Medicom International Conference Series in Oncology

ESMO Congress 2021

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16–21 SEPTEMBER 2021

PEER-REVIEWED CONFERENCE REPORT

Extra Focus on Breast Cancer

Practice-Changing: DESTINY-Breast03

HER2+ metastatic breast cancer in DESTINY-Breast03 demonstrated that T-DXd provided a highly statistically and clinically meaningful improvement in progression-free survival when compared with T-DM1.

read more on PAGE 3

dd-MVAC 'Should Be Gold Standard' for Muscle-Invasive Bladder Cancer

The phase 3 VESPER trial showed that dose-dense methotrexate plus vinblastine, doxorubicin, and cisplatin (dd-MVAC) can improve survival when compared with gemcitabine plus cisplatin in MIBC.

read more on PAGE 26

SARS-CoV-2 Infection/ Vaccine in Cancer Patients

Results from both the VOICE and CAPTURE studies showed that cancer patients in general have an adequate response to SARS-CoV-2 infection and/or SARS-CoV-2 vaccination. Physicians should encourage vaccination.

read more on PAGE 31

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Editor Dr Stefan Rauh, Centre Hospitalier Emile Mayrisch, Luxembourg

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Letter from the Editor

Dr Stefan Rauh

Biography

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

Conflict of Interest Statement:
Nothing to declare.

Dear Reader,

I have again the privilege to present to you our congress report from ESMO 2021 Annual, this time from Paris. We'll wrap up major results even better than Christo's wrapping of the Arc de Triomphe (which took place at the same time). Thanks to COVID-19 this was again a largely virtual event, as audiences on-site mainly consisted of (other) speakers.

A lot to read through? Yes, it is! That's because this congress was again loaded with practice-changing and other relevant studies:

We knew it, studies confirm it:

Cancer patients better get their jab, and better not get into the hospital (due to serious COVID-19 infection).

Chemotherapy is back!

- In form of conjugates: more precise, more lethal (to cancer cells, that is), and less toxic (to their hosts). Here's brand new standards in breast and non-small cell lung cancer. Expect more to come.
- "Vintage chemo" also has a revival: nearly buried by many of us, MVAC made it to the headlines as neoadjuvant standard in early bladder cancer with a relevant survival benefit.
- And upfront chemo may be back in metastatic prostate cancer: The whole works with double hormone blockage AND docetaxel shows highly superior results as compared to less intensive approaches in the PEACE trial.

There's a potent weapon coming up for *KRAS* mutant mCRC, we might get closer to get "cold" MMS colorectal cancer to warm up to immunotherapy, and there are very interesting less toxic schedules to administer TKI's and check-point inhibitors in urothelial cancers…

We take pride in providing you with these and many more important news in professional, peer-reviewed articles. I'm sure you will enjoy our report.

Yours, sincerely
Stefan Rauh

Breast Cancer

Featured interview: Prof. Guy Jerusalem (CHU Liège, Belgium) introduces the chapter on Breast Cancer, featuring 10 articles about updates in Breast Cancer treatment.

Listen to the interview >

Trastuzumab deruxtecan triples PFS

At a prespecified interim analysis of DESTINY-Breast03, comparing trastuzumab deruxtecan (T-DXd) head-to-head with trastuzumab emtansine (T-DM1), T-DXd reduced the risk of disease progression or death by 72% compared with T-DM1. This was presented in the first Presidential Symposium.

The global head-to-head, open-label, randomised, phase 3 DESTINY-Breast03 study (NCT03529110) interim analysis was presented by Dr Javier Cortés (International Breast Cancer Center Barcelona, Spain) [1]. DESTINY-Breast03 evaluated the safety and efficacy of T-DXd (n=261; 5.4 mg/kg) versus T-DM1 (n=263; 3.6 mg/kg) in patients with HER2-positive unresectable and/or metastatic breast cancer previously treated with trastuzumab and a taxane, primarily as their first-line treatment. The primary endpoint of DESTINY-Breast03 was progression-free survival (PFS) based on blinded independent central review. Secondary efficacy endpoints included overall survival (OS), PFS based on investigator assessment, objective response rate, duration of response, clinical benefit rate, and safety.

After 15.5 and 13.9 months of follow-up in the T-DXd and T-DM1 arms respectively, blinded independent central review determined that the median PFS for patients treated with T-DXd was not reached compared with 6.8 months for T-DM1 (HR 0.28; P<0.0001; see Figure). The key secondary endpoint of PFS assessed by investigators showed that patients treated with T-DXd experienced a 3-fold improvement in PFS of 25.1 months versus 7.2 months with T-DM1 (HR 0.26; P<0.0001). PFS benefit was consistent across key subgroups of patients treated with T-DXd, including those with a history of stable brain metastases. Differences in estimated 12-month OS (94.1% with T-DXd vs 85.9% with T-DM1) did not cross the pre-specified boundary for significance (HR 0.56; 95% CI 0.36–0.86) but showed a strong interim trend, and will be followed up as the data mature.

The safety profile of the most common adverse events with T-DXd in DESTINY-Breast03 was consistent with previous data, and no new safety concerns were reported. Interstitial lung disease was reported in 10% of the patients in the T-DXd arm, versus 2% in the T-DM1 arm, yet these numbers are lower than described in earlier trials with T-DXd.

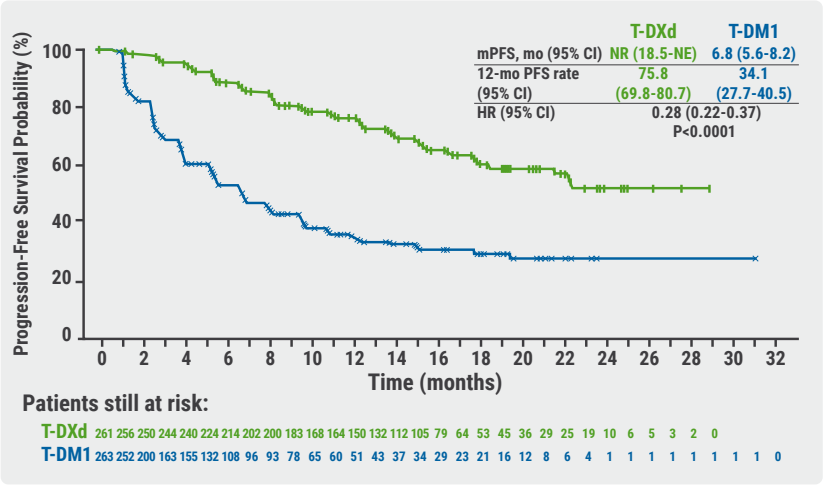
The designated discussant, Dr Shanu Modi (Memorial Sloan-Kettering Cancer Center, New York, USA) declared, "The efficacy seen in this trial is unprecedented."

1. Cortés J, et al. Trastuzumab Deruxtecan (T-DXd) vs Trastuzumab Emtansine (T-DM1) in Patients (Pts) With HER2+ Metastatic Breast Cancer (mBC): Results of the Randomized Phase 3 DESTINY-Breast03 Study. Abstract LBA1, ESMO Congress 2021, 16–21 September.

Novel conjugate meets primary endpoint

The phase 3 TULIP trial, investigating the novel antibody drug conjugate trastuzumab duocarmazine, met its primary endpoint of extended median progression-free survival (PFS) in HER2-positive breast cancer patients, compared with physician's choice, in the third-line setting. These results were presented in the second Presidential Symposium.

Figure: PFS determined by blinded independent central review, the primary endpoint of DESTINY-Breast03 [1]



Trastuzumab duocarmazine is an antibody drug conjugate that targets the HER2 protein with trastuzumab to deliver the cytotoxin duocarmycin after internalisation. Presented by Dr Cristina Saura (Vall d'Hebron Institute of Oncology, Spain), the TULIP trial (NCT03262935) aimed to demonstrate that trastuzumab duocarmazine (1.2 mg/kg every 3 weeks) is superior to physician's choice of treatment in prolonging PFS per blinded independent central review, as its primary endpoint [1].

Eligible patients were randomly assigned 2:1 to receive trastuzumab duocarmazine (n=291) or physician's choice treatment (n=146) until disease progression or unacceptable toxicity. Physician's choice of treatment included lapatinib plus capecitabine, trastuzumab plus capecitabine, trastuzumab plus vinorelbine, or trastuzumab plus eribulin. This randomised, active-controlled, superiority study in patients with unresectable locally advanced or metastatic HER2-positive breast cancer enrolled patients who had either progression during or after at least 2 HER2-targeting treatment regimens for locally advanced or metastatic disease or progression during or after trastuzumab emtansine (T-DM1) treatment. Key secondary endpoints were overall survival (OS), investigator-assessed PFS, objective response rate, and patient-reported outcomes for health-related quality of life.

The primary endpoint of centrally reviewed improved PFS was met, with a median of 7.0 months (95% CI 5.4–7.2 months) for patients in the trastuzumab duocarmazine arm compared with 4.9 months (95% CI 4.0–5.5 months) for physician's choice chemotherapy (P=0.002). Likewise, the secondary endpoint of investigator-assessed PFS was also met; patients in the trastuzumab duocarmazine arm had a median PFS of 6.9 months (95% CI 6.0–7.2 months) versus 4.6 months (95% CI 4.0–5.6 months) in the physician's choice arm.

At the timepoint of this interim analysis, OS was not statistically significant: 20.4 months in the group taking trastuzumab duocarmazine versus 16.3 months in the group following their physician's choice of therapy (HR 0.83; 95% CI 0.62–1.09; P=0.153). The other key secondary endpoints, objective response rate and health-related quality of life, also showed no statistically significant differences between the 2 arms. Final analyses of these endpoints will be evaluated after the data have matured with follow-up.

Safety signals were manageable, and no cardiotoxicity was observed. The most frequent adverse events for trastuzumab duocarmazine were conjunctivitis (38.2%), keratitis (38.2%), and fatigue (33.3%). Interstitial lung disease/pneumonitis occurred in 7.6% of patients on the drug, including 5.2% grade 1-2 events, and 2 grade 5 events.

1. Saura Manich C, et al. Primary outcome of the phase III SYD985.002/TULIP trial comparing [vic-]trastuzumab duocarmazine to physician's choice treatment in patients with pre-treated HER-positive locally advanced or metastatic breast cancer. Abstract LBA15, ESMO Congress 2021, 16–21 September.

Longest survival benefit from first-line CDK4/6 inhibitor

CDK4/6 inhibitor ribociclib added to endocrine therapy extended overall survival (OS) in treatment-naïve postmenopausal patients with HR-positive, HER2-negative, advanced, metastatic breast cancer. Data from the MONALEESA-2 trial showed that after a median follow-up of >6.5 years, median OS was 12 months longer for first-line ribociclib plus letrozole versus placebo plus letrozole.

Prof. Gabriel Hortobagyi (University of Texas MD Anderson Cancer Center, USA) presented the late-breaking results highlighting the final OS analysis of the phase 3 MONALEESA-2 study (NCT01958021), which evaluated ribociclib (oral, 600 mg daily, 3 weeks on/1 week off) plus the aromatase inhibitor letrozole (oral, 2.5 mg daily), compared with placebo plus letrozole [1]. The primary endpoint of MONALEESA-2 (n=668) was met and reported previously, showing that ribociclib plus letrozole improved progression-free survival of postmenopausal women with HR-positive, HER2-negative, metastatic breast cancer [2]. Furthermore, the results of the MONALEESA-7 trial in premenopausal patients with advanced HR-positive, HER2-negative breast cancer reported an improved progression-free survival and OS benefit [3,4]. OS was a key secondary endpoint of MONALEESA-2, and long-term OS data were presented at ESMO 2021.

With a median follow-up of 79.7 months, the final analysis of MONALEESA-2 showed a median OS of 63.9 months with frontline ribociclib and letrozole, compared with 51.4 months with letrozole alone. The estimated 6-year survival rate was 44.2% with ribociclib versus 32% for placebo. MONALEESA-2 is the first trial to demonstrate a survival advantage with a

frontline CDK4/6 inhibitor in combination with an aromatase inhibitor in postmenopausal patients with HR-positive, HER2-negative, advanced breast cancer.

No new safety signals were observed with this longer follow-up, and adverse events were consistent with earlier reported MONALEESA trial results.

Prof. Hortobagyi concluded, "I am very encouraged that metastatic breast cancer patients may have a treatment option that extends survival, delays chemotherapy treatment and preserves their quality of life." To date, this is the first report of a statistically significant and clinically meaningful OS benefit with a first-line CDK4/6 inhibitor in postmenopausal patients with HR-positive, HER2-negative, advanced breast cancer.

1. Hortobagyi GN, et al. Overall survival (OS) results from the phase III MONALEESA-2 (ML-2) trial of postmenopausal patients (pts) with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2−) advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib (RIB). Abstract LBA17_PR, ESMO Congress 2021, 16–21 September.
2. Hortobagyi GN, et al. Ann Oncol. 2019;30(11):1842.
3. Tripathy D, et al. Lancet Oncol. 2018;19(7):904-915.
4. Im SA, et al. N Engl J Med. 2019 Jul 25;381(4):307-316.

Meta-analysis shows 6-months adjuvant trastuzumab is optimal

Adjuvant trastuzumab is just as safe and effective when given to HER2-positive early breast cancer patients for 6, rather than 12 months, according to a meta-analysis of >11,000 participants from 5 major clinical trials. This meta-analysis demonstrated that shorter durations of adjuvant therapy might be as effective.

Prof. Helena Earl (Addenbrooke's Hospital, UK) combined data on more than 11,000 patients who were treated with trastuzumab after surgery for their early HER2-positive breast cancer for 9 weeks or 6 months versus the current standard of 12 months [1]. The rationale for this analysis stemmed from the Finland Herceptin (FinHer) trial, which compared a shorter 9-week treatment protocol against no trastuzumab with promising results [2], and raised the question of whether shorter durations of adjuvant treatment may be just as effective. Additional benefits for patients could be lower toxicity, fewer hospital visits, and a more rapid return to normal life, with considerable societal benefits of reduced costs.

