Medicom International Conference Series in Oncology

# ESMO Congress 2023

European Society of Medical Oncology

20–24 OCTOBER 2023 • MADRID • SPAIN

PEER-REVIEWED CONFERENCE REPORT

## Neoadjuvant LAG-3 inhibitor in MMRd colon cancer

The NICHE-3 trial's first cohort showed 100% pathological complete response rates after nivolumab/relatlimab neoadjuvant treatment of mismatch repair deficient (MMRd) colon cancer, a promising benefit for the next cohort.

read more on PAGE 5

## Perioperative nivolumab boosts event-free survival in NSCLC

Perioperative treatment with chemotherapy plus nivolumab outperformed preoperative chemotherapy alone in participants with resectable non-small cell lung cancer (NSCLC) in the CheckMate 77T trial.

read more on PAGE 8

## Two potential new first-line standards of care in metastatic urothelial cancer

Results from two trials, EV-302/KEYNOTE-A39 and CheckMate 901, demonstrated improved progression-free and overall survival in participants with locally advanced or metastatic urothelial cancer.

read more on PAGE 15

MEDICOM MEDICAL PUBLISHERS

Editor Dr Stefan Rauh, Centre Hospitalier Emile Mayrisch, Luxembourg

## COLOPHON


| | |
|---|---|
| **Editor** | Dr Stefan Rauh<br>Centre Hospitalier Emile Mayrisch, Luxembourg |
| **Reviewer** | Prof. Guy Jerusalem<br>CHU Liège, Belgium |
| **Reviewer** | Dr Joelle Collignon<br>CHU Liège, Belgium |
| **Reviewer** | Prof. Christine Gennigens<br>CHU Liège, Belgium |
| **Publishing Director** | Paul Willers |
| **Medical Science Officer** | Dr Rachel Giles |
| **Medical Project Manager** | Rune Bruls |
| **Editorial Operations Manager** | Dr Rosalie Molenaar |
| **Editorial Coordinators** | Dr Elke Marsch<br>Dr Joery Goossens |
| **Medical Writers** | Dr Marten Dooper |
| **Production Manager** | Anouk Neijenhoff |
| **Graphic Design** | MOOZ grafisch ontwerp |
| **Graphics** | Wim Kempink |
| **Printing** | GVO drukkers & vormgevers B.V. |
| **Cover Photo** | Shutterstock |
| **ISSN** | 2468-8762 23:23 |





MEDICOM
MEDICAL PUBLISHERS

**Head Office**
Medicom Medische Uitgeverij B.V.
Laarderhoogtweg 25
1101 EB Amsterdam
The Netherlands

**Postal address**
Medicom Medical Publishers
PO Box 90
3740 AB Baarn
The Netherlands

Telephone +31 85 4012 560
E-mail publishers@medicom-publishers.com


# Contents

# Letter from the Editor

**Dear colleagues,**

The 2023 ESMO Annual is to be remembered: This year has brought us a rarely precedented load of practice-changing studies including:
A feast for oncologists treating lung cancer with new data on the benefits of peri-operative immune chemotherapy in operable stages, as well as strategies in the adjuvant targeted treatments of oncogene-driven non-small cell lung cancer. News also accumulates in advanced lung cancer disease, from the treatment of niche indications (as *EGFR* exon 20 mutations) as well as antibody-drug-conjugates (ADC).
A dazzling number of ADCs are invading the scene, making it a challenge to remember substance names and correctly attribute them to their indications.
An ADC also represents a new standard in advanced urothelial bladder cancer – with a benefit translated by a hazard ratio rarely witnessed in urothelial cancers – leading to a long enthusiastic standing ovation to the presenter (Prof. T. Powles) by the thousands of attendees during a Presidential Session.
Also surprising, there is progress in areas which have been in hope for good news for a long time – such as systemic induction in locally advanced cervical cancer.

Both research (check out our digest) and educational sessions (which you can check out via OncologyPro on esmo.org) covered a plethora of topics and truly relevant themes. I would like to attract your particular attention to the session on the rechallenge of checkpoint inhibitors and oligometastatic disease.
Likely, not all relevant news will be presented in our report, we apologize, but we were tasked to make difficult choices to stick to our report's content size limits.
Last but not least, in the midst of a horrible year in political and climate change, this congress really brought some good news.

Please, enjoy the read!
Yours, sincerely
**Stefan Rauh**

**Biography**
Dr Stefan Rauh is currently working as a haematooncologist in the oncology department of the Centre Hospitalier Emile Mayrisch, Esch, Luxembourg. He is mainly involved in clinical work but also research and teaching activities and is interested in public policy and international cooperation projects in oncology. He has been a fellow of the European Society of Medical Oncology since 2022. Additionally, he has been a member of the ESMO Practicing Oncologist's Working Group since 2011 (chair 2014–2018) and the ESMO Public Policy Committee, and has been an ESMO Executive Board member in 2015– 2016. He is co-author of the 2017 ESMO European Cancer Patient Coalition (ECPC) Patient Survivorship Guide and an invited expert for the ECPC.

**Conflict of Interest Statement:**
Nothing to declare.

# Breast Cancer

## Benefit of pembrolizumab in TNBC remains after 5 years of follow-up

**The addition of pembrolizumab to both neoadjuvant and adjuvant chemotherapy improves event-free survival in patients with early triple-negative breast cancer (TNBC), as updated results of the KEYNOTE-522 trial showed.**

High-risk early-stage TNBC is associated with early recurrence and high mortality. Neoadjuvant chemotherapy is the preferred treatment approach. Previous results from KEYNOTE-522 (NCT03036488) showed statistically significant and clinically meaningful improvements in pathological complete response (pCR) and event-free survival (EFS) with the addition of pembrolizumab to neoadjuvant platinum-containing chemotherapy followed by adjuvant pembrolizumab in patients with early-stage TNBC [1,2]. Based on these results, the EMA and FDA have approved this treatment for high-risk early-stage TNBC.

Prof. Peter Schmid (Barts Cancer Institute, UK) presented updated results after a median follow-up of 5 years [3]. The phase 3 KEYNOTE-522 trial enrolled 1,174 participants with previously untreated TNBC (stages T1c N1–2 or T2–4 N0–2) who were randomised 2:1 to neoadjuvant pembrolizumab with chemotherapy or placebo with chemotherapy. After surgery, participants received adjuvant pembrolizumab or placebo for 6 months or until recurrence or unacceptable toxicity. Dual primary endpoints were pCR and EFS.

After 5 years of follow-up, EFS rates were 81.3% (95% CI 78.4–83.9) and 72.3% (95% CI 67.5–76.5) respectively for participants treated with pembrolizumab or placebo (HR 0.63; 95% CI 0.49–0.81). For comparison, EFS rates at 3-year follow-up were 84.5% and 76.8%, respectively (HR 0.63; 95% CI 0.48–0.82).

"The curves are starting to flatten out," said Prof. Schmid. The benefit of pembrolizumab was observed within all predefined subgroups, including stratification by PD-L1 expression or nodal status. Overall survival data are not yet mature and were not presented.

"These updated results of KEYNOTE-522 provide further support for neoadjuvant pembrolizumab plus platinum-containing chemotherapy followed by adjuvant pembrolizumab in early-stage TNBC patients," concluded Prof. Schmid.


1. Schmid P, et al. N Engl J Med. 2020;382:810–821.
2. Cortes J, et al. N Engl J Med. 2022;387:217–226.
3. Schmid P, et al. Pembrolizumab or placebo plus chemotherapy followed by pembrolizumab or placebo for early-stage TNBC: Updated EFS results from the phase III KEYNOTE-522 study. Abstract LBA18, ESMO 2023, 20–24 October, Madrid, Spain.


## Addition of pembrolizumab promising in early-stage high-risk ER+/HER2- breast cancer

**The addition of pembrolizumab to neoadjuvant chemotherapy in participants with early-stage, high-risk ER+/HER2- breast cancer leads to a statistically significant increase in pathological complete response (pCR) regardless of PD-L1 status, the first results of the KEYNOTE-756 trial showed.**

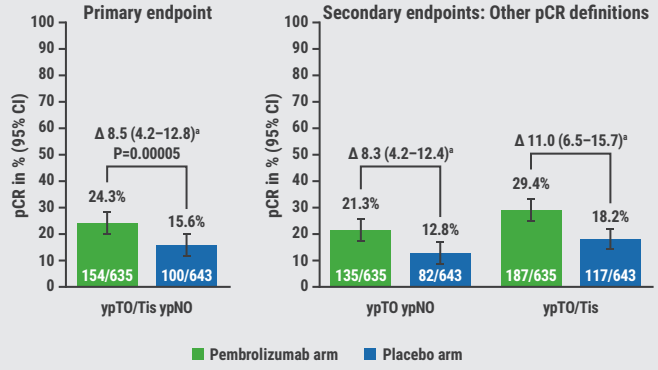
Although patients with early-stage ER+/HER2- breast cancer generally have a better prognosis than those with other breast cancer subtypes, there is a high-risk subpopulation that benefits from neoadjuvant chemotherapy. For this subpopulation, the pCR rates after neoadjuvant chemotherapy range from 0 to 18% [1]. In triple-negative breast cancer (TNBC), the addition of pembrolizumab to neoadjuvant chemotherapy and continued as adjuvant therapy increased pCR and improved event-free survival (EFS) [2]. The current phase 3 KEYNOTE-756 trial (NCT03725059) explores the efficacy and safety of adding pembrolizumab to neoadjuvant chemotherapy and subsequent adjuvant pembrolizumab in participants with early-stage high-risk ER+/HER2- breast cancer. The final pCR results were presented by Dr Fatima Cardoso (Champalimaud Clinical Centre, Portugal) [3].

In KEYNOTE-756, 1278 participants (grade 3 ER+/HER2, T1c-2 N1–2 or T3–4 N0–2) were randomised 1:1 to receiving neoadjuvant chemotherapy with pembrolizumab or placebo, followed by surgery and adjuvant pembrolizumab or placebo. The primary endpoints of the study are pCR and EFS. Results for EFS are not yet mature.

Progression (and discontinuation) during the neoadjuvant treatment was rare in both arms (2.2% in the pembrolizumab arm and 2.0% in the placebo arm). The addition of pembrolizumab to neoadjuvant chemotherapy significantly improved the pCR rate: 24.3% versus 15.6% in the placebo arm

(P=0.00005, see Figure). A pCR benefit from pembrolizumab was observed in all predefined subgroups, including PD-L1 status. In particular, in participants with ER-low (<10%) tumours, the benefit of pembrolizumab was increased compared with neoadjuvant chemotherapy alone. "This particular finding fits in with the idea that ER-low tumours behave more like TNBCs," said Dr Cardoso.

**Figure: Pathological complete response (pCR) achieved by neoadjuvant pembrolizumab or placebo plus chemotherapy followed by adjuvant pembrolizumab or placebo with endocrine therapy at the first interim analysis [3]**




[a] Estimated treatment differences based on the Miettinen & Nurminen method stratified by the analysis randomisation stratification factors. Data cutoff date: May 25, 2023.

IA1, interim analysis 1. pCR, pathological complete response. CI, confidence interval. Δ, difference.

