviving many years after diagnosis, the prevalence is rising. Up to 2005, cancer prevalence in Croatia was under 2 %, while in 2001, there were less than 64 000 persons living with cancer in Croatia.

The cancer prevalence is highest in the 85+ age group (15.2 %), then in the 65-84 age-group (13,2 %), 4,4% in the 40-64, 0,9% in the 20-39 and 0,2% in the 0-19 age group.

As is the case on the global level, the most prevalent cancer in Croatia overall is breast cancer, with 39 036 people (over 99 % women) alive that were diagnosed with breast cancer, followed by colorectal cancer (25 443) and prostate cancer (23 816). Five most prevalent cancer diagnosis in female cancer survivors are breast cancer (35.2 %), colorectal cancer (10.2 %), thyroid cancer (9.3 %), uterine body cancer (8.6 %) and cervical cancer (5.0 %). In men, the most common cancer diagnosis in cancer survivors is prostate cancer (27.1 %), followed by colorectal cancer (16.1 %), bladder cancer (7.2 %), kidney cancer (5.7 %) and melanoma (5.5 %). Cancer sites with a high incidence but relatively low survival, such as lung cancer or pancreatic cancer, will thus have a lower prevalence and are not among the top cancers by prevalence mentioned here.

When we look at the time elapsed since diagnosis (as a surrogate measure of a share of people that might be considered as *cured*), 10.1 % are people in the first year after their diagnosis, 27.6 % are those alive 1-4 years after diagnosis, 23.9 % 5-9 years after diagnosis, and 38.5 % people are alive 10 or more years after diagnosis. In total, for 116,567 people in Croatia more than five years have passed since their cancer diagnosis and they were alive at the end of 2023.

With more people surviving cancer, it is important to recognize specific health care and other needs that cancer survivors have, and provide resources to alleviate the physical, social, and emotional effects of the disease and associated treatment. Given that these needs differ depending on the cancer site, time since diagnosis and age of the patient, comprehensive and timely data on cancer prevalence can help us to better inform the existing policies.

Keywords: cancer, prevalence, cancer survivors, Croatia, cancer registry

REFERENCES:

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229-263. doi:10.3322/caac.21834.
2. De Angelis R, Demuru E, Baili P, Troussard X, Katalinic A, Chirlaque Lopez MD et al. Complete cancer prevalence in Europe in 2020 by disease duration and country (EUROCARE-6): a population-based study. Lancet Oncol. 2024 Mar;25(3):293-307. doi: 10.1016/S1470-2045(23)00646-0.
3. Hrvatski zavod za javno zdravstvo. Rak u Hrvatskoj 2023/2024 (internet]. Šekerija M, ed. Zagreb: Hrvatski zavod za javno zdravstvo; 2026. Available at:https://www.hzjz.hr/periodicne-publikacije/rak-u-hrvatskoj-2023-2024/
4. Šekerija M, Alfirević M, Fabijanić U, Rajačić N, Antoljak N. Epidemiology of cancer in Croatia–recent insights and international comparisons. Libri oncologici: Croatian Journal of Oncology. 2019;47(2-3):84-90.
5. OECD/European Commission (2025), EU Country Cancer Profile: Croatia 2025, EU Country Cancer Profiles, OECD Publishing, Paris. Available at: https://doi.org/10.1787/46c5e70c-en.

S4 – CASE REPORT OF PATIENT WITH METASTATIC EGFR MUTATED LUNG CANCER AND SUCCESSFUL TREATMENT BASED ON COMPRENHENSIVE GENOMIC PROFILING

ANAMARIJA KOVAČ PEIĆ[1], Ivana Canjko[2]

[1]*Department of Hematology and Oncology, General Hospital Dr.Josip Benčević, Slavonski Brod, Croatia*
[2]*Department of Oncology, University Hospital Center Osijek, Osijek, Croatia*

A 65 years old man never smoker with positive familiy history of lung cancer and medical hystory of arterial hypertension was presented with cough, dyspnea and weight loss. In August 2022 right lung adenocarcinoma was diagnosed. CT and MRI scan showed right pleural effusion, bone metastases and pulmonary parenchymal metastases. Initial molecular testing revealed an activating EGFR exon 19 deletion. Clinical stage was T4N2M1c.

In first line of treatment patient received 10 cycles of afatinib from 09/2022 to 06/2023. Cerebellar metastases were identified from June 2023. Plasma testing detected the resistance mutation EGFR T790M and second line with osimertinib was started in July 2023 (1). Total 17 cycles was given till December 2024, patient was asimptomatic for brain metastases and no brain radiotherapy was performed. Best response on CT scan was partial response then stable disease, brain MR confirmed complete response(2). Due to pericardial effusion with impending tamponade, a pericardiocentesis was performed. Systemic chemotherapy with cisplatin/pemetrexed was added for 4 cycles (03/2024-05/2024) with ongoing osimertinib and afterwards patient had stable disease with good quality of life(3). In January 2025 disease progression was confirmed with liver metastases, progression in lung and bones on CT scan and liver biopsy was performed. MRI of brain showed multiple brain metastases, patient was asymptomatic. Liver biopsy confirmed adenocarcinoma and comprehensive tissue based NSG identified EGFR exon deletion and T790M, acquried C797S mutation and EGFR amplification.

Multidiciplinary team recommendation based on NGS results and current guidlines and evidence from MARIPOSA-2 study for patients progressing on osimertinib was amivantanab with chemotherapy in combination(4). The medical record was submitted to the National Committee for treatment approval guided by comprehensive genomic profiling. In February of 2025. amivantantab in combination with carboplatina/pemetrexed was started, then osimetinib monotherapy was continued. Lazertinib was added from October 2025 due to National Committee approval(5). Last CT showed stable disease and this combination treatment is still ongoing.

Keywords: lung cancer, EGFR mutation, osimertinib, amivantantab and lazertinib

REFERENCES:

1. Leonetti A, Sharma S, Minari R, Perego P, Giovannetti E, Tiseo M. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. Br J Cancer. 2019 Oct;121(9):725-737. doi: 10.1038/s41416-019-0573-8.
2. Aibani R, Collins J, Borna AK, Kamran A. Comparative efficacy of osimertinib with and without radiation therapy in EGFR-mutated nonsmall cell lung cancer with brain metastases. Semin Oncol. 2026 Feb;53(1):152436. doi: 10.1016/j.seminoncol.2025.152436.
3. Planchard D, Jänne PA, Cheng Y, Yang JC, Yanagitani N, ... FLAURA2 Investigators et al. Osimertinib with or without Chemotherapy in *EGFR*-Mutated Advanced NSCLC. N Engl J Med. 2023 Nov 23;389(21):1935-1948. doi: 10.1056/NEJMoa2306434.

4. Passaro A, Wang J, Wang Y, Lee SH, Melosky B et al; MARIPOSA-2 Investigators. Amivantamab plus chemotherapy with and without lazertinib in EGFR-mutant advanced NSCLC after disease progression on osimertinib: primary results from the phase III MARIPOSA-2 study. Ann Oncol. 2024 Jan;35(1):77-90. doi: 10.1016/j.annonc.2023.10.117.
5. Besse B, Goto K, Wang Y, Lee SH, Marmarelis ME et al. Amivantamab plus lazertinib in patients with EGFR-mutant NSCLC after progression on osimertinib and platinum-based chemotherapy: results from CHRYSALIS-2 cohort A. J Thorac Oncol. 2025 May;20(5):651-664. doi: 10.1016/j.jtho.2024.12.029.