The meta-analysis included patient data from the PERSEPHONE [3], PHARE [4] and HORG [5] trials, which compared 12 months with 6 months (total n≈11,500), in addition to the SOLD [6] and Short-HER [7] trials, which compared 12 months with 9 weeks (total n≈3,500) adjuvant therapy, respectively. The primary endpoint of the meta-analysis was invasive disease-free survival (IDFS). Secondary outcomes were distant relapse-free survival, overall survival, and breast cancer-specific survival.

The investigators found that treating HER2-positive early breast cancer patients with adjuvant trastuzumab for 6 months was non-inferior to continuing treatment for 12 months, with no significant difference in 5-year IDFS rates (89.26% vs 88.56%, respectively; HR 1.07; 90% CI 0.98–1.17; P=0.02). Importantly, however, when 9 weeks of trastuzumab was compared with 12 months, the IDFS rates were lower for the shorter duration of treatment, not reaching the pre-specified non-inferiority limit, indicating that 9 weeks was not as beneficial as 12 months of treatment (91.40% vs 89.22%, respectively; HR 1.27; 90% CI 1.07–1.49; P=0.56). Combining all 5 trials to compare 12 months of adjuvant therapy versus <12 months showed 5-year IDFS rates of 88.46% versus 86.87%, respectively (HR 1.14; 95% CI 0.88–1.47; P=0.37).

The authors concluded that although efficacy outcomes at 6 months were non-inferior to those at 12 months of adjuvant trastuzumab, 9 weeks of adjuvant treatment was indeed inferior.

1. Earl HM, et al. Individual patient data meta-analysis of 5 non-inferiority RCTs of reduced duration single agent adjuvant trastuzumab in the treatment of HER2 positive early breast cancer. Abstract LBA11, ESMO Congress 2021, 16–21 September.
2. Joensuu H, et al. N Engl J Med. 2006;354(8):809-20.
3. Earl HM, et al. Lancet. 2019;393(10191):2599-2612.
4. Pivot X, et al. Lancet. 2019;393(10191):2591-2598.
5. Mavroudis D, et al. Ann Oncol. 2015;26(7):1333-40.
6. Joensuu H, et al. JAMA Oncol. 2018;4(9):1199-1206.
7. Conte P, et al. Ann Oncol. 2018;29(12):2328-2333.

BrighTNess data may change guidelines

The long-term follow-up (4.5 years) of the phase 3 randomised BrighTNess trial supported that neoadjuvant carboplatin plus paclitaxel is superior to paclitaxel alone, with high pathologic complete response (pCR) rates and event-free survival (EFS) rate benefits in patients with triple-negative breast cancer, including patients with a germline *BRCA* mutation. However, the authors also noted that there were no significant differences in overall survival (OS) at this later timepoint.

Prof. Sibylle Loibl (German Breast Group, Germany) presented the newest update from the BrighTNess trial

(NCT02032277) from patients with previously untreated histologically or cytologically confirmed stage 2 or stage 3 triple-negative breast cancer (n=634) who were candidates for potentially curative surgery and had a good performance status. Participants were randomly assigned to 3 arms: paclitaxel/carboplatin plus a poly(ADP-ribose) polymerase (PARP) inhibitor veliparib (n=316), paclitaxel/carboplatin only (n=160), or paclitaxel only (n=158). All patients then underwent 4 cycles of chemotherapy with doxorubicin and cyclophosphamide. The primary endpoint was pCR, with key secondary endpoints EFS at 4 years, OS, and eligibility for breast conservation after therapy.

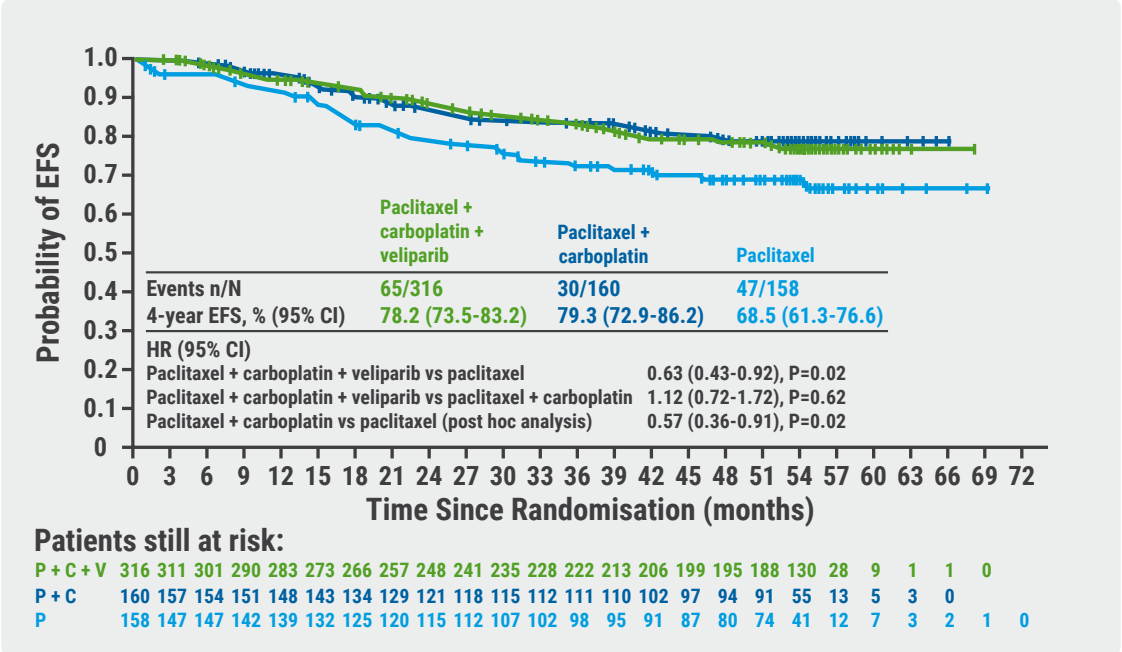
Initial results from this trial had previously shown that the addition of veliparib to carboplatin and paclitaxel improved pCR rates compared with paclitaxel alone, thus meeting the primary endpoint [2]. However, the arm receiving neoadjuvant paclitaxel/carboplatin had similar pCR rates as the triple therapy. Therefore, one of the major conclusions drawn at that time was that the addition of carboplatin to standard neoadjuvant chemotherapy benefitted triple-negative breast cancer patients, not veliparib. There was also no evidence at that time that patients with a germline *BRCA* mutation benefitted from adding carboplatin to paclitaxel in the neoadjuvant setting.

Now, at the ESMO 2021, Prof. Loibl presented longer follow-up results, which refined some of those initial conclusions. After a median follow-up of 4.5 years (see Figure), the EFS with the paclitaxel/carboplatin/veliparib combination was superior to paclitaxel alone (HR 0.63; 95% CI 0.43-0.92; P=0.016). However, the addition of veliparib was still not better than just carboplatin/paclitaxel (HR 1.12; 95% CI 0.72-1.72; P=0.620). Looking at the carboplatin/paclitaxel arm in post hoc analysis, these patients did just as well as the triple therapy arm (HR 0.57; 95% CI 0.36-0.91; P=0.018). These data confirmed and extended the initial analysis.

Very few patients in any of the treatment arms died. The lowest incidence of death occurred in patients randomised to carboplatin/paclitaxel (16/160, 10.0%), followed by carboplatin/paclitaxel/veliparib (38/316, 12.0%), and paclitaxel (22/158, 13.9%). While OS was not statistically different between treatment arms, OS was 18.0% better with carboplatin/paclitaxel/veliparib than with paclitaxel (HR 0.82; P=0.452) and 37.0% better with carboplatin/paclitaxel than with paclitaxel (HR 0.63; P=0.166). Comparing the triple to the double therapy showed that the addition of veliparib was associated with a 25.0% higher OS than carboplatin/paclitaxel, although this was not statistically significant (HR 1.25; P=0.455).

Comparing the initial 309 patients who achieved pCR to those who did not achieve pCR, patients reaching pCR had a 74% improvement in remaining event-free (HR 0.26; P<0.0001). Among patients with germline *BRCA* mutation, those who

Figure: 4-year EFS from the BrighTNess trial [1]



achieved a pCR were similarly likely to remain event-free (HR 0.14; P=0.0004) as those with germline wildtype *BRCA* who had achieved pCR (HR 0.29; P<0.0001). Benefit seemed to be equal for germline *BRCA* mutation carriers as well as germline *BRCA* wildtype carriers.

With regard to safety, there were no significant differences between the groups in the frequency of myelodysplastic syndrome, acute myeloid leukaemia, or other second primary malignancies. Overall, safety signals were manageable and no new safety signals were reported.

In summary, and taken in context of current guidelines, the results from BrighTNess could change guidelines, supporting that patients with high- or moderate-risk triple-negative breast cancer could be treated in the neoadjuvant setting with paclitaxel and carboplatin followed by standard chemotherapy concurrently with pembrolizumab, followed by surgery, and adjuvant therapy with pembrolizumab plus olaparib for patients with germline *BRCA* mutations, or capecitabine for patients without mutations. This trial, however, mainly demonstrated conclusively that there were no short- or long-term benefits to adding veliparib to the combination regimen.

1. Loibl S, et al. Event-free survival (EFS), overall survival (OS), and safety of adding veliparib (V) plus carboplatin (Cb) or carboplatin alone to neoadjuvant chemotherapy in triple-negative breast cancer (TNBC) after ≥4 years of follow-up: BrighTNess, a randomized phase III trial. Abstract 1190, ESMO Congress 2021, 16–21 September.
2. Loibl S, et al. Lancet Oncol. 2018;19(4):497-509.

Double-positive results for triple-negative metastatic breast cancer

According to results of the KEYNOTE-355 trial, adding pembrolizumab to first-line chemotherapy led to statistically significant improvement in the dual primary endpoints of progression-free survival (PFS) and overall survival (OS) among patients with PD-L1-positive metastatic triple-negative breast cancer. Patients had 27% reduced risk for death, although this was only true for the subset of patients with clearly PD-L1-positive tumours.

Prof. Hope Rugo (University of California, San Francisco, USA) presented the data from the randomised, placebo-controlled, double-blind, phase 3 KEYNOTE-355 trial (NCT02819518), in which untreated patients with locally recurrent inoperable or metastatic triple-negative breast cancer were randomised 2:1 to pembrolizumab (200 mg every 3 weeks) plus chemotherapy (nab-paclitaxel; paclitaxel; or gemcitabine plus carboplatin, n=566) or placebo plus chemotherapy (n=281) [1]. Median age of patients was 53 years. Randomisation was stratified by type of on-study chemotherapy (taxane or gemcitabine/carboplatin), PD-L1 expression at baseline (combined positive score [CPS] ≥1 or <1), and previous treatment with the same class of chemotherapy in the neoadjuvant or adjuvant setting.

Dual primary efficacy endpoints were PFS and OS assessed in the PD-L1 CPS ≥10, CPS ≥1, and intention-to-treat populations. The definitive assessment of PFS was reported earlier [2]; OS was reported for the first time at ESMO 2021. Secondary endpoints included objective response rate (ORR), duration of response, disease control rate, and safety.

At the final data cut-off on 15 June 2021, the median follow-up was 44 months in both groups. The findings revealed a median OS of 23.0 months in the pembrolizumab group versus 16.1 months in the placebo group (HR 0.73; 95% CI 0.55-0.95; P=0.0093) among patients with a PD-L1 CPS ≥10. The difference in OS among patients with a CPS ≥1 did not meet the prespecified criteria for statistical significance (17.6 vs 16.1 months; HR 0.86; 95% CI 0.72-1.04; P=0.056). Median OS in the intention-to-treat population was 17.2 months with pembrolizumab versus 15.5 months with placebo (HR 0.89; 95% CI 0.76-1.05), which did not warrant statistical testing. Updated PFS results were similar to previously reported interim data [2], with 65.5% in the pembrolizumab group and 78.6% in the placebo group experiencing a PFS event at data cut-off (HR 0.66; 95% CI 0.50-0.88).

Those with a CPS ≥10 derived the greatest ORR benefit with pembrolizumab versus chemotherapy (52.7% vs 40.8%), followed by patients with a CPS ≥1 (44.9% vs 38.9%), and the intention-to-treat population (40.8% vs 37%). Patients in all 3 groups also had longer duration of response with the pembrolizumab regimen.

Grade 3 or higher treatment-related adverse events occurred among 68.1% of patients in the pembrolizumab group and 66.9% of patients in the placebo group and included anaemia, neutropenia, and nausea. In the pembrolizumab group, 18.3% of patients discontinued the trial due to treatment-related adverse events, as compared with 11% of patients in the chemotherapy group. In total, 2 patients in the pembrolizumab cohort died due to treatment-related adverse events. The safety profile was deemed consistent with previous reports.

In conclusion, pembrolizumab plus chemotherapy showed a significant and clinically meaningful improvement in PFS and OS versus placebo plus chemotherapy among patients with metastatic triple-negative breast cancer and a CPS ≥10. When asked which chemotherapy agent works best with pembrolizumab, Prof. Rugo replied that nab-paclitaxel and paclitaxel were both good options for patients without resistance to taxanes.

1. Rugo HS, et al. KEYNOTE-355: Final results from a randomized, double-blind phase III study of first-line pembrolizumab + chemotherapy vs placebo + chemotherapy for metastatic TNBC. Abstract LBA16, ESMO Congress 2021, 16–21 September.
2. Cortes J, et al. Lancet. 2020;396(10265):1817-1828.