Overall, the supplementation of pembrolizumab to neoadjuvant chemotherapy did not significantly increase adverse event rates (52.5% vs 46.4% grade 3–5 for pembrolizumab vs placebo arm). Immune-mediated adverse events were observed in 32.8% of pembrolizumab-treated participants (7.1% grade 3–5) with hypo- and hyperthyroidism being most prominent.

"The addition of pembrolizumab to neoadjuvant chemotherapy in participants with early-stage, high-risk ER+/HER2- breast cancer leads to a statistically significant increase in pCR regardless of PD-L1 status," concluded Dr Cardoso.


1. Torrisi R, et al. Crit Rev Oncol Hematol. 2021;160:103280.
2. Cortes J, et al. N Engl J Med. 2022;387:217–226.
3. Cardoso F, et al. KEYNOTE-756: Phase III study of neoadjuvant pembrolizumab (pembro) or placebo (pbo) + chemotherapy (chemo), followed by adjuvant pembro or pbo + endocrine therapy (ET) for early-stage high-risk ER+/HER2– breast cancer. Abstract LBA21, ESMO 2023, 20–24 October, Madrid, Spain.


## Long-term air pollution exposure at both residential and workplace locations increases breast cancer risk

**Greater risk for breast cancer is associated with long-term air pollution exposure at both residential and workplace location, results from the prospective French E3N cohort suggest.**

Air pollution, classified as carcinogenic to humans, is a major public health concern [1]. Apart from increasing the risk of lung cancer, chronic exposure to air pollution is also suggested to increase the risk of breast cancer [2,3]. The prospective French E3N cohort (ca 100,000 women) was initiated in 1990 to investigate the risk factors associated with cancer, including breast cancer, and other major non-communicable diseases in women [4].

Prof. Béatrice Fervers (Centre Léon Bérard, France) presented results from a case-control study, based on E3N data, of the association between breast cancer risk and long-term exposure to particulate matters ($PM_{2.5}$, $PM_{10}$) and nitrogen dioxide ($NO_2$), levels of which were estimated at the women's residential and workplace addresses [5].

Participants, aged 40–65 years at inclusion, were followed over the period 1990–2011. Exposure to air pollution was compared in 2419 women with histologically confirmed invasive breast cancer and 2984 individually matched controls. Annual mean $PM_{2.5}$, $PM_{10}$ and $NO_2$ concentration levels were estimated using a Land Use Regression (LUR) model (resolution 50m x 50m) and were assigned to women based on their geocoded residential and workplace addresses. The mean exposure was calculated for each woman from their inclusion into the E3N cohort to their index date (date of diagnosis of cases).

The results showed a statistically significant linear increase in breast cancer risk related to mean exposure to $PM_{2.5}$ (adjusted odds ratio [OR] 1.28; 95% CI 1.00–1.63) for an increment of 10 µg/m$^3$. A numerically, but not statistically significant, increased breast cancer risk was observed for $PM_{10}$ (adjusted OR 1.09; 95% CI 0.92–1.30) and $NO_2$ (adjusted OR 1.05; 95% CI 0.97–1.13) for an increment of 10 µg/m$^3$. No effect of HR status or menopausal status was observed.

"This study is the first to report breast cancer risk to be associated with long-term air pollution exposure at both residential and workplace location histories over 22 years," concluded Prof. Fervers. "Future studies should consider exposure during commuting, the relatively short part of the day that is associated with high exposure to air pollution."


1. Cancer Risk Factors Collaborators. Lancet 2022;400(10352):563–591.
2. Hvidtfeldt UA, et al. Environ Res. 2021;193:110568.
3. White AJ, et al. J Natl Cancer Inst. 2023; Sep 11. DOI: 10.1093/jnci/djad170.
4. Clavel-Chapelon F, et al. Int J Epidemiol. 2015;44(3):801–809.
5. Fervers B, et al. Long-term residential and workplace exposure to air pollution and breast cancer risk: A case-control study nested in the French E3N cohort from 1990 to 2011. Abstract 238MO, ESMO 2023, 20–24 October, Madrid, Spain.

## Third-line datopotamab deruxtecan improves progression-free survival in previously treated metastatic HR+/HER2- breast cancer compared with chemotherapy

**TROPION-Breast01 demonstrated a statistically significant improvement in progression-free survival (PFS) with the TROP2-directed antibody-drug conjugate datopotamab deruxtecan (Dato-DXd) compared with chemotherapy. In addition, Dato-DXd presented with a favourable safety profile.**

Despite new therapeutic options, failure to endocrine and subsequent chemotherapy or CDK4/6-directed therapy remains a clinical problem. Chemotherapy is widely used for the management of endocrine-resistant HR+/HER2- metastatic breast cancer but is associated with low response rates, poor prognosis, and significant toxicity [1]. The current phase 3 TROPION-Breast01 (NCT05104866) trial compared the efficacy and safety of Dato-DXd with chemotherapy.

TROPION-Breast01 enrolled 732 participants with inoperable or metastatic HR+/HER2- breast cancer, who had progression on endocrine therapy, and who had received 1–2 prior lines of systemic chemotherapy. Participants were randomised 1:1 to receiving Dato-DXd or the investigator's choice of chemotherapy (eribulin, vinorelbine, capecitabine, or gemcitabine). The primary endpoints were PFS and overall survival (OS). Dr Aditya Bardia (Massachusetts General Hospital, MA, USA) presented the first results [2].

At the data cut-off, after a median follow-up of 10.8 months, 93 participants in the Dato-DXd arm versus 39 participants in the chemotherapy arm were undergoing treatment. The median PFS was significantly better in the Dato-DXd arm compared with the chemotherapy arm: 6.9 months versus 4.9 months (HR 0.63; 95% CI 0.52–0.76; P<0.0001). At 9 months, 37.5% versus 18.7% of participants were free of progression. The benefit of Dato-DXd over chemotherapy was observed in all prespecified subgroups, including prior use of CDK4/6 inhibitors. In addition, the overall response rate was increased in the Dato-DXd arm, reaching 36.4% versus 22.9% in the chemotherapy arm. OS data are not yet mature and were not presented.

The rate of grade ≥3 treatment-emergent adverse events was lower in the Dato-DXd arm compared with the chemotherapy arm (21% vs 45%), as were rates for dose reduction (21% vs 30%), and dose interruption (12% vs 25%).

Based on these findings, Dr Bardia concluded that "TROPION-Breast01 demonstrated a statistically significant and clinically meaningful improvement of PFS with Dato-DXd, compared with chemotherapy. In addition, Dato-DXd demonstrated a favourable safety profile."


1. Kuderer NM, et al. Nat Rev Clin Oncol. 2022;19:681–697.
2. Bardia A, et al. Datopotamab deruxtecan (Dato-DXd) vs chemotherapy in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2–) breast cancer (BC): Primary results from the randomised phase III TROPION-Breast01 trial. Abstract LBA11, ESMO 2023, 20–24 October, Madrid, Spain.


# Colorectal Cancer

## Neoadjuvant nivolumab/relatlimab demonstrates 100% pathological response in MMRd colon cancer

**Recently, NICHE-2 showed impressive pathological response rates of neoadjuvant nivolumab/ipilimumab in patients with mismatch repair deficient (MMRd) colon cancer. Now, NICHE-3 shows equally impressive pathological complete response (pCR) rates after nivolumab/relatlimab neoadjuvant treatment of MMRd colon cancer.**

MMRd is amongst the best predictive biomarkers of immunotherapy response. Approximately 10–15% of all non-metastatic colon cancers are MMRd. In the NICHE-2 study, neoadjuvant nivolumab/ipilimumab in MMRd colon cancers resulted in 95% major pathologic responses (MPR), including 67% pCR within 6 weeks of treatment [1].

In melanoma patients, the combination of nivolumab and LAG-3 inhibitor relatlimab showed a favourable toxicity profile and promising efficacy in the neoadjuvant setting [2]. Therefore, the NICHE-3 study (NCT03026140) explores the

efficacy and safety of this regimen in participants with non-metastatic MMRd colon cancer. The primary endpoint of NICHE-3 is the pCR. Dr Yara Verschoor (Netherlands Cancer Institute, the Netherlands) presented the results from the stage 1 cohort of NICHE-3 [3].

Stage 1 enrolled 19 participants with resectable, locally advanced (at least cT3 and/or N+), MMRd colon cancer. Participants were treated with 2 doses of nivolumab plus relatlimab at a 4-week interval, followed by surgery within 8 weeks of registration.

With only 5% grade 3 adverse events, neoadjuvant therapy with nivolumab/relatlimab was generally well tolerated. "All participants were fully treated and all participants underwent surgery without delay," said Dr Verschoor. A 100% R0 rate was observed at surgical resection. All participants showed a pathological response (89% MPR, 79% pCR). None of the participants presented lymph node metastases in the surgical resection specimen, therefore none of the participants received adjuvant chemotherapy.

"With 100% of participants revealing a pathological response, stage 1 of NICHE-3 met its endpoint," concluded Dr Verschoor. "As a result, accrual of stage 2 of an extension cohort with 40 participants has started."


1. Chalabi M, et al. Ann Oncol. 2022;33(suppl_7):S1389.
2. Amaria RN, et al. Nature 2022;611:155–160.
3. Verschoor YL, et al. Neoadjuvant nivolumab plus relatlimab (anti-LAG3) in locally advanced MMR-deficient colon cancers: The NICHE-3 study. Abstract LBA31, ESMO 2023, 20–24 October, Madrid, Spain.


## Selective *KRAS*$^{G12C}$ inhibitor sotorasib leads to superior PFS in colorectal cancer

**Patients with *KRAS*$^{G12C}$-mutated, metastatic colorectal cancer (CRC) benefit from the treatment with the combination of sotorasib, a *KRAS*$^{G12C}$ mutation-selective inhibitor, and the EGFR inhibitor panitumumab, first results from the phase 3 CodeBreak300 trial showed. Overall survival data is not yet mature.**

Of all metastatic colorectal tumours, about 3% harbour a *KRAS*$^{G12C}$ mutation, which is associated with poor prognosis [1]. Sotorasib is a selective KRAS inhibitor targeting the protein arising from the *KRAS*$^{G12C}$ mutation. In the phase 1b CodeBreak 101 trial (NCT04185883), the combination of sotorasib with the EGFR inhibitor panitumumab, showed a promising objective response rate (ORR 30%) in participants with advanced *KRAS*$^{G12C}$-mutated CRC [2]. The current CodeBreak300 trial (NCT05198934) is a randomised phase 3 study that further explores the clinical efficacy and safety of the combination of sotorasib and panitumumab in participants with *KRAS*$^{G12C}$-mutated CRC. Dr Filippo Pietrantonio (Istituto Nazionale dei Tumori, Italy) presented the first results [3].

The study enrolled 159 participants who had been previously treated with at least 1 line of therapy for metastatic CRC. Participants were randomised into 3 arms: sotorasib 960 mg daily plus panitumumab (Arm A), sotorasib 240 mg daily plus panitumumab (Arm B) or the control arm (investigator's choice: trifluridine/tipiracil or regorafenib). The primary endpoint of the study is progression-free survival (PFS).

