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PEER-REVIEWED CONFERENCE REPORT

Extra Focus on Breast Cancer

Practice-Changing Results of T-DXd in Breast Cancer

In the DESTINY-Breast04 trial, trastuzumab deruxtecan (T-DXd) outperformed standard-of-care in patients with HER2-low unresectable or metastatic breast cancer who had received 1 or 2 previous lines of chemotherapy.

read more on PAGE 4

Spectacular Results for Dostarlimab in Rectal Cancer

A phase 2 trial investigating neoadjuvant treatment with dostarlimab in patients with mismatch repair deficient (dMMR) rectal cancer showed a response rate of 100% following treatment with this agent in the thus far analysed patients.

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Ifosfamide Performs Well in Recurrent Ewing Sarcoma

Ifosfamide was more efficacious than topotecan plus cyclophosphamide in patients with primary recurrent or refractory Ewing sarcoma, results of the the phase 3 rEECur trial demonstrated.

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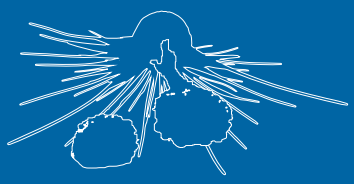

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Letter from the Editor

Dear reader,

It is my pleasure to share with you our summary of this year's annual meeting of the American Society of Clinical Oncology (ASCO), which took place as usual in Chicago.

You will find challenging results, both intellectually speaking as well as clinical: Are there intrinsic differences in CDK4 inhibitors or should we further define hormone receptor-positive metastatic breast cancer (mBC) patients who could best benefit from treatment? We will have to look closer to HER2 status results from our patients, as mBC patients seem to benefit from the targeting conjugate agent trastuzumab deruxtecan – even if they have low expression! Personalised medicine for BC advances with new potentially clinical relevant prognostic biomarkers both in locally advanced BC as well as in ductal carcinoma in situ.

As invasive treatments become safer and easier accessible, there is a tendency to integrate them more and more in oligometastatic disease. A new study provides evidence that this may not be beneficial in BC, underlining the need for evidence-based treatment decision-making rather than "common sense". And maybe I should mention the highly paradigm-changing LUMINA study which may lead to spare patients with very early, good prognosis BC to undergo adjuvant radiotherapy (of course, peer-reviewed published results as well as more long-term follow-up are mandated).

In non-small cell lung cancer, long-term (5 yr) results of the Checkmate 224 trial seem to point to a clear advantage of double checkpoint inhibition over standard chemotherapy with quite impressive overall survival results even in patients with low or absent PD-L1 scores.

New patients with rectal cancer may have lately approached you, declaring that they no longer required surgery nor radiotherapy, just this new drug from America… This somewhat misleading information derives from a phase 2 study with neoadjuvant dostarlimab (a PD-1 inhibitor) in mismatch repair-deficient; stage II and III rectal adenocarcinomas – leading to a 100% response rate (yes it is!) – without concurrent or consecutive chemo- or radiotherapy, clearly showing the power of immune checkpoint blocade in microsatellite instability-high or mismatch repair-deficient tumours. However, it is too early to conclude practice changes for our localised or locally advanced rectum cancer patients.

This is of course just my selection of our selection of ASCO this year. So, please sit back and check out what is new as from today, on your own.

Yours, sincerely
Stefan Rauh

Biography

Dr Stefan Rauh is currently working as haematooncologist 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 coauthor 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

Sacituzumab govitecan meets primary endpoint

Sacituzumab govitecan delivered superior progression-free survival (PFS) data compared with chemotherapy in patients with heavily pre-treated HR-positive/HER2-negative advanced breast cancer. The primary results of the phase 3 TROPiCS-02 trial support the use of this agent in heavily pre-treated breast cancer patients who have limited treatment options.

"In patients with advanced HR-positive/HER2-negative breast cancer who are resistant to endocrine therapy, single-agent chemotherapy is the standard-of-care," mentioned Prof. Hope Rugo (University of California San Francisco, CA, USA). However, chemotherapy options are limited in later lines, resulting in an unmet clinical need [1]. The TROPiCS-02 trial (NCT03901339) randomised patients with HR-positive/HER2-negative metastatic breast cancer, who had received endocrine therapy, a CDK4/6 inhibitor, and 2–4 prior lines of chemotherapy, to sacituzumab govitecan, a first-in-class trop-2-directed antibody-drug conjugate (n=272) or chemotherapy by physician's choice (capecitabine, eribulin, vinorelbine, or gemcitabine; n=271) [2]. The PFS by independent central review was the primary outcome of this study.

The primary endpoint was met: Treatment with sacituzumab govitecan resulted in a significantly improved median PFS compared with chemotherapy (5.5 vs 4.0 months; HR 0.66; P=0.0003), reflecting a 34% reduced risk of disease progression in the sacituzumab govitecan group. In the same line, the 12-month PFS rates were 21.3% for sacituzumab govitecan and 7.1% for chemotherapy. This result was consistent across predefined strata. The overall survival data trended towards a benefit for sacituzumab govitecan (13.9 vs 12.3 months; HR 0.84; P=0.14), however, this data was not yet mature at the time of this analysis. Furthermore, the overall response rate was higher in the experimental arm compared with the control arm (21% vs 14%; P=0.03).

"The safety profile of sacituzumab govitecan in this study was consistent with that observed in previous studies of this agent," said Prof. Rugo. Treatment-emergent adverse events (TEAEs) ≥ grade 3 occurred in 74% and 60% of the patients in the experimental arm and control arm, respectively. The number of TEAEs leading to treatment discontinuation was low, with 6% and 4% in the respective treatment groups. Neutropenia (51%) and diarrhoea (9%) were the most common ≥ grade 3 TEAEs in the experimental arm.

"Sacituzumab govitecan demonstrated statistically significant and clinically meaningful benefits and should be considered as a potential treatment option in the heavily pre-treated advanced breast cancer population with limited treatment options," concluded Prof. Rugo.

1. Gennari A, et al. Ann Oncol. 2021;32(12):1475–1495.
2. Rugo HS, et al. Primary results from TROPiCS-02: A randomized phase 3 study of sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (Pts) with hormone receptor–positive/HER2-negative (HR+/HER2-) advanced breast cancer. LBA1001, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.

Shaky OS results of palbociclib in ER-positive/HER2-negative breast cancer

The overall survival (OS) was not significantly longer for letrozole plus palbociclib than letrozole plus placebo in patients with ER-positive/HER2-negative advanced breast cancer in the PALOMA-2 trial. However, a post-hoc subgroup analysis revealed that patients with a disease-free interval >12 months might live longer if they take additional palbociclib.

The randomised, double-blind, phase 3 PALOMA-2 trial (NCT01740427) was designed to assess the benefits of adding the CDK4/6 inhibitor palbociclib to endocrine therapy. The primary analysis demonstrated that the median progression-free survival (PFS) of patients on palbociclib plus letrozole (n=444) was significantly longer than that of patients who received letrozole and placebo (n=222; 24.8 vs 14.5 months; HR 0.58; P<0.001) [1]. Prof. Richard Finn (David Geffen School of Medicine at UCLA, CA, USA) presented the final OS analysis after a median follow-up of 90 months [2].

The median OS was not significantly longer in the experimental arm compared with the placebo arm (53.9 vs 51.2 months; HR 0.96; P=0.34). Prof. Finn emphasised that missing survival data was substantial and disproportionally divided across the treatment arms, with 21% missing data in the placebo arm and 13% missing data in the palbociclib arm, limiting the interpretation of OS data. A post-hoc

sensitivity analysis, excluding patients of whom survival data was not available, resulted in a median OS of 51.6 months in the palbociclib arm and 44.6 months in the placebo arm (HR 0.87). Additionally, when the authors looked at the subgroup of patients with a disease-free interval >12 months from PALOMA-1 (NCT00721409) and PALOMA-2, the OS data favoured patients on palbociclib over placebo (64.0 vs 44.6 months). Furthermore, in PALOMA-2 the time to chemotherapy appeared to be longer in the experimental arm (38.1 vs 29.8 months), indicating an improved quality-of-life for patients on palbociclib. Finally, the safety profile of the combination therapy remained consistent with long-term use, with no signs of cumulative toxicity.

Prof. Claudine Isaacs (Georgetown University, DC, USA), discussant of this trial, commented that there are several explanations for the lack of OS results of this trial in comparison with the MONALEESA trials (NCT01958021, NCT02422615, NCT02278120), which showed the CDK4/6 inhibitor ribociclib to boost OS [3]. "There could be an intrinsic difference in the efficacy of the 2 CDK4/6 inhibitors. Also, the PALOMA-2 trial included more patients with a disease-free interval ≤12 months, which may reflect greater resistance to endocrine therapy in these patients. This may influence the results. We should therefore await the results of the HARMONIA trial (NCT05207709), comparing ribociclib with palbociclib directly," argued Prof. Isaacs.

1. Finn RS, et al. Overall Survival (OS) With First-Line Palbociclib Plus Letrozole (PAL+LET) Versus Placebo Plus Letrozole (PBO+LET) in Women With Estrogen Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer (ER+/HER2- ABC): Analyses From PALOMA-2. LBA1003, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.
2. Finn RS, et al. N Engl J Med. 2016;375:1925–1936.
3. Hortobagyi G, et al. Ann Oncol. 2021;32(suppl5):S1283–S1346.

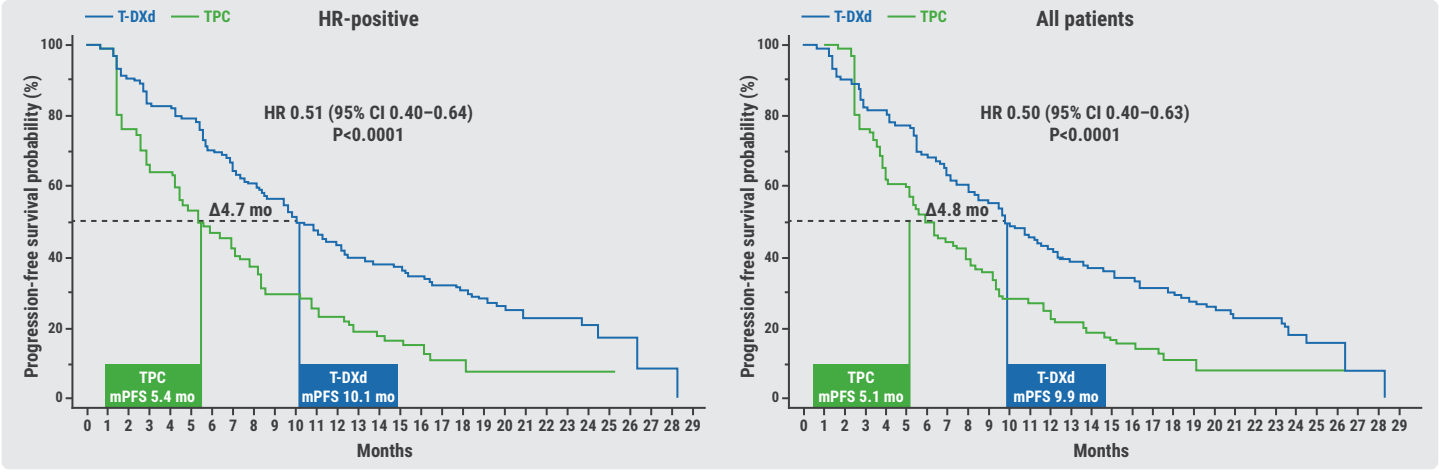
Practice-changing results of T-DXd in HER2-low breast cancer

Trastuzumab deruxtecan (T-DXd) outperformed therapy by physician's choice in patients with HER2-low unresectable or metastatic breast cancer who had received 1 or 2 previous lines of chemotherapy, in the DESTINY-Breast04 trial. T-DXd is the first HER2-targeted therapy to outperform the standard-of-care in terms of progression-free survival (PFS) and overall survival (OS) in the hard-to-treat HER2-low breast cancer population.

"The HER2-status of patients with breast cancer is defined by immunohistochemistry (IHC) scores, with HER2-low being defined as having an IHC score of 1+ or 2+ with in situ hybridisation (ISH)-negative status," explained Prof. Shanu Modi (Memorial Sloan Kettering Cancer Center, NY, USA). The options for these patients, especially in later lines of therapy, are limited [1]. The DESTINY-Breast04 trial (NCT03734029) randomised patients with HER2-low unresectable or metastatic breast cancer to T-DXd (n=373) or chemotherapy by physician's choice (n=184) [2]. Patients had received 1 or 2 prior lines of chemotherapy and were refractory to endocrine therapy if they were HR-positive. PFS by independent central review was the primary endpoint of this study. Of note, approximately 90% of the patients were HR-positive, whereas 10% were HR-negative.

The median PFS of patients on T-DXd was superior to that of patients on chemotherapy (9.9 vs 5.1 months; HR 0.50; P<0.0001) and the same was true for the HR-positive subset of patients (10.1 vs 5.4 months; HR 0.51; P<0.0001; see Figure). Moreover, the median OS favoured T-DXd over chemotherapy in the general population (23.4 vs 16.8

Figure: Progression-free survival of HR-positive patients versus the full analysis set [2]



T-DXd, Trastuzumab deruxtecan; TPC, chemotherapy by physician's choice; mPFS, median progression-free survival; mo, months.

months; HR 0.64; P=0.0010) and in the HR-positive subset of patients (23.9 vs 17.5 months; HR 0.64; P=0.0028). An exploratory analysis displayed that HR-negative patients are likely to benefit from T-DXd as well in terms of PFS (8.5 vs 2.9 months; HR 0.46) and OS (18.2 vs 8.3 months; HR 0.48). The results were consistent across subgroups.

The safety analysis did not reveal new safety issues. Neutropenia was more frequently observed in the chemotherapy arm, whereas nausea was more often reported in the T-DXd arm. Prof. Modi added that the cases of nausea were mostly grade 1 or 2 events, which should be manageable in practice. In total, 16% of the patients in the T-DXd arm experienced treatment-emergent adverse events that led to dose discontinuation, compared with 8% in the chemotherapy arm. ILD/pneumonitis occurred in 12.1% of the patients on T-DXd: 3.5% grade 1, 6.5% grade 2, 1.3% grade 3, and 0.8% grade 5 events. Decreased left ventricular ejection fraction occurred in 4.3% of the patients on T-DXd: 0.3% grade 1, 3.8% grade 2, and 0.3% grade 3.

"T-DXd is the first HER2-targeted therapy to demonstrate improved efficacy in HER2-low metastatic breast cancer, establishing a new standard-of-care for this population, which covers approximately 50% of the total metastatic breast cancer population," concluded Dr Modi.