S5 – COMBINATION OF TARGETED THERAPY AND RADIOTHERAPY IN THE TREATMENT OF METASTATIC NON-SMALL CELL LUNG CANCER

IVANA CANJKO[1], Mirela Šambić Penc[1], Maja Kovač Barić[1], Zdravka Krivdić Dupan[2,3], Luka Perić[1,3], Sebastijan Spajić[1,3], Dominik Seletković[1,3], Laura Zahirović[1,3], Vedrana Pavlović[1]

[1]*Department of Oncology, University Hospital Center Osijek, Osijek, Croatia*
[2]*Department of Diagnostic and Interventional Radiology, University Hospital Center Osijek, Osijek, Croatia*
[3]*Faculty of Medicine, University of J.J.Strossmayer Osijek, Osijek, Croatia*

Lung cancer remains a leading cause of cancer-related mortality worldwide, with many patients presenting with advanced or unresectable disease. Radiotherapy has long been a cornerstone of lung cancer management, providing effective local control and symptom palliation.In recent years, the development of targeted therapies directed against specific molecular alterations particularly tyrosine kinase inhibitors (TKIs) have revolutionized systemic treatment in NSCLC, improving progression-free survival and overall outcomes compared to conventional chemotherapy. Preclinical rationale and retrospective series suggest potential benefits of integrating radiotherapy with EGFR inhibitors and other TKIs in oligometastatic or oligoprogressive disease, although optimal sequencing and toxicity profiles require further clarification.

The integration of radiotherapy with targeted therapy represents a promising therapeutic strategy, aiming to enhance tumor control while minimizing systemic toxicity.Radiotherapy can modulate the tumor microenvironment and potentially increase tumor sensitivity to targeted agents, leading to synergistic antitumor effects. Conversely, targeted therapies may improve radiosensitivity by inhibiting DNA repair pathways and tumor cell proliferation.However, this combination also raises concerns regarding increased toxicity, particularly radiation pneumonitis and esophagitis, necessitating careful patient selection, treatment planning, and timing.

Current research priorities focus on defining biomarkers predictive of response, minimizing overlapping toxicities, and optimizing multimodality treatment schedules. Integrative practice and clinical trials are needed to standardize evidence-based use of radiotherapy plus targeted therapies, with the goal of improving survival and quality of life in lung cancer patients.

Keywords: metastatic non-small cell lung cancer, radiotherapy, targeted therapy, toxicity, biomarkers

REFERENCES:

1. Lee KN, Owen D. Advances in stereotactic body radiation therapy for lung cancer. Cancer J. 2024;30(6):401-6.
2. Utilisation of radiotherapy in lung cancer: a scoping narrative literature review with a focus on Europe. Radiother Oncol. 2024;45:100717.
3. Georgakopoulos I, et al. Combined use of radiotherapy and tyrosine kinase inhibitors in metastatic NSCLC. Crit Rev Oncol Hematol. 2024;204:104520.

4. Bowen Jones S, et al. Emerging role of targeted therapies combined with radiotherapy in inoperable I–III NSCLC: review from IASLC ART. J Thorac Oncol. 2025;20(8):1018-31.
5. Combined use of radiotherapy and TKIs in NSCLC: outcomes in oligometastatic disease and CNS metastases. Crit Rev Oncol Hematol. 2024;S1040-8428(24)00263-4.

S6 – FIRST-LINE IMMUNOTHERAPY FOR METASTATIC NON-SMALL CELL LUNG CANCER: HOW TO CHOOSE BETWEEN SO MANY OPTIONS?

JASNA RADIĆ[1,2]

[1]*Department of Oncology and Nuclear Medicine, Sestre milosrdnice University Hospital Center, Zagreb, Croatia*
[2]*School of Medicine, University of Zagreb, Zagreb, Croatia*

In advanced non–small cell lung cancer (NSCLC), selection of first– line immune checkpoint inhibitors (ICIs) is increasingly individualized, but still anchored first in PDL1 expression and the presence of targetable genomic alterations. High PDL1 expression (≥50%) generally supports singleagent PD1/PDL1 blockade in the absence of actionable drivers, whereas lower or negative PDL1 levels favor chemoimmunotherapy or dual immunotherapy– chemotherapy combinations. Tumor mutational burden (TMB) and clinical surrogates such as smoking status add nuance: smokers typically harbor higher TMB and derive greater relative benefit from ICIs than neversmokers, in whom oncogenic drivers (EGFR, ALK, ROS1) are more prevalent and predict attenuated ICI efficacy, making targeted therapy the preferred initial strategy.

Across histologic subtypes, both nonsquamous and squamous NSCLC benefit from ICIs, though most pivotal trials have enrolled more nonsquamous cases; histology rarely dictates the specific checkpoint agent (although, according to the subgroup analyses some ICIs showed trends toward superior efficacy in particular histological subtype), but can influence the chemotherapy backbone in combination regimens. Brain metastases, once a relative contraindication, are now an important but not exclusionary factor: emerging data suggest that PD1/PDL1 inhibitors alone or with chemotherapy, or combinations of anti PD-1/anti CTLA-4 with or without chemotherapy can achieve intracranial responses and durable control in selected patients, particularly when brain disease is asymptomatic or locally treated, though careful coordination with radiotherapy and steroids remains critical.

Sexbased differences in ICI benefit appear modest and inconsistent; while some metaanalyses hint at slightly greater relative benefit in men, these differences rarely drive drug choice in individual patients and are overshadowed by PDL1 status, driver mutations, and disease burden. TMB, though biologically linked to ICI sensitivity, is not yet a routine standalone decision tool in NSCLC; instead, it is interpreted alongside smoking history, PDL1, and comutational patterns. Lossoffunction genomic alterations in STK11 and KEAP1, often cooccurring with KRAS, have been associated with primary resistance and poorer outcomes on ICIs, prompting consideration of intensified approaches such as combination of dual immunotherapy with chemotherapy and enrollment in clinical trials when feasible.

In practice, the choice of checkpoint inhibitor for NSCLC emerges from an integrated profile: PDL1 level and actionable genomic alterations set the therapeutic "lane" (targeted therapy vs immunotherapy ± chemotherapy), while smoking status, TMB, comutations, brain metastases, and patient factors (performance status, comorbidities, need for rapid response) refine the selection and intensity of ICIbased regimens. This narrative underscores a shift from onesizefitsall immunotherapy toward a layered, biomarker

and contextdriven strategy, with ongoing trials expected to clarify how best to incorporate TMB and resistanceassociated genomic signatures into routine checkpoint inhibitor selection.

Keywords: immune- checkpoint inhibitors, treatment individualization

REFERENCES:

1. Roque K, Ruiz R, Mas L, et al. Update in immunotherapy for advanced non-small cell lung cancer: optimizing treatment sequencing and identifying the best choices. Cancers (Basel). 2023;15(18):4547. doi: 10.3390/cancers15184547.
2. Bronte G, Cosi DM, Magri C, et al. Immune checkpoint inhibitors in *special* NSCLC populations: A viable approach? Int J Mol Sci. 2023;24(16): 12622. doi: 10.3390/ijms241612622.
3. Ghazali N, Garassino MC, Leihgl NB, et al. Immunotherapy in advanced, *KRAS* G12C-mutant non-small-cell lung cancer: current strategies and future directions. Ther Adv Med Oncol. 2025;17. doi: 10.1177/17588359251323985
4. Frost N, Reck M. Non–small cell lung cancer metastatic without oncogenic alterations. Am Soc Clin Oncol Educ Book 2024;44 (3):e432524. doi: 10.1200/EDBK_432524

S7 – HOW TO OPTIMIZE MULTIDISCIPLINARY TREATMENT OF OLIGOMETASTATIC COLORECTAL CANCER?

MAJANA SOČE[1,2]

[1]*Department for Oncology, University Hospital Centre Zagreb, Zagreb, Croatia*
[2]*University of Applied Health Sciences, Zagreb, Croatia*

Optimization of the multidisciplinary approach in the management of oligometastatic colorectal cancer (CRC) is based on timely, coordinated, and personalized care, with the aim of achieving long-term survival and potential cure. Oligometastatic disease, most commonly confined to the liver or lungs, represents an intermediate stage between localized and disseminated disease and therefore requires a truly individualized treatment strategy.

A central role is played by the multidisciplinary team (MDT), which includes a surgeon, an oncologist, a radiologist, a pathologist, and an interventional radiologist. Optimization includes: (1) precise diagnostics and restaging using advanced imaging modalities; (2) patient stratification according to resectability and biological risk; (3) rational use of perioperative or conversion systemic therapy; (4) timely surgical management or application of ablative techniques (RFA, MWA, SBRT); and (5) continuous follow-up and reassessment of therapeutic response.