Survival after neoadjuvant therapy with trastuzumab-lapatinib plus chemotherapy

Survival data from 4 randomised studies of the tyrosine kinase inhibitor lapatinib in combination with neoadjuvant trastuzumab versus trastuzumab (plus anthracycline or paclitaxel chemotherapy) in patients with HER2-positive early breast cancer showed that patients who achieved a pathological complete response (pCR) had a reduced risk of relapse by 65% in patients with hormone receptor-negative tumours and by 40% in patients with hormone receptor-positive disease.

The optimal selection of patients with HER2-positive early breast cancer who may benefit most from de-escalation of treatment remains an unmet need. Prof. Valentina Guarneri (University of Padua, Italy) pointed out that although all studies reported improved outcomes if patients achieved pCR, survival data were not conclusive in any of the individual studies [1]. To address this gap, Prof. Guarneri and colleagues performed a meta-analysis of 4 randomised phase 2 and 3 studies (CALGB40601 [2], CHER-Lob [3], NSABP B-41 [4], NeoALTTO [5]) testing lapatinib in combination with neoadjuvant trastuzumab plus chemotherapy for HER2-positive early breast cancer.

In total, the survival data from 1,410 patients were included in the analysis derived from these 4 studies. Adding lapatinib to trastuzumab improved overall survival (OS) by 35% (HR 0.65; 95% CI 0.43-0.98). In addition, relapse-free survival (RFS) was longer with the combination of lapatinib than with trastuzumab only (HR 0.62; 95% CI 0.46-0.85).

Achievement of a pCR is strongly prognostic for superior outcomes in HER-positive early breast cancers. For all treatments, patients achieving a pCR had better RFS and OS than those with residual disease at surgery (HR 0.45; 95% CI 0.34-0.60 for RFS and HR 0.34; 95% CI 0.23-0.51 for OS). When the researchers stratified the patients who achieved pCR by their tumour's HR status, HR-negative status was associated with a 65% reduction of risk of relapse (HR 0.35; 95% CI 0.23-0.53) and a 73% reduction of risk of death (HR 0.27; 95% CI 0.15-0.47). Patients with HR-positive tumours also had improved RFS (HR 0.60; 95% CI 0.37-0.97), but the benefit was smaller than in patients with HR-negative disease.

In conclusion, these data indicate that neoadjuvant lapatinib-trastuzumab in early HER2-positive breast cancers does provide improved survival outcomes. Furthermore, patients on any treatment who achieve pCR, especially those with HR-negative tumours, may be eligible candidates for treatment de-escalation.

1. Guarneri V, et al. Survival after neoadjuvant therapy with trastuzumab-lapatinib and chemotherapy in patients with HER2-positive early breast cancer: A meta-analysis of randomised trials. Abstract 117O, ESMO Congress 2021, 16–21 September.
2. Fernandez-Martinez A, et al. J Clin Oncol. 2020;38(35):4184-4193.
3. Guarneri V, et al. Eur J Cancer. 2021;153:133-141.
4. Robidoux A, et al. Lancet Oncol. 2013;14(12):1183-92.
5. Venet D, et al. Clin Cancer Res. 2021;27:5607-18.

Postmenopausal breast cancer: extended letrozole reduces recurrence

In postmenopausal patients with breast cancer who received 2–3 years of tamoxifen, treating women with an extended 5-year treatment with the aromatase inhibitor letrozole significantly improved disease-free survival (DFS) compared with the standard approach of 2–3 years of letrozole.

Prof. Lucia Del Mastro (University of Genoa, Italy) presented the results of a multicentre, open-label, randomised phase 3 trial (NCT01064635), which was simultaneously published in the Lancet Oncology [1,2]. Postmenopausal women with stage 1–3 histologically proven and operable invasive HR-positive breast cancer (n=2,056) were enrolled between 1 August 2005 and 24 October 2010 and randomly assigned to receive letrozole (2.5 mg once daily) for 2–3 years (n=1,030, as the control group), or for 5 years (n=1,026, as the "extended" group). The primary endpoint was invasive disease-free survival (IDFS) in the intention-to-treat population.

With a median follow-up of 11.7 years, DFS events occurred in 20.7% of patients in the extended group and 25.4% of patients in the control group. The 12-year DFS rates were

67% and 62%, respectively (HR 0.78; 95% CI 0.65–0.93; P=0.0064). DFS benefit did not change after multivariate Cox analysis (HR 0.79; 95% CI 0.66–0.95; P=0.014), and was consistent across subgroups. The 12-year overall survival rates were 88% in the extended group and 84% in the control group (HR 0.77; 95% CI 0.60–0.98; P=0.036).

Arthralgia (2.2% in the control vs 3.0% in the extended group) and myalgia (0.7% vs 0.9%) were the most common grade 3 and 4 adverse events. Serious treatment-related adverse events occurred in 0.3% of the control group and 0.8% in the extended group. No deaths related to toxic effects occurred. Prof. Del Mastro concluded, "This regimen [sequential endocrine therapy with tamoxifen for 2–3 years followed by letrozole for 5 years] can be considered as one of the optimal standard endocrine treatments for postmenopausal patients with HR-positive breast cancer."

1. Del Mastro L, et al. Extended therapy with letrozole as adjuvant treatment of postmenopausal patients with early-stage breast cancer: A randomised, phase III trial of the Gruppo Italiano Mammella. Abstract 118O, ESMO Congress 2021, 16–21 September.
2. Del Mastro L, et al. Lancet Oncol. 2021;22(10):1458–67.

Asian women also benefit from palbociclib plus letrozole

Results from the PALOMA-4 trial confirmed that palbociclib plus letrozole significantly prolonged progression-free survival (PFS) as compared with placebo plus letrozole in an Asian cohort in the first-line setting for ER-positive, HER2-negative advanced breast cancer.

Prof. Binghe Xu (Peking Union Medical College, Beijing, China) presented results of PALOMA-4 (NCT02297438), currently the largest randomised phase 3 study of a CDK4/6 inhibitor in Asian women with ER-positive, HER2-negative advanced breast cancer in the first-line setting [1]. The multicentre, randomised, double-blind phase 3 study PALOMA-4 was designed to compare the clinical benefit following treatment with letrozole in combination with palbociclib versus letrozole in combination with placebo in Asian postmenopausal women with ER-positive, HER2-negative advanced breast cancer who have not received prior systemic anti-cancer therapies for their advanced/metastatic disease. A previous phase 1 study showed that this combination had similar safety and pharmacokinetic characteristics in Asian women [2].

The experimental arm of palbociclib (125 mg, orally once daily on day 1–21 of every 28-day cycle followed by 7 days off treatment) in combination with letrozole (2.5 mg, orally once daily, continuously) was compared with placebo plus letrozole. The primary endpoint was PFS, with key secondary outcomes being overall survival, number of participants with objective response, duration of response, and quality of life. The primary endpoint was met: median PFS was 21.5 months with palbociclib + letrozole versus 13.9 months with placebo + letrozole (HR 0.677; 95% CI 0.529–0.867; P=0.0012). The PFS benefit of palbociclib + letrozole versus placebo + letrozole was observed across subgroups, except in patients aged ≥65 years.

Febrile neutropenia was reported in 2.4% of patients treated in the experimental arm. Serious adverse events occurred in 15.5% of patients in the palbociclib arm and 9.4% of patients in the placebo arm. Safety was determined to be similar to patients in previous trials with this combination, and no new safety signals were detected.

Prof. Xu concluded that the PFS data from this Asian cohort was consistent with findings from the PALOMA-2 study of mostly White patients. In addition, no new safety concerns associated with palbociclib plus letrozole were identified in Asian women. This study supports the use of palbociclib plus letrozole as first-line therapy in postmenopausal Asian women with ER-positive, HER2-negative advanced breast cancer.

1. Xu B, et al. PALOMA-4: Primary results from a phase III trial of palbociclib (PAL) + letrozole (LET) vs placebo (PBO) + LET in Asian postmenopausal women with estrogen receptor–positive/human epidermal growth factor receptor 2–negative (ER+/HER2–) advanced breast cancer (ABC). Abstract 228MO, ESMO Congress 2021, 16–21 September.
2. Xu B, et al. Cancer Chemother Pharmacol. 2021;88(1):131-141.

No PEARLs of survival with palbociclib plus endocrine therapy compared with capecitabine, but QoL better

Although no overall survival (OS) benefit was observed in the final results of cohort 2 of the phase 3 PEARL study, combination therapy with CDK4/6 inhibitors plus endocrine therapy improved health-related quality of life (HR-QoL) and tolerability over chemotherapy for HR-positive, HER2-negative metastatic breast cancer progressing on aromatase inhibitors. The OS and HR-QoL results were presented for the first time at ESMO 2021 Congress.

The final results of the phase 3 PEARL study (NCT02028507), presented by Prof. Miguel Martín Jiménez (Complutense

University of Madrid, Spain), compared palbociclib plus endocrine therapy versus capecitabine in postmenopausal patients with metastatic breast cancer who progressed on an aromatase inhibitor [1].

With a median follow-up of 28.0 months, the arm treated with palbociclib plus fulvestrant (n=149) had a median OS of 31.1 months, compared with 32.8 months in the arm treated with capecitabine (n=156) (HR 1.10; 95% CI 0.81–1.50; P=0.55; see Table). The results support earlier findings from the trial showing no progression-free survival (PFS) advantage for palbociclib plus fulvestrant over chemotherapy (HR 1.13; 95% CI 0.85–1.50) but an improved toxicity profile and a reduction in the time to deterioration of global health status [2].

Table: OS at median follow-up of 28.0 months shows no significant difference for palbociclib + fulvestrant versus capecitabine [1]

	Patients n	Events n	Censored n	Median OS, months (95% CI)
Palbociclib + fulvestrant	149	85 (57.0%)	64 (43.0%)	31.1 (25.3–38.4)
Capecitabine	156	86 (55.1%)	70 (44.9%)	32.8 (27.5–39.0)

Despite the seemingly disappointing efficacy outcomes, the findings on HR-QoL based on patient-reported outcomes were significant. Differences were observed in the mean change in global health status (GHS)/QoL scores from baseline to treatment cycle 3 (2.9 for palbociclib/endocrine therapy vs -2.1 for capecitabine; P=0.007). Furthermore, the median time to deterioration in GHS/QoL was 8.3 months for palbociclib/endocrine therapy versus 5.3 months for capecitabine (HR 0.70; 95% CI 0.55–0.89; P=0.003). Similar improvements for palbociclib/endocrine therapy were also seen for other scales as physical, cognitive, social functioning, fatigue, nausea/vomiting, and appetite loss.

The most frequent grade 3–4 toxicities with palbociclib plus fulvestrant and capecitabine, respectively, were neutropenia (55.7% and 5.5%), hand/foot syndrome (0% and 23.5%), and diarrhoea (1.3% and 7.6%).

Prof. Martín Jiménez concluded that although there was no statistical superiority of palbociclib plus endocrine therapy over capecitabine with respect to PFS or OS in metastatic breast cancer patients resistant to aromatase inhibitors, palbociclib plus endocrine therapy showed a better safety profile and improved quality of life. The HR-QoL data were published 2 weeks following ESMO 2021 [3].

1. Martín Jiménez M, et al. Overall survival (OS) of palbociclib (P) plus endocrine therapy (ET) versus capecitabine (CAP) in hormone-receptor+/HER2- metastatic breast cancer (MBC) that progressed on aromatase inhibitors (AIs): Final results of the PEARL study. Abstract 229MO, ESMO Congress 2021, 16–21 September.
2. Martin M, Ann Oncol. 2021;32(4):488-499.
3. Kahan Z, et al. Eur J Cancer. 2021;156:70-82.

Gastrointestinal Cancer

Neoadjuvant chemotherapy potential alternative to neoadjuvant chemoradiotherapy in LARC

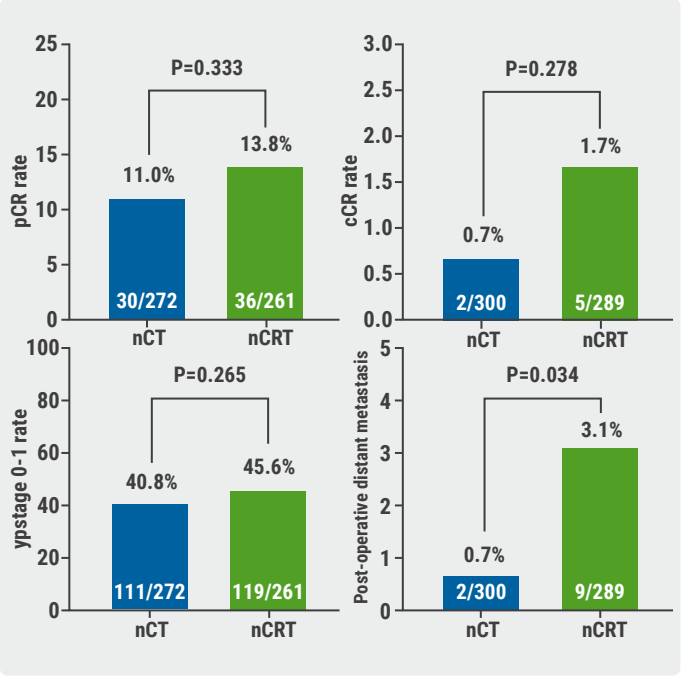
Results from the phase 3, open label CONVERT study suggest neoadjuvant chemotherapy to be non-inferior to neoadjuvant chemoradiation in patients with locally advanced rectal cancer (LARC).

Combined chemoradiation therapy is currently the standard practice for LARC with uninvolved mesorectal fascia. Results from the FOWARC trial were promising for neoadjuvant chemotherapy, but this trial (n=165 patients/arm) was not powered for non-inferiority [1]. The CONVERT study (NCT02288195) was conducted to compare neoadjuvant chemotherapy (capecitabine, oxaliplatin) with standard chemoradiotherapy with capecitabine for these patients. Dr Pei-Rong Ding (Sun Yat-sen University Cancer Center, China) presented the first results [2].