After a median follow-up of 7.8 months, sotorasib (both doses) plus panitumumab significantly improved PFS. Median PFS was 5.6 months, 3.9 months and 2.2 months in Arm A, Arm B and the control arm, respectively (Arm A: HR 0.48; 95% CI 0.30–0.80; P=0.006 and Arm B: HR 0.58; 95% CI 0.36–0.93; P=0.30 vs control arm). PFS benefit was seen in all prespecified subgroups. ORR was significantly improved in Arm A: 26% versus 6% in Arm B and 0% in the control arm. Overall survival data were not mature at the data cut-off date. "Both sotorasib doses plus panitumumab were well tolerated with no new safety signals and no fatal treatment-related adverse events, supporting a dose of 960 mg daily as the sotorasib dose in CRC," highlighted Dr Pietrantonio.

This data suggests that sotorasib plus panitumumab could be a potential new standard of care for patients with pretreated *KRAS*$^{G12C}$-mutated metastatic CRC. "However, overall survival data needs to be awaited," cautioned discussant Dr Miriam Koopmans (University Medical Center Utrecht, the Netherlands).


1. Taieb J, et al. Ann Oncol. Aug 22, 2023. DOI: 10.1016/j.annonc.2023.08.006.
2. Hong DS, et al. J Clin Oncol 2022;40(4_suppl):TPS214.
3. Pietrantonio F, et al. Sotorasib plus panitumumab versus standard-of-care for chemorefractory KRAS G12C-mutated metastatic colorectal cancer (mCRC): CodeBreak 300 phase III study. Abstract LBA10, ESMO 2023, 20–24 October, Madrid, Spain.

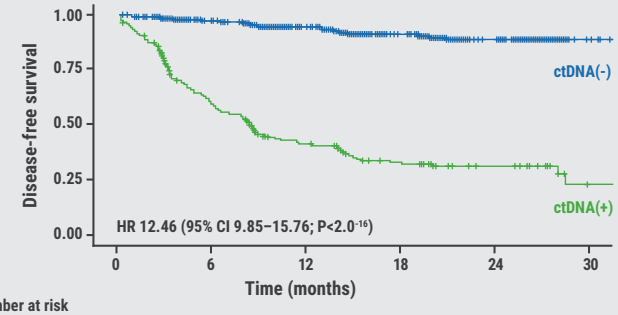

## Postoperative ctDNA predicts survival in colorectal cancer

**Postoperative circulating tumour DNA (ctDNA) has a strong prognostic value for disease-free survival at 24 months, in patients with resectable colorectal cancer (CRC). In addition, in the GALAXY trial, postoperative ctDNA-positive patients, but not ctDNA-negative patients, derived a benefit from adjuvant treatment.**

With the current standard-of-care treatment, more than 30% of patients with resectable CRC relapse. Postoperative ctDNA analysis may enable the identification of molecular residual disease and thus drive subsequent risk stratification and adjuvant chemotherapy treatment decision-making. Preliminary results from the prospective, observational GALAXY study (UMIN000039205) previously demonstrated that postsurgical ctDNA positivity (at 4 weeks after surgery) was associated with higher recurrence risk and was the most significant prognostic factor associated with recurrence risk in patients with stage II or IV CRC [1]. Dr Yoshiaki Nakamura (National Cancer Centre Hospital East, Japan) presented updated results of the GALAXY study [2].

In GALAXY, postoperative ctDNA status was determined at 1, 3, 6, 9, 12, 18, and 24 months after surgery until a recurrence in 2,625 participants with stages II–IV CRC. Participants with ctDNA-negativity at the 4-week timepoint demonstrated a significantly inferior disease-free survival at 24 months compared with ctDNA-positive participants: 89.0% versus 31.4% (HR 12.46; 95% CI 9.85–15.76; P<0.0001, see Figure).

**Figure: CtDNA status linked to disease-free survival during the molecular residual disease window of 30 months [2]**




| Status | ctDNA negative | ctDNA positive |
|---|---|---|
| Events | 7.7% (136/1773) | 59.5% (147/247) |
| 24m DFS (95% CI) | 89% (86.9–90.8) | 31.4% (24.7–38.3) |

ctDNA, circulating tumour DNA. DFS, disease-free survival. CI, confidence interval. HR, hazard ratio.

In stage II–III participants who were negative for ctDNA-negative, postoperative, adjuvant chemotherapy did not improve disease-free survival at 24 months (88.3% vs 89.9%). On the contrary, in stage II–III ctDNA-positive participants, postoperative, adjuvant chemotherapy improved disease-free survival at 24 months (38.6% vs 16.1%).

Based on these results, Dr Nakamura concluded that "postoperative ctDNA has a strong prognostic value for disease-free survival at 24 months. In addition, postoperative ctDNA-positive participants, but not ctDNA-negative participants, derive benefit from adjuvant treatment."


1. Kotani D, et al. Nat Med. 2023;29:127–134.
2. Nakamura Y, et al. Circulating tumor (ct)DNA as a prognostic biomarker in patients (pts) with resected colorectal cancer (CRC): An updated 24 months (mos) disease free survival (DFS) analysis from GALAXY study (CIRCULATE-Japan). Abstract 558MO, ESMO 2023, 20–24 October, Madrid, Spain.


## Overall survival in patients with initially unresectable colorectal liver metastases does not depend on choice of induction regimen

**CAIRO5, the first randomised study to prospectively evaluate 4 systemic induction regiments in patients with initially unresectable colorectal cancer liver metastases (CRLM), did not find differences in overall survival (OS).**

Patients with initially unresectable CRLM might qualify for local treatment with curative intent after reducing the tumour size by induction systemic treatment. The current phase 3 CAIRO5 trial (NCT02162563) aimed to find the optimal systemic induction regimen to convert initially unresectable CRLM to local treatment in 121 participants. Previously, it was reported that the progression-free survival was significantly longer and the complete local treatment (R0/R1 resection and/or ablation) higher with FOLFOXIRI (arm A) versus FOLFOX/FOLFIRI (arm B), both plus bevacizumab for participants with right-sided and/or *RAS/BRAF*$^{V600E}$-mutated tumours [1]. For patients with left-sided and *RAS/BRAF*$^{V600E}$ wildtype tumours, these parameters were not different between adding bevacizumab (arm C) versus panitumumab (arm D) to FOLFOX/FOLFIRI. Prof. Cornelis J. Punt (University Medical Center Utrecht, the Netherlands) presented the OS results from the CAIRO5 trial [2].

The median follow-up was 58 months and the median OS in arm A versus B was 23.6 months versus 24.1 months (HR 0.92; 95% CI 0.70–1.20; P=0.52). In both arms A and B, OS in participants who had local treatment was significantly longer than OS in participants without local treatment (HR 0.27 vs 0.30 in arm A vs arm B, respectively). The median OS in arm C versus D was 40.4 months versus 38.3 months (HR 1.02; 95% CI 0.72–1.46; P=0.89). As for arms A and B, OS in participants who had local treatment in arms C and D was significantly better compared with participants without local treatment (HR 0.22 and HR 0.19). Recurrence within 6 months after complete local treatment occurred in 49% versus 39% of participants in arm A versus B (P=0.28), and 42% versus 39% of participants in arm C versus D (P=0.73).

"In this first randomised study to prospectively evaluate 4 systemic induction regimens in participants with initially unresectable CRLM, no benefit in median OS was observed between FOLFOXIRI-bevacizumab and FOLFOX/FOLFIRI-bevacizumab for right-sided and/or *RAS/BRAF*$^{V600E}$-mutated tumours, nor between adding panitumumab versus bevacizumab to FOLFOX/FOLFIRI for left-sided and *RAS/BRAF*$^{V600E}$ wildtype tumours," concluded Prof. Punt.


1. Bond MJG, et al. Lancet Oncol. 2023;24(7):757–771.
2. Punt CJ, et al. First-line systemic treatment in patients with initially unresectable colorectal cancer liver metastases (CRLM): overall survival of the phase III CAIRO5 study of the Dutch Colorectal Cancer Group. Abstract LBA27, ESMO 2023, 20-24 October, Madrid, Spain.


# Lung Cancer

## Perioperative nivolumab boosts event-free survival in NSCLC

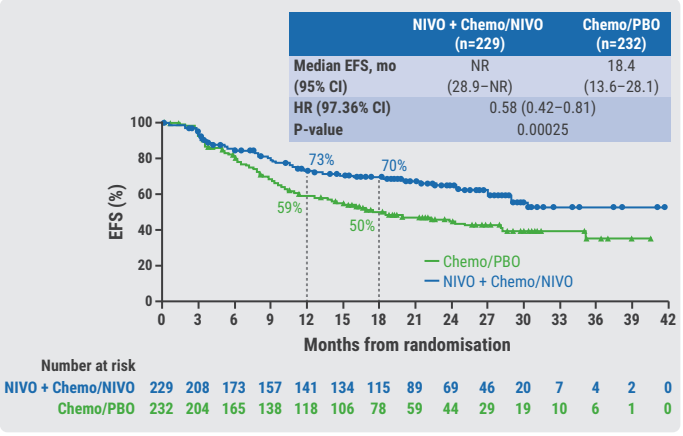
**Perioperative treatment with chemotherapy plus nivolumab outperforms preoperative chemotherapy alone in participants with resectable non-small cell lung cancer (NSCLC), the first results of the CheckMate 77T trial demonstrated.**

In patients with resectable NSCLC, neoadjuvant nivolumab plus chemotherapy previously resulted in significantly longer event-free survival (EFS) and a higher percentage of patients with a pathological complete response (pCR) than chemotherapy alone [1]. The subsequent phase 2 study CheckMate 816 (NCT02998528) showed further improvement with a perioperative approach including adjuvant nivolumab [2]. The current phase 3 CheckMate 77T trial (NCT04025879) is the first study to explore the efficacy and safety of this perioperative approach in participants with resectable stage II–IIIB NSCLC. Dr Tina Cascone (MD Anderson Cancer Center, TX, USA) presented the results from the pre-specified interim analysis [3].

CheckMate 77T enrolled 416 participants with resectable NSCLC (stage IIA–IIIB, without *EGFR* mutation or *ALK* rearrangement) who had no prior systemic anti-cancer treatment. Participants were randomised 1:1 to perioperative nivolumab plus chemotherapy or placebo plus chemotherapy (4 cycles neoadjuvant therapy, followed by surgery and 1-year adjuvant therapy). Of all enrolled participants, 78% underwent surgery, 62–66% received adjuvant therapy and 60% completed adjuvant therapy.

At a median follow-up of 25 months, the trial met its primary endpoint, as EFS was in favour of the nivolumab-treated arm: not reached versus 18.4 months (HR 0.58; 95% CI 0.42–0.81; P=0.00025; see Figure). EFS rates at 18 months were 70% and 50% in the nivolumab and placebo arm, respectively. EFS benefit for nivolumab was observed across subgroups, including stratification by PD-L1 status. Also, pCR was improved in the nivolumab arm (25.3% vs 4.7%; odds ratio 6.64; 95% CI 3.40–12.97). Perioperative nivolumab increased EFS regardless of the pCR status. No new safety issues were observed.

**Figure: EFS per blinded independent central review (BICR) with neoadjuvant nivolumab plus chemotherapy and adjuvant nivolumab versus chemotherapy plus placebo [3]**




EFS, event-free survival. NIVO, nivolumab. PBO, placebo. HR, hazard ratio. Chemo, chemotherapy. CI, confidence interval.