Surgery remains the gold standard for metastasectomy in colorectal cancer (CRC), as it provides the most favorable 5-year overall survival (OS) rates (25–47% in cases of liver metastases). According to available data, the rate of local recurrence (LRR) after stereotactic body radiotherapy (SBRT) was significantly higher than after surgical resection (~28.1% vs. 10.5%). Therefore, surgery may offer more durable long-term local control compared with SBRT; however, it is limited to operable patients and is associated with a higher complication rate compared with ablative treatment options.

Phase I/II studies indicate that SBRT for colorectal liver metastases is associated with favorable local control (LC) and an acceptable toxicity profile. Across various prospective series, 1-year LC rates ranged from approximately 50% to as high as 95%, while median overall survival varied between 16 and 45 months, depending on patient selection and radiation dose. A meta-analysis of 18 studies (656 patients)

reported 1-year overall survival (OS) rates of approximately 67% and solid local control, confirming the efficacy of SBRT in the oligometastatic setting.

Radiofrequency ablation (RFA) and microwave ablation (MWA) are often used for smaller metastases (<3 cm) when surgery is not feasible. In a prospective analysis from the AmCORE registry, SBRT was associated with OS, disease progression outcomes, and local control compared with thermal ablation techniques (RFA/MWA). However, these differences may be partially attributable to significant confounding factors, including older age and more advanced disease in the SBRT-treated cohort. In a retrospective comparison of SBRT versus RFA for intrahepatic metastases, the 2-year local progression-free rate was higher with SBRT (~88%) than with RFA (~74%), particularly for tumors ≥2 cm, with no significant difference observed in OS. These findings suggest a potential advantage of SBRT for larger lesions, where RFA may be more susceptible to the heat-sink effect or limited ablation margins.

In conclusion, a multidisciplinary, personalized, and dynamic therapeutic approach is essential for optimizing outcomes in patients with oligometastatic CRC, with the potential to achieve long-term survival and even cure in carefully selected patients. Centralization of care in high-volume centers, implementation of standardized protocols, and patient enrollment in clinical trials further contribute to improved outcomes.

Keywords: colorectal cancer, ablative methods, SBRT, RFA, MWA

Assessment of resectability and overall patient condition

Technically resectable disease + good ECOG performance status (0–1) + adequate functional parenchyma	Surgical resection (gold standard)
Resectable disease but with high operative risk (comorbidities, advanced age)	SBRT or MWA
Unresectable due to parenchymal volume limitations or unfavorable tumor location	SBRT (particularly if located near major vessels or subdiaphragmatic)
Need for a parenchyma-sparing approach	Combination of surgical resection and ablation (RFA/MWA)

Metastasis size

≤ 2 cm	**RFA/MWA** or SBRT	Very high local control; RFA effective
2 – 3 cm	**MWA or SBRT**	SBRT has stable LC; RFA may be limited
> 3 cm	**SBRT or surgery**	Thermal ablation methods have reduced control due to the heat-sink effect

REFERENCES:

1. Thompson R, Cheung P, Chu W, Myrehaug S, Poon I, Sahgal A, et al. Outcomes of extra-cranial stereotactic body radiotherapy for metastatic colorectal cancer: Dose and site of metastases matter. Radiother Oncol. 2020;142:236-245. doi: 10.1016/j.radonc.2019.08.018.
2. Jan Rodríguez MR, Chen-Zhao X, Hernando O, Flamarique S, Fernández-Letón P, Campo M, et al. SBRT-SG-01: final results of a prospective multicenter study on stereotactic body radiotherapy for liver metastases. Clin Transl Oncol. 2024 Jul;26(7):1790-1797. doi: 10.1007/s12094-024-03403-w.
3. Petrelli F, Comito T, Barni S, Pancera G, Scorsetti M, Ghidini A; SBRT for CRC liver metastases. Stereotactic body radiotherapy for colorectal cancer liver metastases: A systematic review. Radiother Oncol. 2018 Dec;129(3):427-434. doi: 10.1016/j.radonc.2018.06.035.
4. Sheikh S, Chen H, Sahgal A, Poon I, Erler D, Badellino S, et al. An analysis of a large multi-institutional database reveals important associations between treatment parameters and clinical outcomes for stereotactic body radiotherapy (SBRT) of oligometastatic colorectal cancer. Radiother Oncol. 2022 Feb;167:187-194. doi: 10.1016/j.radonc.2021.12.018.
5. Torielli P, McGale J, Liao MJ, Rhaiem R, Bouche O, Botsen D, et al. Hepatic metastases management: A comparative review of surgical resection, thermal ablation, and stereotactic body radiation therapy. Eur J Cancer. 2025 Oct 1;228:115691. doi: 10.1016/j.ejca.2025.115691.

S8 – IMMUNOTHERAPY IN THE TREATMENT OF CERVICAL CANCER: A TURNING POINT IN OUTCOMES?

KRISTINA KATIĆ[1]

[1]*Clinical Department of Gynecology and Obstetrics, Depatment of Gynecologic Oncology, University Hospital Centre Zagreb, Zagreb, Croatia*

Cervical cancer (CC) is the fourth most common cancer and the third cause of cancer– related death among women. While early-stage cancers are often curable with surgery or chemoradiotherapy, the prognosis for locally advanced and metastatic disease remains poor. Many therapeutic options are being investigated for the treatment of patients with CC, and one of the most promising approaches is immunotherapy.

For more than twenty years, the standard treatment for locally advanced CC has been chemoradiotherapy followed by brachytherapy. However, many high-risk patients relapse and die from metastatic disease. Several trials have investigated the addition of immunotherapy to the standard chemoradiation protocol. The KEYNOTE-A18, phase III trial, showed that the addition of pembrolizumab to the standard chemoradiotherapy protocol, followed by pembrolizumab maintenance therapy improves progression-free survival (PFS) and demonstrated positive overall survival (OS) results in high-risk patients, establishing a new treatment standard for patinets with locally advanced CC. In the phase III CALLA trial, the addition of durvalumab to standard chemoradiotherapy did not achieve the primary endpoint of improving PFS in the general population of patients with locally advanced CC, but further exploratory analysis suggests a benefit of durvalumab in patients with high PD-L1 status. Another phase II trial, ATEZOLACC, which investigated the addition of atezolizumab to standard chemoradiotherapy, did not improve 2-year PFS in locally advanced CC. According to these results, several trials are exploring the use of immunotherapy in the neoadjuvant setting before surgery or chemoradiotherapy to shrink tumors, particularly in bulky cases.

Immunotherapy has also changed the treatment of metastatic and recurrent disease. For patients with persistent, recurrent or metastatic disease, the combination of pembrolizumab with chemotherapy and optionally bevacizumab is the preferred first-line regimen in patients with a PD-L1 combined positive score (CPS) ≥1. The KEYNOTE-862 phase III trial demonstrated that this combination significantly improved PFS and OS compared to chemotherapy. The longest median OS has been achieved in patients who received bevacizumab with pembrolizumab and chemotherapy. The phase III BEATcc trial also demonstrated that adding atezolizumab to chemotherapy and bevacizumab improved PFS and OS.

With the aim of further improving outcomes of CC patients, bispecific antibodies are also being explored. The phase III COMPASSION trial explored the efficacy of cadonilimab (a PD-1 and CTLA-4 bispecific antibody) in Chinese population. The trial demonstrated that the combination of cadonilimab with chemotherapy and optionally bevacizumab as a first-line treatment in patients with persistent, metastatic or recurrent disease improved PFS and OS compared to chemotherapy with or without bevacizumab, regardless of PD-L1 status.

Checkpoint inhibitors have also shown effectiveness in second-line metastatic patients. The phase III EMPOWER trial explored the efficacy of cemiplimab in patients with recurrent CC who had progressed after first-line platinum-based chemotherapy and demonstrated improvement in PFS and OS compared to physician's choice chemotherapy, regardless of PD-L1 status.

As a new class of drugs, antibody-drug conjugates, hold promise in treating CC patients, and combinations of immunotherapy and antibody-drug conjugates are also being explored. The phase IB/II Ino-

vaTV 205 trial has explored the efficacy and safety of tisotumab vedotin with pembrolizumab, chemotherapy and bevacizumab for recurrent and metastatic CC. The trial demonstrated that the combination of tisotumab vedotin with pembrolizumab is safe and has promising antitumor activity.

