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PEER-REVIEWED CONFERENCE REPORT

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Breast and Haematological Cancer

Olaparib Benefits Early Breast Cancer Patients

A first interim analysis of the OlympiA trial demonstrated significantly improved invasive disease-free survival in patients with high-risk, HER2-negative, germline *BRCA1/2*-mutated primary breast cancer.

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Immune-Related Adverse Events Associated with Efficacy of Atezolizumab

A pooled analysis of three phase 3 trials in patients with stage IV non-small cell lung cancer showed longer overall survival for patients who experience immune-related adverse events.

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T-DXd Shows Promising Activity in mCRC

In the phase 2, open-label DESTINY-CRC01 trial, treatment of patients with HER2-expressing metastatic colorectal cancer (mCRC) with trastuzumab-deruxtecan (T-DXd) showed promising activity and durability, as well as a manageable safety profile.

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Editor Dr Stefan Rauh, Centre Hospitalier Emile Mayrisch, Luxembourg

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Letter from the Editor

Dr Stefan Rauh

Dear colleagues,

I am delighted to introduce you to our ASCO 2021 Annual Meeting congress report.

Expect plenty of new insights in immunotherapy: checkpoint inhibitors may soon be indicated in (neo) adjuvant treatment, and have become the first anti-neoplastic treatment to provide a benefit in the adjuvant treatment of renal cell carcinoma. New immunologic targets (such as LAG-3) continue to enforce treatment options. You may already have known that toxicity somehow rhymes with treatment efficiency; two studies in checkpoint inhibitors seem to confirm this.

Of course, that's not all there is. HER2 overexpression leads to new treatment options in colorectal cancer. Check out new treatment targets in haematological and solid tumours. The principle of personalised medicine with gene sequencing-based treatment receives further conformation with studies in paediatric cancers.

There's much more in this report – see for yourself!

Wary of visio-conferences? Me, too! Let's hope this will be the last entirely virtual ASCO Annual Meeting… Never-ending COVID is no source for optimism, of course. I also hope that the trend to the more economic all-virtual format will not prevail over the advantage to be in the meeting, listen to the expert Q&A, and spend time with attendees to discuss the topics.

Yours, sincerely

Stefan Rauh

Biography

Dr Stefan Rauh is currently working as haemato-oncologist in the oncology department of Centre Hospitalier Emile Mayrisch, Esch, Luxembourg. He is mainly involved in clinical work but also in research and teaching activities and is interested in public policy and international cooperation projects in oncology. He is member of the ESMO Practicing Oncologist's Working Group since 2011 (chair 2014-2018), member of 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

Excellent prognosis for breast cancer patients with ultra-low-risk gene signature

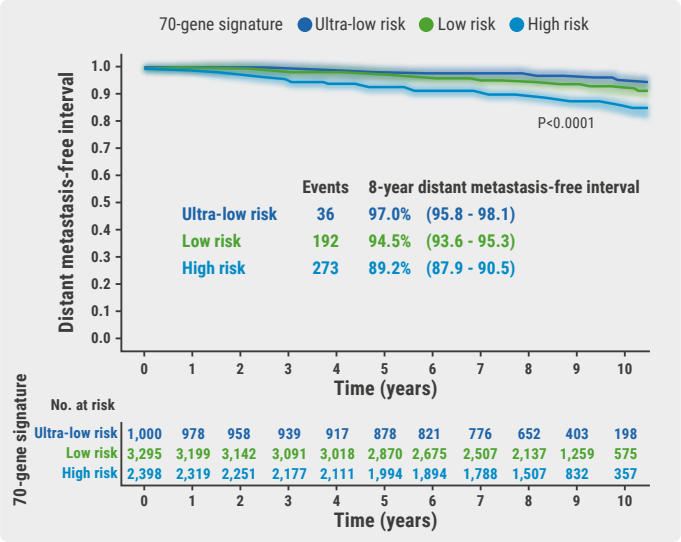
An analysis of 1,000 patients in the MINDACT trial identified patients with ultra-low risk for distant recurrence. These patients could be candidates for further de-escalation of treatment.

Gene signatures have proven successful in identifying patients with a low risk of distant recurrence who could forego chemotherapy [1]. Currently, these signatures are included in international treatment guidelines for breast cancer. For the 70-gene signature (MammaPrint), an additional threshold was established within the low-risk category to identify patients with an ultra-low risk of distant recurrence [2]. In independent cohorts, these patients had excellent breast cancer-specific survival at 15 years, suggesting that ultra-low risk cancers represent indolent diseases [3].

Dr Josephine Lopes Cardozo (Netherlands Cancer Institute, the Netherlands) presented the survival results of patients with an ultra-low-risk 70-gene signature who participated in the randomised, phase 3 MINDACT trial (NCT00433589) [4]. Of the 6,693 patients enrolled, profiling revealed an ultra-low-risk 70-gene signature in 1,000 patients (15%). Among these, 67% were ≥50 years, 81% had tumours <2 cm, 80% were lymph node-negative, 96% had grade 1 or 2 tumours, and 99% were ER-positive. Of patients with an ultra-low risk according to the 70-gene signature, 741 had a low clinical risk and 259 had a high clinical risk. Systemic therapy was received by 83% of patients (69% endocrine therapy, 14% endocrine therapy plus chemotherapy) and 16% received no adjuvant systemic treatment.

After a median follow-up of 8.7 years, 8-year distant metastasis-free interval in the patients with ultra-low risk was 97.0% (vs 94.5% for patients with low-risk signature and 89.2% for patients with high-risk signature; see Figure). Breast cancer-specific survival rate at 8 years was 99.6%, 98.2%, and 93.7%, respectively. The difference in distant metastasis-free interval between patients with ultra-low-risk signature and clinical low risk (n=741) versus ultra-low-risk signature and clinical high risk (n=259) was small: 97.6% versus 95.0%. No difference in breast cancer-specific survival was observed in genomic ultra-low-risk patients by clinical risk: 99.7% versus 99.2%. Distant metastasis-free interval in genomic ultra-low-risk patients who had received no adjuvant systemic treatment was 97.8% versus 97.4% in ultra-low-risk patients who had received adjuvant endocrine systemic therapy and 94.9% in ultra-low-risk patients who had received adjuvant endocrine therapy and chemotherapy.

Figure: Excellent distant metastasis-free interval rates for genomic low-risk and ultra-low-risk patients [4]



Based on these results, Dr Lopes Cardozo concluded that "the 70-gene signature MammaPrint can identify early breast cancer patients who have an ultra-low risk for distant recurrence. These patients could be candidate for further de-escalation of treatment, further reducing overtreatment and the risk of side effects."

1. Piccart M, et al. Lancet Oncol. 2021;22:476-488.
2. Esserman LJ, et al. JAMA Oncol. 2017;3:1503-1510.
3. Delahaye LJMJ, et al. BC Res Treat. 2017;164:461-466.
4. Lopes Cardozo J, et al. Outcome of patients with an ultralow risk 70-gene signature in the MINDACT trial. Abstract 500, ASCO 2021 Virtual Meeting, 4–8 June.

Platinum-based adjuvant chemotherapy in TNBC is not superior or non-inferior to capecitabine

In the ECOG-ACRIN EA1131 trial, platinum-based adjuvant chemotherapy in patients with (basal subtype) triple-negative breast cancer (TNBC) with residual invasive disease did not prove to be non-inferior or

superior to capecitabine adjuvant chemotherapy. The trial was discontinued after the fifth interim analysis.

Patients with TNBC who have residual invasive disease after completion of neoadjuvant chemotherapy have a very high risk of recurrence [1]. Recently, the CREATE-X trial showed this risk is reduced by adjuvant capecitabine, while pre-clinical models suggest TNBC basal subtype has increased sensitivity for platinum-based chemotherapy [2,3].

Therefore, the randomised, phase 3 ECOG-ACRIN EA1131 trial (NCT0244539) tested the hypothesis that invasive disease-free survival would be improved in patients with basal subtype TNBC with residual disease after neoadjuvant chemotherapy with the adjuvant use of platinum-based chemotherapy instead of capecitabine. The trial enrolled 410 patients (recruitment goal: 775) with clinical stage II/III TNBC post-neoadjuvant taxane ± anthracycline-based chemotherapy with at least 1 cm residual disease in the surgical specimen. Patients were randomised 1:1 to receive platinum-based adjuvant chemotherapy (carboplatin or cisplatin once every 3 weeks for 4 cycles) or capecitabine (14 out of 21 days every 3 weeks for 6 cycles). TNBC subtype (i.e basal and non-basal) was analysed in the surgical specimen by PAM50 profiling. The primary endpoint of the trial was invasive disease-free survival. A non-inferiority design (non-inferiority margin of HR of 1.154) with superiority alternative (alternative HR of 0.754) was chosen, assuming a 4-year invasive disease-free survival of 67% for the capecitabine arm. Prof. Ingrid Mayer (Vanderbilt University School of Medicine, TN, USA) presented the results of ECOG-ACRIN EA1131 after the fifth interim analysis [4].

After a median follow-up of 20 months and 120 invasive disease-free survival events (61% of full information) in the 308 (78%) patients with basal subtype TNBC, the 3-year invasive disease-free survival for platinum-treated patients was 42% versus 49% for capecitabine-treated patients (HR 1.06; 95% CI 0.62-1.81).

Grade 3 and 4 toxicities were more common with platinum agents. Based on these interim results, the Data and Safety Monitoring Committee recommended stopping the trial as it was unlikely that further follow-up would show non-inferiority or superiority of platinum-based chemotherapy.

1. Symmans WF, et al. J Clin Oncol. 2017;35:1049-1060.
2. Masuda N, et al. N Engl J Med. 2017;376:2147-2159.
3. Lehmann BD, et al. J Clin Invest. 2011;121:2750-2767.
4. Mayer IA, et al. A randomized phase III post-operative trial of platinum-based chemotherapy (P) versus capecitabine (C) in patients (pts) with residual triple-negative breast cancer (TNBC) following neoadjuvant chemotherapy (NAC): ECOG-ACRIN EA1131. Abstract 605, ASCO 2021 Virtual Meeting, 4–8 June.

Olaparib benefits early breast cancer patients with *BRCA1/2* germline mutation

Featured interview: Dr Judy Garber (Dana-Farber Cancer Institute, MA, USA) discusses the OlympiA trial: Adjuvant olaparib extends disease-free survival in *BRCA* carriers.

read the interview online >

A first interim analysis of the OlympiA trial demonstrated significantly improved invasive disease-free survival in patients with high-risk, HER2-negative, germline *BRCA1/2*-mutated primary breast cancer after 1 year of adjuvant treatment with the PARP inhibitor olaparib.

The PARP inhibitor olaparib is licensed for metastatic HER2-negative breast cancer with *BRCA1/2* germline mutation (gBRCAm). Even with (neo)adjuvant chemotherapy, recurrence rates in patients with gBRCAm early breast cancer can be high, and novel adjuvant treatments are needed.

The OlympiA trial (NCT02032823) explores the efficacy and safety of adjuvant treatment with olaparib in patients with gBRCAm, high-risk, HER2-negative primary breast cancer. The study enrolled 1,836 patients with gBRCAm and HER2-negative (triple-negative or HR-positive), high-risk, early breast cancer after primary local treatment and adjuvant (49.9%) or neoadjuvant (50.1%) chemotherapy. Patients were randomised 1:1 to receive 1 year of continuous oral olaparib (300 mg twice daily) or placebo. Endocrine therapy and bisphosphonates were allowed. The primary endpoint was invasive disease-free survival in the intention-to-treat population. Secondary endpoints included distant disease-free survival, overall survival, and safety. Prof. Andrew Tutt (Institute of Cancer Research, UK) presented the results of the first interim-analysis of OlympiA at 2.5 years median follow-up [1].

Results showed a significant benefit of olaparib versus placebo regarding invasive disease-free survival (HR 0.58; P<0.0001). Three-year invasive disease-free survival was 85.9% versus 77.1%. Distant disease-free survival was also significantly improved with olaparib (HR 0.57; P<0.0001). Three-year distant disease-free survival was 87.5% versus 80.4%. Overall survival was greater for olaparib than placebo but was not statistically significant at the time of the interim analysis. Three-year overall survival was 92.0% versus 88.3%.

No unexpected adverse events of olaparib were observed. Global Health Quality of Life Score was not significantly affected by treatment with olaparib in patients treated with olaparib after adjuvant chemotherapy nor in patients treated with olaparib after neoadjuvant chemotherapy.

Based on these interim-results, Prof. Tutt concluded that "patients with high-risk, HER2-negative, early breast cancer and germline *BRCA1/2* mutations benefit from adjuvant olaparib for 1 year after completion of adjuvant or neoadjuvant chemotherapy."

1. Tutt A, et al. OlympiA: A phase III, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo)adjuvant chemotherapy in patients with germline BRCA1/2 mutations and high-risk HER2-negative early breast cancer. Abstract LBA1, ASCO 2021 Virtual Meeting, 4–8 June.

Dalpiciclib benefits patients with HR-positive, HER2-negative advanced breast cancer

First results of the DAWNA-1 trial showed increased progression-free survival in patients with HR-positive, HER2-negative advanced breast cancer who relapsed on endocrine therapy and who were treated with dalpiciclib, a new CDK4/6 inhibitor.

For patients with HR-positive, HER2-negative advanced breast cancer, treatment with a CDK4/6 inhibitor combined with endocrine therapy is the standard of care, since it achieves a substantial progression-free benefit, significantly increases overall survival, and either maintains or improves quality of life [1]. Dalpiciclib is a novel CDK4/6 inhibitor that has demonstrated tolerability and preliminary anti-tumour activity in pre-treated HR-positive, HER2-negative advanced breast cancer [2].