1. Tarantino P, et al. J Clin Oncol. 2020;38(17):1951–1962.
2. Modi S, et al. Trastuzumab deruxtecan (T-DXd) versus treatment of physician's choice (TPC) in patients (pts) with HER2-low unresectable and/or metastatic breast cancer (mBC): Results of DESTINY-Breast04, a randomized, phase 3 study. LBA3, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.

SET2,3 to inform on chemotherapy decisions in ER-positive breast cancer

The novel SET2,3 genomic test was prognostic for disease-free survival (DFS) and overall survival (OS) in patients with node-positive breast cancer, even after controlling for ROR-PT score. Moreover, in patients with ER-positive breast cancer, SET2,3 results could be utilised to decide which patients were most likely to benefit from dose-dense versus conventional chemotherapy.

The novel SET2,3 genomic test, which measures non-proliferative HR-related transcription, has been validated as a prognostic tool for DFS in patients with ER-positive breast cancer after neo-adjuvant therapy [1]. The ROR-PT and PAM50 intrinsic subtype tests could not predict which patients would benefit from dose-dependent chemotherapy in a previous study [2]. To this end, Dr Otto Metzger (Dana-Farber Cancer Institute, MA, USA) and colleagues aimed to assess the prognostic performance of SET2,3 in patients with ER-positive breast cancer in the phase 3 CALGB9741 trial (n=613; NCT000030880) [3].

A high SET2,3 score was associated with an improved 5-year DFS compared with patients with a low SET2,3 score (86% vs 73%; HR 0.47; 95% CI 0.35–0.64), causing the primary endpoint of this study to be met. Similar results were obtained for the 5-year OS rates (95% vs 85%; HR 0.38; 95% CI 0.27–0.54). Moreover, the prognostic value of SET2,3 was still significant (P<0.0001) after controlling for ROR-PT, showing that SET2,3 is adding independent prognostic value. Furthermore, a significant interaction effect was observed between SET2,3 score and the choice of chemotherapy on DFS (Pinteraction=0.098). In patients with lower SET2,3 scores, dose-dependent chemotherapy would be the preferential option, whereas those with higher SET2,3 scores seem to benefit more from conventional chemotherapy. The interaction effect was even stronger when the investigators looked at OS outcomes (Pinteraction=0.027) and remained significant after controlling for HER2 status.

"The future of SET2,3 may allow us to identify patients who would benefit from dense intense chemotherapy and/or adjuvant abemaciclib," reasoned Prof. Erica Stringer-Reasor (University of Alabama at Birmingham, AL, USA), discussant of this trial. "However, validating this assay in future prospective and retrospective trials is warranted."

1. Du L, et al. Ann Oncol. 2021;32(5):642–651.
2. Liu MC, et al. NPJ Breast Cancer. 2016;2:15023.
3. Metzger O, et al. Measurement of endocrine activity (SET2,3) related to prognosis and prediction of benefit from dose-dense (DD) chemotherapy in estrogen receptor-positive (ER+) cancer: CALGB 9741 (Alliance). Abstract 505, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.

Metastasis-directed therapy fails in oligometastatic breast cancer

Metastasis-directed therapy, either stereotactic ablative radiotherapy (SART) or surgical resection, added to standard-of-care did not provide a significant clinical benefit over standard-of-care alone for patients with oligometastatic breast cancer, according to the results of the phase 2R/3 NRG-BR002 trial.

The phase 2 SABR-COMET trial (NCT01446744) displayed a clinical benefit of SART for patients with oligometastatic cancers [1]. "In oligometastatic breast cancer, phase 3 data

for the efficacy of metastasis-directed therapy is lacking," mentioned Dr Steven Chmura (University of Chicago, IL, USA). The phase 2R stage of the phase 2R/3 NRG-BR002 trial (NCT02364557) randomised 128 patients with oligometastatic breast cancer 1:1 to first-line, standard-of-care systemic therapy with or without additional metastasis-directed therapy (surgical resection or SART) [2]. Previously, the phase 1 NRG-BR001 trial demonstrated the absence of dose-limiting toxicities for the use of SART in patients with multiple metastasis [3]. Progression-free survival (PFS) was the primary endpoint of the current study.

In total, 93% of the patients in the experimental arm received SART and only 2% received surgery. After a median follow-up of 35 months, no significant difference was measured in PFS between the 2 treatment arms (HR 0.92, P=0.36). The 36-month PFS rates were 32.8% in the control arm and 38.1% in the experimental arm, which were not sufficient enough to continue with the phase 3 part of the trial.

Both treatment arms were well tolerated and showed similar safety profiles. In the control arm, 10% of the patients had a grade 3 adverse event, whereas 5% of the patients in the experimental arm experienced a grade 3 adverse event. Only 1 grade 4 adverse event was reported, which occurred in the control arm. Finally, exploratory data showed that patients with >1 metastasis may benefit more from additional metastatic-directed therapy, whereas those with 1 metastasis may be better off with the standard-of-care alone.

"High dose SART was safe in patients with oligometastatic breast cancer, but this metastasis-directed therapy failed to provide a significant PFS benefit for these patients," concluded Dr Chmura.

1. Palma DA, et al. J Clin Oncol. 2020;38:2830–2838.
2. Chmura SJ, et al. NRG-BR002: A phase IIR/III trial of standard of care systemic therapy with or without stereotactic body radiotherapy (SBRT) and/or surgical resection (SR) for newly oligometastatic breast cancer (NCT02364557). Abstract 1007, ASCO 2022 Annual Meeting, 3-7 June, Chicago, IL, USA.
3. Chmura S, et al. J Clin Oncol. 2021; 7(6):845–852.

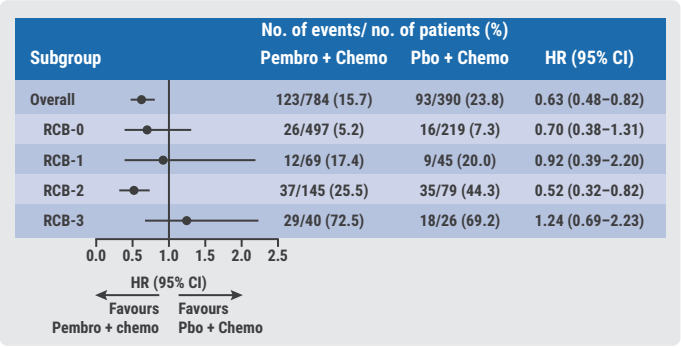
Analysis by residual cancer burden further clarifies effect of pembrolizumab

An exploratory analysis of the KEYNOTE-522 trial showed that patients with triple-negative breast cancer (TNBC) who had residual disease at surgery benefitted from pembrolizumab compared with placebo in terms of event-free survival (EFS) events. This was the case even if the patients did not achieve a pathological complete response (pCR), indicating an effect of the adjuvant pembrolizumab component.

The primary results of KEYNOTE-522 (n=1,174, NCT03036488) demonstrated that neoadjuvant pembrolizumab plus chemotherapy was superior to chemotherapy and placebo in patients with early-stage TNBC in terms of pCR, and in terms of EFS if the neoadjuvant treatment was followed by adjuvant pembrolizumab [1,2]. With the current, prespecified, exploratory analysis, Prof. Lajos Pusztai (Yale School of Medicine, CT, USA) investigated the EFS by treatment arm, within residual cancer burden categories (RCB), ranging from 0 (no residual disease) to 3 (most residual disease) [3].

In each RCB category, fewer patients with residual disease at surgery received pembrolizumab compared with placebo: RCB-1 8.8% vs 11.5%; RCB-2 18.5% vs 20.3%; RCB-3 5.1% vs 6.7%. According to Prof. Pusztai, this indicates that the addition of pembrolizumab did not only increase the pCR rate (RCB-0) but shifted other RCB categories as well, in favour of pembrolizumab. The 36-month EFS analysis showed that patients with RCB-2 (n=224) might benefit most from pembrolizumab (HR 0.52), suggesting that adjuvant pembrolizumab is beneficial for patients who did not achieve a pCR. The corresponding hazard ratios in patients with RCB-0 (n=716), RCB-1 (n=114), and RCB-3 (n=66) were 0.70, 0.92, and 1.24 (see Figure). Notably, within the RCB-3 stratum, patients on placebo had a higher rate of distant recurrence as first EFS event (53.8% vs 35.0%), whereas patients on pembrolizumab more frequently displayed local recurrence as first EFS event (25.0% vs 7.7%).

Figure: Event-free survival analysis by residual cancer burden subgroup [3]



RCB, residual cancer burden; No., number; Pembro, pembrolizumab; Chemo, chemotherapy; Pbo, placebo; HR, hazard ratio.

Dr Erica Michelle Stringer-Reasor (University of Alabama, AL, USA) commented that these results show that RCB is a

more detailed biomarker than pCR and offers new insights in the KEYNOTE-522 trial. "We noticed that patients in the RCB-0 and RCB-1 categories performed very well regardless of adjuvant immunotherapy, raising the question whether these patients should receive this treatment. Also, it would be interesting to see whether we can further stratify patients with residual disease, for example with circulating tumour DNA, to refine additional adjuvant therapy even more."

1. Schmid P, et al. N Engl J Med. 2020;382:810–821.
2. Schmid P, et al. N Engl J Med. 2022;386:556–567.
3. Pusztai L, et al. Event-free survival by residual cancer burden after neoadjuvant pembrolizumab + chemotherapy versus placebo + chemotherapy for early TNBC: Exploratory analysis from KEYNOTE-522. Abstract 503, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.

Contribution of metastatic therapies on mortality reduction in breast cancer

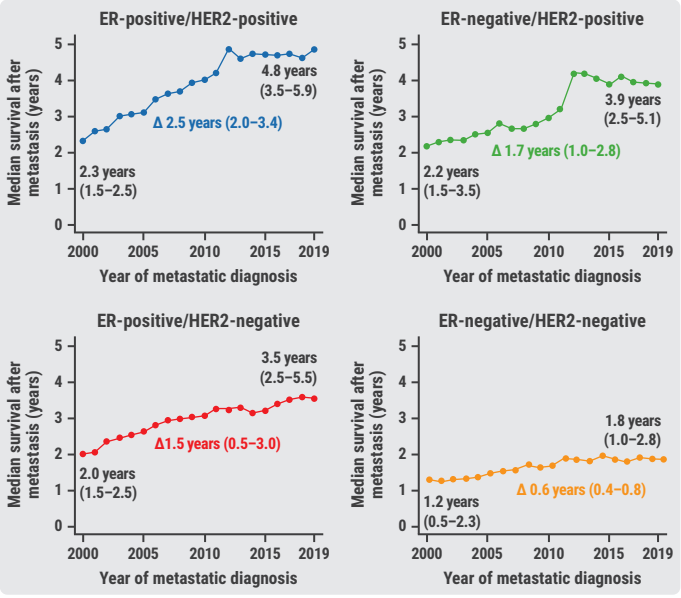
Developments in screening tools, early-stage treatment, and metastatic treatment have resulted in impressive reductions in breast cancer mortality across all molecular subtypes compared with no intervention. In the last 2 decades, the introduction of novel metastatic therapies has been essential to the improved survival of patients with breast cancer.

Based on 6 simulation models of the Cancer Intervention and Surveillance Modelling Network (CISNET), Prof. Jennifer Caswell-Jin (Stanford University, CA, USA) and co-investigators aimed to assess whether advances in metastatic therapies have resulted in a reduced population-level breast-cancer mortality in the last 2 decades [1]. The contribution of screening and early-stage therapy on mortality reduction in patients with breast cancer was assessed in previous research [2].

In 2019, the combination of screening, early-stage treatment, and metastatic treatment resulted in a reduced overall mortality of patients with breast cancer of 58% compared with no intervention. The largest reduction was observed in the ER-positive/HER2-positive subpopulation (71%), whereas the least progress was made in patients with triple-negative breast cancer (40%). In addition, the reduction in mortality rates in patients with ER-negative/HER2-positive or ER-positive/HER2-negative were 61% and 59%, respectively.

According to Prof. Caswell-Jin, the relative contribution of metastatic therapies to reduced mortality varies over time, depending on the distribution of transitioning therapies. When metastatic therapies are transitioned to early-stage therapies, the relative contribution of metastatic therapies to the improvement in overall survival is decreased. In 2019, 19% of the overall mortality reduction was attributed to metastatic therapies. Furthermore, metastatic therapies have improved the median overall survival of patients with ER-positive/HER2-negative breast cancer after distant recurrence from 2.0 to 3.5 years in the last 2 decades. Correspondingly, the median overall survival after distant recurrence increased from 1.2 to 1.8 years in ER-negative/HER2-negative patients, from 2.3 to 4.8 years in ER-positive/HER2-positive patients, and from 2.2 to 3.9 years in ER-negative/HER2-positive patients (see Figure).

Figure: Median survival after distant recurrence for HER2-positive (up) and HER-negative (down) subtypes [1]



"Steady introduction of new metastatic treatments in the last 2 decades has been essential to the observed mortality reduction in patients with breast cancer," concluded Prof. Caswell-Jin.

1. Caswell-Jin J, et al. Contributions of screening, early-stage treatment, and metastatic treatment to breast cancer mortality reduction by molecular subtype in U.S. women, 2000-2017. Abstract 1008, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.
2. Plevritis SK, et al. JAMA. 2018;319(2):154–164.

Radiotherapy may be omitted in breast cancer patients

The prospective cohort study LUMINA found that women ≥55 years with T1N0, G1–2 luminal A breast cancer, who underwent breast-conserving surgery (BCS), had a very low rate of local recurrence if they were treated exclusively with endocrine therapy and

not with radiotherapy. These results indicate that the morbidity and costs of radiotherapy could be avoided in a substantial proportion of women with breast cancer.

"Although the risk of local recurrence after BCS is reduced by approximately 67% with adjuvant radiotherapy, this treatment may be omitted in very-low-risk patients," reasoned Prof. Timothy Whelan (McMaster University, Canada). The LUMINA study (NCT01791829) aimed to determine whether identifying luminal A subtype breast cancer in combination with known clinical pathological factors could identify very-low-risk patients in whom radiotherapy could be omitted after BCS [1]. For this purpose, a prospective analysis was conducted including 500 women ≥55 years with T1N0, G1-2 luminal A-type ductal breast cancer who only followed endocrine therapy, and not radiotherapy, after BCS. Additionally, only patients who had ≤13.25% on a Ki67-test were included in the analysis. The primary endpoint was met if the local recurrence rate was <5% after 5 years.