Immunotherapy has fundamentally changed the treatment of CC patient and has become a standard treatment for both locally advanced and metastatic disease. Despite the positive results of immunotherapy, certain doubts remain, such as how to overcome resistance to immunotherapy and how to identify appropriate predictive biomarkers to further improve outcomes.

Keywords: immunotherapy, cervical cancer, locally advanced disease, metastatic disease

REFERENCES:

1. International Agency for Research on Cancer, WHO; https://gco.iarc.fr/today/home Accessed February 15th, 2026
2. Duska LR, Xiang Y, Hasegawa K, et al. Pembrolizumab with concurrent chemoradiotherapy in participants with high-risk locally advanced cervical cancer: a descriptive analysis of final survival from the phase 3, randomized, double-blind ENGOT-cx11/GOG-3047/KEYNOTE-A18 study. J Clin Oncol. 2025;43(suppl 17):LBA5504. doi:10.1200/JCO.2025.43.17_suppl.LBA5504
3. Monk BJ, Toita T, Wu X, et al Durvalumab versus placebo with chemoradiotherapy for locally advanced cervical cancer (CALLA): a randomised, double-blind, phase 3 trial. Lancet Oncol. 2023 Dec;24(12):1334-1348.
4. Chargari C, Paurtier P, Chaltiel D, ž et al. Academic randomized phase II trial assessing inhibitor of programmed cell death ligand 1 (PD-L1)immune checkpoint atezolizumab in combination with chemoirradiation in locally adanced cervical cancer (ATEZOLACC trial), Int.J Gynecol Cancer 2025;35. doi: 10.1016/j.ijgc.2024.100070.
5. Lorusso D, Colombo N, Dubot C, et al Pembrolizumab plus chemotherapy for advanced and recurrent cervical cancer: final analysis according to bevacizumab use in the randomized KEYNOTE-826 study. Ann Oncol. 2025 Jan;36(1):65-75.
6. Oaknin A, Gladieff L, Martínez-García J, et al; ENGOT-Cx10–GEICO 68-C–JGOG1084–GOG-3030 Investigators. Atezolizumab plus bevacizumab and chemotherapy for metastatic, persistent, or recurrent cervical cancer (BEATcc): a randomised, open-label, phase 3 trial. Lancet. 2024 Jan 6;403(10421):31-43.
7. Wu X, Sun Y, Yang H, et al. Cadonilimab plus platinum-based chemotherapy with or without bevacizumab as first-line treatment for persistent, recurrent, or metastatic cervical cancer (COMPASSION-16): a randomised, double-blind, placebo-controlled phase 3 trial in China. Lancet. 2024 Oct 26;404(10463):1668-1676.
8. Tewari KS, Monk BJ, Vergote I, et al.; Investigators for GOG Protocol 3016 and ENGOT Protocol En-Cx9. Survival with cemiplimab in recurrent cervical cancer. N Engl J Med. 2022 Feb 10;386(6):544-555.
9. Vergote I, Van Nieuwenhuysen E, O'Cearbhaill RE et al. Tisotumab vedotin in combination with carboplatin, pembrolizumab, or bevacizumab in recurrent or metastatic cervical cancer: results from the innovaTV 205/GOG-3024/ENGOT-cx8 study. J Clin Oncol. 2023 Dec 20;41(36):5536-5549.

S9 – PERSONALIZING FIRST-LINE TREATMENT FOR METASTATIC UROTHELIAL CARCINOMA

MARIJANA JAZVIĆ[1], Marijana Udovičić[1], Jure Murgić[1,2], Ana Fröbe[1,3]

[1]*Department of Oncology and Nuclear Medicine, Sestre milosrdnice University Hospital Center, Zagreb, Croatia*
[2]*School of Medicine, Croatian Catholic University, Zagreb, Croatia*
[3]*School of Dental Medicine, University of Zagreb, Zagreb, Croatia*

Bladder cancer is the ninth most common malignancy worldwide, with urothelial carcinoma (UC) accounting for approximately 90% of cases. UC is strongly associated with advanced age – the median age at diagnosis is 73 years – and with comorbidities that create additional challenges for systemic treatment, including reduced fitness and a greater risk of treatment-related toxicity. Cisplatin-based chemotherapy was the cornerstone of first-line treatment for nearly four decades, yet median overall survival (OS) remained limited to 14 – 15 months. Moreover, real-world data suggest that approximately 40% of patients with advanced UC do not receive any systemic treatment, often due to perceived ineligibility or frailty. The emergence of immune checkpoint inhibitors (ICIs) and antibody-drug conjugates (ADCs) has fundamentally reshaped the treatment landscape. With the success of the EV-302 study, the combination of enfortumab vedotin (EV) with pembrolizumab has supplanted platinum-based chemotherapy as the new first-line standard of care. Other recommended first-line options include platinum-based chemotherapy followed by avelumab switch-maintenance in patients without progression, and nivolumab plus cisplatin-gemcitabine followed by nivolumab monotherapy for cisplatin-eligible patients. The availability of multiple effective regimens creates, for the first time, the potential for individualized treatment selection.

The phase III EV-302/KEYNOTE-A39 trial established the combination of enfortumab vedotin plus pembrolizumab (EV+P) as the new standard of care for previously untreated locally advanced or metastatic UC (mUC). Updated data with 29.1 months median follow-up demonstrated a median OS of 33.8 months versus 15.9 months for chemotherapy (HR 0.51; 95% CI 0.43–0.61), with an overall response rate of 67.5% versus 44.2% and a 24-month OS rate of 60% versus 35%. Importantly, these benefits were observed irrespective of cisplatin eligibility or PD-L1 expression status. For cisplatin-eligible patients who cannot receive EV+P, the CheckMate 901 trial demonstrated the efficacy of nivolumab plus gemcitabine-cisplatin, with a median OS of 21.7 versus 18.9 months (HR 0.78). Platinum-based chemotherapy followed by maintenance avelumab remains a further viable option for patients who do not progress on first-line platinum doublets.

An extensive range of first-line systemic treatment options are now available for patients with mUC, creating a favorable dilemma for patients and physicians alike. While EV+P is the current standard of care, alternatives may be more appropriate for individual patients depending on their clinical profile, comorbidities, and treatment priorities.

The identification of predictive biomarkers is emerging as a critical component of treatment personalization, although all currently recommended first-line regimens are approved irrespective of biomarker status. PD-L1 expression does not predict treatment benefit with EV+P, avelumab maintenance, or nivolumab plus cisplatin-gemcitabine in phase 3 trial analyses; nonetheless, PD-L1 status remains required for access to avelumab maintenance in selected countries and for first-line ICI monotherapy in cisplatin-ineligible patients. Nectin-4, the target of enfortumab vedotin, is expressed at moderate-to-high levels in the majority of UCs, but expression may decrease during metastatic progression. Exploratory analyses from EV302 demonstrated that EV+P improved OS over chemotherapy across low, intermediate, and high

Nectin4 expression subgroups, with improved absolute outcomes with higher Nectin-4 expression. Additionally, low membranous Nectin4 expression and absence of NECTIN4 amplification correlated with reduced response rates and shorter OS with laterline EV monotherapy. For treatment sequencing, FGFR3 alteration status – assessed by molecular testing – is required to determine eligibility for erdafitinib, a recommended second-line option after first-line progression. Additionally, HER2 expression assessment may identify patients eligible for trastuzumab deruxtecan in later lines of therapy.