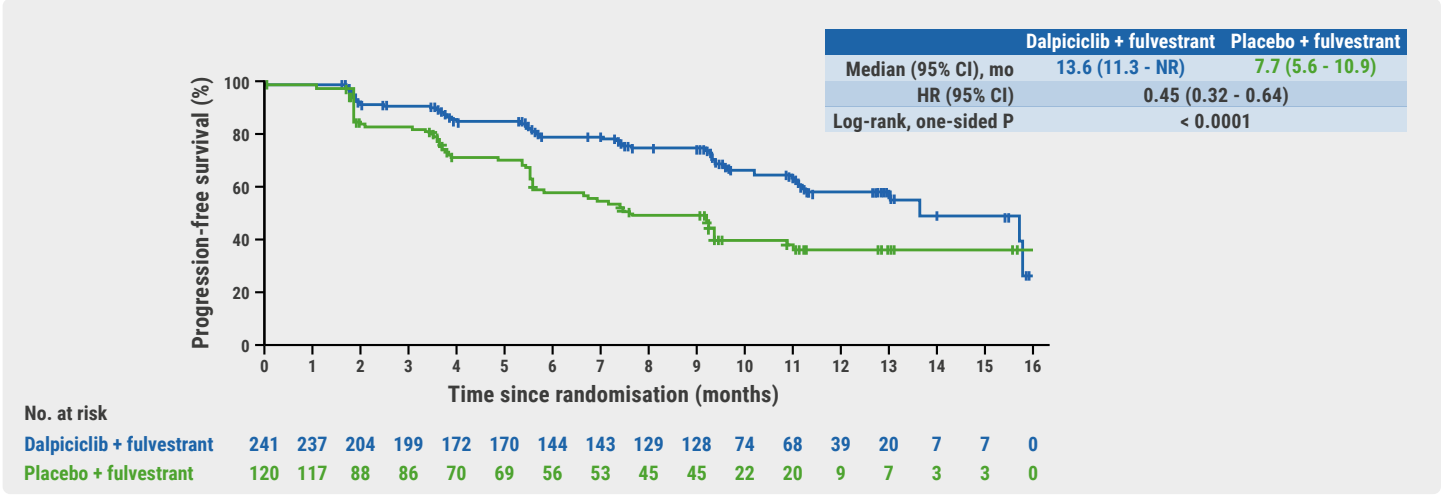
DAWNA-1 (NCT03927456) is a randomised, phase 3 clinical trial evaluating the efficacy and safety of dalpiciclib in HR-positive, HER2-negative advanced breast cancer patients who relapsed or progressed on previous endocrine therapy. The trial enrolled 361 patients who were randomised 2:1 to receive dalpiciclib (150 mg once daily, first 3 weeks of every 4 weeks) plus fulvestrant (500 mg, day 1 and 15 of cycle 1, then day 1 every 4 weeks) or placebo plus fulvestrant. The primary endpoint was progression-free survival. Prof. Binghe Xu (Chinese Academy of Medical Sciences and Peking Union Medical College, China) presented the first results of DAWNA-1 [3].

With a median follow-up of 10.5 months, dalpiciclib plus fulvestrant significantly improved median progression-free survival (per independent review committee): 13.6 months versus 7.7 months (HR 0.45; 95% CI 0.32–0.64; P<0.0001; see Figure). Median time to first subsequent chemotherapy was not reached for dalpiciclib versus 14.2 months for placebo.

Grade 3 or 4 toxicity was increased in patients treated with dalpiciclib compared with placebo: 88.3% versus 11.7%. The most common grade 3 or 4 adverse events with dalpiciclib were neutropenia and leukopenia. Treatment discontinuation due to adverse events was reported for 2.5% of patients treated with dalpiciclib versus 3.3% in the placebo arm.

1. Cardoso F, et al. Ann Oncol. 2020;31:1623-1649.
2. Zhang P, et al. Biomark Res. 2021;9:24.
3. Xu B, et al. Dalpiciclib versus placebo plus fulvestrant in HR+/HER2- advanced breast cancer that relapsed or progressed on previous endocrine therapy (DAWNA-1): A multicenter, randomized, phase 3 study. Abstract 1002, ASCO 2021 Virtual Meeting, 4–8 June.

Figure: Progression-free survival in DAWNA-1 [3]



Trastuzumab-deruxtecan showed clinical activity in patients with brain metastases

Featured interview: Prof. Guy Jerusalem (CHU Liège, Belgium) discusses the DESTINY-Breast01 trial: T-DXd response on brain metastases in HER2+ breast cancer patients.

read the interview online >

A subgroup analysis of the DESTINY-Breast01 trial demonstrated clinical activity of the antibody-drug conjugate trastuzumab-deruxtecan (T-DXd) in patients with HER2-positive metastatic breast cancer who presented with baseline brain metastases.

Patients with HER2-positive metastatic breast cancer are at high risk of developing brain metastases, and treatment options are limited once brain metastases occur [1]. T-DXd is an antibody-drug conjugate composed of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a topoisomerase I inhibitor payload [2].

In the ongoing, phase 2 DESTINY-Breast01 trial (NCT03248492), 184 patients with HER2-positive metastatic breast cancer were enrolled, of whom 24 had a history of brain metastases (17 had brain lesions at baseline). Patients received T-DXd at 5.4 mg/kg every 3 weeks. Overall, T-DXd showed durable anti-tumour activity, and these results led to the approval of T-DXd for the treatment of adult patients with HER2-positive, unresectable or metastatic breast cancer who received 2 or more prior anti-HER2-based regimens (USA and Europe) or had prior chemotherapy and are refractory to or intolerant of standard treatments (Japan) [3].

Prof. Guy Jerusalem (CHU Liège, Belgium) presented the results of a subgroups analysis of the 24 patients with baseline brain metastases [4]. Brain lesions were monitored by MRI or CT every 6 weeks. In these patients, the objective response rate was 58.3% versus 60.9% in all 184 patients treated with T-DXd. Median duration of response was 16.9 months versus 14.8 months in all patients. Median progression-free survival was 18.1 months in the patients with baseline brain metastases versus 16.4 months in all patients. For 15 of the 17 patients who had brain metastases at baseline, data was available to evaluate responses in the brain. Seven patients experienced tumour shrinkage consistent with a partial response in the brain, 7 had stable disease, and 1 had disease progression as the best response.

Based on these results, it was concluded that T-DXd shows a durable systemic disease control in patients with stable treated brain metastases at baseline, with clinical outcomes similar to those of the overall population.

1. Hurvitz SA, et al. Clin Cancer Res. 2019;25:2433-2441.
2. Ogitani Y, et al. Cancer Sci. 2016;107:1039-1046.
3. Modi S, et al. N Engl J Med. 2020;382:610-621.
4. Jerusalem GHM, et al. Trastuzumab deruxtecan (T-DXd) in patients with HER2+ metastatic breast cancer with brain metastases: A subgroup analysis of the DESTINY-Breast01 trial. Abstract 526, ASCO 2021 Virtual Meeting, 4–8 June.

Venetoclax does not benefit ER-positive, HER2-negative metastatic breast cancer

Addition of the BCL2 inhibitor venetoclax to endocrine therapy did not improve clinical benefit in patients with ER-positive, HER2-negative locally advanced/metastatic breast cancer, according to the primary analysis of the phase 2 VERONICA trial.

For patients with ER-positive, HER2-negative metastatic breast cancer, standard first-line treatment consists of CDK4/6 inhibitors combined with single-agent endocrine therapy. Yet, most patients progress. A potential novel therapeutic target is the anti-apoptotic protein BCL2, which is overexpressed in ~85% of primary ER-positive breast cancers. Venetoclax, which has already been approved in several haematological malignancies, is a potent, selective, oral BCL2 inhibitor that has shown promising clinical activity in patients with ER-positive and BCL2-positive metastatic breast cancer who have received prior endocrine therapy [1,2].

The VERONICA trial (NCT03584009) included 103 patients with ER-positive, HER2-negative metastatic breast cancer who had progressive disease after ≤2 lines of treatment (including a CDK4/6 inhibitor). Participants were randomised 1:1 to receive venetoclax (800 mg daily) plus fulvestrant (500 mg day 1 and 15 of cycle 1; day 1 of subsequent 28-day cycles) or fulvestrant alone until disease progression, unacceptable toxicity, withdrawal of consent, death, or predefined study end. The primary endpoint was clinical benefit rate (i.e. complete response, partial response, and stable disease ≥24 weeks). Prof. Geoff Lindeman (Peter MacCallum Cancer Center, Australia) presented the results of the primary analysis [3].

The clinical benefit rate was similar between arms: 11.8% and 13.7% for venetoclax plus fulvestrant and fulvestrant alone, respectively. Median progression-free survival was 2.69 months versus 1.94 months, respectively. Overall survival data were not mature.

1. Rozeboom B, et al. Am J Cancer Res. 2019;9(12):2821–2831.
2. Lok SW, et al. Cancer Discov. 2019;9:354-69.
3. Lindeman GJ, et al. Results from VERONICA: A randomized, phase II study of second-/third-line venetoclax (VEN) + fulvestrant (F) versus F alone in estrogen receptor (ER)-positive, HER2-negative, locally advanced, or metastatic breast cancer (LA/MBC). Abstract 1004, ASCO 2021 Virtual Meeting, 4–8 June.

Lung Cancer

Neoadjuvant nivolumab plus chemotherapy improves surgical outcomes in NSCLC

The results from CheckMate 816 showed that patients with resectable non-small cell lung cancer (NSCLC) who were treated with neoadjuvant nivolumab plus chemotherapy had improved pathologic complete response (pCR) rates and improved surgical outcomes.

The randomised, phase 3 CheckMate 816 trial (NCT02998528) evaluates the efficacy and safety of neoadjuvant therapy with nivolumab plus chemotherapy in patients with resectable NSCLC. Recently, results were presented of the first primary endpoint (pCR, defined as 0% viable tumour cells in lung and lymph nodes): median pCR was 24% in patients (n=179) treated with neoadjuvant nivolumab plus chemotherapy versus 2.2% in patients (n=179) treated with neoadjuvant chemotherapy (HR 13.94; 95% CI 3.49–55.75; P<0.0001) [1]. At the ASCO 2021 Annual Meeting, Dr Jonathan Spicer (McGill University, Canada) presented key surgical outcomes from the study [2].

Definitive surgery rates were 83% with nivolumab plus chemotherapy (n=149) versus 75% with chemotherapy alone (n=135). Reasons for cancelled surgery included disease progression (12 and 17 patients, respectively) and adverse events (2 patients in each arm). Adverse events were responsible for delays of surgery in 6 patients in the nivolumab plus chemotherapy arm and 9 patients in the chemotherapy arm. Minimally invasive surgery rates were 30% and 22%, and conversion from minimally invasive to open surgery rates were 11% and 16% for nivolumab plus chemotherapy and chemotherapy, respectively. Lobectomy was performed in 77% and 61% of patients, and pneumonectomy in 17% and 25% for nivolumab plus chemotherapy and chemotherapy, respectively.

A complete resection (R0) was achieved in 83% versus 78% of patients and median residual viable tumour (RVT) cells in the primary tumour bed were 10% versus 74% for nivolumab plus chemotherapy versus chemotherapy. There was no increase in median duration of surgery and length of hospitalisation between the two arms.

1. Forde PM, et al. Abstract 5218, AACR Annual Meeting 2021, 9–14 April.
2. Spicer J, et al. Surgical outcomes from the phase 3 CheckMate 816 trial: Nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo alone as neoadjuvant treatment for patients with resectable non-small cell lung cancer (NSCLC). Abstract 8503, ASCO 2021 Virtual Meeting, 4–8 June.

Immune-related adverse events are associated with efficacy of atezolizumab in patients with advanced NSCLC

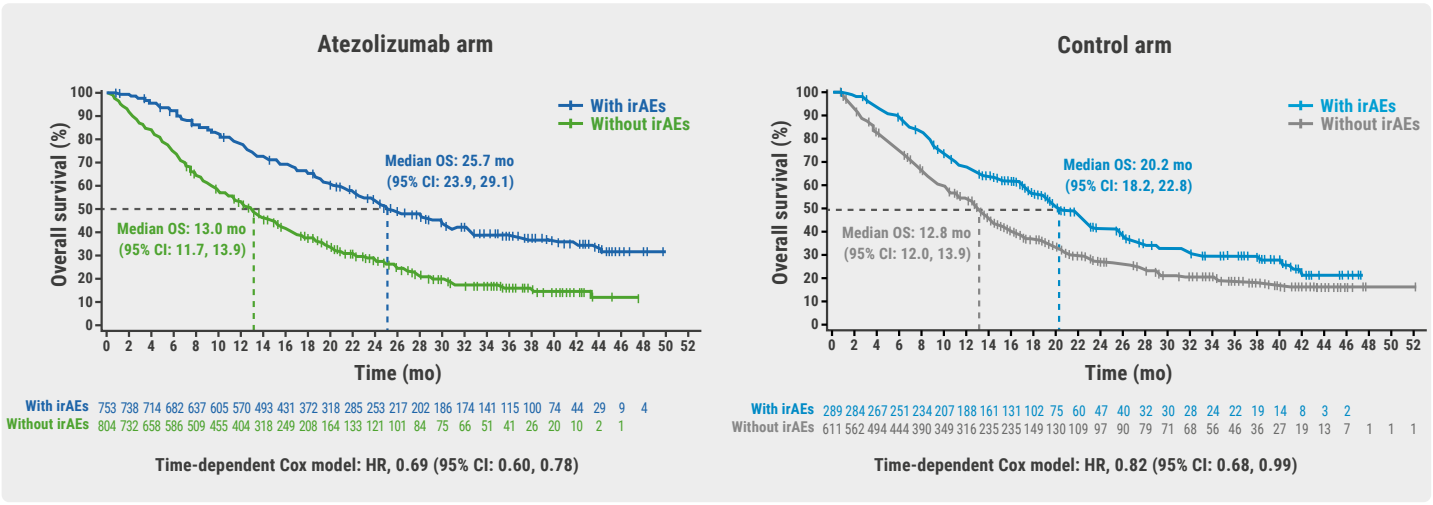
An exploratory, post-hoc, pooled analysis of three phase 3 trials with atezolizumab in patients with stage IV non-small cell lung cancer (NSCLC) – IMpower130, IMpower132, and IMpower150 – showed longer overall survival for patients who experience immune-related adverse events.