After 5 years of follow-up, the local recurrence rate was 2.3% (90% CI 1.3–3.8). Moreover, the rates of contralateral breast cancer (1.9%) and any recurrence (2.7%) were low. The disease-free survival after 5 years was 89.9%, with 47 reported events, of which 23 were second primary non-breast cancers. The overall survival after 5 years was 97.2%, but only 1 out of 13 deaths was breast cancer-related.

"This study showed that the risk for local recurrence after BCS is very low in a substantial proportion of patients with breast cancer," stated Prof. Whelan. "We estimate that radiotherapy could be omitted in approximately 30,000 to 40,000 of the 300,000 patients who are newly diagnosed with invasive breast cancer in North America each year, avoiding the morbidity, inconvenience, and costs of this therapy."

1. Whelan T, et al. LUMINA: A prospective trial omitting radiotherapy (RT) following breast conserving surgery (BCS) in T1N0 luminal A breast cancer (BC). LBA501, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.

Promising data for ribociclib after progression on ET plus CDK4/6 inhibitors in HR-positive/ HER2-negative metastatic breast cancer

Patients with unresectable or HR-positive/HER2-negative metastatic breast cancer who progressed on anti-oestrogen therapy (ET) plus CDK4/6 inhibitors displayed a longer progression-free survival (PFS) when switching to ET plus ribociclib compared with ET plus placebo.

ET plus CDK4/6 inhibition is the standard-of-care for patients with HR-positive/HER2-negative metastatic breast cancer [1]. Although observational data supports switching ET while continuing CDK4/6 inhibitors after patients progress, no prospective, randomised trials have evaluated this approach [2]. The phase 2 MAINTAIN trial (NCT02632045), presented by Prof. Kevin Kalinsky (Winship Cancer Institute of Emory University, GA, USA) randomised 119 patients with HR-positive/ HER2-negative metastatic breast cancer who progressed on ET plus CDK4/6 inhibitors to a switch of ET plus ribociclib or ET plus placebo [3]. PFS was the primary endpoint of this study.

Patients who received ribociclib had a significantly longer median PFS than patients who received placebo (2.76 vs 5.29 months; HR 0.57; P=0.006). In addition, the 12-month PFS rate was approximately 3 times higher in the ribociclib arm (24.6% vs 7.4%). The results appeared to be consistent across subgroups, including the 'prior fulvestrant/exemestane' and 'prior palbociclib/ribociclib' subgroups.

ET plus ribociclib had a manageable safety profile. Neutropenia with a grade ≥3 was more common in patients on ribociclib (38% vs 0%) but only 2 patients experienced febrile neutropenia. Furthermore, 2 patients on ribociclib had pneumonitis (1 grade 3), and 3 patients experienced grade 3 infections, compared with 0 in the placebo group.

Interestingly, an exploratory analysis showed that patients with *ESR1* wildtype mutational status may benefit more from additional ribociclib than patients with *ESR1*-mutated tumours (HR 0.30 vs HR 1.22). Prof. Kalinsky stressed that these were exploratory outcomes and should be interpreted as hypothesis-generating data only.

Prof. Claudine Isaacs (Georgetown University, Washington DC, USA) responded to these results with enthusiasm and caution. "This is the first well-designed, randomised trial to assess the applicability of CDK4/6 inhibitors and switch of ET after disease progression. However, the current study is too small to deliver practice-changing data in my opinion and it remains unclear whether we need to switch both ET and CDK4/6 inhibitors. Fortunately, other phase 2 and 3 trials are underway to investigate these issues."

1. Hortobagyi GN, et al. N Engl J Med. 2022;386:942–950.
2. Wander SA, et al. J Natl Compr Canc Netw. 2021;1–8.
3. Kalinsky K, et al. A randomized, phase II trial of fulvestrant or exemestane with or without ribociclib after progression on anti-estrogen therapy plus cyclin-dependent kinase 4/6 inhibition (CDK 4/6i) in patients (pts) with unresectable or hormone receptor-positive (HR+), HER2-negative metastatic breast cancer (MBC): MAINTAIN trial. LBA1004, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.

7-gene biosignature: Benefits of endocrine therapy and radiotherapy in breast cancer risk groups

A 7-gene predictive ductal carcinoma in situ (DCIS) biosignature named 'DCISionRT with integrated Residual Risk subtype (RRt)' revealed a prognostic and predictive response to radiotherapy for patients who were classified as 'elevated-risk' or 'residual-risk' patients but not for 'low-risk' patients. However, in the residual-risk patients, the risk of recurrence remained high after radiotherapy, irrespective of whether patients received endocrine therapy.

"Clinicopathologic features have not been able to successfully stratify patients with breast cancer into low- and high-risk categories of recurrence after they receive radiotherapy following breast conserving surgery," explained Dr Pat Whitworth (Nashville Breast Cancer Center, TN, USA). A clinically meaningful biomarker could fill this gap.

The 7-gene DCIS biosignature score combines 7 biomarkers and 4 clinicopathologic factors and has been validated as a prognostic tool for ipsilateral breast tumour recurrence (IBTR) and as a predictor for radiotherapy benefit in patients with breast cancer [1]. A central pathology review and biosignature testing was performed on formalin-fixed paraffin embedded tissue at a CLIA-certified lab (Laguna Hills, CA). The biosignature reported a "decision score" and residual risk subtype status. The current study included 926 patients from 4 cohorts with a pre-defined DCIS biosignature risk group of either low-risk (37%), elevated-risk (43%), or residual-risk (20%) to analyse the 10-year IBTR-rate [2]. The low-risk group had a decision score of ≤2.8, the elevated-risk group had a decision score of >2.8 without residual risk subtype, and the residual-risk group had a decision score of >2.8 with residual risk subtype.

IBTR-risk was reduced in the elevated-risk group (4.9% vs 20.6%) and the residual-risk group (14.7% vs 42.1%) but not in the low-risk group (4.8% vs 5.6%) if patients received radiotherapy after breast-conserving surgery compared with patients who had not received radiotherapy after surgery. Importantly, the risk of recurrence after radiotherapy was significantly higher in the residual-risk group compared with the elevated-risk group (P<0.001).

Furthermore, in the elevated-risk group, endocrine therapy reduced the risk of IBTR significantly, regardless of whether patients received radiotherapy (HR 0.34; P=0.023). This was not the case in the residual-risk group (HR 0.76; P=0.46) or in the low-risk group (HR 0.65; P=0.41). If patients in the elevated-risk group had received radiotherapy, the administration of endocrine therapy still trended towards a significant reduction in the IBTR rate (HR 0.40; P=0.059).

In summary, 3 risk groups were identified by means of the 7-gene DCIS biosignature. In the low-risk group, IBTR was not significantly reduced after radiotherapy and/or endocrine therapy, whereas in the elevated-risk group IBTR was reduced. In the residual-risk group, radiotherapy reduced the IBTR rate, but endocrine therapy had no effect.

1. Wärnberg F, et al. Cancers. 2021;13(23):6103.
2. Whitworth P, et al. Assessing the benefit of adjuvant endocrine therapy in patients following breast-conserving surgery with or without radiation stratified by a 7-gene predictive DCIS biosignature. Abstract 502, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.

Lung Cancer

Additional tiragolumab does not help patients with untreated small cell lung cancer

Tiragolumab added to atezolizumab, carboplatin, and etoposide did not improve the progression-free survival (PFS) or overall survival of patients with untreated, extensive-stage, small cell lung cancer (SCLC), as was shown by the primary results of the phase 3 SKYSCRAPER-02 trial.

Tiragolumab is a human anti-TIGIT monoclonal antibody under investigation in several cancer settings, such as non-SCLC and oesophageal cancer. Dr Charles Rudin (Memorial Sloan Kettering Cancer Center, NY, USA) aimed to assess the efficacy of tiragolumab in addition to the standard-of-care (atezolizumab plus carboplatin and etoposide) for patients with extensive-stage SCLC in the SKYSCRAPER-02 trial (NCT04256421) [1,2]. Patients were randomised 1:1 to additional tiragolumab (n=243) or placebo (n=247). PFS was the primary endpoint of the study.

The primary endpoint was not met in the primary analysis set, excluding patients with brain metastases at baseline (± 19%); the median PFS was comparable for patients who received tiragolumab or placebo (5.4 vs 5.6 months; HR 1.11; P=0.35). Similarly, there was no difference in median overall survival between the 2 treatment groups (13.6 vs 13.6 months; HR 1.04; P=0.80). The results did not change when patients with brain metastases were added to the analysis.

The addition of tiragolumab did not substantially change the safety profile of the treatment regimen. "This is important, since tiragolumab is being tested in several other settings as well," explained Dr Rudin. Pruritis was slightly elevated in the tiragolumab arm, a known side effect of this agent.

"Based on the data of the SKYSCRAPER-02 trial, tiragolumab or other TIGIT-targeting agents do not appear to be relevant in patients with extensive-stage SCLC," concluded Dr Rudin.

1. Rudin CM, et al. SKYSCRAPER-02: Primary results of a phase III, randomized, double-blind, placebo-controlled study of atezolizumab (atezo) + carboplatin + etoposide (CE) with or without tiragolumab (tira) in patients (pts) with untreated extensive-stage small cell lung cancer (ES-SCLC). LBA8507, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.
2. Horn L, et al. N Engl J Med. 2018;379:2220–2229.

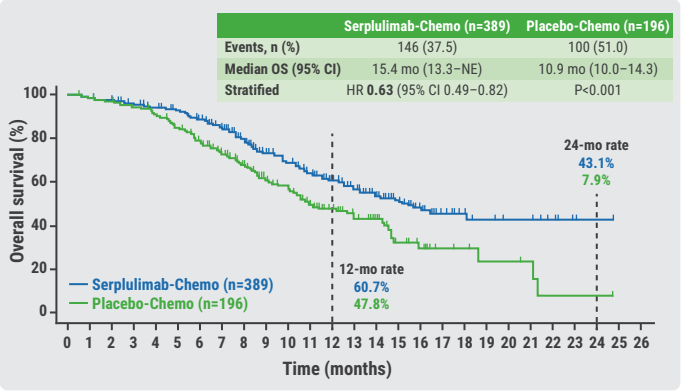
Success for serplulimab plus chemotherapy in small cell lung cancer

Serplulimab plus chemotherapy delivered consistent clinical benefits over chemotherapy alone in the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC), with a manageable safety profile.

"There is still a huge unmet medical need for patients with SCLC," stated Prof. Ying Cheng (Jilin Cancer Hospital, China). In the pivotal ASTRUM-010 study, the novel PD-1 inhibitor serplulimab demonstrated encouraging anti-tumour activity and a manageable safety profile in patients with microsatellite instability-high or mismatch repair-deficient (MSI-H/dMMR) solid tumours [1]. Prof. Cheng presented the primary results of the phase 3 ASTRUM-005 trial (NCT04063163; n=585), which randomised patients with previously untreated ES-SCLC 2:1 to serplulimab plus chemotherapy or placebo plus chemotherapy [2]. The primary endpoint was overall survival (OS).

After a median follow-up of 12.3 months, patients on serplulimab had a significant OS benefit over patients on placebo (median OS 15.4 vs 10.9 months; HR 0.63; P<0.001; see Figure). This result was consistent across subgroups, including patients with various PD-L1 expression levels. Also, the median progression-free survival (5.7 vs 4.3 months; HR 0.48), overall response rates (80.2% vs 70.4%), and median duration of response (5.6 vs 3.2 months; HR 0.48) favoured serplulimab over placebo.

Figure: Overall survival of serplulimab plus chemotherapy versus placebo plus chemotherapy [2]



OS, overall survival; mo, month; NE, not estimable.

The safety profiles of the 2 treatment regimens were mostly comparable. Serious adverse events (AEs) were reported in 35% of the patients in both arms and treatment discontinuations were observed in 4.9% and 4.1% of the patients in the experimental and placebo arm, respectively. Immune-related AEs were more prevalent in the serplulimab group (37.0% vs 18.4%), with hypothyroidism (11.6%), hyperthyroidism (9.0%), and rash (3.1%) being the most commonly identified immune-related AEs in the experimental group.

This survival advantage of nearly 5 months is the highest of any Checkpoint inhibitor in this setting up to now. If confirmed, serplulimab could be the first PD-1 inhibitor in this setting and could outperform previously reported PD-L1 inhibitors.

1. Qin SK, et al. J Clin Oncol. 2021;39(15_suppl):2566–2566.
2. Cheng Y, et al. Serplulimab, a novel anti-PD-1 antibody, plus chemotherapy versus chemotherapy alone as first-line treatment for extensive-stage small-cell lung cancer: An international randomized phase 3 study. Abstract 8505, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.

Adagrasib safe and clinically active in non-small cell lung cancer

In the phase 2 KRYSTAL-1 study, adagrasib showed encouraging clinical activity and a manageable safety profile in patients with previously treated non-small cell lung cancer (NSCLC) bearing a *KRAS-G12C* mutation. The results of this trial have initiated the accelerated approval process of this drug in the USA. The confirmatory phase 3 KRYSTAL-12 trial is currently running to compare adagrasib with docetaxel in this population.

Adagrasib is a covalent inhibitor of *KRAS-G12C* that has demonstrated clinical activity in a variety of *KRAS-G12C*-mutated solid tumours [1,2]. In one cohort of the phase 2 KRYSTAL-1 study (NCT03785249), Dr Alexander Spira (Virginia Cancer Specialists Research Institute, VA, USA) and colleagues tested adagrasib monotherapy (600 mg, oral, twice daily) in patients with previously treated *KRAS-G12C* mutated NSCLC (n=116) [3]. The primary endpoint was the objective response rate (ORR) by blinded independent central review. Results were published in *The New England Journal of Medicine* in June 2022 [4].

An objective response was confirmed in 43% of the participants with measurable disease at baseline (n=112), with 1% of the participants displaying a complete response and 42% of the participants showing a partial response. The disease control rate was 80%. The ORR was 51% if only evaluable participants were included in the calculation. Most of the responses were deep, with 75% of the responders reaching a tumour reduction >50%. The median time to response was 1.4 months and the median duration of response was 8.5 months. After 6 months, 52% of the participants were progression-free. This percentage dropped to 29% at 12 months. The corresponding overall survival rates were 71% at 6 months and 51% at 12 months. Notably, the intracranial response ORR was 33% in participants (n=33) with previously treated, stable CNS metastases, with 15% showing a complete response and 18% showing a partial response. The disease control rate for this subgroup of participants was 85%.

Dr Spira mentioned that the safety profile of adagrasib was manageable in the study cohort. Predominantly grade 3 but also grade 4 adverse events were observed in 43% of the patients. Nausea (4%), fatigue (4%), increased alanine aminotransferase (4%) and aspartate aminotransferase (3%) levels, and decreased appetite (3%) were the most frequently noticed grade 3 or 4 adverse events. Dose reductions or dose interruptions due to treatment-related adverse events occurred in 52% and 61% of the participants. Only 7% of the participants discontinued the study drug after a treatment-related adverse event.