The distinct safety profiles of available regimens are a key consideration: EV+P is associated with skin reactions (67%, grade ≥3 in 15%), cumulative peripheral neuropathy (63%, grade ≥3 in 7%), hyperglycemia, and pneumonitis, whereas platinum-based chemotherapy predominantly causes myelosuppression, and avelumab maintenance has a favorable tolerability profile with low rates of grade ≥3 adverse events (19%). EV-ineligible criteria (EVITA) have been proposed for patients who may not be optimal candidates for EV+P – including those with uncontrolled diabetes, pre-existing grade ≥2 neuropathy, corneal/retinal abnormalities – though these criteria are not yet included in treatment guidelines. Importantly, studies have shown that many patients prioritize treatment experience, including avoidance of adverse events and preservation of quality of life, over maximizing OS alone, underscoring the importance of shared decision-making. The transition from platinum-based chemotherapy to platinum-free therapy is not an all-or-nothing choice but rather the result of precise patient stratification, balancing group-level evidence with individual differences. Future first-line therapy should be centered on tailored treatment, integrating biomarker-driven selection, patient-centered safety considerations, and informed shared decision-making to optimize outcomes for each individual patient.

Keywords: enfortumab vedotin; pembrolizumab; avelumab; cisplatin-eligible; biomarkers; personalized treatment

REFERENCES:

1. Grande E, Hussain SA, Barthelemy P, et al. Individualizing first-line treatment for advanced urothelial carcinoma: A favorable dilemma for patients and physicians. Cancer Treat Rev. 2025;134:102900. doi:10.1016/j.ctrv.2025.102900
2. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer. J Clin Oncol. 2000;18(17):3068-3077.
3. Powles T, Valderrama BP, Gupta S, et al. Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. N Engl J Med. 2024;390(10):875-888. doi:10.1056/NEJMoa2312117
4. Liu Z, Chen C, Yin J, Cong X, Liu Z. Changing landscape of first-line treatment for locally advanced or metastatic urothelial carcinoma: the progression from platinum-based chemotherapy to platinum-free therapy. Front Immunol. 2025;16:1604395. doi:10.3389/fimmu.2025.1604395
5. Powles T, Park SH, Caserta C, et al. Avelumab first-line maintenance for advanced urothelial carcinoma: results from the JAVELIN Bladder 100 trial after ≥2 years of follow-up. J Clin Oncol. 2023;41(20):3486-3492.
6. van der Heijden MS, Sonpavde G, Powles T, et al. Nivolumab plus gemcitabine-cisplatin in advanced urothelial carcinoma. N Engl J Med. 2023;389(19):1778-1789. doi:10.1056/NEJMoa2309863
7. Grande E, Birtle AJ, Kamat AM. Re: Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. Eur Urol. 2024;86(5):e152-e153.
8. Grivas P, Veeranki P, Chiu K, et al. Preferences for first-line treatment of advanced urothelial carcinoma among US practicing oncologists and patients. Future Oncol. 2023;19(36):369-383.

S10 – PRECISION ONCOLOGY IN THE TREATMENT OF ENDOMETRIAL CANCER

MARIJANA MILOVIĆ-KOVAČEVIĆ[1]

[1]*Department of Medical Oncology, Institute of Oncology and Radiology Serbia, Belgrade, Serbia*

The traditional dualistic histopathological classification proposed by Bokhman categorised endometrial carcinoma (EC) into two distinct groups: type I and type II. Endometrioid carcinoma was classified as type I, whereas all non-endometrioid histological subtypes were grouped under type II disease(1).

In recent years, it has become increasingly evident that the traditional histopathological classification demonstrates limited reproducibility and fails to adequately capture the underlying molecular heterogeneity of endometrial cancer. This biological diversity within morphologically defined subgroups has impeded therapeutic stratification and slowed the effective implementation of precision medicine approaches(2).

The molecular classification of endometrial carcinoma (EC) proposed by The Cancer Genome Atlas (TCGA) addresses these limitations by integrating somatic mutational burden and patterns of somatic copy number alterations. This framework stratifies EC into four distinct molecular subgroups:

(1) POLE-ultramutated tumors, characterized by an exceptionally high mutational burden (>100 mutations per megabase) driven by pathogenic variants in the exonuclease domain of DNA polymerase epsilon (POLE);

(2) Microsatellite instability–hypermutated (MSI-H) tumors, exhibiting an intermediate mutational burden (10–100 mutations per megabase) associated with defective mismatch repair;

(3) Copy number–high (serous-like) tumors, defined by extensive somatic copy number alterations and frequent TP53 mutations; and

(4) Copy number–low (endometrioid) tumors, which display low mutational burden and are commonly associated with alterations in the PI3K/AKT pathway and WNT signaling(3).

This pragmatic surrogate approach is based on a limited panel of well-validated immunohistochemical (IHC) markers–MSH6, PMS2, and p53–combined with targeted tumor sequencing for POLE hotspot mutations. Importantly, by incorporating reflex assessment of mismatch repair (MMR) protein expression, this algorithm simultaneously facilitates screening for Lynch syndrome.

Approximately 30% of primary endometrial carcinomas (ECs) exhibit microsatellite instability–high or mismatch repair–deficient (MSI-H/dMMR) status, reflecting underlying immune dysregulation and enhanced tumor immunogenicity. This biological rationale has supported the investigation of immune checkpoint blockade (ICB), administered both as monotherapy and in combination with cytotoxic chemotherapy, other immunotherapeutic strategies, or targeted agents. A major therapeutic milestone was the accelerated approval by the U.S. Food and Drug Administration (FDA) of pembrolizumab, an anti–programmed cell death protein 1 (PD-1) antibody, for the treatment of advanced MSI-H/dMMR solid tumors. Notably, this represented the first tumour-agnostic regulatory approval, in which treatment selection was driven by a shared molecular biomarker rather than by the tumor's tissue of origin(4).

Cyclin-dependent kinases (CDKs) are a family of serine–threonine kinases that play a central role in regulating cell-cycle progression. Palbociclib, a selective CDK4/6 inhibitor, has demonstrated the ability in both preclinical and clinical studies to overcome endocrine resistance and synergistically suppress the

proliferation of estrogen receptor (ER)–positive breast cancer cells when combined with anti-estrogen therapy. Consequently, the combination of palbociclib and letrozole has been approved for the treatment of hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer.

In endometrial cancer, interim results from the phase II ENGOT-EN3 PALEO trial evaluating ER-positive, previously treated endometrioid endometrial carcinoma showed that the addition of palbociclib to letrozole significantly improved progression-free survival (PFS) compared with letrozole plus placebo (median PFS 8.3 vs 3.0 months; hazard ratio 0.56, 95% confidence interval 0.32–0.98; P = 0.041) (5).

The HER2 (ERBB2) gene is amplified in 17%-33% of uterine carcinosarcomas and serous carcinomas. A small randomised phase II trial of carboplatinepaclitaxel with or without trastuzumab in HER2/neu-positive serous EC showed an increase in both PFS and OS for those receiving trastuzumab(6).

Keywords: actionable mutations, endometrial cancer, genomic profiling, precision oncology,

REFERENCE:

1. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983;15(1):10-17.
2. de Boer SM, Wortman BG, Bosse T, et al. Clinical consequences of upfront pathology review in the randomised PORTEC-3 trial for highrisk endometrial cancer. Ann Oncol. 2018;29(2):424-430.
3. Leon-Castillo A, de Boer SM, Powell ME, et al. Molecular classification of the PORTEC-3 trial for high-risk endometrial cancer: impact on prognosis and benefit from adjuvant therapy. J Clin Oncol. 2020;38(29):3388-3397.
4. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol. 2020;21(10):1353-1365.
5. Mirza MR, Bjørge L, Marmé F, et al. LBA28 A randomised doubleblind placebo-controlled phase II trial of palbociclib combined with letrozole (L) in patients (pts) with oestrogen receptor-positive (ERþ) advanced/recurrent endometrial cancer (EC): NSGO-PALEO/ENGOTEN3 trial. Ann Oncol. 2020;31:S1160.
6. Fader AN, Roque DM, Siegel E, et al. Randomized phase II trial of carboplatin-paclitaxel versus carboplatin-paclitaxel-trastuzumab in uterine serous carcinomas that overexpress human epidermal growth factor receptor 2/neu. J Clin Oncol. 2018;36(20):20442051.