Dr Cascone concluded: "These interim results support perioperative nivolumab as a potential new treatment option for patients with resectable NSCLC." However, the study did not yet report whether there is an additional benefit of adjuvant nivolumab in patients who have a pCR after neoadjuvant nivolumab, as discussant Dr Marina Garassino (Instituto Nationale dei Tumori, Italy) remarked.


1. Provencio M, et al. N Eng J Med. 2023;389:504–513.
2. Forde P, et al. N Engl J Med. 2022;386:1973–1985.
3. Cascone T, et al. CheckMate 77T: Phase III study comparing neoadjuvant nivolumab (NIVO) plus chemotherapy (chemo) vs neoadjuvant placebo plus chemo followed by surgery and adjuvant NIVO or placebo for previously untreated, resectable stage II–IIIb NSCLC. Abstract LBA1, ESMO 2023, 20–24 October, Madrid, Spain.

## Selective RET inhibitor selpercatinib doubles progression-free survival in RET-mutated NSCLC

**Compared with the standard of care for patients with RET-fusion-positive metastatic non-small cell lung cancer (mNSCLC), treatment with selpercatinib doubled progression-free survival (PFS), increased response rate (also intracranial) and delayed pulmonary and physical deterioration, results from the LIBRETTO-431 trial showed.**

*RET* gene fusions, when present, are potential targets in patients with NSCLC. Based on the results of KEYNOTE-189 (NCT02578680), the current standard for the treatment of patients with *RET*-fusion-positive mNSCLC (without *EGFR* mutation or *ALK* rearrangement) is a platinum, pemetrexed, pembrolizumab combination [1]. Recently, the single-arm phase 1/2 LIBRETTO-001 (NCT03157128) showed a strong clinical activity of selpercatinib, a selective RET inhibitor, in patients with *RET*-fusion-positive mNSCLC [2].

To further explore the clinical potential of selpercatinib, the current randomised phase 3 LIBRETTO-431 trial (NCT04194944) compared the clinical efficacy and safety of selpercatinib with the standard of care. The study enrolled 261 participants with confirmed *RET*-fusion-positive mNSCLC, of whom 159 were assigned to receive selpercatinib and 102 to the standard of care (platinum, pemetrexed, pembrolizumab). Prof. Herbert Ho Fung Loong (Chinese University of Hong Kong, China) presented the interim results for PFS, the primary endpoint of the study [3].

At a median follow-up of approximately 19 months, selpercatinib demonstrated superior median PFS versus standard of care: 24.8 months versus 11.2 months (HR 0.46; 95% CI 0.31–0.70; P<0.01). The PFS benefit of selpercatinib was observed in all prespecified subgroups. Selpercatinib significantly increased overall response rate (83.7% vs 65.1%), median duration of response (24.2 months vs 11.5 months), intracranial response rate (82.4% vs 58.3%), intracranial complete response rate (35.3% vs 16.7%), and median intracranial PFS (16.1 vs 10.4 months).

Treatment with selpercatinib was relatively well tolerated: median time on selpercatinib was approximately 70% longer than the standard of care (16.7 months vs 9.8 months). The occurrence of adverse events leading to discontinuation was slightly higher in the selpercatinib arm: 10.1% vs 2.0%. Selpercatinib significantly delayed the time-to-deterioration of pulmonary or physical function (HR 0.34 for pulmonary function, HR 0.60 for physical function).

"Selpercatinib should be considered as a first-line standard of care for patients with *RET*-fusion-positive NSCLC," concluded Prof. Ho Fung Loong. "Furthermore, these data reinforce the importance of genomic testing in NCSLC at the time of diagnosis."


1. Gandhi L, et al. N Eng J Med. 2018;378:2078–2092.
2. Drilon A, et al. J Clin Oncol. 2023;41(2):385–394.
3. Ho Fung Loong H, et al. Randomized phase III study of first-line selpercatinib versus chemotherapy and pembrolizumab in RET fusion-positive NSCLC. Abstract LBA4, ESMO 2023, 20–24 October, Madrid, Spain.


## Dato-DXd outperforms docetaxel in previously treated patients with metastatic NSCLC

**The TROP2-directed antibody-drug conjugate datopotamab deruxtecan (Dato-DXd) is a potential new meaningful therapy for patients with previously treated non-squamous non-small cell lung cancer (NSCLC), as was shown in the TROPION-LUNG01 and TROPION-Lung05 trials.**

The standard of care second-line chemotherapy for patients with metastatic NSCLC is associated with modest benefit and substantial toxicity. Dato-DXd, a TROP2-directed antibody-drug conjugate that selectively delivers a potent topoisomerase I inhibitor payload directly into tumour cells, is currently under clinical investigation in multiple tumour types. Promising antitumour activity was observed with Dato-DXd in patients with locally advanced or metastatic NSCLC in the phase 1 TROPION-PanTumor01 Trial (NCT03401385) [1]. Both the phase 3 TROPION-LUNG01 (NCT04656652) and phase 2 TROPION-Lung05 (NCT04484142) trials further evaluated the efficacy and safety of Dato-DXd in previously treated participants with locally advanced or metastatic NSCLC.

The phase 3 TROPION-LUNG01 trial enrolled 604 participants (with or without actionable genomic alterations), who were randomised 1:1 to receive Dato-Dxd or docetaxel until disease progression. The dual primary endpoints were progression-free survival (PFS) and overall survival (OS). Dr Aaron Lisberg (University of California Los Angeles, CA, USA) presented the interim results [2]. Median PFS was significantly improved by treatment with Dato-DXd over docetaxel: 4.4 versus 3.7 months (HR 0.75; 95% CI 0.62–0.91; P=0.004). However, PFS benefit was exclusively observed in participants with non-squamous histology (HR 0.63 vs HR1.38 in participants with squamous histology). OS data are not yet mature.

The phase 2 TROPION-Lung05 trial enrolled 137 participants who had tumours with ≥1 actionable genomic alterations (e.g. *EGFR, ALK, ROS1, NTRK*). All participants were treated with Dato-DXd until progression. The primary endpoint was the objective response rate (ORR). Prof. Luis Paz-Ares (Hospital Universitario 12 de Octubre, Spain) presented the results [3]. ORR in all treated participants was 35.8% (95% CI 27.8–44.4), whereby 3% of participants achieved a complete response and 33% a partial response. The ORR was 43.6% (95% CI 32.4–55.3) in participants with *EGFR* mutations (57% of all participants) and 23.5% (95% CI 10.7–41.2) in participants with *ALK* alterations (25% of all participants). The median PFS in all participants was 5.4 months, and the median duration of response was 7.0 months.

In both trials, Data-DXd had a manageable safety profile, characterised by a low incidence of haematological or drug-related grade ≥3 toxicities. Nausea and stomatitis were the predominant adverse events observed. Grade ≥3 interstitial lung disease (ILD) was reported in 3% of participants, highlighting the need for careful monitoring and adherence to ILD management guidelines.

Based on these interim results, Dr Lisberg concluded that "Dato-DXd is a potential new meaningful therapy for patients with previously treated non-squamous NSCLC."


1. Shimizu T, et al. J Clin Oncol. 2023;41(29):4678–4687.
2. Ahn M-J, et al. L- Datopotamab deruxtecan (Dato-DXd) vs docetaxel in previously treated advanced/metastatic (adv/met) non-small cell lung cancer (NSCLC): Results of the randomized phase III study TROPION-Lung01. Abstract LBA12, ESMO 2023, 20–24 October, Madrid, Spain.
3. Paz-Ares L, et al. TROPION-Lung05: Datopotamab deruxtecan (Dato-DXd) in previously treated non-small cell lung cancer (NSCLC) with actionable genomic alterations (AGAs). Abstract 1314MO, ESMO 2023, 20–24 October, Madrid, Spain.


## First-line and second-line benefit of amivantamab in advanced, *EGFR*-mutated NSCLC

**The bispecific antibody amivantamab showed significant benefit as first-line and second-line treatment versus standard therapy in patients with *EGFR*-mutated, advanced non-small cell lung cancer (NSCLC), results of 3 independent randomised, phase 3 trials showed.**

*EGFR* mutations are present in 15–20% of non-squamous, advanced NSCLC. The standard of first-line treatment for *EGFR*-mutated, advanced NSCLC is osimertinib [1]. However, resistance to the treatment and disease progression are nearly inevitable. Moreover, patients with *EGFR* exon 20 insertions are largely insensitive to the common EGFR tyrosine kinase inhibitors [2]. Secondary *EGFR* and *MET* alterations may account for 25–50% of tumour resistance. Amivantamab is a novel EGFR-MET bispecific antibody with immune cell-directing activity and active against a wide range of *EGFR* and *MET* alterations [3] and was evaluated in the following randomised, phase 3 trials:

Prof. Nicolas Girard (Institut du Thorax Curie-Montsouris, France) presented results from the PAPILLON trial (NCT04538664), a phase 3 study evaluating the efficacy of the addition of amivantamab to standard first-line chemotherapy (carboplatin/pemetrexed) in *EGFR* exon 20 insertion, advanced NSCLC [4]. A total of 308 participants were randomised to amivantamab/chemotherapy or chemotherapy alone. The primary endpoint was progression-free survival (PFS). The addition of amivantamab to the first-line chemotherapy significantly improved median PFS: 11.4 months versus 6.7 months (HR 0.395; 95% CI 0.30–0.53; P<0.001). Also, the overall response rate (ORR), duration of response rate (DoR), and PFS after subsequent therapy (PFS2) were significantly improved in the amivantamab arm.

A significant improvement in PFS (HR 0.70; P<0.001) and PFS2 (HR 0.75; P=0.03) was also observed in MARIPOSA (NCT04487080), a phase 3 trial that evaluated the efficacy of first-line amivantamab/lazertinib versus osimertinib in 878 participants with (any) *EGFR*-mutated advanced NSCLC. Lazertinib is a 3rd generation anti-EGFR tyrosine kinase inhibitor. These results were presented by Prof. Byoung Chul Cho (Yonsei University, Republic of Korea) [5]. The median DoR was improved in the amivantamab/lazertinib arm: 25.8 versus 16.8 months.

MARIPOSA-2 (NCT04988295) evaluated the efficacy of amivantamab/lazertinib/chemotherapy versus amivantamab/chemotherapy versus chemotherapy alone in participants with *EGFR* exon 19 deletion or L858R-mutated advanced NSCLC who progressed on osimertinib monotherapy. Dr Antonio Passaro (European Institute of Oncology IRCCS, Italy) presented the results [6]. The median PFS favoured both amivantamab/chemotherapy and amivantamab/lazertinib/chemotherapy over chemotherapy alone (HR 0.48; 95% CI 0.36–0.64; P<0.001 and HR 0.44; 95% CI 0.35–0.56; P<0.001, respectively). Also, intracranial PFS was improved in both amivantamab-based arms versus chemotherapy alone as were the ORR (64%, 63%, and 36%, respectively) and the median DoR (9.4, 6.9, and 5.6 months, respectively).