A total of 663 patients with LARC within 12 cm from the anal verge and uninvolved mesorectal fascia were 1:1 assigned to receive 4 cycles of chemotherapy alone (nCT arm) or chemoradiotherapy with concurrent capecitabine (nCRT arm). After surgery, patients in the nCT arm were treated with 4 additional cycles of capecitabine/oxaliplatin, whereas patients in the nCRT arm were treated with 6 additional cycles of capecitabine/oxaliplatin. Primary endpoint of the CONVERT study was 3-year locoregional failure-free survival. Of 589 patients who started neoadjuvant treatment, 86.3% of patients accomplished full dose of neoadjuvant therapy in the nCT arm compared with 91.0% in the nCRT arm (P=0.074). Of all patients who received adjuvant chemotherapy (n=457), 52.8% of patients accomplished full dose of adjuvant chemotherapy in the nCT arm compared with 44.1% in the nCRT arm (P=0.065).

The pathologic complete response (pCR) rate was 11.0% in the nCT arm versus 13.8% in the nCT arm (P=0.333). Good downstaging (ypStage 0 to 1) rate was 40.8% versus 45.6% (P=0.265). nCT significantly reduced perioperative distant metastases compared with nCRT (0.7% vs 3.1%; P=0.034; see Figure). Two patients in the nCT arm and 5 patients in the nCRT arm achieved complete clinical response and were treated with a non-operative approach. Fewer preventive ileostomies were observed in nCT arm (52.2% vs 63.6%; P=0.008). Both arms had similar short-term toxicity and postoperative complications, although nCT appeared more toxic (12.3% vs 8.3% of grade 3–4 adverse events). Similar results were observed in subgroup analysis.

Figure: Surgical and pathological results of CONVERT [2]



"nCT achieved similar pCR and good downstaging rate with less peri-operative distance metastasis and preventive colostomy compared with nCRT," concluded Dr Ding. However, pCR, cCR, and downstaging were numerically better for nCRT and nCT remained slightly more toxic. "Long-term follow-up, especially data on disease-free survival and overall survival, is needed to confirm these results."

1. Deng Y, et al. J Clin Oncol. 2019;37: 3223-3323.
2. Ding P-R, et al. Neoadjuvant chemotherapy with oxaliplatin and capecitabine versus chemoradiation with capecitabine for locally advanced rectal cancer with uninvolved mesorectal fascia (CONVERT): Initial results of a multicenter randomised, open-label, phase III trial. Abstract LBA22, ESMO Congress 2021, 16–21 September.

Immune chemo-sensitisation looks promising in microsatellite-stable mCRC

Both MAYA and AtezoTRIBE, phase 2 trials reporting on new immunotherapy-containing approaches to treatment for patients with proficient mismatch repair (pMMR)/ microsatellite-stable (MSS) metastatic colorectal cancer (mCRC), met their primary endpoint of progression-free survival (PFS).

Almost all MSS colorectal cancers are refractory to immunotherapy and combination strategies to turn these so-called 'cold' tumours into 'hot' – i.e. immune-responsive – tumours have failed so far.

Inactivation of the *MGMT* gene by hypermethylation enhances sensitivity for alkylation agents such as temozolomide (TMZ) [1]. Secondary resistance to TMZ may induce a hypermutated status coupled with acquired mutations in MMR genes in diverse tumour types, including CRC [2]. Therefore, the induction of hypermutation by a TMZ priming phase provides the rationale for immune-sensitisation of MSS mCRC.

The single-arm MAYA trial (NCT03832621) enrolled patients with pretreated MSS mCRC and *MGMT* silencing. Patients were treated with 2 priming cycles of TMZ (150 mg/m^2 at day 1–5 every 4 weeks). Patients who showed no progression of disease after the priming phase were treated in addition with ipilimumab (1 mg/kg every 8 weeks) plus nivolumab (480 mg every 4 weeks). Primary endpoint of the trial was 8-month PFS in patients entering the second phase of the trial. Dr Filippo Pietrantonio (Istituto Nazionale dei Tumori di Milano, Italy) presented the results [3].

Of 703 pre-screened patients, 204 (29%) were molecularly eligible; 135 patients entered phase 1 of MAYA, 33 (24%) reached the second treatment phase (immunotherapy). The overall response rate (ORR) in this cohort was 42% (14/33). Median PFS was 7.1 months; 12 of 33 patients who started phase 2 had a PFS >8 months. Therefore, MAYA met its primary endpoint. The safety profile was manageable and consistent with previous data. "Although only 5% of patients with mCRC were eligible for the MAYA study, this strategy is worth of being investigated by RCTs," concluded Dr Pietrantonio. "In addition, biomarkers are needed at the very outset, so that patients unlikely to respond to priming are spared exposure to the primer and its associated toxicities." This study provided proof of concept that TMZ can induce immune-sensitisation in MSS mCRC.

The AtezoTRIBE trial (NCT03721653) prospectively explored the potency of first-line bevacizumab in combination with upfront triplet chemotherapy to turn MSS mCRC into immune-responsive tumours. The scientific rationale is that the addition of a VEGF inhibitor to immune-checkpoint inhibition not only has an additive effect on inhibiting tumour growth, but also induces reprogramming of the immunosuppressive microenvironment.

In the trial, 218 initially unresectable mCRC patients, irrespective of MMR status, were randomised 1:2 to receive up to 8 cycles of FOLFOXIRI/bevacizumab (arm A) or FOLFOXIRI/bevacizumab/atezolizumab (arm B), followed by maintenance with 5-FU/bevacizumab or 5-FU/ bevacizumab/atezolizumab until disease progression. The primary endpoint was PFS. Dr Chiara Cremolini (Azienda Ospedaliero-Universitaria Pisana, Italy) presented the first results of AtezoTRIBE [4].

Addition of atezolizumab to FOLFOXIRI plus bevacizumab led to a 1.6-month increase in median PFS compared with FOLFOXIRI plus bevacizumab (13.1 months vs 11.5 months; HR 0.69; P=0.012). Response rates were comparable between arms (59% vs 64%; HR 0,78; P=0.412). A significant interaction effect between MMR status and treatment arm was found (P=0.010). In the proficient MMR subgroup (n=199; arm A/B: 67/132), significantly longer median PFS was reported in arm B (12.9 vs 11.4 months; HR 0.78; P=0.071). In the deficient MMR subgroup, median PFS was 6.6 months in arm A versus Not Reached in arm B (HR 0.11; P=0.002). Overall survival data are not yet mature.

"In the deficient MMR subgroup, impressive results are reported with FOLFOXIRI plus bevacizumab plus atezolizumab, while in the proficient MMR subgroup the addition of atezolizumab still provides a statistically significant benefit, according to the study design," concluded Dr Cremolini. While not yet practice-changing, this is an important result for a population with an unmet clinical need.

1. Pietrantonio F, et al. Clin Cancer Res. 2020;26:1017-1024.
2. Germano G, et al. Nature 2017;552:116-120.
3. Pietrantonio F, et al. MAYA trial: temozolomide (TMZ) priming followed by combination with low-dose ipilimumab and nivolumab in patients with microsatellite stable (MSS), MGMT silenced metastatic colorectal cancer (mCRC). Abstract 383O, ESMO Congress 2021, 16–21 September.
4. Cremolini C, et al. FOLFOXIRI plus bevacizumab (bev) plus atezolizumab (atezo) versus FOLFOXIRI plus bev as first-line treatmentof unresectable metastatic colorectal cancer (mCRC) patients: Results of the phase II randomized AtezoTRIBEstudy by GONO. Abstract LBA20, ESMO Congress 2021, 16–21 September.

Adagrasib shows promising clinical activity in heavily pretreated *KRAS*-mutated CRC

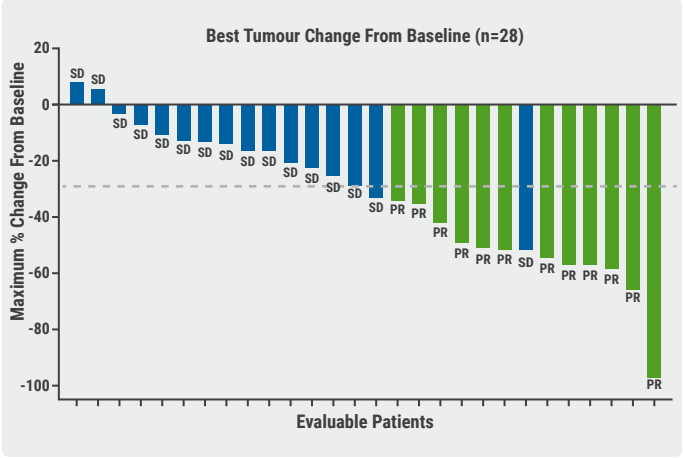
The selective KRAS^{G12C} inhibitor adagrasib, as monotherapy or combined with cetuximab, was well tolerated and demonstrated promising clinical activity in heavily pretreated patients with *KRAS*-mutant colorectal cancer (CRC), first results of the KRYSTAL-1 trial showed.

KRAS^{G12C} mutations, which occur in 3–4% of CRC, act as oncogenic drivers and are a negative predictor of cetuximab efficacy. Adagrasib is a KRAS^{G12C} inhibitor that irreversibly and selectively binds KRAS^{G12C}, locking it in its inactive state. Durable inhibition of KRAS^{G12C} may be particularly important in CRC due to signalling pathways which create a susceptibility to feedback reactivation of KRAS. EGFR signalling is implicated in this reactivation, providing a rational co-targeting strategy for *KRAS*-mutant CRC.

KRYSTAL-1 (NCT03785249) is a multicohort phase 1/2 study evaluating adagrasib in patients with *KRAS*-mutant advanced solid tumours. CRC cohorts include adagrasib 600 mg twice daily monotherapy and adagrasib 600 mg twice daily plus cetuximab. Endpoints include safety, pharmacokinetics, and clinical activity. Dr Jared Weiss (University of North Carolina at Chapel Hill, NC, USA) presented the first results [1].

At data cut-off, 46 patients with CRC (50% female; median age 58 years; 3 median prior lines of therapy) had received adagrasib monotherapy (median follow-up 8.9 months). Among the 45 patients evaluable for clinical activity, the response rate was 22% (10/45, including 1 unconfirmed partial response who remains on study) and disease control rate was 87% (39/45). Median duration of response was 4.2 months; median PFS was 5.6 months. Treatment-related adverse events of any grade occurred in 91% and grade 3/4 events in 30% of patients, with no grade 5 events.

Figure: Overall response of CRC patients on adagrasib plus cetuximab in KRYSTAL-1 [1]



Conversely, 32 patients with CRC (53% female; median age 60 years; 3 median prior lines of therapy) were treated with adagrasib plus cetuximab (median follow-up 7 months). Among the 28 patients evaluable for clinical activity, the response rate was 43% (12/28, including 2 unconfirmed partial response who remain on study) and disease control rate was 100% (see Figure). Data are still unmature for duration of response and PFS. Treatment-related events of any grade occurred in 100% and grade 3/4 events in 16% of patients, with no grade 5 events.

"Adagrasib is well tolerated as monotherapy and combined with cetuximab and demonstrates promising clinical activity in heavily pretreated patients with *KRAS*^{G12C}-mutant CRC," concluded Dr Weiss. The phase 3 KRYSTAL-10 trial (NCT04793958) currently evaluates adagrasib/cetuximab combination versus chemotherapy in the second-line setting in patients with *KRAS*^{G12C}-mutant CRC.

Similar data with another KRAS^{G12C} inhibitor, sotorasib, combined with panitumumab were also presented [2].

1. Weiss J, et al. KRYSTAL-1: Adagrasib (MRTX849) as monotherapy or combined with cetuximab (Cetux) in patients (Pts) withcolorectal cancer (CRC) harboring a KRASG12C mutation. Abstract LBA6, ESMO Congress 2021, 16–21 September.
2. Fakih M, et al. CodeBreaK 101 subprotocol H: Phase Ib study evaluating combination of sotorasib (Soto), a KRASG12C inhibitor, and panitumumab (PMab), an EGFR inhibitor, in advanced KRAS p.G12C-mutated colorectal cancer (CRC). Abstract 434P. ESMO Congress 2021, 16–21 September.

Automated detection of microsatellite status on unstained samples in early colon cancer

Artificial intelligence (AI)-integrated infrared imaging is able to identify microsatellite status with high sensitivity in unstained samples of early colon cancer, a German study showed.

Label-free Quantum Cascade Laser (QCL)-based infrared imaging combined with deep learning provides spatially and molecularly resolved alterations of the genome and proteome in unstained cancer tissue sections. This technique was shown to be able to distinguish between microsatellite instability-high (MSI-H) and microsatellite-stable (MSS) status of sporadic colorectal cancer (CRC) [1]. To verify the method, tissue samples from the prospective, multicentre AIO CPP registry study were analysed.

In detail, images of tissue sections taken in 20 min with QCL infrared microscopes were classified by convolutional neural networks (CNN). An in-house developed segmenting CNN (U-Net) localised tumour regions and a second CNN (VGG-Net) subsequently classified the microsatellite status. Endpoints were area under curve of receiver operating characteristic (AUROC) and area under precision recall curve (AUPRC). Dr Frederik Großerüschkamp (Ruhr-Universität Bochum, Germany) presented the results [2].

The multicentre clinical cohort included 491 patients, of which 100 tumour-free and 391 with tumour. Baseline characteristics of age, sex, stage, location, including *BRAF* mutation status were equally distributed among test cohorts. The U-Net was verified on 294 patients serving as training dataset, 100 as test dataset, and 97 as validation dataset. An AUROC of 0.99 was achieved for the validation dataset. Tumours are thereby precisely spatially resolved in the sections. The microsatellite status classification of the identified tumour regions was verified on 391 patients: 245 served as training dataset, 73 as test dataset, and 73 as validation dataset. In the current study, an AUROC of 0.83 and an AUPRC of 0.64 were achieved.