S11 – RADIOTHERAPY IN BREAST CANCER IN PATIENTS INITIALLY TREATED WITH NEOADJUVANT SYSTEMIC THERAPY

JASENKA GUGIĆ[1]

[1]*Department of Radiotherapy, Institute of Oncology, Ljubljana, Slovenia*

Traditionally, most women diagnosed with breast cancer were treated with upfront surgery as the primary therapeutic approach. Neoadjuvant chemotherapy (NAC) was initially introduced to reduce the disease burden in the breast and axillary lymph nodes and to make previously inoperable or locally advanced cases suitable for surgery, preferably breast conserving surgery (BCS), if possible.

Systemic therapy was typically administered in the adjuvant setting. Clinical trials demonstrated no statistically significant difference in overall or disease-free survival outcomes between patients who received NAC and those treated with adjuvant chemotherapy(1,2). These findings established the safety of administering systemic therapy before surgery. Nowadays, NAC is increasingly used in cases of operable disease, especially in specific biological subtypes, such as triple negative and HER-2 positive tumors, to enable BCS, improve cosmetic outcomes by performing less radical surgery of the breast, prevent also extensive surgery of the axilla and provide in-vivo prognostic information based on tumor response.

Achieving a pathologic complete response (pCR) to NAC is associated with favorable disease-free and overall survival in early stage breast cancer(3,4). The correlation between pathologic response and survival outcomes is strongest for triple negative breast cancer, less for HER-2 positive tumors and weakest for hormone positive tumors. Moreover, pathologic response is becoming increasingly important data for tailoring adjuvant treatment, both locoregional and systemic.

Indications for adjuvant locoregional radiotherapy (RT) in breast cancer have traditionally been based on upfront surgery and the extent of disease at the time of surgery. Although well established for upfront surgery, the role of locoregional RT, especially the role of regional nodal irradiation (RNI) following NAC is not so clear. Disease burden at the time of surgery may no longer reflect the initial extent of disease, both in the primary breast tumor and in the regional lymph nodes. Newest data suggest that decision regarding the administration of locoregional RT in such circumstances should be individually tailored based on tumor biology, the extent of tumor before NAC and at the time of surgery(5).

Whole breast radiotherapy (WBRT) is always indicated after BCS(5). Postmastectomy radiation therapy (PMRT) is recommended after NAC for patients with initial clinical stage III disease, regardless of pathological response and for those with residual nodal disease at the time of surgery(5,6). PMRT is considered for cT1-3N1 or cT3N0 disease and for ypN0 after NAC. According to most guidelines and expert panels, patients with cN2-3 breast cancer should be administered RNI, regardless of their response to NAC(5,6). RNI is also recommended in a case of incomplete axillary nodal staging, for patients with cT4N0-3 and in nearly all cases with residual nodal disease. Patients who are initially presented with cT1-2N0 disease and have a good response to NAC, probably will not benefit from locoregional RT. RNI is rarely administered in this group, unless in cases of high-risk disease.

The main area of clinical uncertainty has been the role of RNI in patients who initially present with cN1 and achieve pathological node negative status after NAC. Retrospective studies have suggested, that RNI can be safely omitted in these cases, without compromising locoregional control(1,7).

This question was specifically addressed in multicentric randomized phase III trial NSABP B-51/RTOG 1304(8). At 5-year follow up, the invasive breast cancer recurrence-free interval (iBCRFI) was com-

parable in both arms, 92.7 % in the RNI group and 91.8 % in the no RNI group (hazard ratio 0.88, p = 0.51). There were no statistically significant differences in secondary outcomes, including locoregional and distant recurrence-free interval, disease-free and overall survival. Locoregional recurrence was rare in both arms (0.8% with RNI and 1.4% without RNI). The study findings suggest the potential for de-escalation of locoregional therapy after NAC; however, these results should be interpreted carefully in a multidisciplinary setting for each specific case, considering individual patient and disease characteristics, such as age or menopausal status, disease burden at presentation, residual disease in the breast, disease subtype and the adjuvant systemic treatment plan.

The issue of de-escalation of radiotherapy was also addressed in RAPCHEM; BOOG 2010-03 – a Dutch prospective multicenter registry study(9). This study evaluated the safety of de-escalated locoregional radiotherapy in patients with cT1-2N1 breast cancer treated with NAC, stratified into predefined risk groups, according to pathologic status at the time of surgery. At 5-year follow up, the overall recurrence rate was 2.2 %, well below the predefined threshold of 4 %.

The landscape of radiotherapy in the era of effective neoadjuvant chemotherapy has fundamentally shifted from the conventional approach towards personalised, response-guided strategies. Generally, the trend is to minimize overtreatment by tailoring radiotherapy based on clinical, pathological, and molecular features, aiming to maintain oncological safety while reducing treatment burden and toxicity.

Keywords: breast cancer; neoadjuvant chemotherapy; locoregional radiotherapy; regional lymph node irradiation; treatment de-escalation.

REFERENCES:

1. Mamounas EP, Anderson SJ, Dignam JJ, Bear HD, Julian TB, Geyer CE Jr, et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. J Clin Oncol. 2012;30(32):3960–3966.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: Meta-analysis of individual patient data from ten randomised trials. Lancet Oncol. 2018;19:27–39.
3. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014;384(9938):164-72.
4. von Minckwitz G, Untch M, Blohmer JU, Costa SD, Eidtmann H, Fasching PA, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol. 2012;30(15):1796-80.
5. National Comprehensive Cancer Network. (2026). NCCN Clinical Practice Guidelines in Oncology: Breast cancer (Version 2.2026). Available on: https://www.nccn.org/guidelines/guidelines-detail?id=1419
6. Rachel BJ, Yara A, Penny A, Parul B, Lisa B, Julie AB, et al. Postmastectomy Radiation Therapy: An ASTRO-ASCO-SSO Clinical Practice Guideline. Journal of Clinical Oncology. 2025;43:30:3292-3311.
7. Shim SJ, Park W, Huh SJ, Choi DH, Shin KH, Lee NK, et al. The role of postmastectomy radiation therapy after neoadjuvant chemotherapy in clinical stage II-III breast cancer patients with pN0: a multicenter, retrospective study (KROG 12–05). Int J Radiat Oncol Biol Phys. 2014;88(1):65–72.
8. Mamounas EP, Bandos H, White JR, Julian TB, Khan AJ, Shaitelman SF, et al. Omitting regional nodal irradiation after response to neoadjuvant chemotherapy. N Engl J Med. 2025;392(21):2113-2124.
9. de Wild SR, de Munck L, Simons JM, Verloop J, van Dalen T, Elkhuizen PHM, et al. De-escalation of radiotherapy after primary chemotherapy in cT1-2N1 breast cancer (RAPCHEM; BOOG 2010-03): 5-year follow-up results of a Dutch, prospective, registry study. Lancet Oncol. 2022;23(9):1201-1210.

S12 – THERAPEUTIC CHALLENGES AND RARE COMPLICATIONS OF IMMUNOTHERAPY IN METASTATIC RENAL CELL CARCINOMA – CASE REPORTS

LANA JAJAC BRUČIĆ[1]

[1]*Department of Hematology, Oncology, Allergology and Clinical Immunology General Hospital of Šibenik-Knin County, Šibenik, Croatia*

Introduction: Renal cell carcinoma accounts for approximately 2–3% of all malignancies, and metastatic disease is present in about 20–30% of patients at the time of diagnosis. Over the past decade, significant progress has been made in the treatment of metastatic renal cell carcinoma with the introduction of immunotherapy. Immune checkpoint inhibitors, particularly PD-1/PD-L1 and CTLA-4 inhibitors, have demonstrated a significant improvement in overall survival compared with previously standard targeted therapy. Today, combinations of immunotherapy with tyrosine kinase inhibitors or dual immunotherapy have become the standard first-line treatment for most patients with advanced disease. Despite substantial therapeutic advances, the clinical course and treatment response remain highly variable, and therapy may be associated with serious adverse events requiring prompt recognition and a multidisciplinary approach. One such complication is the so-called 3M syndrome, a serious immune-related adverse event associated with immune checkpoint inhibitors. It is characterized by the simultaneous occurrence of myocarditis, myositis, and myasthenia gravis. This complication is very rare, occurring in less than 1% of patients treated with immunotherapy, but it is clinically significant due to its high mortality, particularly when myocarditis is present. It most commonly develops within the first few weeks after initiation of immunotherapy.