In all 3 trials, toxicity was significantly increased in experimental arms (amivantamab vs chemotherapy; amivantamab/lazertinib vs osimertinib; amivantamab/lazertinib/chemotherapy and amivantamab/chemotherapy vs chemotherapy), making amivantamab a promising alternative treatment for advanced NSCLC.


1. Soria JC, et al. N Engl J Med. 2018;378:113–125.
2. Ou S-H, et al. JTO Clin Res. 2023;4:100558.
3. Yun J, et al. Cancer Discov. 2020;10(8):1194–1209.
4. Girard N, et al. Amivantamab plus chemotherapy vs chemotherapy as first-line treatment in EGFR Exon 20 insertion-mutated advanced non-small cell lung cancer (NSCLC): Primary results from PAPILLON, a randomized phase III global study. Abstract LBA5, ESMO 2023, 20–24 October, Madrid, Spain.
5. Cho BC, et al. Amivantamab plus lazertinib vs osimertinib as first-line treatment in patients with EGFR-mutated, advanced non-small cell lung cancer (NSCLC): Primary results from MARIPOSA, a phase III, global, randomized, controlled trial. Abstract LBA14, ESMO 2023, 20–24 October, Madrid, Spain.
6. Passaro A, et al. Amivantamab plus chemotherapy (with or without lazertinib) vs chemotherapy in EGFR-mutated advanced NSCLC after progression on osimertinib: MARIPOSA-2, a phase III, global, randomized, controlled trial. Abstract LBA15, ESMO 2023, 20–24 October, Madrid, Spain.


# Upper Gastro-Intestinal Cancer

## Perioperative durvalumab/FLOT improves pCR in gastric cancer

**The addition of the PD-L1 inhibitor durvalumab to chemotherapy showed an improved pathological complete response (pCR) rate when given in the perioperative setting to patients with untreated, resectable gastric/gastro-oesophageal junction (G/GEJ) cancers, results from MATTERHORN showed. The impact on survival is still unknown, as event-free survival data is yet unmature.**

Perioperative FLOT chemotherapy (fluorouracil, leucovorin, oxaliplatin, and docetaxel) has become the standard of care in resectable G/GEJ cancers [1]. However, approximately 50% of patients are expected to eventually relapse. A combination of PD-1 blockade and chemotherapy is the standard first-line treatment in advanced/metastatic G/GEJ cancers [2].

The global, phase 3, randomised, double-blind, placebo-controlled MATTERHORN trial (NCT04592913) assesses perioperative durvalumab with FLOT in participants with resectable G/GEJ cancers. Prof. Salah-Eddin Al-Batran (Northwest Hospital Frankfurt, Germany) presented the results of a pre-planned interim analysis [3].

The MATTERHORN trial randomised 948 participants (resectable stage III–IVA G/GEJ adenocarcinoma) 1:1 to perioperative FLOT (4 doses before, 4 doses after surgery) plus placebo or FLOT plus durvalumab (2 doses before, 2 doses after surgery). Thereafter, durvalumab and placebo were continued for 10 doses. The primary outcome of MATTERHORN is event-free survival; one of the secondary outcomes is the pCR rate.

The combination of durvalumab with FLOT significantly increased the pCR rate from 7% to 19% (odds ratio [OR] 3.08; 95% CI 2.03–4.67; P<0.00001). Likewise, durvalumab significantly increased combined pCR and near-complete response rate: 14% versus 27% (OR 2.19; 95% CI 1.58–3.04; P<0.00001). In the durvalumab arm, more participants presented with downstaging (T0: 23% vs 11%, N0: 52% vs 37%). No unexpected safety signals were observed.

Based on these outcomes, Prof. Al-Batran concluded: "Perioperative treatment with durvalumab plus FLOT leads to a significant improvement of pathological response versus FLOT alone and a significant improvement of downstaging. However, while the results are promising, the event-free survival data are required before any impact on clinical practice can be suggested."


1. Al-Batran S-E, et al. Lancet. 2019;391(10184):1948–1957.
2. Sun JM, et al. Lancet. 2021;398(10302):759–771.
3. Al-Batran S-A, et al. Pathological complete response (pCR) to durvalumab plus 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) in resectable gastric and gastroesophageal junction cancer (GC/GEJC): Interim results of the global, phase III MATTERHORN study. Abstract LBA73, ESMO 2023, 20–24 October, Madrid, Spain.


## Active surveillance after neoadjuvant chemo-radiotherapy in oesophageal cancer

**Data from the SANO trial suggests that active surveillance after neoadjuvant chemoradiotherapy may be an alternative to surgery for some patients with oesophageal cancer.**

Oesophagectomy is the keystone of treatment for patients with oesophageal cancer. This procedure, however, comes with a mortality rate of 1–5%, a complication rate of 59%, persisting symptoms, and decreased quality of life [1].

Previously, the CROSS trial (Netherlands Trial Register NTR487) showed that neoadjuvant chemoradiotherapy improved survival and that 29% of patients had a complete pathological response (49% of patients with squamous cell carcinoma and 23% with adenocarcinoma) after neoadjuvant chemoradiotherapy [2]. This imposed the dilemma of whether all patients should undergo standard surgery after neoadjuvant chemoradiotherapy, or whether active surveillance could provide an organ-sparing alternative strategy.

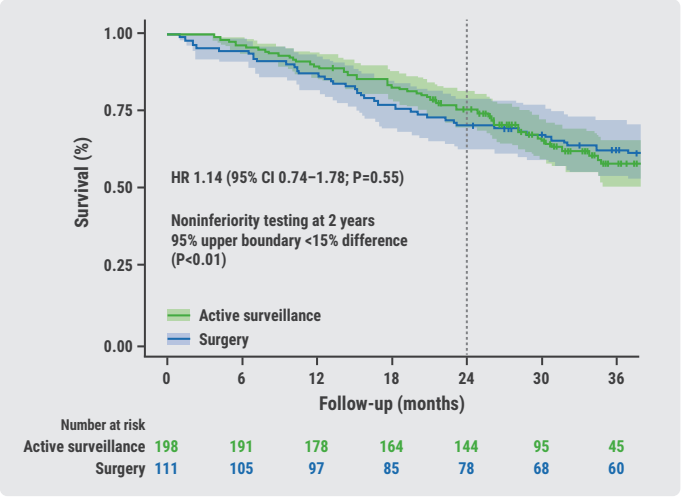
To answer this question, the phase 3 SANO non-inferiority trial (NCT05953181) included 309 participants with locally advanced oesophageal cancer who had a complete pathological response after neoadjuvant chemoradiotherapy (defined as no residual disease at 6 and 12 weeks after neoadjuvant chemoradiotherapy). The participants were randomised 1:1 to standard surgery or active surveillance. Participants in the active surveillance arm underwent a response evaluation every 6 weeks; surgery was only performed in case a (residual) tumour was detected. The primary endpoint was overall survival (OS) from the day of pathological complete response. Non-inferiority was defined as <15% difference in OS at 2 years between study arms. Dr Berend van der Wilk (Erasmus Medical Centre, the Netherlands) presented the first results [3].

After a median follow-up of 38 months, there was no statistically significant difference in OS between the arms (HR 1.14; 95% CI 0.74–1.78; P=0.55). At 2 years, OS in active surveillance was non-inferior to standard surgery (see Figure). In line with this, no statistically significant difference was observed in distant-free survival (HR 1.35; 95% CI 0.89–2.03; P=0.15), or distant metastases rate (odds ratio [OR] 1.45; 95% CI 0.85–2.48; P=0.18). In the active surveillance arm, 35% of participants had persistent complete responses after 2 years. However, no differentiation between adenocarcinoma and squamous cell carcinoma was made in the analysis.

Operative outcomes were comparable in both arms, except for the mean time-to-surgery. This indicates that participants with local regrowth during active surveillance could be operated safely and successfully. At 6 and 9 months after randomisation, global improvement in quality of life appeared to be significantly different and clinically relevant in the active surveillance arm.

"These results suggest that active surveillance offers a potential alternative to surgery for patients with oesophageal cancer who show pathological complete response after neoadjuvant chemoradiotherapy," concluded Dr Van der Wilk.

**Figure: Overall survival does not change with surgery for participants after neoadjuvant chemoradiotherapy in oesophageal cancer [3]**




HR, hazard ratio. CI, confidence interval.


1. Markar SR, et al. Ann Surg Oncol. 2020;27:718–723.
2. Eyck BM, et al. J Clin Oncol. 2021;39(18):1995–2004.
3. Van der Wilk BJ, et al. Neoadjuvant chemoradiotherapy followed by surgery versus active surveillance for oesophageal cancer (SANO-trial): A phase-III stepped-wedge cluster randomised trial. Abstract LBA75, ESMO 2023, 20–24 October, Madrid, Spain.


## FOLFIRINOX equals gemcitabine-based chemoradiotherapy in neoadjuvant setting for pancreatic cancer

**The treatment with neoadjuvant FOLFIRINOX versus gemcitabine-based chemoradiotherapy in patients with borderline resectable or resectable pancreatic cancer was comparably effective concerning overall survival (OS), R0 resection rate, and adverse events, results from the PREOPANC-2 trial showed.**

Previously, PREOPANC (NCT05679583) demonstrated an OS benefit of neoadjuvant gemcitabine-based chemoradiotherapy compared with upfront surgery in participants with borderline resectable and resectable pancreatic cancer [1]. Meanwhile, the treatment with FOLFIRINOX demonstrated survival benefits both in the metastatic and adjuvant settings [2,3]. The current phase 3, randomised PREOPANC-2 trial (EudraCT 2017-002036-17) compared neoadjuvant gemcitabine-based chemoradiotherapy with neoadjuvant FOLFIRINOX in participants with (borderline) resectable pancreatic cancer. Prof. Bas Groot Koerkamp (Erasmus Medical Centre, the Netherlands) presented the first results [4].

PREOPANC-2 enrolled 375 participants who were randomised 1:1 to 8 cycles of FOLFIRINOX followed by surgery without adjuvant treatment (FFX arm), or 3 cycles of neoadjuvant

gemcitabine with hypofractionated radiotherapy followed by surgery and 4 cycles of adjuvant gemcitabine (CRT arm). The primary endpoint was OS.

More participants in the CRT arm completed neoadjuvant treatment (88% vs 62% in the FFX arm); however, 81% of participants in the FFX arm received ≥4 cycles FOLFIRINOX. The resection rate was similar in both arms (77% vs 75% in CRT vs FFX, respectively), as were the rates for R0 resection and pathological complete response. No significant difference was observed in OS between arms. The median OS was 21.9 months in the FFX arm versus 21.3 months in the CRT arm (HR 0.87; 95% CI 0.68–1.12; P=0.28). The OS rates at 1 year were 75.7% and 69.6% respectively, and 35.6% and 32.6% respectively, at 3 years.

Grade 3–4 adverse events rates were comparable in both arms (67% vs 60% in FFX vs CRT, respectively). Diarrhoea was more prominent in the FFX arm (23% vs 0% in CRT).

"Neoadjuvant FOLFIRINOX and gemcitabine-based chemo-radiotherapy are comparably effective regarding overall survival of patients with borderline resectable or resectable pancreatic cancer," concluded Prof. Groot Koerkamp.