Adagrasib is being reviewed by the FDA for accelerated approval as a treatment for patients with *KRAS-G12C* mutated NSCLC who received at least one prior systemic therapy. Also, the confirmatory phase 3 KRYSTAL-12 trial (NCT04685135) is currently running to compare adagrasib with docetaxel in this population.

1. Weiss J, et al. Ann Oncol. 2021;32(suppl_5):S1294.
2. Bekaii-Saab TS, et al. J Clin Oncol. 2022;40(4_suppl):519–519.
3. Spira A, et al. KRYSTAL-1: Activity and safety of adagrasib (MRTX849) in patients with advanced/metastatic non–small cell lung cancer (NSCLC) harboring a KRASG12C mutation. Abstract 9002, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.
4. Jänne PA, et al. N Engl J Med. Jun 3, 2022. DOI: 10.1056/NEJMoa2204619.

Long-term benefits of combined immunotherapy over chemotherapy in non-small cell lung cancer

In the 5-year landmark analysis of the phase 3 CheckMate 227 trial, the first-line immunotherapy combination nivolumab plus ipilimumab demonstrated long-term clinical benefits over chemotherapy in patients with metastatic non-small cell lung cancer (NSCLC), regardless of PD-L1 expression level. A substantial

proportion of responders remained treatment-free for ≥3 years after treatment discontinuation, with a high quality-of-life.

Part 1 of the CheckMate 227 trial (NCT02477826) randomised 1,189 patients with metastatic NSCLC and PD-L1 expression levels ≥1% 1:1:1 to nivolumab plus ipilimumab, nivolumab alone, or platinum-doublet chemotherapy. Part 2 randomised 550 patients with this condition but with PD-L1 expression levels <1% to nivolumab plus ipilimumab, nivolumab plus chemotherapy, or chemotherapy alone. Previous analyses of this trial showed that patients on nivolumab plus ipilimumab had higher overall survival (OS) and progression-free survival (PFS) rates than patients on chemotherapy [1]. Prof. Julie Brahmer (Sidney Kimmel Comprehensive Cancer Center, Australia) presented the 5-year update of CheckMate 227 [2].

In the subgroup of patients with PD-L1 expression levels ≥1%, 24% of the patients on the immunotherapy combination were alive compared with 14% in the chemotherapy arm (median OS 17.1 vs 14.9 months; HR 0.77). After 5 years, 12% of the patients in the immunotherapy combination arm were still progression-free, but only 2% in the chemotherapy arm. Moreover, 28% of the patients in the nivolumab plus ipilimumab arm had an ongoing response, even though the study drug had been discontinued for ≥3 years, and this was only 3% in the chemotherapy arm.

In the stratum of patients that had PD-L1 expression levels <1%, the OS rates after 5 years were 19% and 7%, favouring the combination therapy arm over the chemotherapy arm (HR 0.65). The PFS rates (12% vs 2%) and duration of response rates (21% vs not applicable) after 5 years demonstrated a similar benefit in the combination arm as was seen in the PD-L1 ≥1% subgroup of patients. Interestingly, in 5-year survivors treated with nivolumab plus ipilimumab, the quality-of-life scores were at or above the US norms for up to 4.5 years, irrespective of PD-L1 expression level.

1. Hellman MD, et al. N Engl J Med. 2019;381(21):2020–2031.
2. Brahmer JR, et al. Five-year survival outcomes with nivolumab (NIVO) plus ipilimumab (IPI) versus chemotherapy (chemo) as first-line (1L) treatment for metastatic non–small cell lung cancer (NSCLC): Results from CheckMate 227. LBA9025, ASCO Annual Meeting, 3–7 June, Chicago, IL, USA.

Effect of *KRAS* mutations and PD-L1 expression on therapy response in non-small cell lung cancer

A pooled analysis performed by the FDA showed that chemotherapy plus immunotherapy resulted in a small numerical, but non-significant, overall survival benefit over immunotherapy alone in patients with advanced non-small cell lung cancer (NSCLC) with PD-L1 expression levels ≥50%. Progression-free survival data and overall response rates suggested a more pronounced benefit of the combination therapy in this population. Another pooled analysis displayed that patients with *KRAS*-mutated NSCLC and *KRAS* wildtype NSCLC have similar responses to the combination of chemotherapy and immunotherapy and that patients appear to benefit from the addition of chemotherapy to immunotherapy, irrespective of KRAS mutation status or PD-L1 expression levels.

"Both chemotherapy plus immunotherapy and immunotherapy alone regimens have been approved for the treatment of patients with advanced NSCLC," said Dr Oladimeji Akinboro (US Food and Drug Administration, MD, USA). To date, it is unknown whether patients with PD-L1 expression levels ≥50% benefit more from immunotherapy alone or immunotherapy in combination with chemotherapy. The FDA performed an exploratory-pooled analysis to address this issue [1]. Included were 1,753 patients from 12 different clinical trials with previously untreated advanced NSCLC and PD-L1 expression levels ≥50% who underwent either chemotherapy plus immunotherapy (n=455) or immunotherapy alone (n=1,298). Overall survival (OS) was the primary endpoint.

The median OS data favoured the chemotherapy plus immunotherapy arm numerically, but not statistically significantly, over the immunotherapy alone arm (25.0 vs 20.9 months; HR 0.82; 95% CI 0.62–1.08). The median progression-free survival (9.6 vs 7.1 months; HR 0.69; 95% CI 0.55–0.87) and overall response rates (61% vs 43%; OR 1.2; 95% CI 1.1–1.3) suggested a more pronounced advantage of combination therapies over monotherapies in this population. In contrast, subgroup analysis indicated that patients ≥75 years may benefit more from immunotherapy alone.

A second pooled analysis investigated the outcomes of immunotherapy with or without chemotherapy in patients with advanced NSCLC according to *KRAS* mutation status [2]. Previous studies have suggested that patients with *KRAS*-mutated tumours may benefit more from immunotherapy than monotherapy than patients with *KRAS* wildtype tumours but that patients with *KRAS* mutations and *KRAS* wildtype disease respond equally well to immunotherapy plus chemotherapy [3,4]. However, larger assessments are

needed to confirm these results. For this purpose, included were 1,430 patients with advanced NSCLC and reported *KRAS* mutation status who received first-line immunotherapy, chemotherapy, or a combination of those therapies from 12 clinical trials (*KRAS* wildtype n=875; *KRAS*-mutated n=555 of whom *KRAS-G12C* n=157). Dr Erica Nakajima (US Food and Drug Administration, MD, USA) presented the findings of this study.

The overall response rates (ORR) to therapies were similar for patients with *KRAS* wildtype and *KRAS*-mutated tumours across treatment regimens: immunotherapy 33% versus 37%; chemotherapy 32% versus 33%; combination 51% versus 46%. These results indicate that patients may respond better to the combination of chemotherapy and immunotherapy than to either one of these therapies alone, irrespective of *KRAS* mutation status. Additionally, responses to therapies appeared not to diverge in patients with *KRAS-G12C* mutations. However, this result should be interpreted with caution since the sample size of patients with *KRAS-G12C* mutations was limited.

Importantly, Dr Akinboro and Dr Nakajima emphasised that these were retrospective exploratory analyses and that the results are only hypothesis-generating. Dr Nakjima added that the data of these pooled analyses indicate that chemotherapy plus immunotherapy may be the optimal control arm in trials evaluating first-line therapies in patients with NSCLC.

1. Akinboro O, et al. Outcomes of anti–PD-(L)1 therapy with or without chemotherapy (chemo) for first-line (1L) treatment of advanced non–small cell lung cancer (NSCLC) with PD-L1 score ≥ 50%: FDA pooled analysis. Abstract 9000, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.
2. Nakajima E, et al. Outcomes of first-line immune checkpoint inhibitors with or without chemotherapy according to KRAS mutational status and PD-L1 expression in patients with advanced NSCLC: FDA pooled analysis. Abstract 9001, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.
3. Herbst RS, et al. Ann Oncol. 2019;30(2):281–289.
4. Gadgeel S, et al. Ann Oncol. 2019;30(supp_11):xi64–xi65.

Melanoma

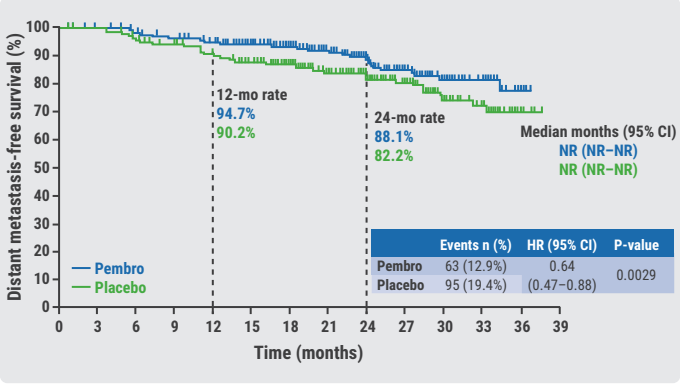
First results on distant metastasis-free survival in stage II melanoma

Results from the KEYNOTE-716 trial showed that patients with resected stage IIB or IIC melanoma had an improved distant metastasis-free survival (DMFS) if they were treated with adjuvant pembrolizumab instead of placebo.

The risk of recurrence is substantial in patients with stage IIB or IIC melanoma [1]. The phase 3 KEYNOTE-716 trial (NCT03553836) randomised 976 patients with resected, high-risk, stage II melanoma 1:1 to pembrolizumab or placebo. Previous results from this trial showed that treatment with adjuvant pembrolizumab improved the recurrence-free survival (RFS) compared with placebo treatment (HR 0.65; P=0.0066) [2]. Prof. Georgina Long (The University of Sydney, Australia) presented the first findings of DMFS from the KEYNOTE-716 trial [3].

After a median follow-up of 27.4 months, the DMFS rate was improved in patients receiving pembrolizumab compared with patients receiving placebo (HR 0.64; P=0.0029; see Figure). Distant metastasis was detected in 12.9% and in 19.4% of the patients in the pembrolizumab arm and placebo arm, respectively. The median DMFS was not reached in either treatment groups. Moreover, the results were consistent across T-subcategories and other key subgroups. This interim analysis showed that RFS continued to favour the pembrolizumab arm over the placebo arm (HR 0.64).

Figure: Distant metastasis-free survival curves for pembrolizumab versus placebo [3]



NR, not reached; mo, month; Prembro, pembrolizumab.

No new safety issues emerged from the current analysis. In total, 17% and 5% of the patients experienced grade ≥3 adverse events (AEs) in the pembrolizumab and placebo group, respectively. In addition, 16% of the patients discontinued pembrolizumab due to AEs compared with 2% in the placebo group. Pruritus, rash, and diarrhoea were the most common grade ≥3 events in the experimental arm.

Dr Charlotte Ariyan (Memorial Sloan Kettering Cancer Center, NY, USA) argued that the risk of recurrence is approximately 40% in stage II patients and that the absolute risk reduction of these patients is 8% if they are treated with pembrolizumab. "Since the rate of grade ≥3 events is 17% and effective post-progression systemic therapies are available for these patients, the overall survival between patients who receive pembrolizumab or systemic therapies may be similar. We should improve the risk estimation of our patients by adding personalised risk calculators, genomic prediction models, and minimal residual disease values to the equation, to calculate which patients would benefit from what treatment."

1. Egger ME, et al. Surgery. 2016;159(5):1412–1421.
2. Luke JJ, et al. Lancet. 2022;399:1718–1729.
3. Long GV, et al. Distant metastasis-free survival with pembrolizumab versus placebo as adjuvant therapy in stage IIB or IIC melanoma: The phase 3 KEYNOTE-716 study. LBA9500, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.

Higher response rates for concurrent triple therapy versus sequential therapy in melanoma

Induction therapy with dabrafenib plus trametinib did not increase the response to subsequent pembrolizumab in patients with *BRAF*-mutated stage III melanoma in the phase 2 NeoTrio trial. Concurrent therapy with dabrafenib, trametinib, and pembrolizumab resulted in the highest pathological response rates, but at a cost of increased toxicity in this population.

The phase 2 NeoTrio trial (NCT02858921) aimed to identify the optimal treatment regimen for patients with *BRAF*-mutated stage III melanoma (n=60). Previous studies have suggested that overall response rates are higher if patients are treated with BRAF plus MEK inhibitors, whereas anti-PD1 therapies demonstrate longer progression-free survival and overall survival rates [1,2]. The participants of the NeoTrio trial were randomised 1:1:1 to pembrolizumab alone, dabrafenib plus trametinib induction therapy followed by pembrolizumab (sequential arm), or simultaneous dabrafenib, trametinib, and pembrolizumab (concurrent arm) [3]. After 6 weeks, all patients could receive surgery for lymph node dissection and adjuvant pembrolizumab. The pathological response at week 6 was the primary outcome. Prof. Georgina Long (The University of Sydney, Australia) presented the results.

The highest pathological response rates were observed in the concurrent arm (80%), whereas participants in the pembrolizumab alone arm (55%) and the sequential arm (50%) displayed lower response rates. The pathological complete response rates were 50%, 30%, and 15% in the concurrent, monotherapy, and sequential arm, respectively. In contrast, the 12-month event-free survival rates (80% in all groups), recurrence-free survival rates (80–89%), and overall survival rates (90–100%) appeared not to differ between treatment groups. Prof. Long added that the pathological responses must be interpreted in the context of received therapy type: "Patients with a pathological complete response or near-pathological complete response with regimens containing BRAF-targeted therapy may recur."

Grade 3/4 treatment-related adverse events were more common in the concurrent arm (55%) than in the pembrolizumab alone (5%) or sequential arm (25%). Correspondingly, treatment discontinuations were more prevalent in the concurrent arm (40%) than in the pembrolizumab arm (5%), or the sequential arm (0%). Pyrexia (15%) and elevated alanine aminotransferase/aspartate transaminase levels (10%) were the most frequently reported grade 3/4 adverse events in the concurrent arm.

Although the first results of the NeoTrio trial indicate that BRAF plus MEK inhibitors do not enhance the response to PD-1 inhibitors in patients with *BRAF*-mutated stage III melanoma, trial follow-up and translational studies are ongoing to gain further insights in the applicability of triple therapies in this population.

1. Robert C, et al. N Engl J Med. 2019;381:626–636.
2. Larkin J, et al. N Engl J Med. 2019;381:1535–1546.
3. Long GV, et al. NeoTrio: Randomized trial of neoadjuvant (NAT) pembrolizumab (Pembro) alone, in sequence (SEQ) with, or concurrent (CON) with dabrafenib plus trametinib (D+T) in resectable BRAF-mutant stage III melanoma to determine optimal combination of therapy. Abstract 9503, ASCO 2022 Annual Meeting, 3-7 June.