Immune-related adverse events have been reported in up to 80% of patients receiving immune checkpoint inhibitor monotherapy and up to 95% of patients receiving immune checkpoint inhibitor combination therapy [1]. Increasing evidence suggests that the occurrence of immune-related adverse events may be predictive of improved outcomes in cancers such as NSCLC [2]. The phase 3 IMpower130 (NCT02367781), IMpower132 (NCT02657434), and IMpower150 (NCT02366143) trials evaluated efficacy and tolerability of atezolizumab in NSCLC [3-5]. These 3 trials enrolled a total of 2,503 patients with stage IV NSCLC: 1,577 patients were treated with atezolizumab, 926 patients were in the control arms.

A post-hoc pooled analysis, presented by Dr Mark Socinski (AdventHealth Cancer Institute, FL, USA), explored the association between immune-related adverse events and efficacy in these trials [6]. In the atezolizumab arm, 753 patients experienced an immune-related adverse event, and 824 patients were without immune-related adverse events. In the control arm, 289 patients experienced an immune-related adverse event, whereas 637 patients did not. Patients who experienced an immune-related adverse event had a longer overall survival than those without immune-related adverse events in both the atezolizumab and control arm (see Figure on the next page).

The median overall survival in the atezolizumab arm was 25.7 months versus 13.0 months for patients with versus without immune-related adverse events (HR 0.69; 95% CI 0.60–0.78). In the control arm, median survival was 20.2 months versus 12.8 months, respectively (HR 0.82; 95% CI 0.68–0.99). In the atezolizumab arm, objective response rate was 61.1% in patients who experienced an immune-related adverse event and 37.2% in patients without immune-related adverse events.

Figure: Overall survival stratified by the occurrence of immune-related adverse events [6]



1. Jamal S, et al. Rheumatol. 2020;47:1656-175.
2. Zhou X, et al. BMC Med. 2020;18:87.
3. West H, et al. Lancet Oncol. 2019;20:924-937.
4. Nishio M, et al. Thorac Oncol. 2021;16:653-664.
5. Socinski MA, et al. N Engl J Med. 2018;378:2288-2301.
6. Socinski MA, et al. Pooled analyses of immune-related adverse events (irAEs) and efficacy from the phase 3 trials IMpower130, IMpower132, and IMpower150. Abstract 9002, ASCO 2021 Virtual Meeting, 4–8 June.

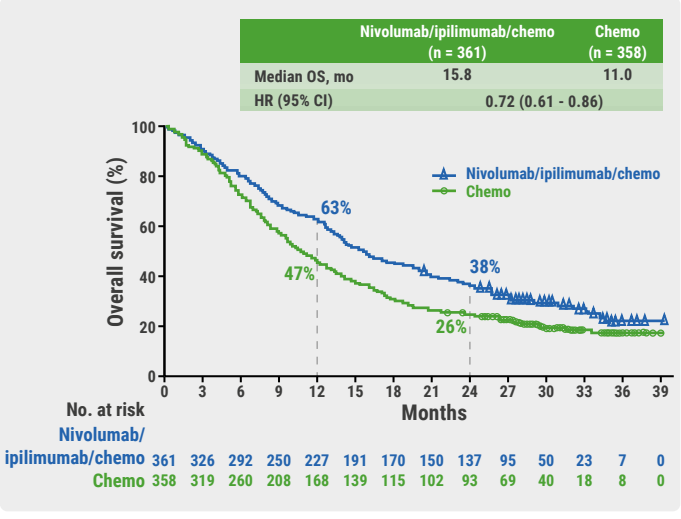
Sustained efficacy of nivolumab/ipilimumab plus 2 cycles of chemotherapy in NSCLC

A 2-year update of the CheckMate 9LA trial showed a sustained benefit of first-line treatment with nivolumab plus ipilimumab plus 2 cycles of chemotherapy versus chemotherapy alone in patients with advanced non-small cell lung cancer (NSCLC).

The combination of nivolumab and ipilimumab, which have distinct but complementary mechanisms of action, has shown improved long-term overall survival benefit in advanced NSCLC [1]. In the randomised, phase 3 CheckMate 9LA trial (NCT03215706), first-line nivolumab plus ipilimumab combined with 2 cycles of chemotherapy significantly improved overall survival, progression-free survival, and objective response rate versus 4 cycles of chemotherapy alone [2]. Clinical benefit was observed regardless of PD-L1 expression level and histology. This regimen is now approved in the USA and Europe, among others, as first-line treatment for adult patients with metastatic NSCLC and no EGFR or ALK genomic tumour aberrations. Prof. Martin Reck (Lung Clinic Grosshansdorf, Germany) presented updated data with a 2-year minimum follow-up from the CheckMate 9LA study, as well as a post-hoc efficacy analysis in patients who discontinued nivolumab/ipilimumab/chemotherapy due to treatment-related adverse events [3].

At a median follow-up of 30.7 months, patients treated with nivolumab/ipilimumab/chemotherapy continued to derive overall survival benefit compared with chemotherapy alone, with a median overall survival of 15.8 months versus 11.0 months, respectively; 2-year overall survival rates were 38% versus 26% (see Figure). The median progression-free survival with nivolumab/ipilimumab/chemotherapy was 6.7 months versus 5.3 months with chemotherapy. A similar clinical benefit was observed in all randomised patients and across the majority of subgroups, regardless of PD-L1 expression and/or histology.

Figure: Updated overall survival in all randomised patients from CheckMate 9LA [3]



Any grade and grade 3–4 treatment-related adverse events were reported in 92% and 48% of patients in the nivolumab/ipilimumab/chemotherapy arm versus 88% and 38% in the chemotherapy arm, respectively. In patients who

discontinued nivolumab/ipilimumab/chemotherapy due to treatment-related adverse events, the median overall survival was 27.5 months (2-year overall survival rate 54%).

"These updated results from CheckMate 9LA continue to support nivolumab/ipilimumab plus 2 cycles of chemotherapy as an efficacious first-line treatment option for patients with advanced NSCLC. In addition, discontinuation due to treatment-related adverse events does not have a negative impact on the long-term benefits seen with this combination," concluded Prof. Reck.

1. Ramalingam SS, et al. J Clin Oncol. 2020;38(supl15):abstract 9500.
2. Paz-Ares L, et al. Lancet Oncol. 2021;22:198-21.
3. Reck M, et al. First-line nivolumab (NIVO) plus ipilimumab (IPI) plus two cycles of chemotherapy (chemo) versus chemo alone (4 cycles) in patients with advanced non-small cell lung cancer (NSCLC): Two-year update from CheckMate 9LA. Abstract 9000, ASCO 2021 Virtual Meeting, 4–8 June.

Patritumab deruxtecan (HER3-DXd) in EGFR TKI-resistant NSCLC

Patritumab deruxtecan (HER3-DXd), an antibody-drug conjugate consisting of a monoclonal antibody to HER3 attached to a topoisomerase I inhibitor, demonstrated anti-tumour activity across various EGFR TKI resistance mechanisms in heavily pretreated, metastatic/locally advanced *EGFR*-mutated non-small cell lung cancer (NSCLC).

EGFR-directed TKIs are the standard of care for patients with *EGFR*-mutated NSCLC. However, the development of various resistance mechanisms commonly leads to progression. Platinum-based chemotherapy following EGFR TKI failure has limited efficacy. Patritumab deruxtecan (HER3-DXd) is an antibody-drug conjugate consisting of a fully human monoclonal antibody to HER3 – expressed in 83% of NSCLC tumours – attached to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker [1].

Dr Jänne Pasi (Dana Farber Cancer Institute, MA, USA) presented efficacy and safety data from an ongoing phase 1 study (NCT03260491) of HER3-DXd in patients with locally advanced or metastatic *EGFR*-mutated NSCLC who had failed on prior EGFR TKI therapy [2]. A total of 57 patients were included, who had a median of 4 prior anti-cancer treatments; 100% had prior EGFR TKI, median treatment duration was 5.5 months, and treatment was ongoing in 18 patients (32%). Participants were treated with HER3-DXd 5.6 mg/kg IV every 3 weeks and followed-up for a median of 10.2 months.

At data cut-off, confirmed objective response rate was 39% (n=22: 1 complete responder, 21 partial responders, 19 with stable disease) with 64% of responses occurring within 3 months of starting HER3-DXd. Disease control rate was 72%, median duration of response was 6.9 months, and median progression-free survival was 8.2 months. Anti-tumour activity was observed across diverse mechanisms of EGFR TKI resistance, including those not directly related to HER3 (*EGFR C797S*, *MET* or *HER2 amp*, and *BRAF* fusion). Among patients with a history of brain metastases and prior platinum-based chemotherapy, objective response rate was 37%.

HER3-DXd had a manageable safety profile and a low rate of discontinuation due to adverse events. The most common grade ≥3 adverse events were thrombocytopenia (30%), neutropenia (19%), and fatigue (14%). Drug-related interstitial lung disease by central adjudication occurred in 4 patients (7%; 1 grade ≥3; no grade 5); 6/57 pts (11%) had adverse events associated with treatment discontinuation (none were due to thrombocytopenia).

1. Scharpenseel H, et al. Sci Rep. 2019;9:7406.
2. Pasi AJ, et al. Efficacy and safety of patritumab deruxtecan (HER3-DXd) in EGFR inhibitor-resistant, EGFR-mutated (EGFRm) non-small cell lung cancer (NSCLC). Abstract 9007, ASCO 2021 Virtual Meeting, 4–8 June.

Melanoma

Long-term results from ground-breaking melanoma trials

After initial results over 5 years ago, long-term follow-up data from 3 clinical trials – CheckMate 067, COLUMBUS, and ABC – showed a durable and sustained clinical benefit for patients with melanoma.

In the phase 3 CheckMate 067 trial (NCT01844505), first-line treatment with nivolumab plus ipilimumab or nivolumab alone demonstrated a durable and sustained survival benefit compared with ipilimumab alone in patients with unresectable stage III or IV melanoma [1]. Results from the phase 3 COLUMBUS trial (NCT01909453) showed improved survival of patients with advanced/metastatic *BRAF* V600-mutant melanoma when treated in first line with encorafenib plus binimetinib versus encorafenib (or vemurafenib) [2]. The phase 2 ABC trial (NCT02374242) showed good intracranial responses in melanoma patients with asymptomatic brain metastases [3]. Now, long-term follow-up data of these trials are available.

Dr Jedd Wolchok (Memorial Sloan Kettering Cancer Center, NY, USA) presented overall survival data of the CheckMate 067 trial [4]. At the time of analysis, all patients (n=945), who were 1:1:1 randomised to nivolumab plus ipilimumab, nivolumab alone, or ipilimumab alone, had a minimum follow-up of 6.5 years. Median overall survival was 72.1 months with nivolumab plus ipilimumab, 36.9 months with nivolumab, and 19.9 months with ipilimumab. Survival rates at 6.5 years were 49%, 42%, and 23%, respectively. Survival rates at 6.5 years in *BRAF*-mutated patients were 57%, 43%, and 25%, respectively. Median treatment-free intervals following study therapy discontinuation were 27.6 months, 2.3 months, and 1.9 months, respectively.

Prof. Reinhard Dummer (University Hospital Zürich, Switzerland) reported on a 5-year update from the COLUMBUS trial [5]. In this trial, 577 patients were randomised 1:1:1 to encorafenib plus either binimetinib, encorafenib, or vemurafenib. Median overall survival was 33.6 months, 23.5 months and 16.9 months, respectively. At 5 years, the overall survival rates were 34.7%, 34.9%, and 21.4% respectively. Objective response rates were 64.1%, 51.5%, and 40.8%, respectively.

Prof. Georgina Long (Melanoma Institute, Australia) presented the 5-year overall survival data from the ABC trial [6]. In this randomised phase 2 trial, melanoma patients with untreated brain metastases were treated with nivolumab plus ipilimumab (n=35) or nivolumab (n=25). Median overall survival in the nivolumab plus ipilimumab arm was not reached compared with 26.1 months in the nivolumab arm. At 5 years, overall survival rates were 51% and 34%, respectively. Intracranial progression-free survival rates were 52% and 14%, respectively.

1. Wolchok JD, et al. N Engl J Med. 2017;377:1345-1356.
2. Dummer R, et al. Lancet Oncol. 2018;19:1315-1327.
3. Long GV, et al. Lancet Oncol. 2018;19:672-681.
4. Wolchok JD, et al. CheckMate 067: 6.5-year outcomes in patients (pts) with advanced melanoma. Abstract 9506, ASCO 2021 Virtual Meeting, 4–8 June.
5. Dummer R, et al. Five-year overall survival (OS) in COLUMBUS: A randomized phase 3 trial of encorafenib plus binimetinib versus vemurafenib or encorafenib in patients (pts) with BRAF V600-mutant melanoma. Abstract 9507, ASCO 2021 Virtual Meeting, 4–8 June.
6. Long GV, et al. Five-year overall survival from the anti-PD1 brain collaboration (ABC Study): Randomized phase 2 study of nivolumab (nivo) or nivo+ipilimumab (ipi) in patients (pts) with melanoma brain metastases (mets). Abstract 9508, ASCO 2021 Virtual Meeting, 4–8 June.