1. Versteijne E, et al. J Clin Oncol. 2022;40(11):1220–1230.
2. Conroy T, et al. JAMA Oncol. 2022;8(11):1571–1578.
3. Conroy T, et al. N Engl J Med. 2011;364:1817–1825.
4. Groot Koerkamp B, et al. Neoadjuvant chemotherapy with FOLFIRINOX versus neoadjuvant gemcitabine-based chemoradiotherapy for borderline resectable and resectable pancreatic cancer (P75 REOPANC-2): A multicenter randomized controlled trial. Abstract LBA83, ESMO 2023, 20–24 October, Madrid, Spain.


## Modified FLOT regime outperforms FOLFOX in advanced/metastatic gastric/gastroesophageal junction adenocarcinoma

**In participants with advanced HER2-negative gastric/gastroesophageal junction (G/GEJ) adenocarcinoma, a modified FLOT regimen (mFLOT) demonstrated significant and clinically meaningful improvement in progression-free survival (PFS) and overall survival (OS) versus FOLFOX, as was demonstrated by the GASTROFOX study.**

The preferred first-line chemotherapy regimen for irresectable locally advanced or metastatic G/GEJ adenocarcinoma is a platinum/fluoropyrimidine combination, such as FOLFOX [1]. For localised G/GEJ adenocarcinomas, perioperative FLOT triplet has become the standard of care [2]. The current phase 3 GASTROFOX study (NCT03006432) explored the efficacy and safety of mFLOT with a modified dose of 5FU (2400 mg/m$^2$/46 hr) versus FOLFOX in participants with advanced G/GEJ adenocarcinomas [3].

GASTROFOX randomised 506 participants with HER2-negative, locally advanced unresectable or metastatic G/GEJ adenocarcinoma 1:1 to FOLFOX or mFLOT. The primary endpoint was PFS and the secondary endpoints included OS and safety. For survival outcomes, HR and 95% CI were estimated by a Cox proportional hazard (PH) model. In the case of non-PH, the restricted mean survival time was used to evaluate the treatment effect. Prof. Aziz Zaanan (Université Paris Cité, France) presented the results [4].

After a median follow-up of 42.8 months, PFS was in favour of mFLOT with 7.59 versus 5.98 months (non-PH). Restricted mean survival time at 12 months was 7.52 versus 6.62 months (P=0.007). mFLOT also significantly improved OS: 15.08 versus 12.65 months (HR 0.82; 95% CI 0.68–0.99; P=0.04).

"In participants with advanced HER2-negative G/GEJ adenocarcinoma, mFLOT demonstrated significant and clinically meaningful improvement in PFS and OS versus FOLFOX," said Prof. Zaanan. "Therefore, mFLOT can be considered as a new therapeutic option for patients eligible for a triplet regimen."


1. Lordick F, et al. Ann Oncol. 2022;33(10):1005–1020.
2. Al-Batran S-A, et al. Lancet. 2019;391(10184):1948–1957.
3. Van Cutsem E, et al. Ann Oncol. 2015;26(1):149–156.
4. Zaanan A, et al. 5-fluorouracil and oxaliplatin with or without docetaxel in the first-line treatment of HER2 negative locally advanced (LA) unresectable or metastatic gastric or gastro-esophageal junction (GEJ) adenocarcinoma (GASTFOX-PRODIGE 51): A randomized phase III trial sponsored by the FFCD. Abstract LBA77, ESMO 2023, 20–24 October, Madrid, Spain.

# Melanoma

## Lifileucel induces a durable response in heavily pretreated mucosal melanoma

**In a subgroup analysis of the phase 2 C-144-01 study, the one-time treatment with lifileucel induces a strong and durable response in patients with advanced mucosal melanoma.**

Advanced mucosal melanoma is rare and difficult to treat, with worse outcomes after anti-PD-1 therapy than non-mucosal melanoma [1,2]. In pooled analyses, the objective response rate (ORR) is about 20%, and the median overall survival (OS) is 11–16 months. Lifileucel is a one-time, autologous tumour infiltrating lymphocyte (TIL) cell therapy that uses TILs recovered from a patient's tumour tissue to produce polyclonal patient-specific TILs during a 22-day centralised manufacturing process. Recently, results of the phase 2 C-144-01 trial (NCT02360579) showed an ORR of 31.4% in 153 heavily pretreated patients with advanced melanoma (all subtypes but uveal melanoma) after a single infusion of lifileucel [3]. Dr Evidio Domingo-Musibay (Masonic Cancer Center, MN, USA) reported results from a subgroup of 12 participants with advanced mucosal melanoma [4].

The median age of the participants was 61 years, the number of prior therapies ranged from 1–6, and all participants were *BRAF*$^{V600}$ wildtype. The median applied dose of lifileucel was 26.1 x 109 cells. All participants had a high disease burden.

After a median follow-up of 35.7 months, ORR was 50% (95% CI 21.1–78.9), 1 participant had a complete response, and 5 participants presented with a partial response. The median duration of response was not yet reached. "The duration of response was more than 6 months in all responders, more than 12 months in 5 responders, and more than 24 months in 4 responders," highlighted Dr Domingo-Musibay.

In contrast to the participants with cutaneous melanoma, the participants with mucosal melanoma had a low tumour mutational burden (2.145 mutations/Mb vs 10.47 mutations/Mb). TIL persistence was comparable in mucosal and cutaneous melanoma beyond month 12. The most common non-haematological adverse events of grade 3–4 were febrile neutropenia (58.3%) and hypotension (33.3%). All participants presented with haematological adverse events of grades 3–4, which was expected because of the non-myeloablative lymphodepletion required for TIL harvest for lifileucel manufacturing.

Dr Domingo-Musibay explained: "These results further support the potential benefit of lifileucel as a one-time treatment, a feature that makes it different from other immunotherapies."


1. D'Angelo SP, et al. J Clin Oncol. 2017;35(2):226–235.
2. Hamid O, et al. Br J Cancer. 2018;119:670–674.
3. Chesney J, et al. J Immunother Cancer. 2022;10(12):e005755.
4. Domingo-Musibay E, et al. Lifileucel tumour-infiltrating lymphocyte (TIL) cell therapy in patients (pts) with advanced mucosal melanoma after progression on immune checkpoint inhibitors (ICI): Results from the phase II C-144-01 study. Abstract 1086O, ESMO 2023, 20–24 October, Madrid, Spain.


## Darovasertib/crizotinib combination: a potential first-line therapy in metastatic uveal melanoma

**The initial evaluation of darovasertib/crizotinib in both first-line and pretreated participants with metastatic uveal melanoma (MUM) showed a manageable safety profile and clinical efficacy. The levels of circulating tumour DNA (ctDNA) were reduced in almost all participants.**

Approximately 50% of patients with uveal melanoma will eventually develop metastatic disease which has a poor prognosis and a median overall survival of approximately 1 year. Currently, MUM has limited effective (and approved) therapies. In over 95% of MUM cases, the driver mutations in *GNAQ/GNA11* occur, which activate protein kinase C (PKC) signalling. In a first-in-human study, the selective PKC inhibitor darovasertib demonstrated clinical responses in MUM [1]. Moreover, the oncogene *cMET* is overexpressed in MUM and can additionally drive cell growth and survival pathways. The current phase 1/2 study (NCT03947385) consequently evaluated the efficacy and safety of the darovasertib combined with the potent cMET inhibitor crizotinib. Dr Meridith McKean (Tennessee Oncology, TN, USA) presented results from the expansion cohort [2].

The participants had a large tumour burden, where 66% of them presented with the largest metastatic lesions over 3 cm, 65% had hepatic and extrahepatic disease, and 60% had

elevated lactate dehydrogenase (LDH) levels. Participants were treated with the darovasertib/crizotinib combination until progression of disease or signs of toxicity occurred.

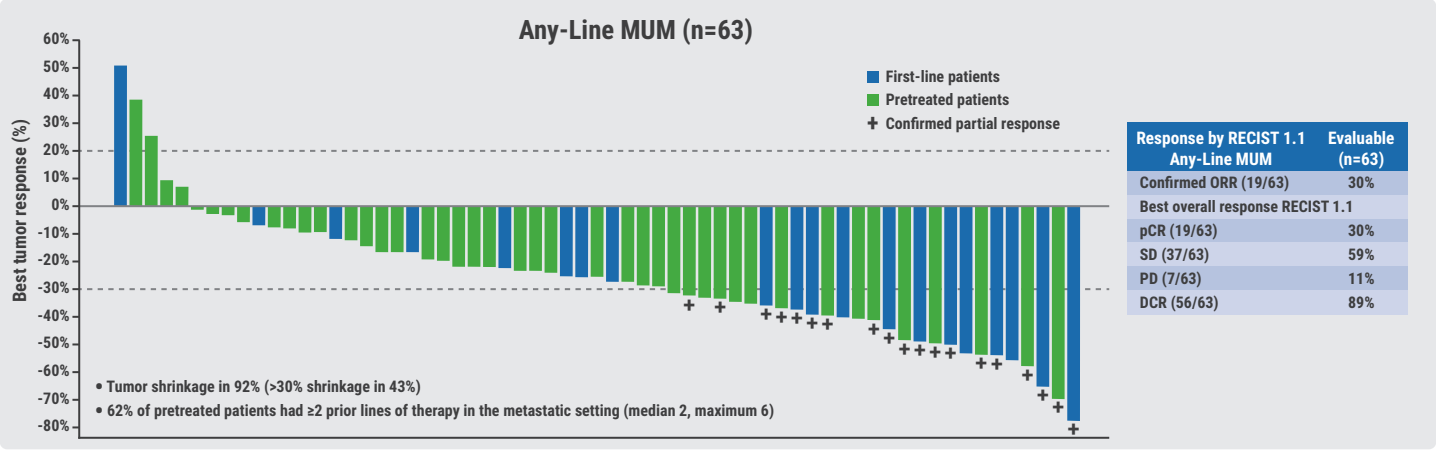
A clinical partial response was observed in 30% of the participants, stable disease in 59%, and tumour shrinkage in 92% (see Figure). These responses were noted regardless of prior lines of treatment (62% of participants had ≥2 prior treatment lines in the metastatic setting), LDH status, and HLA-A*02.01 status. A deep and sustained decrease in plasma ctDNA levels was observed in 94% of the participants. The depth of this molecular response correlated with the best overall response (RECIST 1.1). The interim median progression-free survival was 7.1 months in the first-line setting (n=20), 6.8 months in the any-line setting (n=63), and 11.0 months in participants with hepatic-only (i.e. early phase) metastatic disease (n=19).

The combination of darovasertib/crizotinib had a manageable safety profile. Serious treatment-related adverse events were seen in 10.3% of the participants and adverse events led to discontinuation in 7.4% of the participants.

Based on these results, Dr McKean concluded that "the efficacy and safety of darovasertib/crizotinib in first-line and hepatic-only participants support the ongoing registration study (NCT05987332) of darovasertib/crizotinib in first-line MUM."


1. Piperno-Neumann S, et al. Br J Cancer. 2023;128:1040–1051.
2. McKean M, et al. ctDNA reduction and clinical efficacy of the darovasertib + crizotinib (Daro + Crizo) combination in metastatic uveal melanoma (MUM). Abstract 1081O, ESMO 2023, 20–24 October, Madrid, Spain.