Based on these results, Dr Großerüschkamp concluded that "MSI-H was identified with high sensitivity but low specificity and demands therefore longer training phases and larger sample numbers for training. Both are currently under work."

1. Kallenbach-Thieltges A, et al. Sci Rep. 2020;10:10161.
2. Großerüschkamp F, et al. Automated detection of microsatellite status in early colon cancer (CC) using artificial intelligence (AI) integrated infrared (IR) imaging on unstained samples from the AIO ColoPredictPlus 2.0 (CPP) registry study. Abstract 385O, ESMO Congress 2021, 16–21 September.

Consistent benefit of anti-PD-1 therapy for oesophageal and gastric cancer

Updated results from the CheckMate649 study report continued overall survival (OS) benefit of nivolumab/chemotherapy versus chemotherapy alone in patients with advanced gastric cancer (GC)/gastroesophageal junction cancer (GEJC)/oesophageal adenocarcinoma (EAC). In contrast, there was no OS benefit with nivolumab/ipilimumab versus chemotherapy.

Recently, results from the randomised, global, phase 3 CheckMate649 study (NCT02872116) demonstrated superior OS with first-line nivolumab/chemotherapy versus chemotherapy in patients with advanced GC/GEJC/EAC, leading to FDA approval [1]. Dr Yelena Janjigian (Memorial Sloan Kettering Cancer Center, NY, USA) presented updated results from CheckMate649 with longer follow-up for nivolumab/chemotherapy versus chemotherapy and first results for nivolumab/ipilimumab versus chemotherapy [2].

In CheckMate649, 2,031 patients with previously untreated, unresectable advanced or metastatic GC/GEJC/EAC were enrolled regardless of PD-L1 expression. Patients with known HER2-positive status were excluded. Patients were randomised to nivolumab (360 mg every 3 weeks or 240 mg every 2 weeks)/chemotherapy (XELOX every 3 weeks or FOLFOX every 2 weeks) (n=789), nivolumab (1 mg/kg)/ipilimumab (3 mg/kg every 3 weeks, 4 doses, then nivolumab 240 mg every 2 weeks) (n=409), or chemotherapy alone (n=833). Dual primary endpoints were OS and progression-free survival (PFS) per blinded independent central review for nivolumab/chemotherapy versus chemotherapy in patients with PD-L1 combined positive score (CPS) ≥5 (n=955). Hierarchically tested secondary endpoints included OS in nivolumab/chemotherapy versus chemotherapy in patients with CPS ≥1 (n=1,581) and OS in nivolumab/ipilimumab versus chemotherapy (CPS ≥5, n=473).

Nivolumab/chemotherapy continued to show improvement in OS versus chemotherapy alone with an additional 12 months of follow-up from the primary analysis: median OS was 14.4 months versus 11.1 months (HR 0.70) in CPS ≥5 patients and 13.8 months versus 11.6 months (HR 0.79) in all randomised patients. 2-year OS rates were 31% versus 19% (CPS ≥5), and 28% versus 19% (all randomised). Median OS in microsatellite instability-high (MSI-H) patients (n=44) was 38.7 months versus 12.3 months (HR 0.38).

The secondary endpoint of OS in patients with CPS ≥5 for nivolumab/ipilimumab versus chemotherapy was not met (11.2 vs 11.6 months; HR 0.89). Median OS in MSI-H patients (n=21) was not reached versus 10.0 months (HR 0.28). No new safety signals were identified.

"These updated results from CheckMate649 continue to demonstrate clinically meaningful long-term survival benefit from first-line nivolumab/chemotherapy versus chemotherapy alone and an acceptable safety profile," concluded Dr Janjigian. "This further supports the use of nivolumab/chemotherapy as a new standard first-line treatment in patients with advanced GC/GEJC/EAC, with best benefit in CPS ≥5 patients."

1. Janjigian YY, et al. Lancet 2021;398:27-40.
2. Janjigian YY, et al. Nivolumab (NIVO) plus chemotherapy (Chemo) or ipilimumab (IPI) vs chemo as first-line (1L) treatment foradvanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): CheckMate649 study. Abstract LBA7, ESMO Congress 2021, 16–21 September.

HIPEC in gastric cancer with peritoneal metastases

Hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with peritoneal metastases from gastric cancer did not improve overall survival (OS). However, the procedure is safe and improves progression-free survival (PFS), results from GASTRIPEC I showed.

About 30% of patients with gastric cancer present with synchronous peritoneal metastases [1]. Cytoreductive surgery combined with perioperative systemic chemotherapy can improve survival in selected patients [2]. The randomised GASTRIPEC I trial (NCT02158988) aimed to evaluate the efficacy and safety of additional HIPEC to cytoreductive surgery and perioperative systemic chemotherapy in patients with peritoneal metastases from gastric cancer.

Patients were enrolled and randomised 1:1 to perioperative chemotherapy (epirubicin/oxaliplatin/capecitabin or cisplatin/capecitabin/trastuzumab depending on HER2 status) and cytoreductive surgery or perioperative chemotherapy, cytoreductive surgery, and HIPEC. Recruitment was stopped due to slow recruitment. Primary endpoint was OS, secondary endpoints were (amongst others) 30-day morbidity, PFS, toxicity, and hospital stay. Prof. Beate Rau (Charité University Hospital Berlin, Germany) presented the results of GASTRIPEC I [3].

In total, 55 patients stopped treatment before cytoreductive surgery because of disease progression or death. The primary endpoint was not met: median OS for both groups was 14.9 months. However, in patients with complete cytoreduction (CCR=0) HIPEC significantly improved OS: at 30 months, 30% of patients treated with HIPEC were still alive versus 0% of patients not treated with HIPEC (see Figure). Median PFS was significantly improved from 3.5 months in the non-HIPEC arm to 7.1 months in the HIPEC arm (P=0.0472). HIPEC had no impact on morbidity, complications, and/or hospital stay.

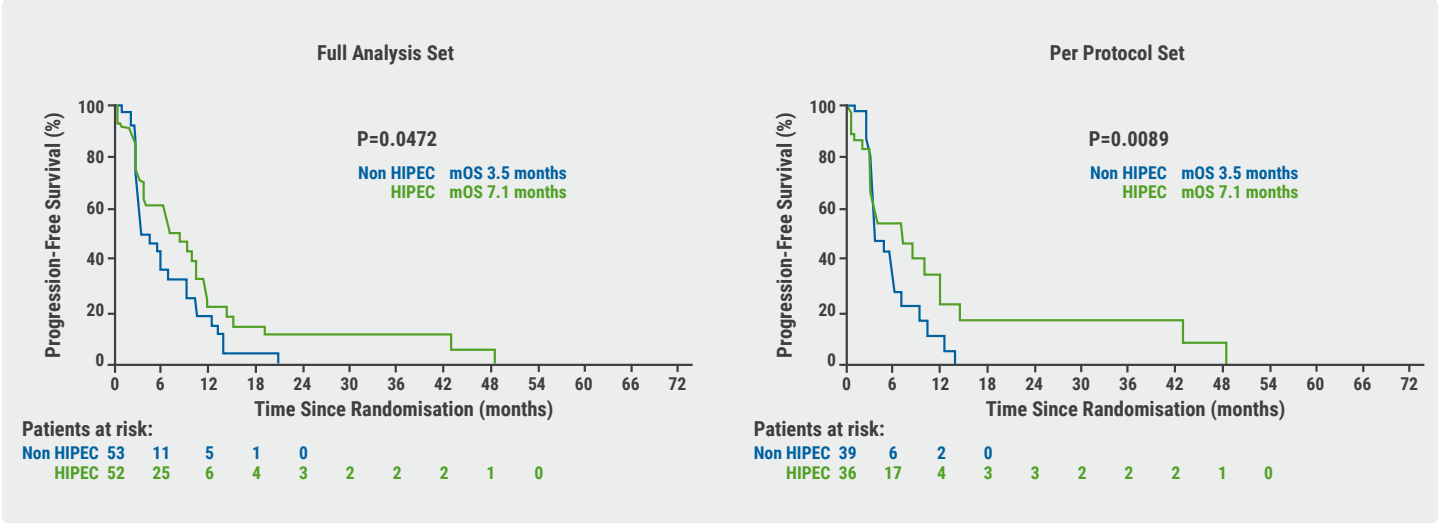
Based on these results, Prof. Rau concluded that "addition of HIPEC to perioperative systemic chemotherapy and cytoreductive surgery does significantly improve PFS and OS after complete cytoreductive surgery. Additional HIPEC did not compromise patient's safety." HIPEC can be used in selective patients able to undergo a complete cytoreduction.

1. Tan HL, et al. Asia Pac J Clin Oncol. 2019;15:10-17.
2. Yarema R, et al. World J Gastrointest Oncol. 2020;12:569-58.
3. Rau B, et al. The effect of hyperthermic intraperitoneal chemotherapy (HIPEC) upon cytoreductive surgery (CRS) in gastric cancer (GC) with synchronous peritoneal metastasis (PM): A randomized multicentre phase III trial (GASTRIPEC-I-trial). Abstract 1376O, ESMO Congress 2021, 16–21 September.

ctDNA highly predictive in HER2-positive, advanced gastric or gastro-oesophageal junction cancer

First-line trastuzumab/nivolumab/FOLFOX6 outperforms trastuzumab/nivolumab/ipilimumab in HER2-positive, advanced gastric or gastro-oesophageal cancer, first results from INTEGA showed. In addition, circulating tumour (ct)DNA appeared to be highly predictive, independent of treatment arm.

Figure: PFS, secondary endpoint of GASTRIPEC I [3]



Previously, results from the ToGA trial showed survival benefit for first-line trastuzumab in combination with chemotherapy in patients with HER2-positive, advanced gastric or gastro-oesophageal junction cancer [1]. In addition, immunotherapy has been shown to be superior to chemotherapy as a first-line treatment in patients with gastro-oesophageal adenocarcinoma [2]. The phase 2 INTEGA trial (NCT03409848) compared different immunotherapy regimens in first-line treatment of HER2-positive gastro-oesophageal adenocarcinoma.

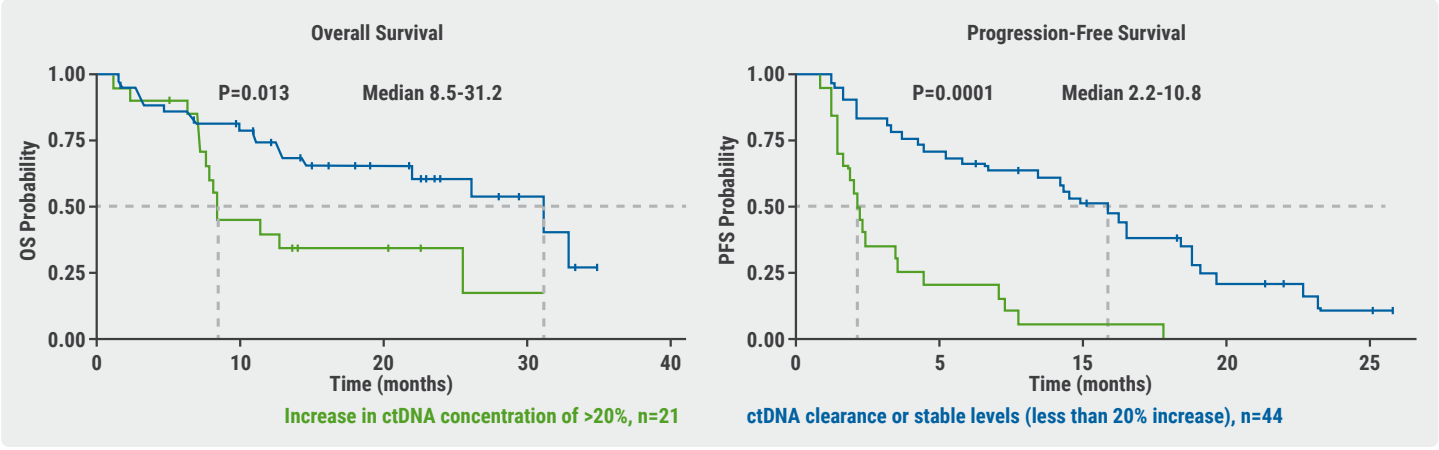
A total of 88 patients with previously untreated HER2-positive gastro-oesophageal adenocarcinoma were randomised 1:1 to receive trastuzumab/nivolumab in combination with either ipilimumab (arm A) or mFOLFOX6 (arm B) for up to 12 months. The first endpoint was to increase the 12-month overall survival (OS) rate from 55% (trastuzumab /chemotherapy with the ToGA regimen) to 70% in each arm. Dr Alexander Stein (University Cancer Center Hamburg, Germany) presented the first results [3].

The first endpoint of 70% OS rate at 12 months was reached in arm B, but not in arm A (57%). In addition, median progression-free survival (PFS) was improved in arm B versus arm A (10.7 vs 3.2 months). Liquid biopsy analyses showed strong correlation of high ctDNA load after first treatment with shorter PFS and OS, independent of treatment arm (see Figure).

"Trastuzumab/nivolumab/FOLFOX showed increased efficacy compared with the ToGA regimen, whereas trastuzumab/nivolumab/ipilimumab did not improve OS over trastuzumab/chemotherapy," concluded Dr Stein. "In addition, ctDNA was observed to be highly predictive of prognosis independent of treatment arm."

1. Bang Y-J, et al. Lancet 2010;376:687-697.
2. Tabernero J, et al. J Clin Oncol. 2019;37(18_suppl):LBA4007.
3. Stein A, et al. Ipilimumab or FOLFOX in combination with nivolumab and trastuzumab in previously untreated HER2 positive locally advanced or metastastic esophagogastric adenocarcinoma (EGA): Results of the randomized phase II INTEGA trial (AIO STO 0217). Abstract LBA54, ESMO Congress 2021, 16–21 September.