Novel dual checkpoint blockade improves progression-free survival in melanoma

First results of the phase 3 RELATIVITY-047 trial validated the efficacy of dual checkpoint blockade demonstrated with the LAG-3 inhibitor relatlimab and nivolumab in patients with advanced melanoma.

Lymphocyte-activation gene 3 (LAG-3) regulates an immune checkpoint pathway that inhibits T-cell activity and is upregulated in many tumour types including melanoma [1]. Relatlimab, a human IgG4 LAG-3-blocking antibody, restores effector function of exhausted T cells [2]. Relatlimab in combination with nivolumab modulates potentially synergistic immune checkpoint pathways and can enhance anti-tumour immune responses [3].

RELATIVITY-047 (NCT03470922) is a global, randomised, double-blind, phase 2/3 study evaluating the combination of relatlimab plus nivolumab treatment in first-line advanced melanoma. In this trial, 714 patients with previously untreated advanced melanoma were randomised 1:1 to receive relatlimab (160 mg) plus nivolumab (480 mg) every 4 weeks or nivolumab alone. Patients were stratified by LAG-3 expression, PD-L1 expression, and *BRAF* mutation status. The primary

endpoint was progression-free survival. Secondary endpoints were overall survival and objective response rate. Dr Evan Lipson (Johns Hopkins University, MD, USA) presented the first results of RELATIVITY-047 [4].

At a median follow-up of 13.2 months, progression-free survival in the relatlimab plus nivolumab arm was significantly improved compared with the nivolumab monotherapy arm (10.1 months vs 4.6 months, respectively). Progression-free rate at 12 months was 47.7% in the relatlimab/nivolumab arm versus 36.0% in the nivolumab arm. Progression-free survival favoured relatlimab/nivolumab regardless of age, LDH, tumour burden, *BRAF*-mutation status, PD-L1 expression, and LAG-3 expression.

The incidence of grade 3/4 treatment-related adverse events was higher in the relatlimab/nivolumab arm versus the nivolumab arm (18.9% vs 9.7%). Treatment-related adverse events of any grade led to treatment discontinuation in 14.6% and 6.7% of patients in the relatlimab/nivolumab arm and nivolumab arm, respectively.

1. Durham NM, et al. PLOS One. 2014;9(11):e109080.
2. Yu X, et al. MAbs. 2019;11(6):1139-1148.
3. Ascierto PA, et al. Abstract 4998, ESMO 2017, 8–12 Sept, Madrid, Spain.
4. Lipson E, et al. Relatlimab (RELA) plus nivolumab (NIVO) versus NIVO in first-line advanced melanoma: Primary phase III results from RELATIVITY-047 (CA224-047). Abstract 9503, ASCO 2021 Virtual Meeting, 4–8 June.

Neoadjuvant therapy with nivolumab plus relatlimab is safe and effective in patients with stage III melanoma

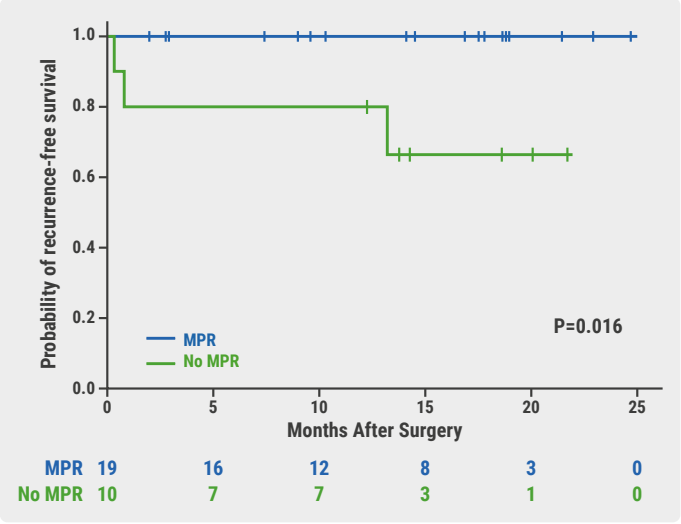
Neoadjuvant and adjuvant treatment with nivolumab plus the LAG-3 inhibitor relatlimab achieved high pathologic complete response (pCR) and major pathologic response rates with a favourable toxicity profile. This was shown in a multi-institutional, investigator-initiated, single-arm study.

A pooled analysis of 192 patients from 6 trials has shown improved recurrence-free survival and overall survival in patients with clinical stage III melanoma who achieved a pCR after neoadjuvant immunotherapy or targeted therapy [1]. In addition, a combination of neoadjuvant immunotherapy regimens has shown robust pathologic response with acceptable toxicity in stage III melanoma patients [2]. Also, nivolumab combined with the LAG-3 antibody relatlimab has demonstrated a favourable toxicity profile and responses in both checkpoint-naïve and refractory metastatic melanoma [3].

To evaluate the efficacy and safety of neoadjuvant nivolumab plus relatlimab followed by adjuvant nivolumab plus relatlimab, a single-arm study (NCT02519322) was conducted in 30 patients with clinical stage IIIB/IIIC/IIID/IV surgically-resectable melanoma. The primary endpoint of the trial was pCR rate. Secondary endpoints were relapse-free, event-free, and overall survival, objective response rate, and safety. Patients received nivolumab (480 mg) and relatlimab (160 mg) in weeks 1 and 5. Surgery was conducted at week 9 and specimens were assessed for pathologic response per established criteria. Patients received up to 10 additional doses of nivolumab and relatlimab after surgery. Dr Rodabe Amaria (MD Anderson Cancer Center, TX, USA) presented the first results [4].

The rate of pCR was 59%, and 7% achieved near pCR (<10% viable tumour), resulting in a major pathologic response (pCR + near pCR) of 66%. In addition, 7% of patients achieved a pathologic partial response (10–50% viable tumour) and 27% no pathologic response (≥50% viable tumour). RECIST objective response rate was 57%. The 1-year relapse-free survival for patients with major pathologic response was 100% compared with 80% for patients without (P=0.016; see Figure).

Figure: Improved RFS outcomes for patients with major pathologic response [4]



No treatment-related grade 3/4 adverse events occurred during neoadjuvant treatment, and 26% of patients reported a grade 3/4 adverse event that began during adjuvant treatment.

1. Menzies AM, et al. Nat Med. 2021;27:301-309.
2. Rozeman EA, et al. Lancet Oncol. 2019;20:948-960.
3. Ascierto PA, et al. Abstract 4998, ESMO 2017, 8–12 Sept, Madrid, Spain.
4. Amaria RN, et al. Neoadjuvant and adjuvant nivolumab (nivo) with anti-LAG3 antibody relatlimab (rela) for patients (pts) with resectable clinical stage III melanoma. Abstract 9502, ASCO 2021 Virtual Meeting, 4–8 June.

Genitourinary Cancers

Abiraterone added to ADT + docetaxel nearly doubles survival in *de novo* mCSPC

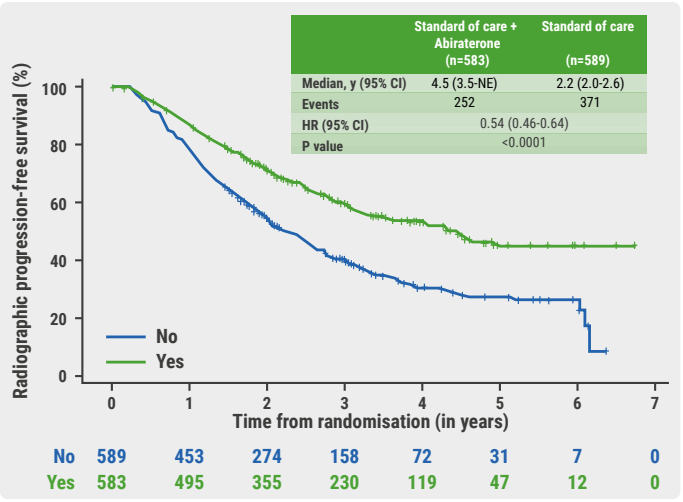
First results from the phase 3 PEACE-1 trial showed that adding abiraterone to androgen deprivation therapy (ADT) plus docetaxel significantly improved progression-free survival in patients who present with *de novo* metastatic castration-sensitive prostate cancer (mCSPC), without meaningful added short-term toxicity.

Historically, ADT was the standard of care for men with mCSPC. Since 2015, combining ADT with either docetaxel, novel hormonal therapies (abiraterone, enzalutamide), or radiotherapy to the primary tumour has shown to improve overall survival and, thus, became the new standard of care [1-4]. However, it was unknown whether combining these new treatments on top of ADT further increments outcomes.

The primary goal of the PEACE-1 trial (NCT01957436) is to evaluate the efficacy and safety of the addition of abiraterone, radiotherapy, or abiraterone plus radiotherapy to standard of care. A total of 1,173 men with *de novo* mCSPC were randomised to standard of care, standard of care plus abiraterone, standard of care plus radiotherapy, or standard of care plus abiraterone plus radiotherapy. No interaction was detected between the effect of abiraterone and that of radiotherapy (P=0.64), allowing to pool the abiraterone arms for comparisons: 589 patients were enrolled in the standard of care (± radiotherapy) arm and 583 patients were enrolled in the standard of care (± radiotherapy) plus abiraterone arm. The trial has 2 co-primary endpoints of radiographic progression-free survival and overall survival. Dr Karim Fizazi (Institut Gustav Roussy, France) presented the first results of PEACE-1 [5].

After a median follow-up of 3.5 years, median radiographic progression-free survival was 4.5 years in the standard of care plus abiraterone arm versus 2.2 years in the standard of care arm (see Figure). Median castration-resistant-free survival was 3.8 years and 1.5 years, respectively. The relative improvement of progression-free survival was comparable in patients treated with or without docetaxel. No meaningful additional toxicity was observed in patients treated with standard of care plus abiraterone.

Figure: Radiographic progression-free survival in the overall population of PEACE-1 [6]



1. Sweeney CJ, et al. N Engl J Med. 2015;373:737-746.
2. Fizazi K, et al. N Engl J Med. 2017;377:352-360.
3. Davis ID, et al. N Engl J Med. 2019;381:121-131.
4. Parker CC, et al. Lancet 2018;392:2353-2366.
5. Fizazi K, et al. A phase 3 trial with a 2x2 factorial design of abiraterone acetate plus prednisone and/or local radiotherapy in men with de novo metastatic castration-sensitive prostate cancer (mCSPC): First results of PEACE-1. Abstract 5000, ASCO 2021 Virtual Meeting, 4–8 June.

VISION trial shows improved survival with ^{177}Lu-PSMA-617 in mCRPC

Addition of ^{177}Lu-PSMA-617 radioligand therapy to standard of care for patients with metastatic castration-resistant prostate cancer (mCRPC) significantly improved survival, according to results from the randomised, phase 3 VISION trial.

Despite recent therapeutic advances, mCRPC remains invariably fatal. Prostate-specific membrane antigen (PSMA) is highly expressed in mCRPC lesions. The targeted radioligand ^{177}Lu-PSMA-617 delivers β-particle radiation to PSMA-expressing cells and the surrounding microenvironment [1].

The VISION trial (NCT03511664) is an international, randomised, open-label, phase 3 study evaluating ^{177}Lu-PSMA-617 in men with PSMA-positive mCRPC, previously treated with next-generation androgen receptor signalling inhibition and 1–2 taxane regimens. The trial randomised 831 patients 2:1 to ^{177}Lu-PSMA-617 (7.4 GBq every 6 weeks x 6 cycles) plus standard of care or standard of care alone (investigator determined

but excluding cytotoxic chemotherapy and radium-223). The alternate primary endpoints were radiographic progression-free survival and overall survival. Key secondary endpoints were objective response rate, disease control rate, and time to first symptomatic skeletal event. Dr Michael Morris (Memorial Sloan Kettering Cancer Center, NY, USA) presented the results of the VISION trial after a median follow-up of 20.9 months [2].

The addition of ^{177}Lu-PSMA-617 therapy to standard of care significantly improved median radiographic progression-free survival versus standard of care alone (8.7 months vs 3.4 months). The alternate primary endpoint of overall survival was also significantly improved versus standard of care (median 15.3 vs 11.3 months, respectively). All key secondary endpoints were statistically significant between the treatment arms in favour of ^{177}Lu-PSMA-617 plus standard of care, including overall response rate (51.0% vs 3.1%) and disease control rate (86.3% vs 50.0%).

While a higher rate of high-grade treatment-emergent adverse events was observed with ^{177}Lu-PSMA-617 (any grade: 85.3% vs 28.8%; grade 3-5: 28.4% vs 3.9%), therapy was generally well tolerated.

1. Kratochwil C, et al. J Nucl Med. 2016 Aug;57(8):1170-6.
2. Morris MJ, et al. Phase III study of lutetium-177-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION). Abstract LBA4, ASCO 2021 Virtual Meeting, 4–8 June.