**Figure: Overall response and disease control rates in participants with any-line MUM [2]**




| Response by RECIST 1.1 Any-Line MUM | Evaluable (n=63) |
|---|---|
| Confirmed ORR (19/63) | 30% |
| Best overall response RECIST 1.1 | |
| pCR (19/63) | 30% |
| SD (37/63) | 59% |
| PD (7/63) | 11% |
| DCR (56/63) | 89% |

MUM, metastatic uveal melanoma. ORR, objective response rate. pCR, pathological complete response. SD, stable disease. PD, progressive disease. DCR, disease control rate (pCR+SD).

# Genito-Urinary Cancers

## Two potential new first-line standards of care in metastatic urothelial cancer

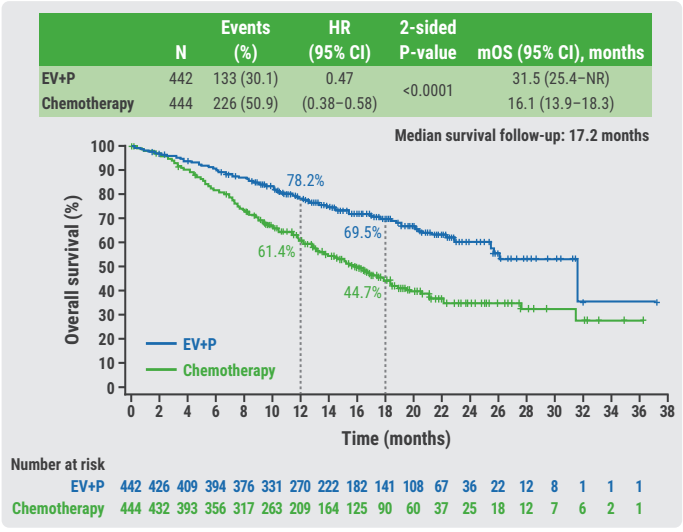
**Results from two trials, the EV-302/KEYNOTE-A39 and CheckMate 901 trials, demonstrated significantly improved progression-free (PFS) and overall survival (OS) in participants with locally advanced or metastatic urothelial cancer.**

For decades, platinum-based chemotherapy has been the first-line treatment for patients with locally advanced or metastatic urothelial cancer. Previous studies, evaluating chemotherapy concurrently with immunotherapy, have failed to demonstrate improved survival in these patients [1,2]. The current phase 3 EV-302/KEYNOTE-A39 (NCT04223856) explored the efficacy and safety of first-line enfortumab vedotin (EV) in combination with pembrolizumab compared with chemotherapy alone. The first results were presented by Prof. Thomas Powles (Queen Mary University of London, UK) [3].

A total of 886 participants with previously untreated locally advanced or metastatic urothelial cancer were randomised 1:1 to first-line EV/pembrolizumab until progression (max 35 cycles of pembrolizumab) or 6 cycles platinum-based chemotherapy (maintenance avelumab permitted). The primary endpoints were PFS and OS.

EV/pembrolizumab outperformed chemotherapy in both PFS and OS. Median PFS was 12.5 versus 6.3 months (HR 0.45; 95% CI 0.38–0.54; P<0.00001) and median OS was 31.5 versus 16.1 months (HR 0.47; 95% CI 0.38–0.58; P<0.00001) in the EV/pembrolizumab arm and chemotherapy arm, respectively (see Figure). The benefit of EV/pembrolizumab over chemotherapy was observed in all prespecified subgroups, including stratification by PD-L1 status and cisplatin eligibility. In addition, EV/pembrolizumab was superior to chemotherapy regarding objective response rate (ORR, 67.7% vs 44.4%). Moreover, the complete response rate more than doubled with EV/pembrolizumab (29.1% vs 12.5%). The rate of adverse events grade ≥3 was highest in the chemotherapy arm (70% vs 56% in the EV/pembrolizumab arm).

**Figure: Overall survival was reduced by 53% in participants who received EV/pembrolizumab compared with chemotherapy alone, results from the EV-302/KEYNOTE-A39 showed [3]**




HR, hazard ratio. mOS, median overall survival. CI, confidence interval. EV+P, enfortumab vedotin/pembrolizumab. NR, not reached. N, number.

Alternatively, the CheckMate 901 trial (NCT03036098), a randomised, phase 3 trial, combined chemotherapy (gemcitabine/cisplatin) with nivolumab. The trial enrolled 608 participants with previously untreated unresectable or metastatic urothelial cancer and randomised them 1:1 to gemcitabine/cisplatin for 6 cycles or nivolumab plus gemcitabine/cisplatin for 6 cycles followed by nivolumab until disease progression or a maximum of 1 year. The primary endpoints were PFS and OS. The results were presented by Dr Michiel van der Heijden (Netherlands Cancer Institute, the Netherlands) [5].

Nivolumab plus chemotherapy significantly outperformed chemotherapy alone both for PFS and OS. The median OS was 21.7 versus 18.9 months (HR 0.78; 95% CI 0.63–0.96; P=0.0171) and the median PFS was 7.9 versus 7.6 months (HR 0.72; 95% CI 0.59–0.88; P=0.0012) for nivolumab plus chemotherapy and chemotherapy alone, respectively. The benefit in the nivolumab arm was observed in all prespecified subgroups, including stratification by PD-L1 expression and liver metastasis.

The ORR was also improved in the nivolumab arm: 57.6% (21.7% complete responders) versus 43.1% (11.8% complete responders). Responses were rapidly achieved (median time-to-response 2 months in both arms) and the median duration of response was longer in the nivolumab arm (9.5 vs 7.3 months). The median duration of complete response was 37.1 versus 13.2 months, respectively. "Nivolumab plus gemcitabine/cisplatin is associated with rapid, deep, and durable responses," said Dr Van der Heijden.

The rate of treatment-related adverse events was almost similar in both arms: 57% versus 48% (any grade) and 22% versus 18% (grade ≥3) for nivolumab plus chemotherapy versus chemotherapy alone, respectively. The most prominent adverse events were chemotherapy-related.

Based on these results, both Prof. Powles and Dr Van der Heijden concluded that, at last, the bar for OS in locally advanced or metastatic urothelial cancer has been raised. Both EV/pembrolizumab and chemotherapy/nivolumab could become a new first-line standard of care.

Discussant Dr Andrea Apolo (NCI Bethesda, MD, USA) fully agreed. "However, with new standards of care come new questions, such as 'What will be the best second line?' And 'What will be the role of checkpoint inhibition in later lines?'"


1. Powles T, et al. Lancet Oncol. 2021;22(7):931–945.
2. Galsky MD, et al. Lancet. 2020;395(10236):1547–1557.
3. Powles TB, et al. 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). Abstract LBA6, ESMO 2023, 20–24 October, Madrid, Spain.
4. Van der Heijden MS, et al. Nivolumab plus gemcitabine-cisplatin versus gemcitabine-cisplatin alone for previously untreated unresectable or metastatic urothelial carcinoma: Results from the phase III CheckMate 901 trial. Abstract LBA7, ESMO 2023, 20–24 October, Madrid, Spain.

## LuPSMA and enzalutamide: a promising combination

**The combination of enzalutamide and lutetium-177-PSMA-617 (LuPSMA) enhanced anticancer effects in prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) participants, the first results of the ENZA-p trial showed.**

Both the nonsteroidal antiandrogen enzalutamide and PSMA-specific radionucleotide treatment LuPSMA improve overall survival (OS) in mCRPC [1,2]. It is also known that treatment with enzalutamide upregulates PSMA expression in tumour cells. Therefore, combining enzalutamide and LuPSMA could be synergistic. This hypothesis was tested in the randomised phase 2 ENZA-p trial (NCT04419402). The results from the first interim analysis at a median follow-up of 20 months were presented by Prof. Louise Emmett (St Vincent's Hospital Sydney, Australia) [3].

A total of 162 participants with mCRPC, rising prostate-specific antigen (PSA) levels, at least 2 high-risk factors for early enzalutamide failure, and a positive $^{68}$Ga-PSMA scan were randomised 1:1 to enzalutamide or enzalutamide plus LuPSMA. LuPSMA was given 15 days after the start of enzalutamide and again 6 weeks later. Participants in the LuPSMA arm who had maintained a positive PSMA scan at day 92 were offered 2 extra LuPSMA doses. The primary endpoint is PSA-progression-free survival (PSA-PFS). The secondary endpoints include radiological PFS (rPFS), PSA50% and PSA90% response rates (PSA50RR, PSA90RR), adverse events, and OS.

LuPSMA favoured PSA-PFS as the primary endpoint. The median PSA-PFS was 13 months in the LuPSMA arm versus 7.8 months in the enzalutamide alone arm (HR 0.43; 95% CI 0.29–0.63; P<0.00001). The PSA response rates were also in favour of LuPSMA, where PSA50RR was 93% versus 67% in the LuPSMA and enzalutamide arms, respectively. PSA90RR was 78% versus 37%. Adverse events were similar in both arms.

"These results provide strong evidence that the combination of enzalutamide and LuPSMA has enhanced anticancer effects in PSMA-positive mCRPC patients," Prof. Emmett concluded. "In addition, the adaptive LuPSMA dosing has the potential to reduce toxicity by only administering in patients with persistent PSMA-avid disease." The progression-free and overall survival data are planned for July 2024.


1. Beer TM, et al. N Engl J Med. 2014;371:424–433.
2. Sartor O, et al. N Engl J Med. 2021;385:1091–1103.
3. Emmett L, et al Enzalutamide and 177Lu-PSMA-617 in poor-risk, metastatic, castration-resistant prostate cancer (mCRPC): A randomised, phase II trial: ENZA-p (ANZUP 1901). Abstract LBA84, ESMO 2023, 20–24 October, Madrid, Spain.


## No benefit of erdafitinib over pembrolizumab in urothelial cancer second-line therapy

**While superior to chemotherapy, erdafitinib did not outperform pembrolizumab as second-line treatment in participants with *FGFR3/2*-altered, metastatic urothelial carcinoma, results from Cohort 2 of the THOR trial showed.**

Despite much progress in first-line treatment of metastatic urothelial cancer, improved second-line treatment remains an unmet clinical need [1]. Selective FGFR inhibition is becoming an increasingly important focus of novel drug development for this population [2]. Erdafitinib is a US-approved oral pan-FGFR tyrosine kinase inhibitor to treat locally advanced/metastatic urothelial carcinoma in patients with susceptible *FGFR3/2* alterations who progressed after platinum-containing chemotherapy. Erdafitinib's accelerated approval was based on outcomes from a phase 2, single-arm trial [3].

The recent phase 3, randomised THOR trial (NCT03390504) investigates the efficacy of erdafitinib as a second-line treatment versus standard of care in participants with unresectable, advanced or metastatic urothelial cancer. Results from Cohort 1 showed that erdafitinib significantly improved progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) versus chemotherapy in participants with an *FGFR* alteration [4]. In the current Cohort 2, erdafitinib was compared with pembrolizumab in the same participant group. Prof. Arlene Siefker-Radtke (MD Anderson Cancer Centre, TX, USA) presented the results [5].