Figure: Correlation ctDNA concentration after first treatment with OS and PFS [3]



Lung Cancer

Robust anticancer activity of trastuzumab deruxtecan in *HER2*-mutated NSCLC

Primary data from the DESTINY-Lung01 trial demonstrated trastuzumab deruxtecan (T-DXd) to be safe and effective in heavily pretreated patients with *HER2*-mutated non-small cell lung cancer (NSCLC).

HER2 mutations occur in ~3% of patients with NSCLC, indicating poor prognosis and an increased incidence of brain metastases [1]. T-DXd is a novel antibody-drug conjugate consisting of a humanised, anti-HER2 monoclonal antibody, a topoisomerase I inhibitor payload, and an exatecan derivative [2]. The phase 2 DESTINY-Lung01 trial (NCT03505710)

assessed the efficacy and safety of T-DXd in heavily pretreated (up to 8 lines) patients with *HER2*-mutated NSCLC.

A total of 91 patients (median age 60 years; 93.4% had a *HER2* mutation; 36.3% had asymptomatic central nervous system metastasis) were treated with T-DXd (6.4 mg/kg every 3 weeks). Primary endpoint was objective response rate (ORR), secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. Dr Bob Li (Memorial Sloan Kettering Cancer Center, NY, USA) presented the primary data [3].

Centrally confirmed ORR was 54.9% (49 partial responders, 1 complete responder); disease control rate was 84%. Responses were observed across all *HER2* mutation subtypes, as well as in patients with no detectable HER2 expression or *HER2* gene amplification. Efficacy was consistent across subgroups, including patients previously treated with a HER2 tyrosine kinase inhibitor or with brain metastasis. Median PFS was 8.2 months; median OS was 17.8 months.

Treatment-related adverse events (any grade) occurred in 96.7% of patients, treatment-related adverse events grade ≥3 were observed in 46.2% of patients. Adjudicated drug-related interstitial lung disease (ILD) occurred in 24 patients. "T-DXd demonstrated robust and durable activity in patients with previously treated *HER2*-mutated NSCLC," concluded Dr Li. "T-DXd has a manageable safety profile; however, ILD remains an important risk. Effective early detection and management are critical in preventing high-grade ILD."

1. Offin M, et al. Cancer. 2019;125:4380-4387.
2. Ogitani Y, et al. Clin. Cancer Res. 2016;22:5097–5108.
3. Li B, et al. Primary data from DESTINY Lung01:a phase 2 trial of trastuzumab deruxtecan (T DXd) in patients with HER2 mutated (HER2 m) metastatic non small cell lung cancer (NSCLC). Abstract LBA45, ESMO Congress 2021, 16–21 September.

Nivolumab/ipilimumab continues to provide survival benefit in unresectable MPM

In the 3-year update from CheckMate743, nivolumab/ipilimumab continued to be superior to chemotherapy in patients with unresectable malignant pleural mesothelioma (MPM). Exploratory analyses suggest a high inflammatory gene signature score to be predictive for survival benefit with nivolumab/ipilimumab in these patients.

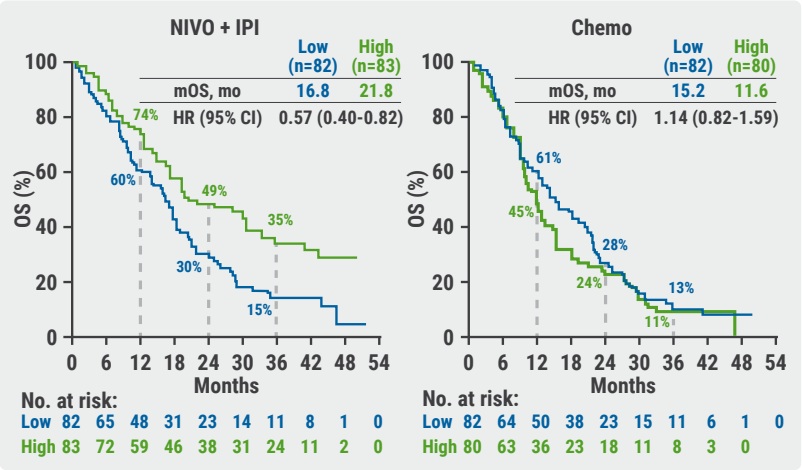
In the randomised, phase 3 CheckMate743 trial (NCT02899299), first-line nivolumab plus ipilimumab significantly improved overall survival (OS) over chemotherapy in patients with unresectable MPM (18.1 vs 14.1 months; HR 0.74; P=0.0020) [1]. This regimen is now approved in EU & USA, amongst others, as first-line treatment for (adult) patients with unresectable MPM. However, no long-term outcomes of immunotherapy in MPM had been reported. Prof. Solange Peters (Lausanne University Hospital, Switzerland) presented the 3-year update of efficacy and safety results from CheckMate743 as well as results from exploratory biomarker analyses.

The study enrolled 606 patients with untreated MPM, stratified by histology (epithelioid vs non-epithelioid) and sex. Patients were randomised 1:1 to nivolumab (3 mg/kg every 2 weeks)/ipilimumab (1 mg/kg every 6 weeks) up to a maximum of 2 years or to chemotherapy (every 3 weeks, 6 cycles). The primary endpoint was OS, safety and biomarker assessments were prespecified exploratory endpoints. OS association with a 4-gene inflammatory gene expression signature (CD8A, PD-L1, STAT-1, LAG-3) was estimated by RNA sequencing and categorised as high versus low relative to median score.

With a minimum follow-up of 35.5 months, nivolumab/ipilimumab continued to provide OS benefit versus chemotherapy (HR 0.73). OS rates were 41% versus 27% at 24 months and 23% versus 15% at 36 months. Progression-free survival (PFS) rates at 36 months were 14% versus 1%. Of note, treatment with nivolumab/ipilimumab stopped at a maximum of 24 months. OS rates in the nivolumab/ipilimumab-treated population were irrespective of histology. Median duration of response was 11.6 months for nivolumab/ipilimumab versus 6.7 months for chemotherapy. In a post hoc analysis, discontinuation of nivolumab/ipilimumab due to treatment-related adverse events did not have a negative impact on the long-term benefits seen in all randomised patients.

Exploratory biomarker analyses showed that median OS was longer for patients with high inflammatory gene signature score (21.8 months vs 16.8 months for low inflammatory gene signature score) in the nivolumab/ipilimumab-treated population. At 3 years, 35% of nivolumab/ipilimumab-treated patients with a high inflammatory gene signature score

Figure: OS by 4-gene inflammatory signature score [2]



were still alive versus 15% of patients with a low score. The inflammatory gene signature score was not associated with prolonged OS for chemotherapy (see Figure).

"These updated data further reinforce previously published findings and support the benefit of giving patients immunotherapy instead of chemotherapy," concluded Prof. Peters.

1. Baas P, et al. Lancet 2021;397:375-386.
2. Peters S, et al. First-line nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) in patients (pts) with unresectable malignant pleural mesothelioma (MPM): 3-year update from CheckMate743. Abstract LBA65, ESMO Congress 2021, 16–21 September.

Adjuvant atezolizumab lowers relapse rate in resected NSCLC

An exploratory analysis from the Impower010 trial added support for the use of adjuvant immunotherapy post-chemotherapy for selected early-stage non-small cell lung cancer (NSCLC).

Despite treatment with curative intent, up to 60% of patients with stage I-III NSCLC still experience disease relapse [1]. Impower010 (NCT02486718) is the first randomised phase 3 study to show significant disease-free survival (DFS) improvement with adjuvant cancer immunotherapy (atezolizumab) after adjuvant chemotherapy in patients with early-stage resected NSCLC [2].

Enrolled patients had completely resected stage IB-IIIA NSCLC and ECOG performance status 0–1. A total of 1,280 patients received up to four 21-day cycles of cisplatin-based chemotherapy (plus pemetrexed, docetaxel, gemcitabine, or vinorelbine). Next, 1,005 patients without progression after adjuvant chemotherapy were randomised 1:1 to atezolizumab (1,200 mg every 3 weeks) for 16 cycles or until disease relapse or unacceptable toxicity or to best supportive care (BSC). The primary endpoint was DFS which was hierarchically tested in PD-L1 TC ≥1% (SP263) stage II-IIIA patients (n=476), then in all randomised stage II-IIIA patients (n=882), and then in intention-to-treat patients (n=1,005).

As previously reported, median DFS was significantly improved by atezolizumab in PD-L1 TC ≥1% patients (HR 0.66; P=0.004), and in all randomised patients (HR 0.79; P=0.02), but not in the ITT population (HR 0.81; P=0.04) [2]. Dr Enriqueta Felip (Vall d'Hebron Institute of Oncology, Spain) presented additional results from exploratory analyses in Impower010 [3].

In all randomised stage II-IIIA patients, DFS improvement was seen with increasing PD-L1 expression: TC <1% (n=383) HR 0.97; TC 1–49% (n=247) HR 0.87; and TC ≥50% (n=229) HR 0.43. Among PD-L1 TC ≥1% stage II-IIIA patients (n=676), 73 patients (29%) relapsed in the atezolizumab arm versus 102 patients (45%) in the BSC arm. Sites of relapse in both arms were comparable. Time to relapse appeared to favour the atezolizumab arm over the BSC arm in the PD-L1 TC ≥1% stage II-IIIA patients, with minimal differences seen in the all-randomised and intention-to-treat populations. A higher rate of post-relapse immunotherapy was seen in the BSC arm.

Dr Felip summarised that "in this interim DFS analysis, relapse rate was higher in the BSC arm versus the atezolizumab arm. However, there was no clear difference in pattern of relapse between the arms among patients who relapsed."

1. Vansteenkiste J, et al. Ann Oncol. 2019;30:1244-1253.
2. Wakelee HA, et al. J Clin Oncol 39, 2021 (suppl 15; abstr 8500)
3. Felip E, et al. Impower010: patterns of relapse and subsequent therapy from a Phase III study of atezolizumab (atezo) vs best supportive care (BSC) after adjuvant chemotherapy (chemo) in stage IB-IIIA non-small cell lung cancer (NSCLC). Abstract LBA9, ESMO Congress 2021, 16–21 September.

Three-year OS follow-up from CASPIAN trial

The phase 3 CASPIAN trial demonstrated first-line treatment with durvalumab/platinum-etoposide to improve overall survival (OS) versus etoposide alone in patients with extensive stage small-cell lung cancer (ES-SCLC). Three-year median follow-up demonstrated sustained OS benefit.

Recently, the phase 3 CASPIAN trial (NCT03043872) demonstrated first-line treatment of ES-SCLC with durvalumab plus etoposide to improve OS versus etoposide alone (HR 0.73; P=0.0047) [1]. This benefit was sustained with more than 2 years follow-up [2]. In addition, a numerical, not statistically significant improvement in OS was observed with durvalumab plus tremelimumab plus etoposide versus etoposide alone [2].

Updated OS results of CASPIAN after a median of more than 3 years follow-up were presented by Dr Luis Paz-Ares (Hospital Universitario 12 de Octubre, Spain). In CASPIAN, 805 patients with treatment-naïve ES-SCLC were randomised 1:1:1 to durvalumab/etoposide (every 3 weeks), durvalumab/tremelimumab/etoposide (every 3 weeks), or etoposide (every 3 weeks, 6 cycles). Patients in the immunotherapy arms received 4 cycles of etoposide/durvalumab ± tremelimumab, followed by maintenance durvalumab (every 4 weeks). The primary endpoints were OS for durvalumab/etoposide versus etoposide and for durvalumab/tremelimumab/etoposide versus etoposide.

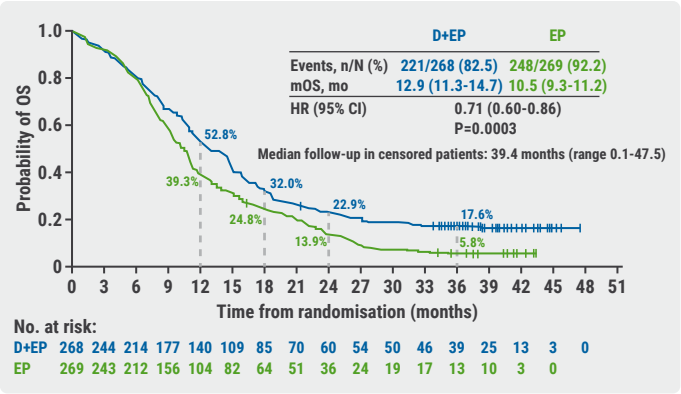
At a median follow-up of 39.4 months (86% maturity), durvalumab/etoposide continued to demonstrate improved OS versus etoposide (HR 0.71; P=0.0003). Median OS was 12.9 versus 10.5 months. At 24 months, 22.9% versus 13.9% of patients were alive, and at 36 months 17.6% versus 5.8% of patients were alive with durvalumab/etoposide versus etoposide, respectively (see Figure).

Durvalumab/tremelimumab/etoposide also continued to improve OS versus etoposide (HR 0.81; P=0.02). Median OS was 10.4 months versus 10.5 months. At 24 months, 22.9% versus 13.9% of patients were alive, and at 36 months 15.3% and 5.8% of patients were alive with durvalumab/tremelimumab/etoposide versus etoposide alone, respectively.

Safety profiles were consistent with previous analyses. "Three times more patients were estimated to be alive at 3 years follow-up when treated with durvalumab/etoposide versus etoposide alone, further establishing durvalumab/etoposide as standard of care for first-line treatment of ES-SCLC," concluded Dr Paz-Ares. "Addition of tremelimumab to durvalumab/etoposide does not further improve OS."

1. Paz-Ares L, et al. Lancet. 2019;394:1929-1939.
2. Goldman JW, et al. Lancet Oncol. 2021;22:51–65.
3. Paz-Ares L, et al. Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): 3-year overall survival update from the phase III CASPIAN study. Abstract LBA61, ESMO Congress 2021, 16–21 September.