Genitourinary Cancers

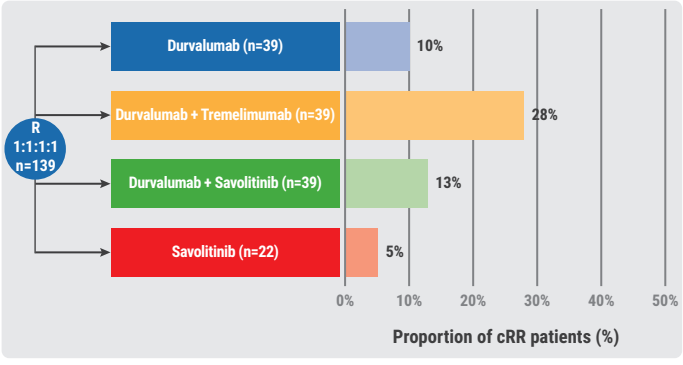
Exploratory treatment options fail in ccRCC

Although the 4 tested treatment regimens – durvalumab alone, durvalumab plus tremelimumab or savolitinib, or savolitinib alone – of the phase 2 CALYPSO trial appeared to be safe in patients with previously treated advanced clear cell renal cell carcinoma (ccRCC), the primary efficacy endpoint was not met for any treatment regimen.

The CALYPSO trial (NCT02819596) randomised 139 patients with vascular endothelial growth factor (VEGF) refractory ccRCC to 1 of 4 treatment arms: PD-L1 inhibitor durvalumab alone (n=39), durvalumab plus the CTLA-4 inhibitor tremelimumab (n=39), durvalumab plus the MET inhibitor savolitinib (n=39), or savolitinib alone (n=19). Prof. Thomas Powles (University of London, UK), who presented the results of the trial, added that the savolitinib monotherapy arm was closed early, because the standard-of-care treatment had changed during the course of the study [1]. The primary efficacy endpoint was a confirmed response rate ≥50%.

Confirmed response rates ranged from 5% in the savolitinib alone arm to 28% in the durvalumab plus tremelimumab arm, with no arm reaching the prespecified confirmed response rate ≥50% (see Figure). Prof. Powles argued that the confirmed response rates in the durvalumab plus tremelimumab arm may seem promising, but that nivolumab alone reached a confirmed response rate of 25% in the CheckMate025 trial (NCT01668784) in previously treated patients with ccRCC [2]. Furthermore, savolitinib-containing regimens did not appear to perform better in patients with MET-driven RCC.

Figure: Confirmed response rates in the CALYPSO trial [1]



R, randomised; cRR, confirmed response rate.

Serious adverse event rates occurred in around 30% of participants in the durvalumab alone and durvalumab plus tremelimumab arms, 49% in the durvalumab plus savolitinib arm, and 16% in the savolitinib monotherapy arm. There was 1 treatment-related death in the durvalumab plus tremelimumab arm and none in the other arms.

1. Powles T, et al. CALYPSO: A three-arm randomised phase II study of Durvalumab alone or with Savolitinib or tremelimumab in previously treated advanced clear cell renal cancer. LBA 4503, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.
2. Motzer RJ, et al. NEJM. 2015;373(19):1803–1813.

Adjuvant everolimus did not benefit high-risk renal cell carcinoma

In patients with renal cell carcinoma (RCC), adjuvant everolimus after nephrectomy did not provide a statistically significant benefit over placebo in terms of recurrence-free survival (RFS). However, the observed numerical benefit, especially in the very high-risk subgroup of patients, warrants further investigation into the role that everolimus may play in the adjuvant treatment of patients with RCC after nephrectomy.

"Approximately one-third of the patients with RCC relapses after nephrectomy," explained Dr Christopher W. Ryan (Oregon Health & Science University, OR, USA) [1]. Since 2006, a new generation of adjuvant trials has emerged to improve the standard-of-care for these patients, which was 'surveillance alone'. Everolimus is a mechanistic target of rapamycin (mTOR) inhibitor, approved for the treatment of metastatic RCC [2]. The phase 3 EVEREST trial (NCT01120249) randomised patients with RCC who underwent nephrectomy and have high risk of recurrence to everolimus (n=775) or placebo (n=770). The primary endpoint was RFS and Dr Ryan presented the final analysis of the trial [1].

After a median follow-up of 6.3 years, the primary endpoint narrowly missed the prespecified P-value for statistical significance of 0.022 (HR 0.85; $P_{1\text{-sided}}$=0.025). Notably, the numerical benefit of everolimus over placebo appeared to be more pronounced in the very high-risk patient population (HR 0.79; $P_{1\text{-sided}}$=0.011) compared with the intermediate high-risk population (HR 0.99; $P_{1\text{-sided}}$=0.48), although no significant interaction effect of risk stratification on treatment outcome

was reported ($P_{interaction}$=0.20). Furthermore, the results of the trial did not favour everolimus over placebo with respect to overall survival (HR 0.90; $P_{1\text{-sided}}$=0.178).

Adverse events (AEs) of all grades were more frequently observed in patients on everolimus (96%) than in patients on placebo (81%), predominantly due to a higher rate of gastrointestinal or cutaneous AEs. Similarly, grade 3 or higher AEs were noted in 46% of the patients in the experimental arm and in 11% of the patients in the placebo arm. In total, 14% of the patients on everolimus experienced oral mucositis of grade 3 or higher, compared with 0% in the placebo group. Also, diarrhoea (33% vs 15%), nausea (24% vs 17%), maculo-papular rash (31% vs 8%), acneiform rash (29% vs 5%), and pruritus (18% vs 8%) of any grade were more common in patients receiving everolimus than placebo. As a result, the percentage of the discontinuation rate not due to progression or death was higher in the experimental arm than in the placebo arm (47% vs 17%).

"The effect of everolimus was especially pronounced in patients with very high-risk disease. Further analyses are needed to establish which subgroups of patients may benefit the most from adjuvant treatment with everolimus," argued Dr Ryan. "In addition, the high discontinuation rate in the everolimus group puts the therapy duration into question."

1. Ryan CW, et al. Everolimus for Renal Cancer Ensuing Surgical Therapy—A Phase III Study. LBA 4500, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.
2. https://www.ema.europa.eu/en/medicines/human/EPAR/afinitor

Cabozantinib fails as first-line maintenance therapy in urothelial cancer

The phase 2 ATLANTIS study did not demonstrate a clinical benefit of cabozantinib over placebo as maintenance therapy after platinum-based chemotherapy in patients with advanced urothelial cancer. Moreover, placebo is no longer an acceptable control arm for patients with this condition.

Until January of last year, platinum-based chemotherapy followed by surveillance was the standard first-line treatment for patients with advanced urothelial cancer. In the current phase 2 ATLANTIS screening trial (ISRCTN25859465), Prof. Robert Jones (University of Glasgow, UK) and colleagues evaluated whether patients with advanced urothelial cancer who are ineligible for inclusion in precision-medicine arms of maintenance therapy trials respond to cabozantinib [1]. Patients with advanced urothelial cancer received 4–8 cycles of first-line chemotherapy and were subsequently randomised 1:1 to cabozantinib (40 mg, oral, once daily) or placebo if they tested negative for all biomarkers. Recruitment of patients was stopped early, because research in the meantime demonstrated that avelumab may become the standard-of-care in the maintenance setting of patients with this indication [2]. Therefore, it was unethical to randomise patients to the placebo arm, leaving the total number of randomised patients to 61. Progression-free survival (PFS) was the primary outcome.

The median PFS was 13.7 months in the cabozantinib arm and 15.8 months in the placebo arm (HR 0.89; P=0.35), not reaching the primary endpoint. The median overall survival rates demonstrated similar results (cabozantinib 75.5 months vs placebo 82.9 months; HR 0.80; P=0.25). In terms of safety, anorexia, diarrhoea, fatigue, hypertension, hypothyroidism, rash, and neutropenia were more common in the cabozantinib arm. According to Prof. Jones, these were all known and manageable adverse events of this agent.

"This study does not support further investigation of cabozantinib as single agent maintenance therapy after platinum-based chemotherapy in patients with advanced urothelial cancer," concluded Prof. Jones.

1. Jones RJ, et al. A randomised, double blind, phase II clinical trial of maintenance cabozantinib following chemotherapy for metastatic urothelial carcinoma (mUC): Final analysis of the ATLANTIS cabozantinib comparison. LBA4505, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.
2. Powles T, et al. N Engl J Med. 2020;383(13):1218–1230.

^{177}Lu-PSMA-617 is a valid treatment option for PSMA-positive mCRPC

^{177}Lu-PSMA-617 (LuPSMA) displayed a higher prostate-specific antigen response, a larger progression-free survival (PFS) benefit, more quality-of-life improvements, a favourable safety profile, and similar survival outcomes compared with cabazitaxel in patients with PSMA-positive, progressive metastatic castration-resistant prostate cancer (mCRPC) who progressed on docetaxel and androgen-receptor pathway inhibitors, supporting the choice for LuPSMA in these patients.

LuPSMA is a radioligand therapy that has demonstrated to deliver greater prostate-specific antigen reductions (66% vs 37%), improved 12-month PFS rates (19% vs 3%), and fewer grade 3–4 adverse events (33% vs 53%) compared

with cabazitaxel in the randomised, phase 2 TheraP trial (NCT03392428), including 200 patients with PSMA-positive, progressive mCRPC [1]. Here, Prof. Michael Hofman (Peter McCallum Cancer Centre, Australia) presented the 3-year overall survival (OS) results [2].

The updated PFS results confirmed the superiority of LuPSMA over cabazitaxel (restricted mean survival time 7.1 vs 5.0 months; HR 0.62; P=0.0028). In contrast, the OS data did not demonstrate a difference between the 2 treatment regimens (19.1 vs 18.6 months; HR 0.97; P=0.99). According to Prof. Hofman, withdrawals from the cabazitaxel arm after randomisation and post-protocol cross-over confounded the OS results. Furthermore, no new safety issues emerged in this updated analysis.

"With greater activity, fewer adverse events, similar OS results as cabazitaxel, and a life prolonging treatment by itself, LuPSMA appears to be the preferred choice in patients with PSMA-positive mCRPC who progressed on docetaxel," stated Prof. Hofman.

1. Hofman MS, et al. Lancet. 2021;397(10276):797–804.
2. Hofman M, et al. TheraP: 177Lu-PSMA-617 (LuPSMA) versus cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel—Overall survival after median follow-up of 3 years (ANZUP 1603). Abstract 5000, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.

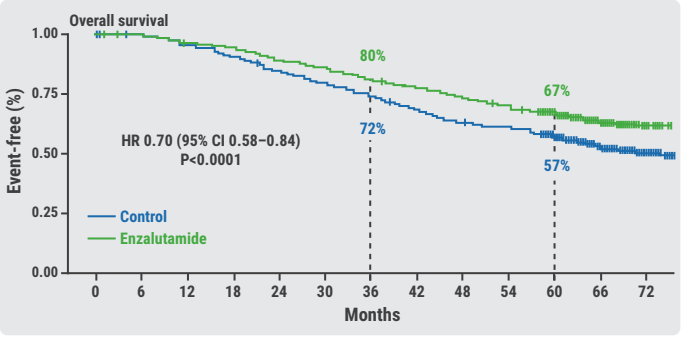
Enzalutamide performs well in metastatic hormone-sensitive prostate cancer

Enzalutamide added to testosterone suppression outperformed testosterone suppression plus standard nonsteroidal anti-androgen (NSAA) therapy in patients with metastatic hormone-sensitive prostate cancer (mHSPC) in the ENZAMET trial. The benefits in overall survival (OS) were most pronounced in patients with low-volume disease who did not receive early or concurrent docetaxel.

The phase 3 ENZAMET trial (NCT02446405) randomised 1,125 patients with mHSPC to testosterone suppression plus standard NSAA therapy (control arm) or testosterone suppression plus enzalutamide (experimental arm). The administration of prior or concurrent docetaxel was allowed at investigator's discretion. The first interim analysis of this trial, performed in 2019, displayed an OS benefit for patients in the enzalutamide arm, but not if these patients were planned to receive early docetaxel [1]. At ASCO 2022, Prof. Ian Davis (Monash University, Australia) presented the second interim analysis of this trial [2].

After a median follow-up of 68 months, the OS benefit of patients in the enzalutamide arm was maintained (median OS 73.2 months vs 'not reached'; HR 0.70; P<0.0001, see Figure). In addition, the corresponding 5-year OS rates were 67% and 57%. Prof. Davis added that 76% of the patients in the control arm received enzalutamide or abiraterone after progression compared with 26% of the patients in the experimental arm. Prespecified subgroup analyses suggested that the OS benefits of enzalutamide were apparent across subgroups, but that patients with low-volume disease who were not planned for early docetaxel (55%) may benefit the most from enzalutamide. Importantly, a clear benefit of enzalutamide on top of testosterone suppression and docetaxel was observed in patients with synchronous de novo disease (n=362; HR 0.73; 95% CI 0.55–0.99). The study was however not powered for the subgroup analyses so these results should be interpreted with caution.

Figure: Overall survival outcomes of ENZAMET [2]



"Although enzalutamide was already used widely in patients with mHSPC, largely because of the results of the ENZAMET study, the current analysis provides more rationale for the use of enzalutamide after docetaxel or with concurrent docetaxel," argued Prof. Russel Szmulewitz (University of Chicago, IL, USA), discussant of this presentation.

1. Davis ID, et al. N Engl J Med. 2019;381(2):121–131.
2. Davis ID, et al. Updated overall survival outcomes in ENZAMET (ANZUP 1304), an international, cooperative group trial of enzalutamide in metastatic hormone-sensitive prostate cancer (mHSPC). LBA5004, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.

Haematologic Malignancies

Autologous stem cell transplantation plus RVd improves PFS in multiple myeloma

Lenalidomide-bortezomib-dexamethasone (RVd) plus autologous stem cell transplantation (ASCT) delivered superior progression-free survival (PFS) in patients with newly diagnosed multiple myeloma compared with dexamethasone alone in the phase 3 DETERMINATION trial. However, no difference in overall survival (OS) was observed between the 2 regimens after 6 years of follow-up.

The phase 3 DETERMINATION trial (NCT01208662) randomised patients with newly diagnosed multiple myeloma to RVd alone (n=357) or RVd plus ASCT (n=365). After the induction phase, ASCT, and consolidation therapy, all patients received lenalidomide maintenance therapy. The primary outcome measure was PFS. Prof. Paul Richardson (Harvard Medical School, MA, USA) presented the results [1].