Case 1: A female patient born in 1942 had previously undergone left nephrectomy for clear cell renal cell carcinoma (pT1N0). During follow-up imaging in February 2020, a new lesion was detected in the right kidney along with multiple pulmonary lesions suspicious for metastatic disease. In March 2022, treatment with sunitinib was initiated, resulting in a good initial response with regression of pulmonary metastases. During therapy, adverse events including pancytopenia and cutaneous toxicity developed, requiring dose reduction. Due to worsening renal function and the development of moderate proteinuria, treatment was temporarily interrupted. In September 2022, disease progression in the lungs was documented. Considering the progression (despite the treatment break) and the significant toxicity of sunitinib, second-line treatment with nivolumab was initiated. The therapy was well tolerated, and follow-up imaging demonstrated stable disease until February 2024, when oligoprogression with a metastasis in the right clavicle was detected. Palliative radiotherapy with conventional fractionation was administered while continuing systemic therapy for a total duration of two years. In February 2026, progression of the bone metastasis in the right clavicle was observed, while disease control at other sites was maintained. The patient remains in good general condition, with preserved quality of life six years after the diagnosis of metastatic disease. The question of further treatment remains open, including the possibility of radiosurgery, repeat conventional radiotherapy, or reintroduction of systemic therapy.

Case 2: A male patient born in 1949 initially presented in December 2022 with macroscopic hematuria. Radiological evaluation revealed an irregular tumor mass measuring 6 × 3 cm in the medial part of the left kidney with suspected capsular invasion but without evidence of metastatic spread. In February 2023, a left nephrectomy was performed, and histopathology confirmed clear cell renal cell carcinoma measuring 5.5 × 5 cm with invasion into the surrounding adipose tissue and high nuclear grade (grade 3). Follow-

up imaging in April 2023 demonstrated multiple bilateral pulmonary metastases. Treatment with dual immunotherapy was indicated, and in June 2023 therapy with ipilimumab and nivolumab was initiated. After the first cycle, the patient developed general weakness, diplopia, and lower limb weakness. Laboratory findings showed markedly elevated levels of high-sensitivity troponin (up to 7000), creatine kinase (up to 4700), and liver enzymes (AST up to 280, ALT up to 420). The initial ECG demonstrated sinus rhythm with right bundle branch block, which subsequently progressed to left bundle branch block and then to a "stable" complete atrioventricular block with a ventricular rate of 32–48 beats per minute. NT-proBNP levels also increased (200–1100). Due to suspected immune-related cardiotoxicity with myocarditis progressing to complete AV block, high-dose corticosteroids were initiated and the patient was transferred to University Hospital Split, where a pacemaker was implanted. Upon return, the patient complained of dyspnea and, due to global respiratory failure, was admitted to the intensive care unit and subsequently intubated. Treatment was managed by a multidisciplinary team including an anesthesiologist, cardiologist, oncologist, neurologist, and nephrologist. The patient received pulse-dose corticosteroids (500 mg intravenous methylprednisolone daily) for three days without clinical improvement. Neurological evaluation raised suspicion of an immunotherapy-induced myasthenic crisis, and treatment with plasmapheresis was recommended; an acetylcholinesterase inhibitor was also initiated. The clinical course was further complicated by pneumonia. Due to the lack of improvement, intravenous immunoglobulin therapy was initiated, again without clinical benefit. Subsequent treatment with rituximab was indicated; however, after three administrations, no improvement was observed and the patient unfortunately died.

Conclusion: The presented cases illustrate the heterogeneity of the clinical course in metastatic renal cell carcinoma. The use of modern metastasis-directed treatment techniques, such as stereotactic radiosurgery, is increasingly finding a place in everyday clinical practice. Systemic therapies such as immunotherapy may enable long-term disease control, but can also cause severe adverse events that require prompt recognition and aggressive immunosuppressive treatment.

Keywords: renal cell carcinoma, imunotherapy, 3M overlap syndrome, metastases-directed therapy

REFERENCES:

1. Tannir NM, Albigès L, McDermott DF, Burotto M, Choueiri TK, Hammers HJ, et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 8-year follow-up results of efficacy and safety from the phase III CheckMate 214 trial. Ann Oncol. 2024;35(11):1026-1038. doi:10.1016/j.annonc.2024.07.727.
2. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2019;380(12):1116-1127. doi:10.1056/NEJMoa1816714.
3. Lipe DN, Qdaisat A, Krishnamani PP, Nguyen TD, Chaftari P, El Messiri N, et al. Myocarditis, myositis, and myasthenia gravis overlap syndrome associated with immune checkpoint inhibitors: a systematic review. Diagnostics. 2024;14(16):1794. doi: 10.3390/diagnostics14161794
4. Rose TL, Kim WY. Renal cell carcinoma: a review. JAMA. 2024;332(12):1001–1010. doi:10.1001/jama.2024.12848
5. Powles T, Albiges L, Bex A, Grünwald V, Porta C, Procopio G, et al. ESMO Clinical Practice Guideline update on the use of immunotherapy in early-stage and advanced renal cell carcinoma. Ann Oncol. 2021;32(12):1511-1519. doi:10.1016/j.annonc.2021.09.014.

S13 – THE ERA OF PRECISION ONCOLOGY IN THE TREATMENT OF BILIARY TRACT TUMORS

JOSIPA FLAM[1,2], Andreja Bartulić[1,2], Luka Perić[1,2], Vedrana Pavlović[1], Laura Zahirović[1], Dino Belić[1,2], Ilijan Tomaš[1,2]

[1]*Department of Radiotherapy and Oncology, University Hospital Center Osijek,*
[2]*Department for Oncology, Faculty of Medicine, University of J.J.Strossmayer Osijek, Osijek, Croatia*

Tumors of the biliary tract represent a heterogeneous group of malignant diseases that include intrahepatic and extrahepatic cholangiocarcinoma as well as gallbladder carcinoma. These tumors have an extremely poor prognosis and limited therapeutic options in the advanced stage. The traditional standard of care for unresectable or metastatic disease has long been systemic chemotherapy based on gemcitabine and cisplatin; however, patient survival has remained modest. In recent years, the addition of durvalumab to the treatment of metastatic or advanced disease has improved survival in these patients, but there is still a need for better treatment options, particularly in the second line after progression on chemoimmunotherapy. The development of molecular diagnostics and the growing understanding of the genomic profile of these tumors have led to the emergence of the era of precision oncology, which enables an individualized treatment approach based on specific molecular alterations of the tumor.

Genomic analyses have shown that a significant proportion of biliary tract tumors contain potentially targetable molecular alterations. Particularly important are FGFR2 gene fusions, IDH1 mutations, alterations in BRAF, HER2 amplifications, and microsatellite instability (MSI-H) or high tumor mutational burden (TMB-high). These discoveries have enabled the development of targeted therapies that selectively inhibit key signaling pathways responsible for tumor growth and progression.

In patients with intrahepatic cholangiocarcinoma and FGFR2 fusions, FGFR inhibitors have demonstrated significant clinical activity, with prolonged progression-free survival compared with historical standards of treatment. Similarly, IDH1 inhibitors provide a new therapeutic option for patients with the corresponding mutations, while targeted therapies directed at HER2 or BRAF represent promising approaches in smaller, molecularly defined subgroups of patients. In addition, immunotherapy with checkpoint inhibitors has shown efficacy in patients with MSI-H or TMB-high tumors, further expanding the therapeutic arsenal.

The integration of molecular profiling into routine clinical practice is becoming a key component of the modern management of biliary tract cancers (BTC). Comprehensive genomic testing is increasingly recommended already at the diagnosis of advanced disease in order to identify targetable mutations in a timely manner and enable access to personalized therapies or clinical trials. A multidisciplinary approach, including oncologists, pathologists, molecular biologists, and hepatobiliary surgeons, is essential for the optimal management of these diseases.

In conclusion, precision oncology is significantly changing the therapeutic approach to biliary tract tumors. Although the proportion of patients with targetable molecular alterations is still relatively limited, continuous advances in genomic profiling, the development of new targeted agents, and combination therapies offer a realistic possibility of improving treatment outcomes in this prognostically unfavorable group of malignant diseases.