Post-nephrectomy pembrolizumab improves disease-free survival

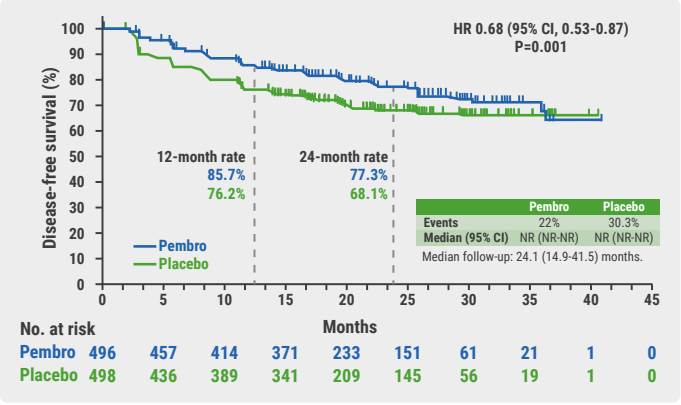
First results of the phase 3 KEYNOTE 564 trial showed that adjuvant therapy with pembrolizumab after nephrectomy enhanced disease-free survival of patients treated for locoregional clear cell renal cell cancer (RCC).

Nephrectomy is the standard-of-care treatment for locoregional RCC. However, nearly half of the patients eventually experience disease recurrence after surgery which is associated with shortened life expectancy. Effective perioperative therapy to reduce this risk remains an unmet need.

The phase 3, randomised KEYNOTE 564 trial (NCT03142334) evaluates the effect of pembrolizumab versus placebo as adjuvant therapy for patients with RCC. The study enrolled 994 patients with histologically confirmed clear cell RCC (intermediate-high risk [pT2, grade 4, or sarcomatoid, N0 M0; or pT3, any grade, N0 M0], high risk [pT4, any grade, N0 M0; or pT any stage, any grade, N+ M0], or M1 NED [no evidence of disease after primary tumour + soft tissue metastases completely resected ≤1 year from nephrectomy]). Participants were randomised 1:1 to pembrolizumab (200 mg every 3 weeks for 1 year) or placebo. The primary endpoint was disease-free survival in all randomised patients. Overall survival was a key secondary endpoint, as well as safety/tolerability. Dr Toni Choueiri (Dana-Farber Cancer Institute, MA, USA) presented the results of the first interim analysis of KEYNOTE 564 [1].

At a median follow-up of 24.1 months, the primary endpoint of disease-free survival was met (median not reached for both arms, HR 0.68; P=0.001; see Figure). The estimated disease-free survival rate at 24 months was 77.3% versus 68.1% in the pembrolizumab and placebo arm, respectively. Overall survival data are not yet mature.

Figure: Disease-free survival in the intention-to-treat population of KEYNOTE 564 [1]



All-cause adverse events were observed in 470 patients (96.3%) treated with pembrolizumab and 452 patients (91.1%) treated with placebo. Grade 3-5 all-cause adverse events occurred in 158 patients (32.4%) with pembrolizumab and 88 patients (17.7%) with placebo.

1. Choueiri TK, et al. Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for patients with renal cell carcinoma: Randomized, double-blind, phase III KEYNOTE-564 study. Abstract LBA5, ASCO 2021 Virtual Meeting, 4–8 June.

Glutaminase inhibitor telaglenastat does not improve survival mRCC

First results of the phase 3 CANTATA trial showed no survival benefit of treatment with the glutaminase inhibitor telaglenastat plus cabozantinib versus cabozantinib alone in patients with previously treated metastatic renal cell cancer (mRCC).

Renal cell cancer is a highly metabolic tumour with high expression of glutaminase, a key enzyme in glutamine metabolism.

Telaglenastat is a potent glutaminase inhibitor showing promising anti-tumour effect in heavily pretreated mRCC patients when combined with everolimus or cabozantinib [1,2]. The phase 3 CANTATA trial (NCT03428217) evaluated the efficacy and safety of the combination telaglenastat plus cabozantinib in patients with previously treated mRCC.

Eligible patients had 1 or 2 prior lines of systemic therapy for mRCC, including at least 1 anti-angiogenic therapy or nivolumab/ipilimumab. A total of 444 patients were enrolled and randomised to receive cabozantinib (60 mg once daily) with either telaglenastat (800 mg twice daily) or placebo, until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival by BICR. Dr Nizar Tannir (Houston University, TX, USA) presented the first results [3].

Median progression-free survival was 9.2 months for cabozantinib/telaglenastat versus 9.3 months for cabozantinib/placebo (HR 0.94; 95% CI 0.74–1.21; P=0.65). The overall response rate was 31% with cabozantinib/telaglenastat versus 28% with cabozantinib/placebo. Overall survival was not mature at data cut-off. In a prespecified subgroup analysis in patients with prior immune checkpoint inhibition, median progression-free survival was numerically longer in the telaglenastat arm than in the placebo arm (11.1 versus 9.2 month, respectively; HR 0.77; 95% CI 0.56–1.06). Rates of adverse events were similar between arms.

1. Motzer R, et al. Abstract 811, ESMO 2019 Annual Meeting, 27 Sept–1 Oct, Barcelona, Spain.
2. Meric-Bernstam F, et al. Abstract 549, ASCO-GU 2019, 17–19 Feb, San Fransico, USA.
3. Tannir NM, et al. CANTATA: Primary analysis of a global, randomized, placebo (Pbo)-controlled, double-blind trial of telaglenastat (CB-839) + cabozantinib versus Pbo + cabozantinib in advanced/metastatic renal cell carcinoma (mRCC) patients (pts) who progressed on immune checkpoint inhibitor (ICI) or anti-angiogenic therapies. Abstract 4501, ASCO 2021 Virtual Meeting, 4–8 June.

Promising efficacy and safety of feladilimab in recurrent/metastatic urothelial carcinoma

Results from the phase 1 INDUCE-1 trial showed promising activity and manageable safety of the ICOS agonist feladilimab as monotherapy or combined with pembrolizumab in patients with recurrent/metastatic urothelial carcinoma.

Inducible T-cell co-stimulator (ICOS) is a member of the CD23 receptor superfamily, which includes CTLA4 and PD-1, and has a pivotal role in stimulating T-cell proliferation, differentiation, survival, and function [1]. ICOS is highly expressed in all stages of urothelial cancer.

The phase 1 INDUCE trial (NCT02723955) evaluates feladilimab as monotherapy and in combination with pembrolizumab in selected advanced solid tumours. Eligible patients had recurrent/metastatic urothelial carcinoma of the upper or lower urinary tract, 6 or fewer prior systemic therapy lines in the advanced setting, measurable disease, and no active autoimmune disease. Anti-PD-(L)1-experienced patients (n=14) received monotherapy feladilimab (0.3 mg/kg every 3 weeks), and anti-PD-(L)1-naïve patients (n=32) received feladilimab plus pembrolizumab (200 mg every 3 weeks) for up to 35 cycles until disease progression or unacceptable toxicity. Dr Arjun Balar (Perlmutter Cancer Center, NY, USA) presented preliminary results from the urothelial carcinoma expansion cohorts [2].

In the monotherapy arm, median duration of follow-up was 12.6 months; overall response rate was 7% (1 partial responder) with a duration of response of 6.1 months. Disease control rate was 21%, and median overall survival was 14.5 months, with 77% of patients alive at 6 months. In the combination arm, median duration of follow-up was 9.6 months; overall response rate was 22% (7 partial responders) with a median duration of response of 8.3 months. Disease control rate was 63%, and median overall survival was 10.7 months, with 64% of patients alive at 6 months.

Grade ≥3 treatment-related adverse events were reported for 0% and 9% of patients in the monotherapy arm and combination arm, respectively. A trend was observed for enrichment of clinical activity in patients with tumours expressing PD-L1, ICOS, or both.

1. Simpson TR, et al. Curr Opin Immunol. 201;22:326-332.
2. Balar AV, et al. Inducible T-cell co-stimulatory (ICOS) receptor agonist, feladilimab (fela), alone and in combination (combo) with pembrolizumab (P): Results from INDUCE-1 urothelial carcinoma (UC) expansion cohorts (ECs). Abstract 4519, ASCO 2021 Virtual Meeting, 4–8 June.

Gastrointestinal Cancers

Pembrolizumab benefits survival in MSI-H/dMMR metastatic colorectal cancer

First-line treatment of patients with microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC) with pembrolizumab improved overall survival, but the prespecified threshold for significance was not reached. These were the final results of the phase 3 KEYNOTE 177 trial.

Immune checkpoint blockade has a predicted clinical benefit in patients with MSI-H/dMMR mCRC [1]. In the phase 3 KEYNOTE 177 trial (NCT02563002), 307 treatment-naïve patients with MSI-H/dMMR mCRC were randomly assigned 1:1 to receive pembrolizumab (200 mg every 3 weeks up to 35 cycles) or chemotherapy every 2 weeks. Results from an interim analysis showed significant prolonged progression-free survival in patients treated with pembrolizumab versus chemotherapy (median 16.6 months vs 8.2 months) [2]. Prof. Thierry André (Sorbonne University, France) presented the final results of KEYNOTE 177, after 190 overall survival events [3].

The median study follow-up was 44.5 months in the pembrolizumab arm versus 44.4 months in the chemotherapy arm. In the chemotherapy arm, 56 (36%) patients crossed over to pembrolizumab, with 37 more receiving anti-PD-(L)1 therapies off-study (60% effective crossover rate in the intention-to-treat population). Median overall survival was not reached in the pembrolizumab arm versus 36.7 months in the chemotherapy arm. The hazard ratio for overall survival favoured pembrolizumab versus chemotherapy with a trend toward reduction in the risk of death (HR 0.74). However, this difference did not reach prespecified statistical significance. At 3 years, the overall survival rate was 61% in the pembrolizumab arm versus 50% in the chemotherapy arm.

1. Le DT, et al. Science 2017;357:409-413.
2. André T, et al. N Engl J Med. 2020;383:2207-2218.
3. André T, et al. Final overall survival for the phase III KN177 study: Pembrolizumab versus chemotherapy in microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC). Abstract 3500, ASCO 2021 Virtual Meeting, 4–8 June.

Panitumumab added to 5-FU/LV effective as maintenance therapy in patients with mCRC

Progression-free survival in patients with *RAS* wildtype metastatic colorectal cancer (mCRC) improved with the addition of panitumumab to maintenance therapy with 5-FU/LV versus 5-FU/LV alone, demonstrated results from the phase 3 PANAMA trial.

Currently, the preferred maintenance therapy regimen in mCRC is fluoropyrimidine ± bevacizumab, with improved progression-free but not overall survival [1]. Maintenance concepts in the context of EGFR monoclonal antibody-based first-line therapy are still the subject of scientific debate. Although EGFR-antibodies may provide activity during maintenance therapy, 5-FU/LV appears necessary [2].

The phase 3 PANAMA trial (NCT01991873) evaluated the efficacy and safety of maintenance therapy with panitumumab plus 5-FU/LV versus 5-FU/LV alone in patients with *RAS* wild-type mCRC who showed a clinical response on induction therapy with 6 cycles of FOLFOX (5-FU/LV, oxaliplatin) plus panitumumab. The primary endpoint was progression-free survival. Prof. Dominik Modest (Charité Universitätsmedizin Berlin, Germany) presented the first results [3].

Of the 377 patients treated with induction therapy, 248 were randomised to receive maintenance therapy with either 5-FU/LV plus panitumumab (n=125) or 5-FU/LV alone (n=123). At data cut-off, median progression-free survival was improved with 5-FU/LV plus panitumumab versus 5-FU/LV alone (8.8 vs 5.7 months; HR 0.72; 80% CI 0.60–0.85; P=0.014). Data for the key secondary endpoint of overall survival is immature, but currently shows a small trend towards a better outcome with 5-FU/LV plus panitumumab. Re-induction therapy was initiated less frequently in the 5-FU/LV plus panitumumab arm and was also associated with less objective responses compared to the 5-FU/LV alone arm. Maintenance therapy with 5-FU/LV plus panitumumab was well tolerated, with expected adverse events with special interest to panitumumab.

1. Sonbol MB, et al. JAMA Oncol. 2020 Mar 1;6(3):e194489
2. Pietrantonio F, et al. JAMA Oncol. 2019;5:1268-1275.
3. Modest DP, et al. Maintenance therapy with 5-fluoruracil/leucovorin (5-FU/LV) plus panitumumab (pmab) or 5-FU/LV alone in RAS wildtype (WT) metastatic colorectal cancer (mCRC) - the PANAMA trial (AIO KRK 0212). Abstract 3503, ASCO 2021 Virtual Meeting, 4–8 June.

Trastuzumab-deruxtecan showed promising activity in patients with HER2-expressing mCRC

In the phase 2, open-label DESTINY-CRC01 trial, treatment of patients with HER2-expressing metastatic colorectal cancer (mCRC) with trastuzumab-deruxtecan (T-DXd) showed promising activity and durability, as well as a manageable safety profile.

Of all patients with mCRC, less than 5% have a HER2-expressing tumour [1]. Currently, no approved HER2-targeted therapies exist for mCRC. T-DXd is an antibody-drug conjugate of a humanised anti-HER2 antibody bound to a topoisomerase I inhibitor by a cleavable linker. The previously published primary results of the DESTINY-CRC01 trial (NCT03384940) demonstrated anti-tumour activity of T-DXd in patients with HER2-expressing mCRC [2]. Dr Takayuki Yoshino (National Cancer Center Hospital East, Japan) presented updated results [3].

Enrolled were 86 patients with *RAS* wildtype mCRC that progressed in 2 or more prior regimens. Patients in cohort A (n=53) were HER2-positive (IHC3+ or IHC2+/ISH+), patients in Cohort B (n=15) were HER2-borderline (IHC2+/ISH-), and patients in Cohort C (n=18) were HER2-negative (IHC1+). Patients were treated with 6.4 mg/kg of T-DXd every 3 weeks. The primary endpoint was confirmed objective response rate in cohort A.

The objective response rate was 45.3% in Cohort A versus 0% in both Cohort B and Cohort C. Disease control rate was 83.0%, 60.0%, and 22.2% in the respective cohorts. The median duration of response in Cohort A was 7.0 months. Median progression-free and overall survival results are summarised in the Figure.