The median PFS was significantly improved in patients who underwent ASCT in addition to RVd therapy compared with those who did not (67.5 vs 46.2 months; HR 1.53; P<0.0001). Interestingly, this effect appeared to be more pronounced in patients with international staging system (ISS) I disease (HR 1.83) than in patients with ISS II (HR 1.38) or ISS III disease (HR 1.14). Also, patients with a high cytogenetic risk benefitted relatively more from early ASCT (HR 1.99) than those with standard risk (HR 1.38). Another remarkable observed subgroup difference was that Black patients (20% of the included patients; HR 1.07) benefitted less from early ASCT than White patients (HR 1.67). Furthermore, a preliminary analysis of MRD status showed that a higher number of patients in the ASCT group reached MRD-negative status (54.4% vs 39.8%) and that MRD-negativity was associated with longer PFS, regardless of received treatment. Importantly, after a median follow-up of 76 months, OS was not improved in the ASCT arm compared with the control arm (80.7 vs 79.2 months; HR 1.10; P=0.99).

RVd plus ASCT was associated with higher but mostly manageable rates of toxicity. In total, 1.6% and 0.3% of the patients experienced fatal adverse events (AEs) in the ASCT plus RVd arm and RVd alone arm, respectively. In addition, grade ≥3 events (94.2% vs 78.2%) and haematologic grade ≥3 events (89.9% vs 60.5%) were more common in the combination arm.

"The PFS benefit with early ASCT in the first-line treatment of patients with multiple myeloma reaffirms ASCT as a standard-of-care. However, the similar OS results for both treatment arms supports the use of a personalised approach. Furthermore, we should investigate the impact of quadruplet therapies and perform whole-genome sequencing analyses to gain better insights in which patients should be selected for ASCT," concluded Prof. Richardson.

1. Richardson PG, et al. Lenalidomide, bortezomib, and dexamethasone (RVd) ± autologous stem cell transplantation (ASCT) and R maintenance to progression for newly diagnosed multiple myeloma (NDMM): The phase 3 DETERMINATION trial. LBA4, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.

Novel first-line treatment option for mantle cell lymphoma

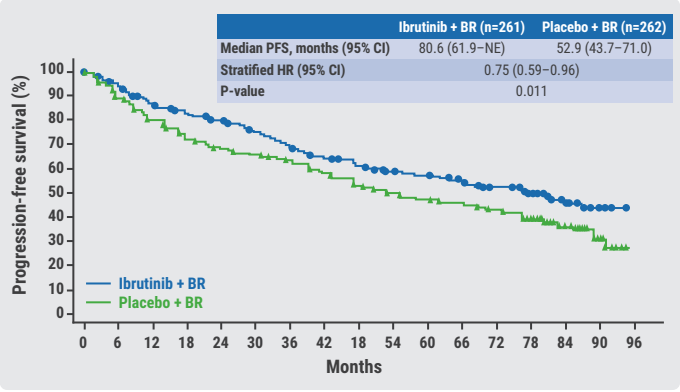
Bendamustine-rituximab chemotherapy plus ibrutinib outperformed bendamustine-rituximab alone as a first-line treatment for older patients with mantle cell lymphoma. The phase 3 SHINE trial demonstrated a meaningful benefit of the combination therapy over the monotherapy in terms of progression-free survival (PFS) but not in overall survival (OS). Nonetheless, bendamustine-rituximab plus ibrutinib displayed itself as a highly effective option for the mantle cell lymphoma population.

Bendamustine-rituximab has become the most commonly used first-line regimen for older patients with mantle cell lymphoma [1]. The Bruton's tyrosine kinase (BTK) inhibitor ibrutinib has transformed the care of patients with relapsed/refractory mantle cell lymphoma [2]. The phase 3 SHINE trial (NCT01776840), presented by Prof. Michael Wang (Anderson Cancer Center, TX, USA), randomised 523 older patients (≥65 years) with untreated mantle cell lymphoma 1:1 to 6 cycles of bendamustine-rituximab plus ibrutinib and rituximab maintenance therapy or bendamustine-rituximab plus placebo and rituximab maintenance therapy [3]. The primary endpoint was PFS.

After a median follow-up duration of 7.1 years, the PFS was significantly higher in the ibrutinib arm than in the

placebo arm (6.7 vs 4.4 years; HR 0.75; P=0.011; see Figure), representing a 25% reduction in risk of disease progression or death in the combination therapy arm. The results were mostly consistent across subgroups, with the exception of high-risk patients, in whom the PFS results were comparable (HR 1.02). Notably, the OS appeared not to differ between the experimental arm and the placebo arm, with 55% and 57% survival after 84 months, respectively. However, the OS results were not yet mature at the time of the presentation.

Figure: Progression-free survival of ibrutinib versus placebo in addition to bendamustine-rituximab [3]



PFS, progression-free survival; BR, bendamustine-rituximab.

Neutropenia was the most common adverse event, occurring in approximately 50% of the patients in each arm. Rash and pneumonia were more common in the experimental arm, as well as atrial fibrillation (13.9% vs 6.5%), and bleeding of any grade (42.9% vs 21.5%). However, the rate of major bleedings was comparable (5.8% vs 4.2%).

Prof. Kerry Savage (University of British Columbia, Canada), discussant of this trial, argued that the results of the SHINE trial support bendamustine-rituximab plus ibrutinib as a first-line treatment option for older or transplant-ineligible patients with mantle cell lymphoma, especially for those who display a good performance status. "Careful selection of patients is still needed, since the safety analysis showed increased rates of neutropenia, infections, and cardiac complications in the combination arm. Finally, mantle cell lymphoma is clinically and biologically diverse and we need to implement the use of BTK inhibitors in personalised approaches for our patients."

1. Martin P, et al. J Clin Oncol. 2021;(39):7504–7504.
2. Wang ML, et al. N Engl J Med. 2013;369:507–516.
3. Wang ML, et al. Primary Results From the Double-Blind, Placebo-Controlled, Phase III SHINE Study of Ibrutinib In Combination With Bendamustine-Rituximab and Rituximab Maintenance as a First-Line Treatment for Older Patients With Mantle Cell Lymphoma. LBA 7502, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.

Promising results for novel CAR-T therapy in relapsed/refractory multiple myeloma

GC012F, a dual CAR-T therapy, showed favourable safety outcomes and a high response rate in a population of patients with heavily pre-treated relapsed/refractory multiple myeloma (RRMM) in an update of the first-in-human study testing this BCMA/CD19-targeting therapy.

"FasTCAR GC012F is a CAR-T therapy that targets both BCMA and CD19 in order to establish fast, deep, and durable responses in patients with MM," explained Prof. Juan Du (Shanghai Chang Zheng Hospital, China). With a time from isolation until freezing of only 22–36 hours, the current therapy establishes a fast vein-to-vein time, potentially eliminating the need for a bridging therapy prior to CAR-T infusion, which is often needed in conventional CAR-T therapy. The current, open-label, single arm, investigator-initiated trial subjected 28 patients with heavily pre-treated (≥3 lines of therapy) RRMM to GC012F dual CAR-T therapy. Safety was the primary endpoint of this study. Of note, 89% of the patients had a high-risk profile.

According to Prof. Du, the safety profile of the CAR-T therapy was favourable. Grade ≥3 haematologic adverse events ranged from 36% for anaemia to 82% for neutropenia. The cases of cytokine release syndrome were mostly low grade (0–2: 93%) and only 2 patients experienced a grade 3 cytokine release syndrome event. No cases of immune effector cell-associated neurotoxicity syndrome were reported.

In total, an impressive 89.3% of the patients responded to the therapy, with 75% of the patients displaying a minimal residual disease (MRD) complete response or stringent complete response and 86% of the patients demonstrating a very good partial response (VGPR) or better. In addition, after a median follow-up of 6.3 months, the median duration of response was not reached.

Prof. Du summarised that the updated results of this first-in-human study assessing FasTCAR GC012F dual CAR-T therapy showed very promising activity in a heavily pre-treated, high-risk population of patients with RRMM, with a favourable safety profile. "Fast, deep, and durable responses were achieved with this novel CAR-T therapy."

1. Du J, et al. Updated results of a multicenter first-in-human study of BCMA/CD19 dual-targeting fast CAR-T GC012F for patients with relapsed/refractory multiple myeloma (RRMM). Abstract 8005, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.

Gastrointestinal Cancers

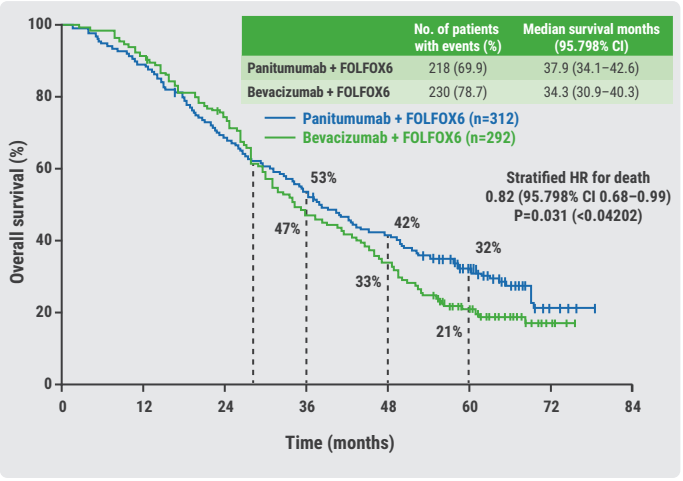
Panitumumab beats bevacizumab in *RAS* wildtype left-sided metastatic colorectal cancer

Panitumumab was superior to bevacizumab when added to mFOLFOX6 as first-line therapy in patients with *RAS* wildtype metastatic colorectal cancer (mCRC), especially in patients with left-sided tumours. The results of the phase 3 PARADIGM trial support mFOLFOX6 plus panitumumab as first-line therapy in patients with *RAS* wildtype left-sided mCRC.

Adding an EGFR inhibitor or VEGF inhibitor to chemotherapy improves the overall survival (OS) of patients with mCRC significantly [1]. In patients with *RAS* wildtype, left-sided, colorectal tumours, the benefit of an EGFR inhibitor may be enriched, based on retrospective analysis [2]. The phase 3 PARADIGM trial assessed this matter by randomising 823 patients with RAS wildtype mCRC 1:1 to mFOLFOX6 plus the EGFR inhibitor panitumumab or to mFOLFOX6 plus the VEGF inhibitor bevacizumab [3]. In total, 604 patients had left-sided tumours. The primary endpoints of this trial were OS in the left-sided population and OS in the overall population. Dr Takayuki Yoshino (National Cancer Center Hospital East, Japan) presented the results.

After 5 years of follow-up, panitumumab performed better than bevacizumab in terms of median OS in both the left-sided population (37.9 vs 34.3 months; HR 0.82; P=0.031; see Figure) and the overall population (36.2 vs 31.3 months; HR 0.84; P=0.030). The OS curves of the 2 treatment regimens separated after 28 months. In contrast, the median progression-free survival did not differ between treatment regimens: left-sided population (13.7 vs 13.2 months; HR 0.98); overall population (12.9 vs 12.0 months; HR 1.01). According to Dr Yoshino, the research group expected this result. Other efficacy outcomes favoured the panitumumab arm, especially in the left-sided sub-population, in whom response rates were 80.2% versus 68.6%. Interestingly, an exploratory analysis of OS in the right-sided population did not display a benefit of panitumumab over bevacizumab (20.2 vs 23.2 months; HR 1.09).

Figure: Overall survival of panitumumab versus bevacizumab in left-sided population [3]



No new safety issues were observed for the treatment regimens. In the panitumumab arm, 71.8% of the patients experienced grade ≥3 adverse events compared with 64.9% of the patients in the bevacizumab arm. The treatment discontinuation rates due to adverse events were 23.8% and 18.4% in the panitumumab arm and bevacizumab arm, respectively. Acne-like dermatitis, paronychia, dry skin, and hypomagnesaemia were more often observed in patients on panitumumab.

"These results support panitumumab plus mFOLFOX6 as first-line therapy for patients with *RAS* wildtype and left-sided mCRC," concluded Dr Yoshino. "A large-scale biomarker analysis is currently ongoing (NCT02394834) to gain in-depth understanding of these results."

1. Venook AP, et al. JAMA. 2017;317(23):2392–2401.
2. Arnold D, et al. Ann Oncol. 2017; 28(8):1713–1729.
3. Yoshino T, et al. Panitumumab (PAN) plus mFOLFOX6 versus bevacizumab (BEV) plus mFOLFOX6 as first-line treatment in patients with RAS wild-type (WT) metastatic colorectal cancer (mCRC): Results from the phase 3 PARADIGM trial. LBA1, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.

Spectacular results for dostarlimab in mismatch repair deficient rectal cancer

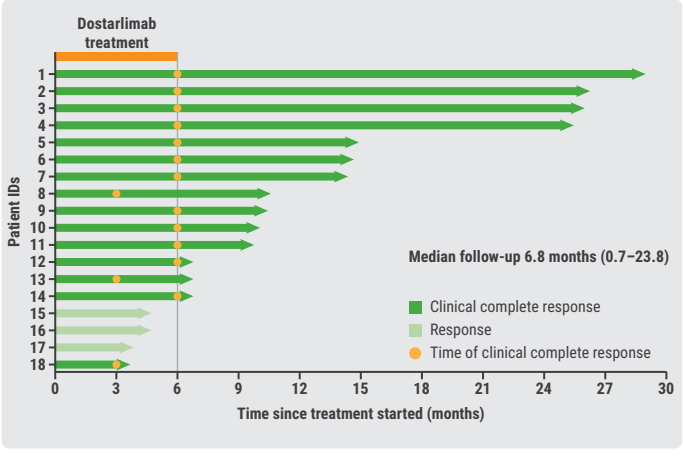
A phase 2 trial investigating neoadjuvant treatment with the PD-1 inhibitor dostarlimab in patients with stage II

or III mismatch repair deficient (dMMR) rectal cancer showed a response rate of 100% following treatment with this agent in the thus far analysed patients. Off-protocol use of neoadjuvant immunotherapy in this population is likely to occur.

"Locally advanced rectal cancer is treated with a combination of chemotherapy, radiation, and optional surgery, with all its costs and life-altering consequences," said Dr Andrea Cercek (Memorial Sloan Kettering Cancer Center, NY, USA) [1]. Patients with dMMR rectal cancer are relatively resistant to chemotherapy but are responsive to checkpoint inhibitors [2,3]. The current phase 2 study aimed to assess whether neoadjuvant PD-1 inhibition may be able to replace chemotherapy, chemo- and radiation therapy, or chemotherapy, radiation therapy, and surgery in patients with dMMR rectal cancer.