Cohort 2 enrolled 351 (checkpoint inhibitor-naïve) participants who had progressed on first-line treatment. Participants were randomised 1:1 to erdafitinib or pembrolizumab. The primary endpoint was OS. "In contrast to the results from Cohort 1, the trial did not meet its primary endpoint for Cohort 2," summarised Prof. Siefker-Radtke. Neither the median OS nor the median PFS were statistically different between the groups. She continued: "This was somewhat unexpected because *FGFR*-altered tumours are known as 'cold' tumours, i.e. unresponsive for immune therapy. In line with this, we observed a significantly lower ORR in participants treated with pembrolizumab. However, the duration of response was longer in the pembrolizumab arm than in the erdafitinib arm."


1. Zheng X, et al. Front Oncol. 2022;12:907377.
2. Garje R, et al. Oncologist. 2020;25(11):e1711–e1719.
3. Loriot Y, et al. N Engl J Med. 2019;381:338–348.
4. Loriot Y, et al. J Clin Oncol. 2023;41(17_suppl):LBA4619–LBA4619.
5. Siefker-Radtke AO, et al. Phase III THOR study: Results of erdafitinib (erda) vs pembrolizumab (pembro) in pretreated patients (pts) with advanced or metastatic urothelial cancer (muc) with select fibroblast growth factor receptor alterations (FGFRalt). Abstract 2359O, ESMO 2023, 20–24 October, Madrid, Spain.

# Gynaecological Cancers

## Addition of atezolizumab to chemotherapy and maintenance PARP inhibitor has no benefit in ovarian cancer

**Combining atezolizumab with chemotherapy and maintenance PARP inhibitor niraparib in late-relapsing recurrent chemotherapy-sensitive ovarian cancer does not significantly improve progression-free survival (PFS) nor objective response rate (ORR), results of the phase 3 ANITA trial showed.**

The standard therapy for ovarian cancer with a treatment-free interval of more than 6 months (late-relapsing) is chemotherapy followed by PARP inhibitor maintenance, in case a response to chemotherapy is observed. Despite a strong preclinical rationale, most previous phase 3 studies failed to show the benefit of the addition of a PD-L1 inhibitor to this standard treatment [1–4].

The current phase 3 ANITA trial (NCT03598270) evaluated the effectiveness of PD-1 checkpoint inhibitor atezolizumab in participants treated with chemotherapy and subsequent maintenance PARP inhibition using niraparib. ANITA enrolled 417 participants with high-grade late-relapsing recurrent ovarian cancer who were randomised 1:1 to 6 cycles of chemotherapy with or without atezolizumab followed by maintenance niraparib with or without atezolizumab in case of chemotherapy sensitivity. The primary endpoint was PFS. Prof. Antonio Gonzalez Martin (Cancer Centre Clinica Universidad de Navarre, Spain) presented the first results [5].

The addition of atezolizumab did not significantly improve median PFS: 11.2 versus 10.2 months (HR 0.89; 95% CI 0.71–1.10; P=0.28). No benefit of atezolizumab was observed in any of the prespecified subgroups, including PD-L1 status. Also, atezolizumab did not improve ORR (45% versus 43%) or any other secondary endpoint available at this point.

Placing these results in the context of other studies on this subject, discussant Prof. Charley Gourley (University Edinburgh, UK) suggested that the (negative) results of ANITA fit the idea that bevacizumab is required to 'unlock' the synergy of the PARP inhibitor and immune checkpoint inhibitor combination. The role of bevacizumab in the treatment of this ovarian cancer setting is however not clear [6]. Yet, in both the DUO-O (NCT03737643) and MEDIOLA trials (NCT02734004), triplet therapy (PARP inhibitor, immune checkpoint inhibitor, bevacizumab) showed benefits in ORR or PFS over doublet therapy [6,7].


1. Monk BJ, et al. Lancet Oncol. 2021;22(9):1275–1289.
2. Pujade-Lauraine E, et al. Lancet Oncol. 2021;22(7):1034–1046.
3. Moore KN, et al. J Clin Oncol. 2021;39(17):1842–1855.
4. Kurtz JE, et al. J Clin Oncol. 2023;41(30):4768–4778.
5. Gonzalez Martin A, et al. Atezolizumab (atezo) combined with platinum-based chemotherapy (CT) and maintenance niraparib for recurrent ovarian cancer (rOC) with a platinum-free interval (TFIp) >6 months: Primary analysis of the double-blind placebo (pbo)-controlled ENGOT-Ov41/GEICO 69-O/ANITA phase III trial. Abstract LBA37, ESMO 2023, 20–24 October, Madrid, Spain.
6. Harter P, et al. J Clin Oncol. 2023;41(17_suppl): LBA5506–LBA5506.
7. Drew Y, et al. Ann Oncol. 2020;31(suppl_4): S615–S616.


## Short-induction chemotherapy improves survival in advanced cervical cancer

**The addition of 6 cycles of carboplatin/paclitaxel induction chemotherapy, directly followed by standard chemoradiotherapy, improved progression-free survival (PFS) and overall survival (OS) in participants with locally advanced cervical cancer by almost 40%, results of the phase 3 INTERLACE trial showed.**

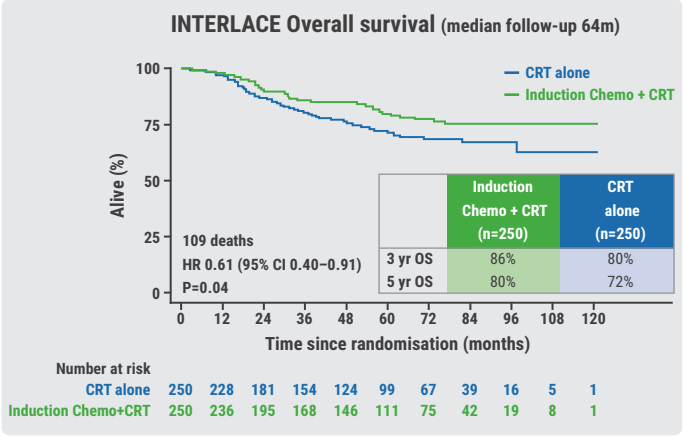
For more than 2 decades, chemoradiotherapy followed by brachytherapy has been the standard of care for patients with locally advanced cervical cancer (FIGO IB3–IVA). Although the local control of disease has increased over time, up to 30% of patients eventually relapse and die from metastatic disease. A recent phase 2 study showed the feasibility and a good response rate of induction chemotherapy using weekly paclitaxel and carboplatin for 6 cycles, immediately followed by standard chemoradiotherapy [1].

The current phase 3 INTERLACE trial (EudraCT: 2011-001300-35) randomised 500 participants with locally advanced cervical cancer (stage IB1 node positive–IVA) to standard chemo-radiotherapy or induction chemotherapy followed by standard chemoradiotherapy. The primary endpoints were PFS and OS. Results were presented by Dr Mary McCormack (University College London, UK) [2].

About 75% of enrolled participants presented with stage IIA or IIB disease, 82% showed squamous histology and almost 60% of participants and tumours were node-negative. The

adherence to induction chemotherapy was high, with more than 90% of participants having received at least 5 cycles of induction chemotherapy. Also, more than 90% of participants adhered to radiotherapy in both study arms. Induction chemotherapy substantially increased both PFS and OS. At the 5-year follow-up, 73% of participants in the induction arm were progression-free versus 64% in the control arm (HR 0.65; 95% CI 0.46–0.91; P=0.013). At the same follow-up time point, 86% of participants in the induction arm were still alive versus 80% in the control arm (HR 0.61; 95% CI 0.40–0.91; P=0.04, see Figure). "OS in the control arm was similar to that in the recent literature," remarked Dr McCormack. Total local relapse rates after 5 years were 16% in both arms. In contrast, the total distant relapse rate after 5 years was 12% in the induction arm versus 20% in the control arm.

**Figure: Overall survival results from the INTERLACE trial over time [2]**




HR, hazard ratio. CRT, chemoradiotherapy. Chemo, chemotherapy. OS, overall survival. Yr, year. CI, confidence interval. FU, follow-up.

"In conclusion, the INTERLACE trial showed that short induction chemotherapy with paclitaxel and carboplatin can significantly improve PFS and OS and decrease distant relapses. This induction protocol is feasible across different healthcare settings and should be considered the new standard in locally advanced cervical cancer," summarised Dr McCormack.


1. McCormack M, et al. Br J Cancer. 2013;108:2464–2469.
2. McCormack M, et al. A randomised phase III trial of induction chemotherapy followed by chemoradiation compared with chemoradiation alone in locally advanced cervical cancer: The GCIG INTERLACE trial. Abstract LBA8, ESMO 2023, 20–24 October, Madrid, Spain.


## Neoadjuvant immune checkpoint blockade safe and effective in MMRd endometrial cancer

**In mismatch repair-deficient (MMRd) endometrial cancer, neoadjuvant immune checkpoint blockade with pembrolizumab is safe and feasible, the first results of the phase 1 PAM study demonstrated.**

Recent studies suggest neoadjuvant immune checkpoint blockade may be more efficacious than adjuvant treatment in (MMRd) cancers [1,2]. However, neoadjuvant immune checkpoint blockade in local MMRd has not been explored for endometrial cancer. The recent PAM study (NCT04262089) aimed to establish proof of concept for the use of immune checkpoint blockade as novel neoadjuvant therapy in patients with endometrial cancer characterised by either MMRd or mutations in the exonuclease (proofreading) domain of DNA polymerase epsilon. Dr Marco de Bruyn (University Medical Center Groningen, the Netherlands) presented results from the MMRd cohort [3].

Participants (n=4 stage I–II, n=6 stage III) at intent-to-treat with primary surgery (minimally a hysterectomy) were treated with 2 x 3-weekly cycles of pembrolizumab before standard of care resection and adjuvant treatment if indicated. The radiologic and pathologic response rates, treatment-related adverse events and immune correlates of treatment were assessed.

In participants with measurable disease on MRI (n=8), a partial radiologic response was observed in 3 of 8 participants (objective response rate [ORR] 37.5%). A pathological response (<90% viable cancer cells) was observed in 5 of 10 participants, with 2 major pathologic responses (<10% viable cancer cells). Up to the date of presentation of the results, no recurrences have been observed, with a median and longest disease-free survival of 17 and 26 months, respectively.

The safety profile was as to be expected. Grade 1–2 treatment-related adverse events were observed in 9 of 10 participants. A treatment-induced immunological response was detected in 9 of 10 participants with increased lymphoid infiltrates, clonal T cell expansion and diverse T cell phenotypes in post-treatment samples. Monoclonal T cell expansion of predominantly CD8-positive cells was observed in responding participants. In tumour-draining (sentinel) lymph nodes, a significant clonal overlap with treatment-induced intratumoral T cell expansion was demonstrated.

"Neoadjuvant immune checkpoint blockade is safe and feasible in MMRd endometrial cancer," concluded Dr De Bruyn. An investigation of extended neoadjuvant treatment (9 cycles) is currently being evaluated.


1. Chalabi M, et al. Ann Oncol. 2022;33(suppl_7):S1389.
2. Reijers ILM, et al. Nat Med. 2022;28:1178–1188.
3. De Bruyn M, et al. Neoadjuvant immune checkpoint blockade in mismatch repair deficient endometrial cancer. Abstract 742MO, ESMO 2023, 20–24 October, Madrid, Spain.