Figure: 3-year overall survival update of CASPIAN [3]



TCR clonality predicts pembrolizumab response in NSCLC

Pre-treatment T-cell receptor (TCR) clonality and reduced diversity predicted response rate in non-small cell lung cancer (NSCLC) patients with high PD-L1 treated with pembrolizumab.

Due to recombination and cellular selection, the immune system is able to produce up to 10^{11} different TCRs. Increased clonality, reduced diversity, and increased convergence of TCRs have been suggested to reflect clonal expansion of antigen-specific T cells in the tumour microenvironment and to correlate with improved overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). Moreover, increased clonality has been linked to increased risk of developing immune related toxicity.

To further explore the association between TCR repertoire and treatment outcomes, Australian investigators analysed the pre-treatment TCR repertoire in 29 patients with NSCLC (PD-L1 ≥50%) treated with single-agent pembrolizumab and follow-up for at least 18 months. Dr Afef Abed (Edith Cowan University, Australia) presented the results [1].

Reduced number of unique clones and reduced Shannon diversity was found to be associated with improved ORR to pembrolizumab (P=0.038 and P=0.021, respectively). Moreover, there was a significantly longer PFS in patients with reduced number of unique clones (HR 0.40; P=0.040), reduced Shannon diversity (HR 0.44; P=0.044), reduced Evenness (HR 0.31; P=0.033), and elevated clonality (HR 2.45; P=0.044). None of these parameters were statically significant in relation to OS. Three TCR families (TRBV6-4, TRBV10-2, and TRBV10-3) were observed to occur significantly more frequently among non-responders.

"So, increased pre-treatment TCR clonality and reduced diversity are associated with improved response rate and PFS, but not OS, in NSCLC patients with high PD-L1 treated with pembrolizumab monotherapy," concluded Dr Abed. "Further maturation of this cohort will demonstrate whether the circulating pre-treatment TCR repertoire is a prognostic factor for immune checkpoint inhibition."

1. Abed A. et al. Clinical value of pre-treatment T-cell receptors (TCR) repertoire in non-small cell lung cancer (NSCLC) patients treated with single agent immunotherapy. Abstract LBA68, ESMO Congress 2021, 16–21 September.

Melanoma

Adjuvant immunotherapy reduces risk of disease recurrence in stage II melanoma

The first interim analysis of KEYNOTE-716 suggests adjuvant pembrolizumab to be superior to standard-of-care observation for adult and children with completely resected high-risk melanoma.

Patients with stage IIB-C melanoma are at high risk of disease recurrence and survival outcomes are similar to stage IIIA-B melanoma [1]. In patients with stage III melanoma, adjuvant therapy with pembrolizumab prolonged recurrence-free survival (RFS) as well as distant metastasis-free survival (DMFS) [2]. The phase 3, double-blind KEYNOTE-716 trial (NCT03553836) evaluated pembrolizumab versus placebo in patients with resected stage IIB or IIC melanoma. Dr Jason Luke (UPMC Hillman Cancer Center, PA, USA) presented results from the first interim analysis of KEYNOTE-716 [3].

A total of 976 patients (64% stage IIB, 34.8% stage IIC; aged ≥12 years with complete resection of cutaneous melanoma and with negative sentinel lymph node biopsy) were enrolled and randomised 1:1 to pembrolizumab (200 mg; 2 mg/kg for paediatric patients) or placebo every 3 weeks for 17 cycles (up to 1 year). Treatment continued until disease recurrence or unacceptable toxicity. The primary endpoint was RFS per investigator assessment. Secondary endpoints were DMFS, overall survival (OS), safety, and quality of life.

At median follow-up of 14.4 months, pembrolizumab significantly prolonged RFS versus placebo (HR 0.65; P=0.00658; median not reached for both). The 12-month RFS rate was 90.5% versus 83.1%. At data cut-off, 11.1% of patients treated with pembrolizumab had a recurrence versus 16.8% of patients treated with placebo. Pembrolizumab almost halved the distant recurrence rate (4.7% vs 7.8%).

The incidence of grade ≥3 adverse events (AEs) was higher with pembrolizumab than with placebo, both for any-cause AEs (25.9% vs 17.1%) and for drug-related AEs (16.1% vs 4.3%). Altogether, 15.3% of patients discontinued pembrolizumab due to a drug-related AE, compared with 2.5% receiving placebo. Immune-mediated AEs occurred in 36.2% versus 8.4%, most commonly hypothyroidism (15.7% vs 3.5%) and hyperthyroidism (10.4% vs 0.6%). Most were grade 1–2 in severity. Quality of life was maintained with both adjuvant pembrolizumab and placebo.

"Adjuvant pembrolizumab is an effective treatment option with a favourable benefit risk profile for patients with high-risk stage II melanoma," concluded Dr Luke.

1. Luke JJ, et al. Nat Rev Clin Oncol. 2017;14:463–482.
2. Eggermont AMM, et al. Lancet Oncol. 2021;22:643–654.
3. Luke JJ, et al. Pembrolizumab versus placebo after complete resection of high-risk stage II melanoma: Efficacy and safety results from the KEYNOTE-716 double-blind phase III trial. Abstract LBA3_PR, ESMO Congress 2021, 16–21 September.

IFN-γ signature predicts response to immunotherapy

Preliminary results of the phase 1b DONIMI trial showed that the interferon (IFN)-γ signature is useful to discriminate between melanoma patients who will benefit from neoadjuvant therapy with nivolumab alone and patients who might need an escalated therapy.

Neoadjuvant immunotherapy with ipilimumab plus nivolumab induces high pathologic response rates (72–78%) in stage IIIB-D melanoma and is strongly associated with long-term relapse-free survival (RFS) [1]. Patients with a low baseline IFN-γ signature are known to be less likely to respond to immunotherapy [2]. The class I histone deacetylase inhibitor domatinostat has previously demonstrated to increase intertumoral T-cell infiltration and IFN-γ sign expression

in melanoma. The DONIMI trial (NCT04133948) tests neoadjuvant combinations of nivolumab plus ipilimumab with domatinostat in melanoma patients stratified according to IFN-γ signature from tumour biopsies. Aim of the trial is to de-escalate neoadjuvant immunotherapy in patients with a high IFN-γ signature, whereas in patients with a low IFN-γ signature neoadjuvant immunotherapy will be escalated.

In the DONIMI study, stage III *de novo* or recurrent melanoma patients with a high IFN-γ signature (n=20) were randomised to arm A (2 cycles nivolumab 240 mg, every 3 weeks) or arm B (2 cycles nivolumab 240 mg plus domatinostat 200 mg twice daily, days 1–14, every 3 weeks), whereas patients with a low IFN-γ (n=20) were randomised to arm C (same treatment regimen as arm B) or arm D (2 cycles nivolumab 240 mg plus ipilimumab 80 mg plus domatinostat 200 mg once daily, days 1–14, every 3 weeks). Surgery and lymph node dissection was planned after 6 weeks. Adjuvant nivolumab 480 mg every 4 weeks or dabrafenib plus trametinib (in non-responding *BRAF*-mutated patients) started at week 12, for 52 weeks.

Prof. Christian Blank (Netherlands Cancer Institute, the Netherlands) presented the first results of the DONIMI trial [3]. All treatment regimens were feasible as surgery was performed on time in all patients (week 6 ± 1 week). Grade 3–4 systemic treatment-related adverse events during the first 12 weeks occurred in 0% in arm A, 20% in arm B, 40% in arm C, and 20% in arm D. Except for grade 2–3 domatinostat-related rash, no unexpected treatment-related adverse events were observed.

Pathologic response rate was 90% (70% pCR) in arm A and 80% (50% pCR) in arm B (high IFN-γ signature patients). This was 30% (10% pCR) in arm C, and 40% (30% pCR) in arm D (low IFN-γ signature patients). In arm D, 2 patients developed distant metastases before surgery. At data cut-off, estimated 6-month relapse-free survival rate was 100% in patients with high IFN-γ signature and 79.4% in patients with low IFN-γ signature.

Based on these preliminary results, Prof. Blank concluded that "neoadjuvant therapy with nivolumab plus domatinostat plus ipilimumab appears safe and feasible. Moreover, DONIMI shows prospectively the discriminative ability of the IFN-γ signature. It adequately identified patients who can benefit from nivolumab alone versus patients who might need an alternative scheme."

1. Menzies AA, et al. Nat Med. 2021;27:301-309.
2. Karachaliou N, et al. Ther Adv Med Oncol. 2018;10:1758834017749748.
3. Blank CU, et al. Personalized combination of neoadjuvant domatinostat, nivolumab (NIVO) and ipilimumab (IPI) in stage IIIB-D melanoma patients (pts) stratified according to the interferon-gamma signature (IFN-γ sign): The DONIMI study. Abstract LBA39, ESMO Congress 2021, 16–21 September.

Updated results of SECOMBIT trial

First OS data of the SECOMBIT trial did not (yet) show the optimum sequential approach with immunotherapy and targeted therapy in patients with *BRAF*-mutated metastatic melanoma.

Treatment with targeted therapy (BRAF and MEK inhibitors) and immune-checkpoint inhibitors (anti-CTLA4, anti-PD-1) have improved the outcome of *BRAF*-mutated metastatic melanoma patients in first line, but the best sequencing remains an open question. In the SECOMBIT trial (NCT02631447) immunotherapy and targeted therapy were given sequentially [1]. This phase 2 study included 251 patients with untreated, metastatic *BRAF*-mutated melanoma, who were randomised 1:1:1 to 3 arms: encorafenib plus binimetinib until progression, followed by ipilimumab plus nivolumab (arm A); ipilimumab plus nivolumab until progression, followed by encorafenib plus binimetinib (arm B); or encorafenib plus binimetinib for 8 weeks, followed by ipilimumab plus nivolumab until progression, followed by encorafenib plus binimetinib (arm C). Primary endpoint of SECOMBIT is overall survival (OS), secondary endpoints are total PFS, PFS until second progression, and best ORR. First results (median PFS) of SECOMBIT were presented at ESMO 2020 [1]. Prof. Paolo Ascierto (Istituto Nazionale Tumori "Fondazione Pascale", Italy) presented updated results [2].

The study primary endpoint was met in each arm, with at least 30 patients alive at 24 months; median OS was not reached in any of the treatment arms. The survival rate at 2 and 3 years was 65% and 54% in arm A, 73% and 62% in arm B, and 69% and 60% in arm C, respectively. Total PFS rate at 2 and 3 years was 46% and 41% in arm A, 65% and 53% in arm B, and 57% and 54% in arm C.

"With a median follow-up of 32.2 months, 2- and 3-year rates of both total PFS and OS show a better trend in arm B and C," concluded Prof. Ascierto. "Longer follow-up is required to better define the data and monitor the trend. In addition, biomarkers analysis is ongoing."

1. Ascierto PA, et al. ESMO 2020 Virtual Meeting, abstract LBA45, 19–21 Sep.
2. Ascierto PA, et al. SECOMBIT: The best sequential approach with combo immunotherapy [ipilimumab (I) /nivolumab (N)] and combo target therapy

[encorafenib (E)/binimetinib (B)] in patients with BRAF mutated metastatic melanoma: A phase II randomized study. Abstract LBA40, ESMO Congress 2021, 16–21 September.

Combining T-VEC and pembrolizumab does not significantly improve survival in advanced, unresectable melanoma

First and second interim analyses of the MASTERKEY-265 trial showed no significant benefit for the combination of T-VEC and pembrolizumab over pembrolizumab alone in patients with unresectable stage IIIB/IVM1c melanoma.

Previous research showed that oncolytic virotherapy with talimogene laherparepvec (T-VEC) may improve the efficacy of anti-PD-1 therapy in patients with advanced melanoma by changing the tumour microenvironment [1]. In the phase 3 MASTERKEY-265 trial (NCT02263508), 692 patients with unresectable stage IIIB-IVM1c, anti-PD-1-naïve melanoma with injectable lesions were randomised 1:1 to T-VEC/pembrolizumab or placebo/pembrolizumab. T-VEC was given at ≤4x10^6 plaque-forming units (PFU) followed by ≤4x10^8 PFU 3 weeks later and every 2 weeks until dose 5, and every 3 weeks thereafter. Pembrolizumab was given intravenously 200 mg every 3 weeks. Dual primary endpoints were progression-free survival (PFS) and overall survival (OS). Secondary endpoints included objective response rate (ORR), complete response rate (CRR), durable response rate (DRR), duration of response (DOR), and safety. Dr Helen Gogas (National and Kapodistrian University of Athens, Greece) presented the first results of MASTERKEY-265 [2].

The primary endpoints did not reach statistical significance. After a median follow-up of 31.0 months, median PFS was 14.3 months for the T-VEC/pembrolizumab-treated patients and 8.5 months for the placebo/pembrolizumab-treated patients (HR 0.86; P=0.13); 1-and 2-year PFS rates were 53.8% versus 45.7% and 41.9% versus 38.6%, respectively (see Figure).

Median OS was not reached for the T-VEC/pembrolizumab arm and 49.2 months for the placebo/pembrolizumab (HR 0.96; P=0.74). OS was not expected to achieve statistical significance at the primary OS analysis. Safety profiles were generally comparable between treatment arms.

"Combining T-VEC and pembrolizumab does not significantly improve PFS or OS in patients with unresectable stage III/IVM1 melanoma," concluded Dr Gogas.

1. Ribas A, et al. Cell. 2017;170:1109-1119.
2. Gogas HJ, et al. MASTERKEY-265: A phase III, randomized, placebo (Pbo)-controlled study of talimogene laherparepvec (T) plus pembrolizumab (P) for unresectable stage IIIB–IVM1c melanoma (MEL). Abstract 1037O, ESMO Congress 2021, 16–21 September.