For this purpose, 30 patients received dostarlimab (500 mg, intravenous, every 3 weeks) for 6 months followed by radiologic and endoscopic evaluation. If a clinical complete response was achieved, a wait-and-see approach was installed with 4-monthly follow-up visitations. If residual disease was detected, patients received chemoradiation. After completion of this therapy, another evaluation would decide if surgery was needed. The primary objectives were the overall response rate of PD-1 blockade with or without chemoradiation and the pathologic or clinical complete response rate at 12 months after PD-1 therapy with or without chemoradiation.

Figure: Duration of clinical complete response on dostarlimab treatment [3]



Spectacularly, all 14 patients that have been analysed to date reached a clinical complete response on dostarlimab therapy alone. Moreover, the responses were ongoing in all assessed patients after a median follow-up of 6.8 months (see Figure). Furthermore, no grade 3 or 4 adverse events were reported in these patients.

According to Dr Cercek, PD-1 inhibition may eliminate the need for chemotherapy and radiation in patients with early-stage dMMR rectal cancer and may rapidly translate to areas without access to modern chemotherapy, radiation, and surgery. It will spare patients from toxicity and late effects of chemo- and radiation therapy and surgery.

"Based on the data of this study, off-protocol use of neoadjuvant immunotherapy in this population is likely to occur," expected Dr Kimmie Ng (Dana-Farber Cancer Institute, MA, USA), who commented on this late-breaking abstract. Dr Ng commented that the results are spectacular, but that larger sample sizes, longer follow-up time, and results from other endpoints are needed before standard-of-care may be changed in this population.

1. Cercek A, et al. Single agent PD-1 blockade as curative-intent treatment in mismatch repair deficient locally advanced rectal cancer. LBA5, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.
2. Cercek A, et al. Clin Can Res. 2020;26(13):3271–3279.
3. Andre T, et al. NEJM. 2020;383:2207–2218.

Triplet chemotherapy beats doublet chemotherapy in colorectal cancer liver metastases

The CAIRO5 trial showed triplet chemotherapy to be superior to doublet chemotherapy in terms of efficacy in patients with initially unresectable colorectal cancer liver metastases (CRLM) and right-sided and/or *RAS/BRAFV600E*-mutated primary tumours, at the expense of increased but manageable toxicity. The use of a liver expert panel increased the selection of patients who received local treatment with curative intent.

Patients with initially unresectable CRLM are treated with induction systemic treatment, however there is no consensus on the criteria for resectability of CRLM and on the systemic induction regimen that should be administered to these patients. The phase 3 CAIRO5 trial (NCT02162563) installed a liver panel to confirm the unresectability (by surgery-only in one stage) of patients with initially unresectable CRLM [1]. Hereafter, those with *RAS/BRAFV600E*-mutated and/or right-sided primary tumours (n=294) were randomised to FOLFOX/FOLFIRI plus bevacizumab (doublet chemotherapy)

or FOLFOXIRI plus bevacizumab (triplet chemotherapy). Progression-free survival (PFS) was the primary endpoint. Results were presented by Prof. Cornelis Punt (University Medical Center Utrecht, the Netherlands).

After a median follow-up of 41 months, the median PFS was significantly longer in patients who had received FOLFOXIRI than in those that had received doublet chemotherapy (10.6 vs 9.0 months; HR 0.77; P=0.038). At this point in time, the overall survival data was not yet mature. Furthermore, the subgroup analysis did not demonstrate an association between baseline unresectability status or mutation status and PFS. The overall response rate was higher in the triplet chemotherapy arm (53.5% vs 33.3%; P<0.001). However, grade ≥3 adverse events were more common in patients who underwent triplet chemotherapy than in those who underwent doublet chemotherapy (75.7% vs 59.2%; P=0.003), mostly due to an increased rate of neutropenia (38.2% vs 12.9%) and diarrhoea (19.4% vs 3.4%).

CAIRO5 is the first randomised trial to prospectively demonstrate the clinical benefit of triplet versus doublet chemotherapy in patients with initially unresectable CRLM and right-sided and/or *RAS/BRAFV600E*-mutated primary tumours. Prof. Punt added that the use of a liver expert panel is feasible and allows the selection of an increased number of patients who are suitable to receive local treatment with curative intent.

1. Punt CJA, et al. FOLFOXIRI + bevacizumab versus FOLFOX/FOLFIRI + bevacizumab in patients with initially unresectable colorectal liver metastases (CRLM) and right-sided and/or RAS/BRAFV600E-mutated primary tumor: Phase III CAIRO5 study of the Dutch Colorectal Cancer Group. LBA3506, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.

To resect or not to resect primary tumours in stage IV colon cancer?

In patients with colon cancer or high rectal cancer and synchronous unresectable metastases, resection of the primary tumour did not prolong the overall survival (OS) time compared with chemotherapy only. Chemotherapy demonstrated to be the most important factor to influence OS in these patients.

"Resection of the primary tumour in patients with stage IV colorectal cancer is debated," said Prof. Jürgen Weitz (Technische Universität Dresden, Germany) at the start of his presentation [1]. It may prevent primary tumour complications, but increases the risk of surgical complications. Current evidence is unclear on whether the primary tumour should be resected in this population [2]. To address this gap in the literature, the SYNCHRONOUS trial (ISRCTN30964555) randomised 393 patients with colon cancer or high rectal cancer, synchronous metastases, and asymptomatic primary tumours to resection plus chemotherapy by physician's choice or chemotherapy alone [1]. OS was the primary endpoint of this trial.

After a median follow-up of 36 months, no significant difference in OS was measured between the resection plus chemotherapy arm and the chemotherapy alone arm (16.7 vs 18.6 months; P=0.685). Notably, in a subgroup of patients that did not receive chemotherapy (24.1% in resection plus chemotherapy and 6.4% in chemotherapy alone arm), the OS decreased significantly (HR 5.32; P<0.001). In addition, no subgroup appeared to benefit from surgery in addition to chemotherapy in terms of OS.

Serious adverse events were more common in the chemotherapy arm (18.0% vs 10.2%), mainly due to an increased number of gastrointestinal tract-related events (10.7% vs 4.8%; P=0.031).

Prof. Weitz concluded that the addition of resection of the primary tumour to chemotherapy does not prolong OS in patients with colon cancer or high rectal cancer, asymptomatic primary tumours, and synchronous unresectable metastases. In fact, chemotherapy was the most important factor to impact the OS time of these patients.

1. Rahbari NN, et al. Randomized clinical trial on resection of the primary tumor versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases. LBA3507, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.
2. Cirocchi R, et al. Cochrane Database Syst Rev. 2012;8:CD008997.

Novel treatment option for *KRAS* wildtype pancreatic cancer

Gemcitabine plus nimotuzumab demonstrated overall survival (OS) benefits over gemcitabine alone for patients with *KRAS* wildtype metastatic pancreatic ductal adenocarcinoma (mPDAC) or locally advanced pancreatic cancer (LAPC). The results of the phase 3 Notable trial show the value of determining *KRAS* status in pancreatic cancer.

Activation of the epidermal growth factor receptor (EGFR)-Ras-Raf-MEK-ERK pathway plays a part in patients with

KRAS wildtype pancreatic cancer [1]. Therefore, the phase 3 Notable trial (NCT02395016) randomised patients with *KRAS* wildtype locally advanced or metastatic pancreatic cancer to gemcitabine and placebo (n=41) or gemcitabine plus nimotuzumab (n=41), which is an EGFR-targeting monoclonal antibody. OS was the primary endpoint of this study. Prof. Shukui Qin (Cancer Center of Jinling Hospital, China) presented the results [2].

The combination therapy arm outperformed the placebo arm significantly for OS (10.9 vs 8.5 months; HR 0.50; P=0.024), decreasing the risk of mortality by 50%. In addition, the 1-year and 3-year OS rates were 43.6% and 13.9% for patients treated with nimotuzumab and 26.8% and 2.7% for patients who received placebo.

Importantly, the combination therapy was well tolerated and no substantial increase in grade 3 adverse events was observed among patients who received nimotuzumab. The most frequently reported adverse events in the nimotuzumab arm were neutropenia (11.1%), leukopenia (8.9%), and thrombocytopenia (6.7%). Prof. Qin added that the OS curves of the 2 treatment arms separated rather late, suggesting there might be subgroups within the *KRAS* wildtype subgroup of tumours that behave differently in response to nimotuzumab.

This trial demonstrated that it is worth determining *KRAS* status in pancreatic cancer. Gemcitabine plus nimotuzumab displayed itself as a novel option for patients with *KRAS* wildtype mPDAC/LAPC who otherwise would have received only gemcitabine. "It would be interesting to see how combination chemotherapy would behave in the *KRAS* wildtype mPDAC population," concluded Thomas Seufferlein (Ulm University Hospital, Germany), discussant of this session [3].

1. Luchini C, et al. J Exp Clin Cancer Res. 2020;39(1):227.
2. Qin S, et al. Nimotuzumab combined with gemcitabine versus gemcitabine in KRAS wild-type locally advanced or metastatic pancreatic cancer: a prospective, randomized-controlled, double-blinded, multicenter, and phase III clinical trial. J Clin Oncol. LBA4011, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.
3. Seufferlein T, et al. Is it worth determining KRAS Status in Pancreas Cancer? Discussant LBA 4011, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.

Gynaecological Cancers

Primary results of rucaparib in ovarian cancer

First-line rucaparib maintenance therapy after platinum-based chemotherapy improved the progression-free survival (PFS) of patients with stage III–IV ovarian cancer in the ATHENA-MONO trial. Further tumour reductions were reported following treatment with rucaparib.

The efficacy of the PARP inhibitor rucaparib has been established in patients with platinum-sensitive recurrent ovarian cancer [1]. Also, PARP inhibitors have delivered PFS benefits as first-line maintenance treatment [2]. However, the optimal first-line maintenance strategy for patients with advanced ovarian cancer is still unclear.

The phase 3 ATHENA trial (NCT03522246) randomised patients with FIGO stage III or IV ovarian cancer, who responded to first-line platinum-based doublet chemotherapy, 4:4:1:1 to rucaparib plus nivolumab (arm A), rucaparib plus placebo (arm B), placebo plus nivolumab (arm C), and placebo plus placebo (arm D). Prof. Bradley Monk (University of Arizona, AZ, USA) discussed the results of the ATHENA-MONO trial, comparing arm B (n=427) with arm D (n=111) [3]. Investigator-assessed PFS was the primary outcome of the trial.

Rucaparib was associated with an improvement in the median PFS of patients with homologous recombination deficiency-positive tumours (28.7 vs 11.3 months; HR 0.47; P=0.0004) and in the median PFS of the intention-to-treat population (20.2 vs 9.2 months; HR 0.52; P<0.0001). The PFS per blinded, independent, central review demonstrated similar results. Furthermore, the PFS benefit of rucaparib was consistent among *BRCA*-mutated (HR 0.40), *BRCA* wildtype/loss of heterozygosity high (HR 0.58), and homologous recombination deficiency-negative patients (HR 0.65). Prof. Monk pointed out that patients with the highest risk (residual disease, stage IV, abnormal CA-125 levels) appeared to benefit more from treatment with rucaparib.

In total, 60.5% of the patients on rucaparib experienced grade ≥3 adverse events (AEs) compared with 22.7% of the patients in the placebo arm. Most treatment-emergent AEs in the active arm were of gastrointestinal origin or marrow-related, and could be mitigated with dose reductions or dose interruptions. The discontinuation rate was 11.8% in patients receiving rucaparib.

Rucaparib showed to be effective as first-line maintenance monotherapy with significant benefits over placebo in the intention-to-treat and homologous recombination deficiency patients.

1. Coleman RL, et al. Lancet. 2017;390:1949–1961.
2. Moore K, et al. N Engl J Med. 2018;379:2495–2505.
3. Monk BJ, et al. ATHENA–MONO (GOG-3020/ENGOT-ov45): A randomized, double-blind, phase 3 trial evaluating rucaparib monotherapy versus placebo as maintenance treatment following response to first-line platinum-based chemotherapy in ovarian cancer. LBA5500, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.

Trabectedin not superior to chemotherapy in recurrent epithelial ovarian cancer

Trabectedin failed to show a clinical benefit over standard-of-care chemotherapy in patients with *BRCA*-mutated or BRCAness phenotype, recurrent epithelial ovarian cancer. Nonetheless, translational studies are ongoing to identify potential predictive biomarkers of response to trabectedin.

Trabectedin in combination with pegylated liposomal doxorubicin (PLD) is an approved treatment for patients with platinum-sensitive recurrent ovarian cancer [1]. Dr Domenica Lorusso (San Raffaele Scientific Institute, Italy) presented the phase 3 MIT023 trial results which assessed the efficacy and safety of trabectedin in patients with *BRCA*-mutated or BRCAness phenotype recurrent epithelial ovarian cancer [2]. In total, 244 patients were randomised 1:1 to trabectedin or investigator's choice chemotherapy. The primary endpoint was overall survival (OS).

After a median follow-up of 18.8 months, trabectedin failed to demonstrate an OS benefit over chemotherapy (15.8 vs 17.9 months; HR 1.15; P=0.304). Similarly, progression-free survival rates (4.9 vs 4.4 months) and overall response rates (17.1% vs 21.4%) did not show a substantial difference between the 2 treatment arms. In addition, no subgroup appeared to benefit more from trabectedin than from chemotherapy.

Serious adverse events were observed in 24.8% of the patients on trabectedin and in 5.1% of the patients on chemotherapy. The rate of treatment discontinuations was higher in the experimental arm (15.7% vs 5.9%). Febrile neutropenia (4.1%), neutropenia (34.7%), hepatic toxicity (14.9%), fatigue (15.7%), and nausea (7,4%) were the most distinctive grade ≥3 adverse events in the experimental arm.

Dr Lorusso commented that trabectedin did show a retained clinical activity comparable with chemotherapy, despite the fact that this study analysed patients that were heavily pre-treated. Therefore, translational studies are ongoing to detect which patients are more likely to respond to trabectedin.

1. Poveda A, et al. Ann Oncol. 2011;22(1):39–48.
2. Scambia G, et al. Randomized phase III trial on trabectedin (ET-743) single agent versus clinician's choice chemotherapy in recurrent ovarian, primary peritoneal, or fallopian tube cancers of BRCA-mutated or BRCAness phenotype patients (MITO23). LBA5504, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.