REFERENCES

1. Farha N, Dima D, Ullah F, Kamath S. Precision oncology targets in biliary tract cancer. Cancers (Basel). 2023;15(7):2105.
2. Tomczak A, et al. Precision oncology for intrahepatic cholangiocarcinoma in clinical practice. Br J Cancer. 2022;127:1289–1298.
3. Abou-Alfa GK, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a phase III randomized trial. Lancet Oncology. 2020 Jun;21(6):796-807. doi: 10.1016/S1470-2045(20)30157-1.
4. Saboor F, et al. Recent advances in molecular classification and multimodal treatment of intrahepatic cholangiocarcinoma. World Journal of Surgical Oncology. 2026;24:art.76. doi: 10.1186/s12957-025-04188-0

S14 – TREATMENT APPROACHES FOR STAGE III PATIENTS IN THE IMMUNOTHERAPY ERA

MARIJO BOBAN[1,2]

[1]*Department of Oncology, University Hospital of Split, Split, Croatia*
[2]*School of Medicine,University of Split, Split, Croatia*

Immunotherapy, primarily utilizing immune checkpoint inhibitors (ICIs), has revolutionized stage III non-small cell lung cancer (NSCLC) treatment by improving outcomes in both unresectable and resectable disease settings.

The standard of care for patients with a good performance status (ECOG 0-1) with unresectable NSCLC was establish in the PACIFIC trial in which patients, without disease progression following concurrent chemoradiotherapy (CRT), were randomized to receive one year of durvalumab or placebo(1). Consolidation therapy with durvalumab significantly extended the progressionfree survival (PFS) (median 16.9 vs. 5.6 months, HR 0.55, 95% CI 0.45 to 0.68) and the overall survival (OS) (median 47.5 vs 29.1 months, HR 0.72, 95% CI 0.59 to 0.89), increasing the 5year survival rate by 10% (42.9% vs. 33.4%). Patients without disease progression following sequential CRT should also receive consolidation immunotherapy with durvalumab. Post hoc exploratory analysis in the PACIFIC trial did not demonstrate benefit in patients with PD-L1 expression <1% so this therapy is only approved for those with PD-L1 positive tumors.

The optimal integration of ICIs with definitive CRT for unresectable stage III NSCLC remains an area of active investigation. Phase III clinical trials utilizing ICIs concurrently with definitive CRT resulted in increased toxicity without improving efficacy compared to the PACIFIC regimen(2). It is worth noting the encouraging results of the multicenter retrospective analysis comparing the outcomes between neoadjuvant ICI-chemotherapy (ChT) followed by definitive CRT (NEO) and CRT followed by adjuvant immunotherapy (ADJ, the PACIFIC regimen). The treatment sequence in NEO group was associated with significantly improved PFS and OS compared to the standard adjuvant immunotherapy approach, without a definitive increase in the incidence of severe pneumonitis(3).

Patients with a good performance status (ECOG 0-1) who, due to comorbidities and/or tumor characteristics, are ineligible for CRT, but have PD-L1 positive tumor without EGFR, ALK and ROS1 alterations, should receive cemiplimab either as monotherapy (PD-L1 >=50%) or in combination with chemotherapy(4).

All patients with a good performance status with resectable stage II or III tumors, without EGFR and ALK alterations and without contraindications for ICI administration, should receive such therapy. The addition of ICIs to ChT, whether in the neoadjuvant, perioperative, or adjuvant setting, significantly improves treatment outcomes for these patients. Despite the fact that there are no randomized clinical trials

comparing the efficacy of different immunotherapy administration settings, indirect comparisons suggest greater efficacy of perioperative/neoadjuvant immunotherapy compared to the adjuvant approach. For instance, available therapeutic options with perioperative pembrolizumab (KEYNOTE-671, OS HR 0.74, 95% CI 0.59 to 0.92, 5y OS rate 64.6% vs. 53.6%) or neoadjuvant nivolumab (CheckMate 816, OS HR 0.72, 95% CI 0.523 to 0.998, 5y OS rate 65.4% vs. 55.0%) have demonstrated a significant improvement in overall survival, whereas this has not been achieved in any clinical trial involving adjuvant immunotherapy(5,6). In cases where individual patients do not receive perioperative or neoadjuvant immunotherapy, they should receive adjuvant therapy with pembrolizumab (if PD-L1 <50%) or atezolizumab (if PD-L1 ≥50%) (7,8). There are many open questions regarding the treatment of these patients as we lack clinical trials that would allow for reliable individualization (escalation/de-escalation) of therapy based on the results achieved with neoadjuvant treatment. For instance, should adjuvant immunotherapy be administered to a patient who has achieved a pathologic complete response (pCR) following neoadjuvant treatment and has negative circulating tumor DNA (ctDNA)? Alternatively, how should postoperative treatment be intensified for patients with an unsatisfactory response to neoadjuvant therapy (non-pCR, positive ctDNA)?

The lack of sufficiently precise criteria defining tumor resectability poses a significant challenge in daily clinical practice. Currently, there is no consensus on whether NSCLC with multi-station N2 disease or bulky N2 disease should be considered resectable. Therefore, whether these patients should be treated with concurrent CRT followed by durvalumab, or with neoadjuvant/perioperative ChT–ICI followed by surgery, remains a subject of ongoing controversy. The decision-making process is further complicated in institutions with limited resources for optimal and timely staging (EBUS, PET/CT).

The optimal treatment for patients with stage III small-cell lung cancer is based on the positive results of the ADRIATIC trial, in which consolidation immunotherapy with durvalumab following concurrent CRT led to a significant improvement in PFS (median 16.6 vs. 9.2 months, HR 0.76, 97.195% CI 0.59 to 0.98) and OS (median 55.9 vs. 33.4 months, HR 0.73, 98.321% CI 0.54 to 0.98)(9).

Keywords: non-small cell lung cancer, small cell lung cancer, immunotherapy, treatment strategy

REFERENCES:

1. Spigel DR, Faivre-Finn C, Gray JE, et al. Five-year survival outcomes from the PACIFIC trial: durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. J Clin Oncol. 2022;40(12):1301-1311.
2. Bradley JD, Sugawara S, Lee KH, et al. Simultaneous durvalumab and platinum-based chemoradiotherapy in unresectable stage III non-small cell lung cancer: The phase III PACIFIC-2 study. J Clin Oncol. 2025;43(33):3610-3621.
3. Li G, Liu C, Xi P, et al. Neoadjuvant immunotherapy plus chemotherapy in locally advanced stage III NSCLC patients undergoing definitive chemo-radiotherapy---a realworld multicenter retrospective study. Lung Cancer. 2026;211:108883. doi: 10.1016/j.lungcan.2025.108883.
4. Kalinka E, Bondarenko I, Gogishvili M, et al. First-line cemiplimab for locally advanced NSCLC: updated subgroup analyses from the EMPOWER-lung 1 and EMPOWER-lung 3 trials. JTO Clinical and Research Reports 2026. doi: 10.1016/j.jtocrr.2025.100947.
5. Wakelee H, Spicer JD, Gao S, et al. Perioperative pembrolizumab in early-stage non-small– cell lung cancer (NSCLC): 5-year follow-up from KEYNOTE-671. Annals of Oncology (2025) 36 (suppl_2): S1-S60. doi: 10.1016/annonc/annonc1965
6. Forde PM, Spicer JD, Provencio M, et al. Overall survival with neoadjuvant nivolumab plus chemotherapy in lung cancer. N Engl J Med. 2025;393(8):741-752.
7. O'Brien M, Paz-Ares L, Marreaud S, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. Lancet Oncol. 2022;23(10):1274-1286.
8. Felip E, Altorki N, Zhou C, et al. Five-year survival outcomes with atezolizumab after chemotherapy in resected stage IB-IIIA non-small cell lung cancer (IMpower010): An open-label, randomized, phase III trial. J Clin Oncol. 2025;43(21):2343-2349.
9. Cheng Y, Spigel DR, Cho BC, et al. Durvalumab after chemoradiotherapy in limited-stage small-cell lung cancer. N Engl J Med. 2024;391(14):1313-1327.