The safety profile was consistent with the known safety profile of T-DXd. An adverse event of special interest is interstitial lung disease, which occurred in 8 of 86 patients (4 patients grade 2, 1 patient grade 3, and 3 patients grade 5). These results are promising and support future trials with T-DXd in HER2-positive mCRC.

1. Siena S, et al. Ann Oncol. 2018;29:1108-1119.
2. Siena S, et al. Lancet Oncol. 2021;22:779-789.
3. Yoshino T, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients (pts) with HER2-expressing metastatic colorectal cancer (mCRC): Final results from a phase 2, multicenter, open-label study (DESTINY-CRC01). Abstract 3505, ASCO 2021 Virtual Meeting, 4–8 June.

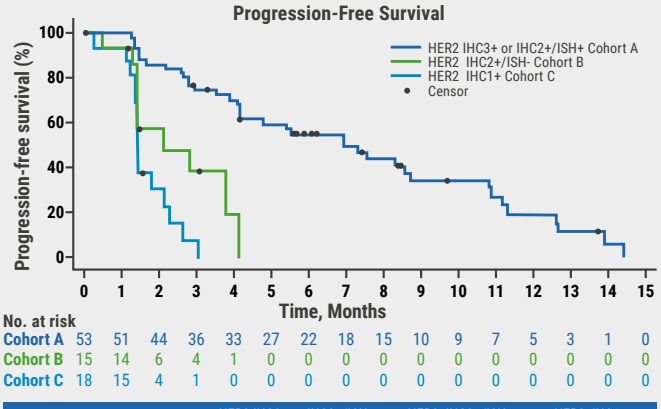
Benefit of both I-O/chemo combo and I-O/I-O combo over chemotherapy alone in oesophageal squamous cell cancer

First results of the randomised, phase 3 CheckMate 648 study demonstrated superior overall survival of first-line treatment with nivolumab plus ipilimumab or nivolumab plus chemotherapy versus chemotherapy alone.

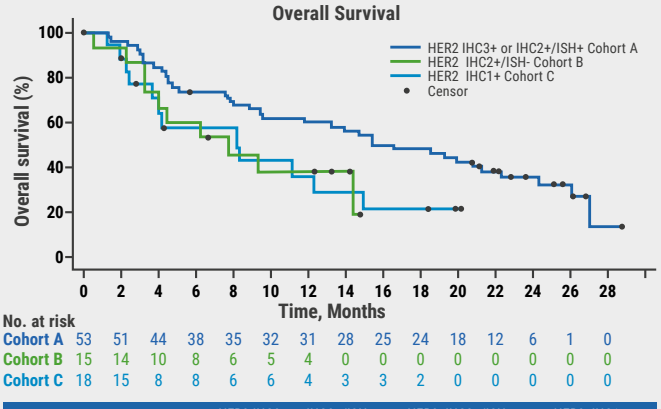
Standard first-line chemotherapy for advanced or metastatic oesophageal squamous cell cancer (ESCC) results in poor overall survival [1]. Recently, first-line treatment with the PD-1 inhibitor nivolumab demonstrated superior overall survival versus chemotherapy in previously treated patients with ESCC in the ATTRACTION-3 trial (NCT02569242) [2].

The randomised, phase 3 ChecMate 648 trial (NCT03143153) explored the efficacy and safety of first-line treatment in ESCC

Figure: Progression-free and overall survival in DESTINY-CRC01 [3]



	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n=53)	HER2 IHC2+/ISH- Cohort B (n=15)	HER2 IHC1+ Cohort C (n=18)
mPFS (95% CI), months	6.9 (4.1-8.7)	2.1 (1.4-4.1)	1.4 (1.3-2.1)

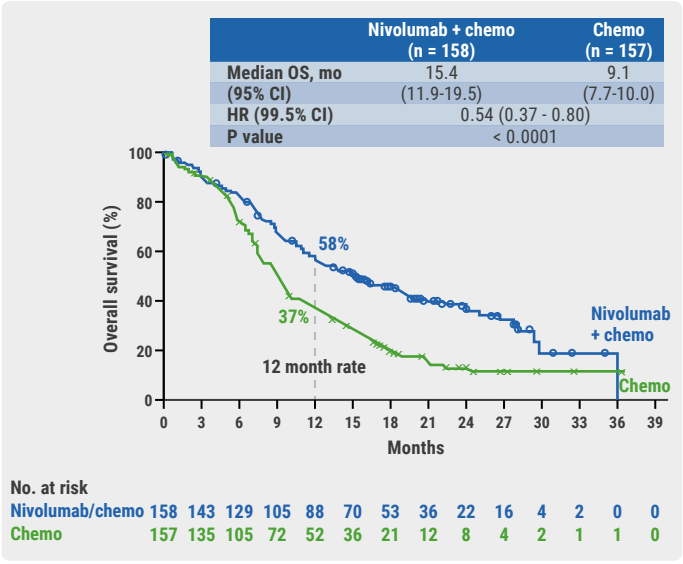


	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n=53)	HER2 IHC2+/ISH- Cohort B (n=15)	HER2 IHC1+ Cohort C (n=18)
mOS (95% CI), months	15.5 (8.8-20.8)	7.3 (3.0-NE)	7.7 (2.2-13.9)

with 2 combination therapies: nivolumab plus ipilimumab (I-O/I-O combo) and nivolumab plus chemotherapy (I-O/chemo combo). Enrolled were 970 patients with previously untreated, unresectable advanced, recurrent, or metastatic ESCC regardless of PD-L1 expression. Patients received either nivolumab (240 mg every 2 weeks) plus chemotherapy (fluorouracil plus cisplatin every 4 weeks), nivolumab (3 mg/kg every 2 weeks) plus ipilimumab (1 mg/kg every 6 weeks), or chemotherapy alone. Primary endpoints for both comparisons were overall survival and progression-free survival in patients with tumour cell PD-L1 ≥1%. Secondary endpoints were overall and progression-free survival in all randomised patients. Dr Ian Chau (Royal Marsden Hospital, UK) presented the results of the first interim analysis at a minimum follow-up of 12.9 months [3].

Both the I-O/chemo combo and the I-O/I-O combo led to statistically significant improvement in overall survival versus chemotherapy alone. Median overall survival was 15.4 months, 13.7 months, and 9.1 months for treatment with I-O/chemo combo, I-O/I-O combo, and chemotherapy alone, respectively (see Figure).

Figure: Interim overall survival data of CheckMate 648 for patients with PD-L1 ≥1% [3]



A statistically significant progression-free survival benefit was also observed for I-O/chemo combo versus chemotherapy alone, but this did not meet the prespecified boundary for significance for I-O/I-O combo versus chemotherapy alone. The objective response rate (per BICR) was 53% (I-O/chemo combo), 35% (I-O/I-O combo), and 20% (chemotherapy alone). The median duration of response was 8.4 months, 11.8 months, and 5.7 months for treatment with I-O/chemo combo, I-O/I-O combo, and chemotherapy alone, respectively. Secondary endpoint of overall survival was also met, showing clear superiority in all randomised patients regardless of PD-L1 expression. No new safety signals were identified for the combination treatments. In conclusion, nivolumab + chemotherapy and nivolumab + ipilimumab each represent a new potential standard of care for patients with advanced ESCC.

1. Moehler MH, et al. Ann Oncol. 2020;31(2):228-235.
2. Kato K, et al. Lancet Oncol. 2019;20:1506-1517.
3. Chau I, et al. Nivolumab (NIVO) plus ipilimumab (IPI) or NIVO plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced esophageal squamous cell carcinoma (ESCC): First results of the CheckMate 648 study. Abstract LBA4001, ASCO 2021 Virtual Meeting, 4–8 June.

Benefit of I-O/chemo combo over chemotherapy alone in advanced GC/GEJC/EAC

The addition of nivolumab to chemotherapy demonstrated improved survival benefit along with an acceptable safety profile, while maintaining tolerability and quality of life in patients with gastric cancer/gastric-oesophageal junction cancer and oesophageal adenocarcinoma (GC/GEJC/EAC), additional data from CheckMate 649 showed.

Standard chemotherapy for advanced GC/GEJC/EAC results in poor overall survival (median <1 year) [1]. Recently, the CheckMate 649 trial (NCT02872116) demonstrated a survival benefit of nivolumab/chemotherapy versus chemotherapy alone in patients with advanced GC/GEJC/EAC [2]. Prof. Markus Moehler (Mainz University Clinic, Germany) presented additional data [3].

CheckMate 649 enrolled 789 patients in the nivolumab/chemotherapy arm and 792 patients in the chemotherapy alone arm. At 12.1 months minimum follow-up, nivolumab/chemotherapy treatment continued to have a statistically significant overall survival benefit versus chemotherapy alone (HR 0.80; 99.3% CI 0.68–0.94; P=0.0002). Progression-free survival benefit was also seen (HR 0.77; 95% CI 0.68–0.87). An overall survival benefit was observed in multiple prespecified subgroups. The objective response rate was 58% in the nivolumab/chemotherapy arm versus 46% in the chemotherapy alone arm.

Treatment-related adverse events grade 3-4 with potential immunologic aetiology were observed in 16% of patients treated with nivolumab/chemotherapy. Treatment with nivolumab/chemotherapy was associated with maintaining

health-related quality of life and a decreased risk of symptom deterioration versus chemotherapy alone. This data supports nivolumab/chemotherapy as a new first-line standard therapy in advanced non-HER2-positive GC/GEJC/EAC.

1. Fuchs CS, et al. Lancet Oncol. 2019;20:420-435.
2. Moehler MH, et al. Abstract LBA6, ESMO 2020, 19-21 Sept.
3. Moehler MH, et al. First-line (1L) nivolumab (NIVO) plus chemotherapy (chemo) versus chemo in advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): Expanded efficacy and safety data from CheckMate 649. Abstract 4002, ASCO 2021 Virtual Meeting, 4–8 June.

Perioperative chemotherapy and neoadjuvant multimodality therapy appear equally effective

First results of the phase 3, open-label Neo-AEGIS trial demonstrated no evidence that perioperative chemotherapy (i.e. modified MAGIC or FLOT regimen) was inferior to multimodal therapy (i.e. CROSS regimen) in patients with oesophageal adenocarcinoma (EAC) and gastric-oesophageal junction cancer (GEJ).

The optimum combination curative approach to locally advanced GEJ/EAC is unknown. A key question is whether neoadjuvant multimodal therapy, specifically the CROSS regimen (i.e. carboplatin/paclitaxel, 41.4Gy radiation therapy), is superior to optimum perioperative chemotherapeutic regimens including modified MAGIC (i.e. epirubicin, cisplatin [oxaliplatin], 5-FU [capecitabine]) and more recently FLOT (i.e. docetaxel, 5-FU, leucovorin, oxaliplatin).

The Neo-AEGIS trial (NCT01726452) is the first randomised controlled trial designed to address this question. At 24 European sites, 377 patients with cT2-3N0-3M0 EAC or GEJ were randomly assigned to CROSS or perioperative chemotherapy. The primary outcome was overall survival. The initial power calculation was based on CROSS superiority of 10%. After the first futility analysis (70 events), this was modified to a non-inferiority margin of 5%. Secondary endpoints included toxicity, pathologic measures of response, and postoperative complications. Prof. John Reynolds (Trinity St James Cancer Institute, Ireland) presented the results of the second futility analysis [1].

A total of 362 patients were evaluated; 178 receiving CROSS, 184 receiving MAGIC/FLOT (157/27), 90% male, median age 64 years, 84% cT3, and 58% cN1. At a median follow-up of 24.5 months, 143 deaths occurred (70 in the CROSS and 73 in the MAGIC/FLOT arm). The second futility analysis (60% of planned events) showed a 3-year estimated survival probability of 56% in the CROSS arm and 57% in the MAGIC/FLOT arm (HR 1.02; 95% CI 0.74–1.42). Markers of response (pathologic complete response, major pathologic response, R0 rate, and nodal downstaging) were significantly better in the CROSS arm. Neutropenia, diarrhoea, and vomiting were significantly increased in the chemotherapy arm compared with CROSS. However, there were no differences in toxic deaths, neutropenic sepsis, or pulmonary embolism. Based on the absence of futility, evidenced recruitment was closed in December 2020.

1. Reynolds JV, et al. Neo-AEGIS (Neoadjuvant trial in Adenocarcinoma of the Esophagus and Esophago-Gastric Junction International Study): Preliminary results of phase III RCT of CROSS versus perioperative chemotherapy (Modified MAGIC or FLOT protocol). Abstract 4004, ASCO 2021 Virtual Meeting, 4–8 June.

Haematological Cancers

Olutasidenib demonstrates efficacy in patients with relapsed/refractory *IDH1* mutant AML

First results of a phase 2 study demonstrated durable complete remissions in patients with relapsed/refractory *IDH1* mutant acute myeloid leukaemia (AML) after monotherapy with IDH1 inhibitor olutasidenib.

Isocitrate dehydrogenase 1 (IDH1) is a key enzyme in cellular metabolism, epigenetic regulation, redox states, and DNA repair. *IDH1* mutations are causal in the development and/or progression of various types of cancer due to the supraphysiological production of D-2-hydroxyglutarate (2HG). *IDH1* mutations occur in 6–10% of AML patients [1]. Olutasidenib is a highly potent selective and orally active inhibitor of IDH1 mutants, inhibiting 2HG over-production.