Encouraging results of relacorilant in ovarian cancer

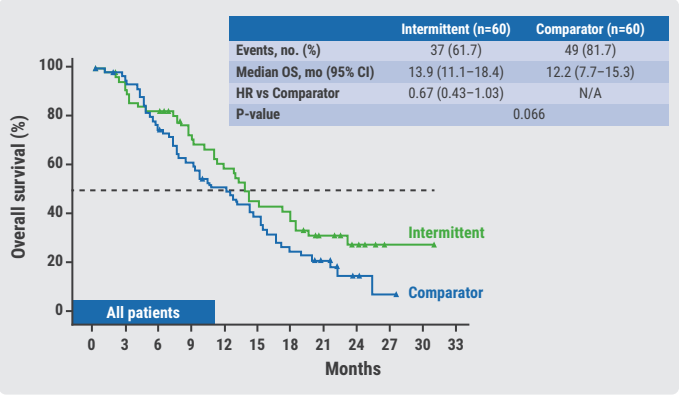
The glucocorticoid receptor modulator relacorilant added to nab-paclitaxel demonstrated an overall survival (OS) benefit over nab-paclitaxel alone in patients with platinum-resistant/refractory ovarian cancer. These results provide evidence that cortisol modulation is a promising novel modality in oncology.

A phase 2 study randomised 178 patients with recurrent platinum-resistant ovarian cancer to intermittent relacorilant plus nab-paclitaxel, continuous relacorilant plus nab-paclitaxel, or nab-paclitaxel alone. The primary analysis showed a significantly improved median progression-free survival (PFS) for patients in the intermittent arm compared with the nab-paclitaxel alone arm (5.55 vs 3.76 months; HR 0.66; log-rank P=0.038). Prof. Nicoletta Colombo (University of Milan, Italy) presented the final results of the study, including mature OS results [1].

The updated PFS rates were similar with those of the primary analysis, with a median PFS of 5.6 months in the intermittent arm and a median PFS of 3.8 months in the control arm (HR 0.66; P=0.038). Prof. Colombo mentioned that the overall response rates were similar in the 2 arms, but that the duration of response was significantly longer in the intermittent arm (HR 0.36; P=0.006). Importantly, the trend towards an improved OS in the intermittent arm compared with the control arm that was observed in the primary

analysis was maintained in this analysis, with a median OS of 13.9 versus 12.2 months (HR 0.67; P=0.066; see Figure).

Figure: Positive overall survival for intermittent relacorilant plus nab-paclitaxel [1]



OS, overall survival; mo, months; no., number; N/A, not applicable.
Intermittent, intermittent relacorilant + nab-paclitaxel; Comparator, nab-paclitaxel monotherapy.

At 24 months, 27% and 14% of the patients were still alive in the intermittent and control arm, respectively. This result was consistent when patients with primary platinum-refractory disease were excluded from the analysis (HR 0.63; P=0.045). Finally, the updated safety analysis demonstrated that intermittent relacorilant does not come with additional safety issues compared to nab-paclitaxel alone.

The promising results of relacorilant in this phase 2 study initiated the development of the phase 3 ROSELLA trial to assess this agent in patients with ovarian cancer.

1. Colombo N, et al. Overall survival data from a 3-arm, randomized, open-label, phase 2 study of relacorilant, a selective glucocorticoid receptor modulator, combined with nab-paclitaxel in patients with recurrent platinum-resistant ovarian cancer. LBA5503, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.

Miscellaneous Topics

Bacterial decolonisation effective against radiation dermatitis

Bacterial decolonisation of *Staphylococcus aureus* could effectively decrease the severity of radiation dermatitis and prevent moist desquamation in patients with breast or head-and-neck cancer who received radiotherapy. Moreover, this approach is safe, easy, and cost-effective, according to the authors.

Ms Yana Kost (Albert Einstein College of Medicine, NY, USA) and colleagues demonstrated that nasal colonisation with *Staphylococcus aureus* prior to radiotherapy is a predictor of grade ≥2 radiation dermatitis. Therefore, a randomised phase 2 trial (NCT03883828) was developed to compare a strategy of bacterial decolonisation with standard-of-care in patients (n=80) with breast cancer or head-and-neck cancer who were planned to receive fractionated radiotherapy (≥15 fractions) [1]. Patients in the bacterial decolonisation arm received intranasal mupirocin ointment, twice daily, and chlorhexidine body wash, once daily, for 5 consecutive days prior to radiotherapy initiation. This strategy was repeated every other week for 5 days during radiotherapy.

The median radiation dermatitis grade was significantly lower in the bacterial decolonisation arm than in the standard-of-care arm (1.19 vs 1.58; P=0.019), meeting the primary endpoint of this trial. In addition, grade ≥2 moist desquamation could effectively be prevented by the bacterial decolonisation approach (0% vs 23.68%; P=0.002). Furthermore, the data showed that nasal *Staphylococcus aureus* colonisation rates were decreased in the bacterial decolonisation arm from baseline to post-radiotherapy (13.16% to 7.89%), whereas an opposite pattern was noted in the standard-of-care arm (15.79% to 23.68%). Despite these results, no significant differences in quality-of-life between the 2 patient groups were reported.

Ms Kost concluded that bacterial decolonisation was an effective strategy to reduce radial dermatitis severity and prevent moist desquamation in the study population. She argued that bacterial decolonisation is safe, easy, cost-effective, and avoids infection and skin atrophy, concerns that are associated with the use of topical steroids.

1. Kost Y, et al. Bacterial decolonization to prevent acute radiation dermatitis: A randomized controlled trial. LBA12003, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.

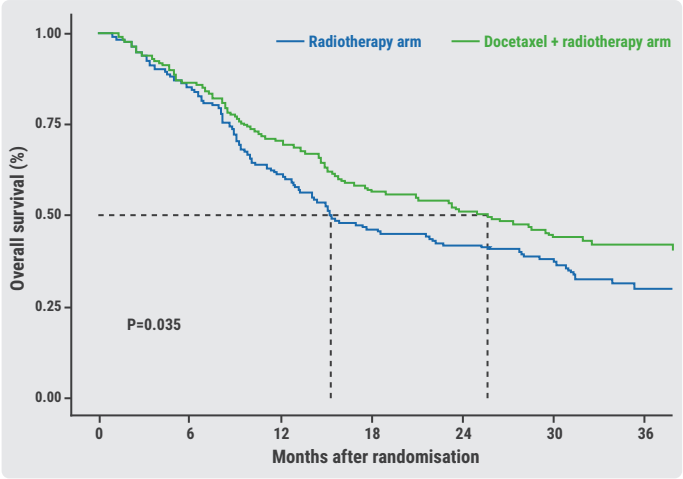
New standard-of-care for cisplatin-ineligible locally advanced head and neck squamous cell carcinoma

Docetaxel added to radiation improved the disease-free survival (DFS) and overall survival (OS) of patients with locally advanced head-and-neck squamous cell carcinoma (LAHNSCC). The current randomised trial is the first study to assess docetaxel as a radiosensitiser in cisplatin-ineligible patients with LAHNSCC and resulted in the presentation of a new reference standard-of-care for this population.

Although chemoradiation with cisplatin is a main standard therapy for patients with LAHNSCC, patients who are unsuitable to receive cisplatin are not uncommon. Prof. Vanita Noronha (Tata Memorial Hospital, India) discussed a phase 3 trial that randomised patients with LAHNSCC, who were ineligible for cisplatin, to radiotherapy alone (n=176) or docetaxel and radiotherapy (n=180) [1]. The main outcomes of the trial were DFS and OS after 2 years, quality-of-life, and adverse events (AEs).

The 2-year DFS was significantly higher in participants who received docetaxel and radiotherapy than in participants who received radiotherapy alone (42% vs 30.3%; HR 0.67; P=0.0021). Likewise, the 2-year OS data favoured participants who received docetaxel over those who did not (50.8% vs 41.7%; HR 0.75; P=0.035; see Figure). The results of these efficacy endpoints were consistent across prespecified subgroups. Furthermore, the functional assessment of cancer therapy – general (FACT-G) score displayed lower reductions in quality-of-life for patients receiving docetaxel at 6 months (-25.4 vs -40.5; P=0.035).

Figure: Overall survival results of docetaxel plus radiotherapy versus radiotherapy alone [1]



AEs that were more common in the docetaxel-radiotherapy arm than in the radiotherapy alone arm included grade 3–5 mucositis (49.7% vs 22.2%; P<0.001), grade 3–5 odynophagia (52.5% vs 33.5%; P<0.001), grade 3–5 dysphagia (49.7% vs 33.0%; P=0.002), and any grade weight loss (51.4% vs 36.4%; P=0.005). Grade 3–5 hyponatraemia was also more frequently observed in the docetaxel-radiotherapy arm (30.2% vs 19.3%; P=0.02).

"The improved DFS and OS in cisplatin-ineligible patients with LAHNSCC who received the addition of docetaxel to radiation represents a new reference standard-of-care for this group of patients," concluded Prof. Noronha.

1. Noronha V, et al. Results of phase 3 randomized trial for use of docetaxel as a radiosensitizer in patients with head and neck cancer unsuitable for cisplatin-based chemoradiation. LBA 6003, ASCO 2022 Annual meeting, 3–7 June, Chicago, IL, USA.

Ifosfamide is likely to be the go-to therapy in recurrent Ewing sarcoma

Ifosfamide was more efficacious than topotecan plus cyclophosphamide in patients with primary recurrent or refractory Ewing sarcoma, despite a higher discontinuation rate due to toxicity in the ifosfamide arm. The phase 3 rEECur trial is the first randomised study to deliver efficacy, safety, and quality-of-life data to inform physicians on chemotherapy treatment decisions for patients with recurrent Ewing sarcoma.

No established standard-of-care exists for patients with recurrent/refractory Ewing sarcoma, because there have not been any randomised trials comparing different chemotherapy regimens in this population. Therefore, the phase 3 rEECur trial, presented by Dr Martin McCabe (University of Manchester, UK), randomised patients with previously treated Ewing sarcoma to ifosfamide (n=78) or topotecan plus cyclophosphamide (n=162). The primary outcome was event-free survival (EFS) [1].

The median EFS was numerically higher in the ifosfamide arm (5.7 months) than in the topotecan plus cyclophosphamide arm (3.5 months) and trended towards significance (HR 0.73; 95% CI 0.51–1.05). In addition, the 6-month EFS rates were 47% and 37% in the ifosfamide and topotecan plus cyclophosphamide arm, respectively. Interestingly, exploratory subgroup analysis revealed that the effect appeared to be more pronounced in younger patients (<14 years; HR 0.37) than in older patients (HR 0.93). The overall

survival (OS) analysis displayed similar results, with a median OS of 15.4 months in the ifosfamide arm and a median OS of 10.5 months in the topotecan plus cyclophosphamide arm, with a trend towards a significant difference (HR 0.73; 95% CI 0.50–1.08).

The rate of grade ≥3 adverse events (AEs) was higher in the ifosfamide arm (57%) than in the topotecan plus cyclophosphamide arm (44%), mainly due to a higher rate of nervous system (8% vs 3%) and renal/urinary disorders (8% vs 0%) in the ifosfamide arm. In the topotecan plus cyclophosphamide arm, 53% of the patients discontinued due to progression compared with 22% in the ifosfamide arm. However, 26% of the patients in the ifosfamide group discontinued due to AEs but no patients in the topotecan plus cyclophosphamide group did so. Dr McCabe commented that this was a high-dose trial and that dose reductions were not allowed in the ifosfamide arm. In the topotecan plus cyclophosphamide arm, dose reductions were allowed. Finally, quality-of-life data suggested that improvements were made in the ifosfamide arm but not in the topotecan plus cyclophosphamide arm.

1. McCabe MG, et al. Phase III assessment of topotecan and cyclophosphamide and high-dose ifosfamide in rEECur: An international randomized controlled trial of chemotherapy for the treatment of recurrent and primary refractory Ewing sarcoma (RR-ES). LBA2, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.

Dabrafenib plus trametinib candidates for standard-of-care in *BRAF V600*-mutated paediatric low-grade glioma

The non-chemotherapeutic combination of dabrafenib and trametinib outperformed standard-of-care chemotherapy in paediatric patients with *BRAF V600*-mutated low-grade glioma. With the manageable safety profile, it shows potential as a new standard-of-care for this population.

Gliomas, accounting for approximately 45% of all paediatric central nervous system tumours, are surgically treated if possible [1]. Unfortunately, about 50% of these tumours cannot be resected, because the tumours are too large or inaccessible. Chemotherapy is the first-line standard of care in these patients. However, paediatric patients with *BRAF V600E* mutations show a less favourable response to chemotherapy and novel therapeutic options are needed for these patients [2]. Prof. Eric Bouffet (University of Toronto, Canada) presented results from a phase 2 trial (NCT02684058) which randomised patients with *BRAF V600*-mutant low-grade glioma to dabrafenib plus trametinib (n=73) or chemotherapy (carboplatin plus vincristine; n=37) [3]. Objective response rate (ORR) per central independent review was the primary endpoint.

The experimental arm showed superior ORR compared with the chemotherapy arm (47% vs 11%; OR 7.2; P<0.001). Most objective responses were partial responses in the experimental arm (44%) and in the chemotherapy arm (8%). The differences between the treatment arms were the most pronounced in ganglioglioma (ORR 38% vs 0%), low-grade glioma not otherwise specified (ORR 86% vs 17%), pilocytic astrocytoma (ORR 41% vs 8%), and pleomorphic xanthoastrocytoma (ORR 33% vs 0%). Furthermore, the progression-free survival (PFS) after 12 months favoured the experimental arm over the placebo arm (66.6% vs 26.1%; HR 0.31; P<0.001). These results were also reflected in the reported quality-of-life scores, which were improved in the experimental arm compared with the chemotherapy arm.

The safety analysis displayed that grade ≥3 adverse events (AEs) were more common in the chemotherapy arm (94% vs 47%). Similarly, treatment-related discontinuation rates were higher in the chemotherapy arm (9% vs 3%). Pyrexia (68%), headache (47%), and dry skin (26%) were more frequently reported in the experimental arm, whereas vomiting, nausea, and marrow-related issues were more common in the chemotherapy arm.

"In paediatric patients with *BRAF V600*-mutant low-grade glioma, the combination of dabrafenib plus trametinib was superior to standard-of-care frontline chemotherapy, with a manageable safety profile, demonstrating potential as a new standard-of-care for this population," concluded Prof. Bouffet.

1. Ostrom QT, et al. Neuro Oncol. 2021;23:301–305.
2. Lassaletta A, et al. J Clin Oncol. 2017;35(25):2934–2941.
3. Bouffet E, et al. Primary analysis of a phase II trial of dabrafenib plus trametinib (dab + tram) in BRAF V600–mutant pediatric low-grade glioma (pLGG). LBA2002, ASCO 2022 Annual Meeting, 3–7 June, Chicago, IL, USA.