The phase 2, multicohort 2102M 101 trial (NCT02719574) is evaluating olutasidenib as a single agent and in combination with azacitidine in *IDH1* mutant AML patients. Dr Stéphane de Botton (Institute Gustave Roussy, France) presented interim results from cohort 1 in which 153 patients with relapsed or refractory AML received olutasidenib alone at the dose of 150

milligrams twice daily over continuous 28-day cycles [2]. The primary endpoint was complete remission (CR) plus complete remission with partial haematological recovery (CRh). Additional endpoints included overall response rate, duration of response, overall survival, transfusion independence, and safety.

At a median duration of treatment of 5.5 months, a total of 123 patients were evaluable for efficacy. The CR+CRh rate was 33%, including 30% of patients achieving CR. Composite CR (CR+CRh+CR with incomplete recovery) was 45%. The median duration of CR+CRh was not reached. The median duration of overall response was 11.7 months. The median overall survival for CR+CRh patients was not reached. For non-CR+CRh patients, the median overall survival was 15.0 months, for non-responders it was 4.1 months. Transfusion independence was achieved in all response groups, particularly those achieving CR.

Serious adverse events were reported in the majority of patients; the most frequent being febrile neutropenia, anaemia, and thrombocytopenia. Treatment-related adverse events of special interest included differentiation syndrome, which was reported in 21 patients (14%).

1. Molenaar RJ, et al. Oncogene 2018;37:1949–1960.
2. De Botton S, et al. Effect of olutasidenib (FT-2102) on complete remissions in patients with relapsed/refractory (R/R) mIDH1 acute myeloid leukemia (AML): Results from a planned interim analysis of a phase 2 clinical trial. Abstract 7006, ASCO 2021 Virtual Meeting, 4–8 June.

Acalabrutinib as effective but better tolerated than ibrutinib in CLL

Featured interview: Dr John Byrd (Ohio State University College of Medicine, OH, USA) discusses the ELEVATE-RR trial: Acalabrutinib demonstrates similar efficacy and better safety compared with ibrutinib. read the interview online >

In the first head-to-head trial of BTK inhibitors in previously treated chronic lymphocytic leukaemia (CLL), acalabrutinib demonstrated non-inferior progression-free survival with less cardiotoxicity and fewer discontinuations due to adverse events compared with ibrutinib.

Bruton tyrosine kinase (BTK) is critical for CLL tumour cell proliferation and survival [1]. Ibrutinib, the first BTK inhibitor approved for adults with CLL, is associated with adverse events, particularly cardiovascular toxicities, that can lead to treatment discontinuation [2].

The randomised, non-inferiority, phase 3 ELEVATE-RR trial (NCT02477696) compared ibrutinib and acalabrutinib, a second-generation BTK inhibitor, in previously treated patients with CLL requiring therapy. The study randomised 533 patients 1:1 to receive acalabrutinib (100 mg twice daily) or ibrutinib (420 mg once daily) until progression or unacceptable toxicity. The primary endpoint was progression-free survival; secondary endpoints were incidence of all-grade atrial fibrillation, grade ≥3 infection, Richter transformation, and overall survival. Prof. John Byrd (Ohio State University Comprehensive Cancer Center, OH, USA) presented the first results of this head-to-head trial [3].

At a median follow-up of 40.9 months, progression-free survival was 38.4 months in both arms (HR 1.00; 95% CI 0.79-1.27), so the primary endpoint of non-inferiority was met. Acalabrutinib was statistically superior to ibrutinib in all-grade atrium fibrillation incidence (9.4% vs 16.0%; P=0.023). Among the other secondary endpoints, incidences of grade ≥3 infection and Richter transformation were comparable between arms. Median overall survival was not reached in either arm (HR 0.82; 95% CI 0.59–1.15), with 63 (23.5%) deaths in the acalabrutinib arm and 73 (27.5%) in the ibrutinib arm.

Acalabrutinib was associated with a lower incidence of hypertension (8.6% vs 22.8%), arthralgia (15.8% vs 22.8%), and diarrhoea (34.6% vs 46.0%), but a higher incidence of headache (34.6% vs 20.2%) and cough (28.9% vs 21.3%). Adverse events led to treatment discontinuation in 14.7% of acalabrutinib-treated patients versus 21.3% of ibrutinib-treated patients. Among any-grade events, both cardiac and bleeding events were less frequent with acalabrutinib (24.1% vs 30.0% and 38.0% vs 51.3%, respectively; see Table).

Table: Events of clinical interest [2]

	Any Grade		Grade ≥3	
Events, n (%)	**Acalabrutinib (n=266)**	**Ibrutinib (n=263)**	**Acalabrutinib (n=266)**	**Ibrutinib (n=263)**
Cardiac events	64 (24.1)	79 (30.0)	23 (8.6)	25 (9.5)
Atrial fibrilation	25 (9.4)	42 (16.0)	13 (4.9)	10 (3.8)
Ventricular arrhythmias	0	3 (1.1)	0	1 (0.4)
Bleeding events	101 (38.0)	135 (51.3)	10 (3.8)	12 (4.6)
Major bleeding events	12 (4.5)	14 (5.3)	10 (3.8)	12 (4.6)
Hypertension	25 (9.4)	61 (23.2)	11 (4.1)	24 (9.1)
Infections	208 (78.2)	214 (81.4)	82 (30.8)	79 (30.0)
ILD/pneumonitis	7 (2.6)	17 (6.5)	1 (0.4)	2 (0.8)
SPMs excluding NMSC	24 (9.0)	20 (7.6)	16 (6.0)	14 (5.3)

1. Vitale C, Burger JA. Expert Opin Pharmacother. 2016;17:1077-1189.
2. Dickerson T, et al. Blood 2019;134:1919-1928.
3. Byrd, JC, et al. First results of a head-to-head trial of acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia. Abstract 7500, ASCO 2021 Virtual Meeting, 4–8 June.

Gynaecological Cancers

Novel drug combination for recurrent ovarian cancer

Mirvetuximab soravtansine, a folate receptor-targeting antibody-drug conjugate, in combination with bevacizumab, demonstrated impressive anti-cancer activity in the phase 1b FORWARD II trial.

Mirvetuximab soravtansine is an antibody-drug conjugate comprising a folate receptor α (FRα)-binding antibody, cleavable linker, and the maytansinoid DM4, a potent tubulin-targeting agent. Prior research showed that mirvetuximab soravtansine has encouraging anti-tumour activity in platinum-resistant ovarian cancer, either as monotherapy or in combination with bevacizumab [1,2].

As part of the phase 1b FORWARD II trial (NCT02606305), the combination of mirvetuximab soravtansine with bevacizumab was evaluated in patients with FRα-positive, platinum-agnostic ovarian cancer. This was defined as patients who had medium/high expression of FRα (≥50%/≥75% of cells with PS2+ staining intensity) and who were either platinum-resistant or platinum-sensitive. Enrolled were 60 patients (32 platinum-resistant and 28 platinum-sensitive). Patients received mirvetuximab soravtansine (6 mg/kg) and bevacizumab (15 mg/kg) on day 1 of a 21-day cycle. Prof. David O'Malley (Ohio State University, OH, USA) presented the results of the study [3].

At a median follow-up of 17.5 months, objective response rate in the total population was 50%; 33% in patients with medium FRα expression and 64% in patients with high FRα expression. Objective response rate was 59% in patients who were platinum-resistant (and had high FRα expression) and 69% in patients who were platinum-sensitive (and had high FRα expression). Median duration of response was 9.7 months in the total population and 11.8 months in the patients with high FRα expression (12.7 months in the platinum-sensitive patients and 9.4 months in the platinum-resistant patients of those with high FRα expression). Of patients who had high FRα expression, 32/33 (99%) showed a deep and rapid anti-tumour response regardless of platinum status.

The most common treatment-related adverse events were diarrhoea (62%), blurred vision (60%), fatigue (60%), and nausea (57%). The most common treatment-related grade 3/4 adverse events were hypertension (17%) and neutropenia (13%).

1. Moore K, et al. Ann Oncol. 2019;30(suppl 5):V403.
2. O'Malley DM, et al. Gyn Oncol. 2020;157:379-385.
3. O'Malley DM, et al. Mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients (pts) with platinum-agnostic ovarian cancer: Final analysis. Abstract 5504, ASCO 2021 Virtual Meeting, 4–8 June.

Adjuvant chemotherapy does not improve outcome in patients with locally advanced cervical cancer

Results of the randomised, phase 3 OUTBACK trial do not support the use of adjuvant chemotherapy after chemoradiation in women with locally advanced cervical cancer. At 5 years, both overall and progression-free survival were similar in the respective treatment arms.

The standard treatment for locally advanced disease is chemoradiation followed by brachytherapy. However, a significant percentage of women still relapse and die from the development of distant metastatic disease [1]. A randomised trial suggested additional benefit of the use of concurrent cisplatin-gemcitabine and radiation followed by 2 cycles of cisplatin-gemcitabine [2].

The randomised, phase 3 OUTBACK trial (ACTRN12610000732088) was designed to determine the effects of adjuvant chemotherapy after chemoradiation on survival. Eligible women (n=919) had locally advanced cervical cancer (FIGO 2008 stage IB1 and node positive, IB2, II, IIIB, or IVA) that was suitable for primary treatment with chemoradiation with curative intent. The participants were randomised 1:1 to either standard cisplatin-based chemoradiation (control) or standard cisplatin-based chemoradiation followed by adjuvant chemotherapy with 4 cycles of carboplatin and paclitaxel. Adjuvant chemotherapy was started in 361 (78%) women assigned to receive it. The median follow-up was 60 months. The primary endpoint was overall survival at 5 years. Secondary endpoints included progression-free survival, adverse events, and patterns of disease recurrence. Prof. Linda Mileshkin (Peter MacCallum Cancer Center, Australia) presented the results [3].

At 5 years, overall survival was similar in both arms (71% vs 72%). Progression-free survival was also similar (63% vs 61%). Adverse events of grade 3–5 within a year of randomisation occurred in 81% of patients who were assigned and received adjuvant chemotherapy versus 62% assigned control. There was no evidence of differences between treatment groups in adverse events beyond 1 year of randomisation. Global Health Quality of Life Scores were worse during adjuvant therapy and 3 to 6 months thereafter but similar from months 12 to 36.

1. Narayan K, et al. Int J Gynecol Cancer. 2009;19(5):912-918.
2. Dueñas-González A, et al. J Clin Oncol. 2011;29:1678–1685.
3. Mileshkin LR, et al. Adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone: The randomized phase III OUTBACK Trial (ANZGOG 0902, RTOG 1174, NRG 0274). Abstract LBA3, ASCO 2021 Virtual Meeting, 4–8 June.

Dual HER2-blockade shows anti-tumour activity in patients with uterine cancer

In the phase 2 TAPUR basket trial, the combination of pertuzumab and trastuzumab demonstrated anti-tumour activity in heavily pre-treated patients with uterine cancer with *HER2* amplification and/or specific mutations. Additional study is warranted to confirm the efficacy of pertuzumab and trastuzumab in this patient population.

Unlike in breast cancer, the clinical significance of *HER2* gene amplification in uterine cancer is controversial since the single-agent trastuzumab has shown little activity in *HER2*-positive endometrial cancer. TAPUR is a phase 2 basket study (NCT02693535) evaluating the anti-tumour activity of commercially available targeted agents in patients with advanced solid cancers harbouring genomic alterations known to be drug targets. The primary endpoint of TAPUR is disease control, defined as objective response, or stable disease for at least 16 weeks. Dr Eugene Ahn (Cancer Treatment Centers of America, IL, USA) presented results from the uterine cancer cohort of TAPUR [1].

Enrolled were 28 heavily pretreated patients with advanced uterine cancer with *HER2* or *HER3* amplification or over-expression or a pre-specified *HER2* mutation. Eligible participants had no standard treatment options, measurable disease, ECOG PS 0-2, and adequate organ function. They were treated with pertuzumab and trastuzumab (every 3 weeks) until disease progression.

The disease control rate was 37%, and the objective response rate was 7%. At 16 weeks, 2 patients had a partial response, and 8 patients achieved stable disease. Median progression-free survival was 28.1 weeks; median overall survival was 60.9 weeks. One patient experienced grade 3 muscle weakness, which was at least possibly related to pertuzumab/trastuzumab.

1. Hussein MA, et al. Pertuzumab plus trastuzumab (P+T) in patients (Pts) with uterine cancer (UC) with ERBB2 or ERBB3 amplification, overexpression or mutation: Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) study. Abstract 5508, ASCO 2021 Virtual Meeting, 4–8 June.

Paediatric Cancer

Molecular tumour profiling impacts the diagnosis and treatment of solid tumours

The first results of the GAIN/iCAT2 Consortium trial showed the importance of molecular profiling of solid tumours in young patients.

Next-generation sequencing (NGS) assays are now a standard part of clinical care for many adult solid cancers. The significance of molecular tumour profiling for the care of children with cancer is not well understood. To determine the clinical impact of identifying genomic alterations by NGS for young patients with relapsed, refractory, or high-risk extracranial solid tumours, the GAIN/iCAT2 Consortium study (NCT02520713) was started. Dr Alanna Church (Boston Children's Hospital, MA, USA) reported on the first 389 participants (of estimated 825 patients) in this prospective cohort study enrolling patients at 12 institutions in the USA with extracranial solid tumours diagnosed at age 30 years or less [1].

Targeted DNA NGS was performed on ≥1 tumour samples from each patient. Selected patients also had tumours subjected to

RNA sequencing. Test results were returned to the treating oncologist and follow-up treatment and response data were collected. Genomic alterations were classified according to evidence of impact on diagnosis, prognosis, or response to targeted therapy matched to an identified alteration (matched targeted therapy, MTT) using established guidelines. Response to MTT was determined and reported as a response if either there was a radiographic response according to RECIST or the duration of therapy was over 4 months. Molecular tumour profiling was successful in 345 (89%) patients (mean age 11 years at diagnosis; 65% with sarcoma). Of these, 299 (87%) had 1 or more alterations of clinical significance. Genomic alterations with diagnostic, prognostic, or therapeutic significance were present in 208 (60%), 51 (15%), and 240 (70%) patients, respectively. Of the 240 patients with tumours harbouring genomic alterations designated as having therapeutic impact, 23 (11%) had Tier 1 molecular findings (clinical evidence same/similar alteration, same disease).

In total, 205 patients were eligible to receive MTT based on having a molecular alteration with therapeutic significance and sufficient follow-up; 31 of these patients (15%) received MTT. Seven patients (23%) receiving MTT responded, 6 of these were kinase fusions (i.e *TCF12-NOTCH1* fusion, *KHDRBS2-BRAF* fusion, *RBPMS-NTRK2* fusion, *SEPT17-BRAF* fusion, *CCDC6-ALK* fusion, *MYH10-RET* fusion). All of the responders received targeted therapy matched to a fusion (respectively: crenigacestat, trametinib, larotrectinib, trametinib, crizotinib, and vendetinib). Furthermore, 78% of diagnostically significant alterations were fusions.

1. Church AJ, et al. Clinical impact of molecular tumour profiling in pediatric, adolescent, and young adult patients with extra-cranial solid malignancies: An interim report from the GAIN/iCat2 study. Abstract 10005, ASCO 2021 Virtual Meeting, 4–8 June.

Circulating tumour DNA to evaluate response in children with neuroblastoma

In the phase 2 NANT2011-01 trial, levels of circulating tumour DNA (ctDNA) were evaluated during treatment. In patients with a clinical response, ctDNA became undetectable over time.

Neuroblastoma is the most common extracranial solid tumour in paediatrics. High-risk disease comprises about half of all diagnoses and long-term survival is poor. Plasma ctDNA has been demonstrated to be present at high levels in neuroblastoma and provides an important tool and surrogate for tumour molecular analyses [1].

The multicentre, open-label, randomised, phase 2 NANT2011-01 trial (NCT02035137) evaluated the diagnostic and therapeutic agent metaiodobenzylguanidine (MIBG) with or without radiation sensitisers for patients with relapsed or refractory neuroblastoma. In a pre-planned exploratory analysis, presented by Dr Kevin Campbell (Dana-Farber Cancer Institute, MA, USA), plasma samples from the NANT2011-01 trial, were used to evaluate the potential use of ctDNA as a biomarker to evaluate response to MIBG [2]. Plasma was collected at baseline prior to MIBG and at 4, 5, 15, and 50 days after MIBG. Samples were analysed for percentage ctDNA levels using ultra-low passage whole-genome sequencing.

This analysis included 84 patients with a median age of 6.25 years. Of the 37 patients (44%) with detectable ctDNA at baseline, the median ctDNA level was 32%. Baseline ctDNA levels showed a significant positive correlation with percentage involvement in bone marrow and Curie score but not RECIST sum of diameters for soft tissue sites. Following therapy, the proportions of patients with detectable ctDNA were 47% at day 4, 62% at day 5, 33% at day 15, and 14% at day 50. The rate of ctDNA detection was similar between responders and non-responders at baseline, day 4, and day 5, but undetectable in responders at day 15 and day 50 versus 37% and 20% in non-responders (see Table).

Table: Proportion of patients with detectable ctDNA according to response to first course [2]

	Baseline	Day 4	Day 5	Day 15	Day 50
Total	37/84 (44%)	34/73 (47%)	26/42 (62%)	7/21 (33%)	3/21 (14%)
Responders	8/19 (42%)	9/17 (53%)	6/14 (43%)	0/2 (0%)	0/6 (0%)
Non-Responders	29/65 (45%)	25/56 (45%)	20/38 (53%)	7/19 (37%)	3/15 (20%)

Dr Campbell concluded that these results warrant further use of ctDNA to evaluate the response to treatment in children with relapsed or refractory neuroblastoma. For example, it should be investigated how copy number alterations or segmental chromosomal aberrations detectable in ctDNA might be associated with differential response to MIBG therapy.

1. Klega K, et al. JCO Presic Oncol. 2018;2:PO.17.00285.
2. Campbell KM, et al. Changes in ctDNA levels after MIBG therapy in patients with relapsed or refractory neuroblastoma. Abstract 10012, ASCO 2021 Virtual Meeting, 4–8 June.

Basic Science

PARP7 inhibitor shows promising results in first-in-human trial

RBN-2397 is a potent, selective inhibitor of PARP7 that could potentially release the brake on the anti-tumour immunity. It was well tolerated and demonstrated proof of mechanism in a first-in-human trial.

Targeting cytosolic nucleic acid sensing pathways and the Type I interferon response is an emerging therapeutic strategy in oncology. PARP7 is a member of the poly-ADP-ribose polymerases (PARP) enzymes and acts as a brake on the cellular stress response by negatively regulating the Type I interferon response. PARP7 expressed in cancer cells blocks anti-tumour immunity and is, therefore, a potential novel therapeutic target. RBN-2397 is a potent, selective inhibitor of PARP7 that could potentially release the brake on the anti-tumour immunity. In preclinical models, RBN-2397 restored Type I interferon signalling in tumours, caused complete tumour regressions, and induced adaptive immunity [1].

Dr Gerald Falchook (Sarah Cannon Research Institute at HealthONE, CO, USA) presented the results of the first-in-human phase 1 study (NCT04053673) of RBN-2397 in patients with solid tumours [2]. Patients (n=47) were treated with RBN-2397 on either a continuous or 14-of-21-day intermittent schedule using a 3 plus 3 dose-escalation design; 25 patients were treated with the intermittent schedule (25 to 500 mg twice daily) and 22 patients with the continuous schedule (100 to 400 mg twice daily). Most common cancer types were breast cancer (n=8), lung cancer (n=7), endometrial cancer (n=4), colon cancer (n=4), and pancreatic cancer (n=4). The primary objective was to establish maximum tolerated dose, dose-limiting toxicity, and the recommended phase 2 dose. Secondary objectives were to characterise the safety profile of RBN-2397, preliminary anti-tumour activity, and to examine pharmacokinetics of micronised tablets.

The most frequent treatment-related adverse events (all grades) were dysgeusia (36%), decreased appetite (16%), fatigue (14%), and nausea (12%). Grade 3/4 treatment-related adverse events all occurred in 8 patients (16%) at doses ≥200 mg: diarrhoea (n=2), anaemia (n=2), fatigue (n=1), increased AST (n=1), neutropenia (n=1), and thrombocytopenia (n=1). The maximum tolerated dose was 400 mg twice daily on a continuous dosing schedule, recommended phase 2 dose was 200 mg twice daily on a continuous dosing schedule with micronised tablets.

In 5 evaluable tumour biopsy pairs, increases in interferon-stimulated gene expression were observed post RBN-2397, consistent with activation of Type I interferon. An increase was observed in immune response-related genes and CD8+ T cells in a patient with metastatic squamous non-small cell lung cancer (NSCLC) who has been on study for >16 months. One patient with HR-positive, HER2-negative breast cancer achieved a confirmed partial response at 100 mg RBN-2397, and 9 patients had stable disease for over 4 months. At data cut-off, 3 patients had an ongoing response. In the expansion phase, which is currently ongoing, patients with squamous NSCLC, HR-positive breast cancer, and PARP7-amplified tumours are included.

1. Vasbinder MM, et al. Tumour Biol. 2020;80:DDT02-01.
2. Falchook GS, et al. A first-in-human phase 1 study of a novel PARP7 inhibitor RBN-2397 in patients with advanced solid tumours. Abstract 3000, ASCO 2021 Virtual Meeting, 4–8 June.

IACS-6274 is well tolerated and biologically active in selected advanced tumours

Results from a biomarker-driven phase 1 trial showed treatment with IACS-6274, a potent oral glutaminase-1 (GLS1) inhibitor, to be safe and well tolerated up to a dose of 180 mg twice daily. Preliminary anti-tumour activity was observed.

Deregulated cellular metabolism is a key hallmark of cancer, in particular for tumours harbouring *KEAP1/NFE2L2* mutations or those expressing low Asparagine Synthetase (ASNS) levels, leaving these tumours subject to glutaminolysis for bioenergetics. GLS1 is a key enzyme in glutaminolysis, converting glutamine into glutamate.

IACS-6274 is a potent oral GLS1 inhibitor with excellent pharmacokinetics and anti-tumour activity in biomarker-defined preclinical models. Dr Timothy Yap (MD Anderson Cancer Center, TX, USA) presented the results of a phase 1 trial (NCT03894540) of IACS-6274 in patients with molecularly

selected advanced solid tumours [1]. Primary endpoints were safety and tolerability, maximum tolerated dose, and recommended phase 2 dose. One secondary endpoint was preliminary anti-tumour activity.

The trial enrolled 22 patients with advanced ovarian cancer (n=8), non-small cell lung cancer (n=7), melanoma (n=2), gastric cancer, anal cancer, endometrial cancer, leiomyosarcoma, and head and neck squamous cell carcinoma (all n=1). Molecular alterations assessed included ASNS loss (n=6), *STK11* (n=5), *KEAP1* (n=5), *NFE2L2* (n=4), and *NF1* (n=1). A total of 12 patients had 2–4 prior lines of therapy, 10 patients had ≥5. Patients received IACS-6274 at escalating doses ranging from 20–240 mg twice daily.

The most common grade 1-2 treatment-related adverse events were very transient photophobia and photopsia, observed mainly at the highest doses of 180 mg and 240 mg. Grade 3-4 treatment-related toxicities were mainly seen at the dose of 240 mg (i.e. acute renal failure, nausea, hypokalaemia, hypertension, PRES syndrome, and seizures, all of which fully resolved). Glutamate to glutamine ratios decreased in plasma samples in patients at day 14. Compared with baseline, patients at doses of 120, 180, and 240 mg had inhibition of 82.5% (P<0.0001), 83.9% (P<0.0001), and 85.3% (P<0.0001), respectively. The recommended phase 2 dose was 180 mg twice daily. Best response was stable disease in 17 of 20 evaluable patients. Disease control rate at 12 weeks was 60%. Durable stable disease for more than 6 months was observed in 6 patients (2 patients with advanced ASNS-loss ovarian cancer, 2 patients with PD1 inhibitor-resistant melanoma, 1 patient with *NF1*-mutant leiomyosarcoma, and 1 patient with *STK11*-mutant non-small cell lung cancer).

1. Yap TA, et al. First-in-human biomarker-driven phase I trial of the potent and selective glutaminase-1 (GLS1) inhibitor IACS-6274 (IPN60090) in patients (pts) with molecularly selected advanced solid tumours. Abstract 3001, ASCO 2021 Virtual Meeting, 4–8 June.

CYT-0851 shows promising anti-tumour activity across different tumour types

CYT-0851 is the first DNA-damage repair therapeutic with demonstrated clinical activity in both haematologic malignancies and solid tumours, as results from a phase 1-2 trial showed.

Homologous recombination is an essential, high-fidelity mechanism to repair DNA double-strand breaks. Over-expression of the cytidine deaminase family of DNA damaging enzymes in subsets of cancers leads to increased DNA damage and subsequent dependence on homologous recombination-mediated DNA repair. Inhibition of homologous recombination in cancer cells leads to accumulation of unrepaired DNA double-strand breaks and tumour cell death. RAD51 is a key enzyme involved in homologous recombination. CYT-0851 is an oral, first-in-class, small-molecule inhibitor of RAD51-mediated DNA repair. Previously, CYT-0851 showed anticancer activity in preclinical models of solid and haematological cancer [1,2].

Dr Ryan Lynch (Fred Hutchinson Cancer Research Center, WA, USA) presented the first results of a phase 1-2 trial (NCT03997968) of CYT-0851 in patients with advanced solid and haematologic cancers [3]. Primary objectives included safety, maximum tolerated dose, recommended phase 2 dose, and anti-tumour activity. Secondary and exploratory objectives included pharmacokinetics, pharmacodynamics, and predictive biomarkers of response.

At data cut-off, 39 patients were enrolled of whom 35 were treated with CYT-0851. Diagnoses were sarcoma (n=12), non-Hodgkin lymphoma (n=8), breast cancer (n=5), pancreatic cancer (n=4), ovarian cancer (n=3), head and neck cancer (n=1), small cell lung cancer (n=1), and mucoepidermoid carcinoma (n=1). Dosing ranged from 15–45 mg twice daily to 90–3,000 mg once daily.

No patients experienced dose-limiting toxicity. A total of 13 patients (37%) experienced a CYT-0851-related adverse event with only 1 patient experiencing a grade ≥3 adverse event (fatigue). No clinically significant myelosuppression or treatment-related discontinuation was observed. Preliminary pharmacokinetic analyses showed dose-proportional systemic exposure with a half-life of ~3 days, supporting the transition from twice-daily to once-daily dosing.

A total of 21 patients were response-evaluable; 3 partial responses were observed (2 patients with non-Hodgkin lymphoma, 1 patient with soft-tissue sarcoma), and 10 patients had stable disease. Dose escalation continues to establish the recommended phase 2 dose, with planned expansion in 7 disease-specific cohorts in haematological and solid cancers.

1. Day M, et al. Cancer Res. 2019;79(suppl):C14.
2. Day M, et al. Blood 2019;134(suppl 1):2080.
3. Lynch RC, et al. First-in-human phase I/II study of CYT-0851, a first-in-class inhibitor of RAD51-mediated homologous recombination in patients with advanced solid and hematologic cancers. Abstract 3006, ASCO 2021 Virtual Meeting, 4-8 June.