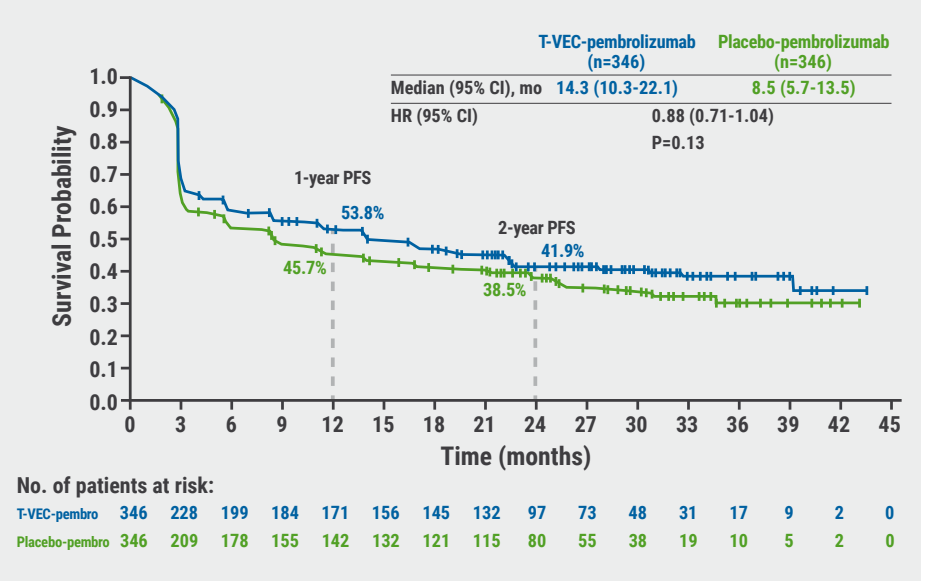
Durable intracranial responses with nivolumab/ipilimumab

Melanoma patients with brain metastases can have a durable intracranial response with first-line nivolumab/ipilimumab, long-term results of CheckMate204 showed.

Brain metastases are a common complication of solid tumours and remain a major cause of disabling neurologic complications and death in patients with cancer. Surgical resection and stereotactic radiotherapy are highly effective treatments for local control. However, these treatments do not have any effect on the risk of the development of new brain metastases, on the control of extracranial disease, or on overall survival (OS).

The open-label, phase 2 CheckMate204 trial (NCT02320058) evaluated efficacy and safety of nivolumab/ipilimumab as treatment in melanoma patients with brain metastases. Previous results showed clinically meaningful intracranial efficacy, concordant with extracranial activity, and a safety profile similar to that reported in patients with melanoma

Figure: PFS, primary endpoint of MASTERKEY-265 [2]



who do not have brain metastases [1]. Dr Kim Margolin (City of Hope, CA, USA) now presented 3-year response and survival outcomes of CheckMate204.

In this study, patients with metastatic melanoma and ≥1 nonirradiated brain metastasis 0.5–3 cm in diameter received 4 cycles nivolumab (1 mg/kg)/ipilimumab (3 mg/kg) every 3 weeks, followed by nivolumab (3 mg/kg every 2 weeks) until progression or unacceptable toxicity. The primary endpoint was intracranial clinical benefit rate (CBR), defined as the proportion of patients with complete response (CR), partial response (PR), or stable disease (SD) ≥6 months. A total of 101 patients with asymptomatic brain metastases (cohort A) and 18 patients with symptomatic brain metastases (cohort B) were enrolled. Median follow-up was 34 months in cohort A and 7.5 months in cohort B.

For cohort A, 36-month intracranial progression-free survival (PFS) was 54%, and OS was 72%. Intracranial CBR was 57%; of patients with objective response, 85% had an ongoing response at 36 months. For cohort B, 36-month intracranial PFS was 19%, and OS was 37%. Intracranial CBR was 17%; of patients with objective response, 100% had an ongoing response at 36 months. The toxicity profile of nivolumab/ipilimumab for both asymptomatic and symptomatic patients with brain metastases was similar to that of patients without brain metastases.

"These results show durable 3-year PFS and OS rates for the asymptomatic cohort, supporting the use of first-line nivolumab/ipilimumab," concluded Dr Margolin. "Patients with symptomatic brain metastases remain difficult to treat, but some can also derive long-term benefit from first-line nivolumab/ipilimumab."

1. Tawbi HA, et al. N Engl J Med. 2018; 379:722-730.
2. Margolin KA, et al. CheckMate204: 3-year outcomes of treatment with combination nivolumab (NIVO) plus ipilimumab (IPI) for patients (pts) with active melanoma brain metastases (MBM). Abstract 039MO, ESMO Congress 2021, 16–21 September.

Genitourinary Cancer

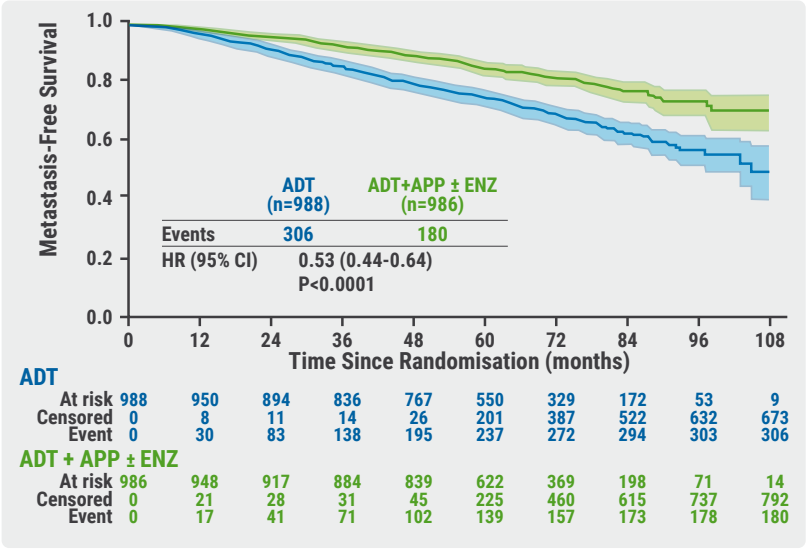
Both men with high-risk non-metastatic prostate cancer and men with metastatic prostate cancer benefit from intensified hormone treatment

Three trials – PEACE-1, two combined STAMPEDE cohorts, and ARCHES – highlighted the benefits of treatment intensification with androgen receptor signalling inhibitors in patients with hormone-sensitive prostate cancer (HSPC).

Although treatment with androgen deprivation therapy (ADT) and local radiotherapy has improved outcome of patients with high-risk non-metastatic (M0) prostate cancer, post-treatment failure rates are high. In patients with metastatic prostate cancer, addition of abiraterone-acetate/prednisone (AAP) to ADT has proven to increase overall survival (OS). However, due to low numbers of events, no statistically significant benefit of addition of AAP to ADT was shown in patients with M0 prostate cancer [1]. To power the endpoint of metastases-free survival (MFS) in M0 patients, the STAMPEDE investigators combined M0 patients from 2 comparisons in the STAMPEDE platform protocol (NCT00268476), creating a cohort of 1,974 patients with M0 prostate cancer [2]. Patients were randomised 1:1 to ADT plus AAP (or ADT plus AAP plus enzalutamide) versus ADT alone. Of note, previous analysis of STAMPEDE showed that addition of enzalutamide to AAP did not prolong survival in men with metastatic castration-resistant prostate cancer [3]. Prof. Gerhardt Attard (UCL Cancer Institute, UK) presented the results of this analysis [4].

AAP-based therapy improved MFS, the primary endpoint (180 vs 306 events; HR 0.53; P<0.0001). At 6 years follow-up, AAP (± enzalutamide) improved MFS from 69% to 82% (see Figure 1). In addition, OS was improved by combining AAP (± enzalutamide) with ADT (HR 0.60; P<0.0001); 6-year OS rates improved from 77% to 86%; 6-year prostate cancer-specific survival improved from 85% to 93%. As expected, no extra benefit was observed from combining AAP/ADT with enzalutamide versus AAP/ADT. Extra toxicity from AAP addition was as expected, with no apparent synergistic adverse events from the combination. "These results clearly

Figure 1: MFS in combined STAMPEDE cohorts [4]



show that 2 years of AAP-based therapy significantly improves MFS and OS in men with high-risk M0 prostate cancer versus ADT alone. Therefore, this should be a new standard of care," concluded Prof. Attard. "Adding enzalutamide to AAP increases toxicity, but has no discernible effect of efficacy."

The phase 3 PEACE-1 trial (NCT01957436) investigated the addition of AAP (± local radiotherapy) to ADT/docetaxel in men with *de novo* metastatic HSPC. A total of 355 patients was treated with ADT/docetaxel ("doublet") and 355 patients were treated with AAP/ADT/docetaxel ("triplet"). Prof. Karim Fizazi (Institut Gustave Roussy, France) presented the results [5].

Like in non-metastatic men, both (radiographic) PFS and OS was improved with the addition of AAP. Median radiographic PFS was 4.5 years versus 2.0 years (HR 0.50; P<0.0001); median OS was not evaluable versus 4.4 years (HR 0.75; P=0.017). More benefit of AAP addition, both for radiographic PFS and OS, was observed in patients with high-volume metastatic burden compared with low-volume metastatic burden (median PFS: HR 0.47 vs 0.58, respectively; median OS: HR 0.72 vs 0.83, respectively). Prof. Fizazi concluded that "these results are practice changing: at least men with *de novo*, high-volume metastatic HSPC should be offered triple therapy."

The randomised phase 3 ARCHES trial (NCT02677896) aimed to evaluate the efficacy and safety of the addition of enzalutamide to ADT in men with metastatic HSPC. Previous results from ARCHES showed that enzalutamide/ADT significantly reduced the risk of radiographic disease progression by 61% (P<0.001) and improved key secondary endpoints (time to PSA progression, time to initiation of new antineoplastic therapy, time to first symptomatic skeletal event, time to castration resistance, and reduced risk of pain progression), while maintaining a high quality of life versus placebo plus ADT [6]. Dr Andrew Armstrong (Duke Cancer Institute, NC, USA) presented final OS data from ARCHES [7]

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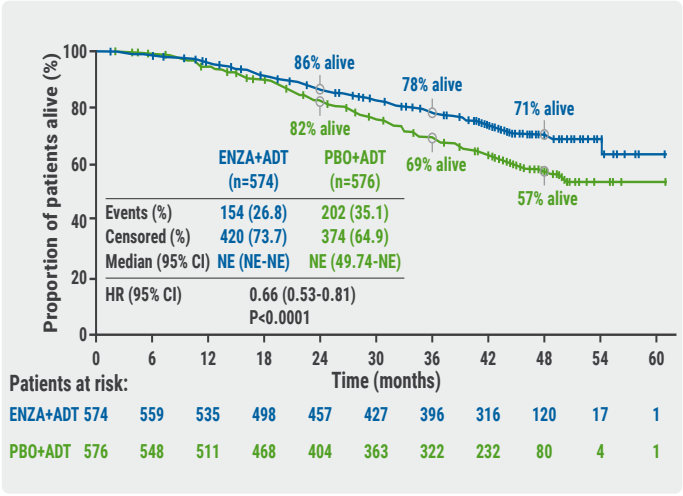
In the study, 1,150 patients were randomised 1:1 to ADT/enzalutamide or ADT alone. After study unblinding, 184 patients (31.9%) randomised to ADT alone remained progression-free and crossed over tot ADT/enzalutamide. Median time to crossover was 21.5 months. Addition of enzalutamide significantly prolonged OS (HR 0.66; P<0.0001). After 4 years of follow-up, 71% of patients in the enzalutamide/ADT arm were still alive, versus 57% in the ADT alone arm (see Figure 2). Also, time to subsequent antineoplastic therapy was increased with enzalutamide/ADT versus ADT alone (HR 0.38). Benefit of enzalutamide was irrespectively of disease volume, prior local therapy, age, Gleason score, disease localisation, and PSA. Safety and toxicity were consistent with findings from the primary analysis.

Figure 2: OS in intention-to-treat population of ARCHES [7]



"The final analysis of ARCHES demonstrates that enzalutamide/ADT has a long-term survival benefit versus ADT alone in men with metastatic HSPC," concluded Dr Armstrong.

1. James ND, et al. N Eng J Med. 2017;377:338–351.
2. Attard G, et al. Eur Urol. 2021;80:522-523.
3. Morris MJ, et al. J Clin Oncol. 2019;37:5008.
4. Attard G, et al. Abiraterone acetate plus prednisolone (AAP) with or without enzalutamide (ENZ) added to androgen deprivation therapy (ADT) compared to

ADT alone for men with high-risk non-metastatic (M0) prostate cancer (PCa): Combined analysis from two comparisons in the STAMPEDE platform protocol. Abstract LBA4, ESMO Congress 2021, 16–21 September.
5. Fizazi K, et al. A phase 3 trial with a 2x2 factorial design in men with de novo metastatic castration-sensitive prostate cancer (mCSPC): Overall survival with abiraterone acetate plus prednisone in PEACE-1. Abstract LBA5, ESMO Congress 2021, 16–21 September.
6. Armstrong AJ, et al. J Clin Oncol. 2019;37:2974–2986.
7. Armstrong AJ, et al. Final overall survival analysis from ARCHES: A phase 3, randomized, double blind, placebo-controlled study of enzalutamide plus androgen deprivation therapy in men with metastatic hormone sensitive prostate cancer. Abstract LBA25, ESMO Congress 2021, 16–21 September.

TKI drug-free interval strategy not detrimental to conventional continuation strategy in RCC

First results from the phase 2/3 STAR trial showed that a drug-free interval strategy in tyrosine kinase inhibitor (TKI)-therapy in patients with advanced/metastatic renal cell carcinoma (RCC) is not detrimental to overall survival (OS) and quality of life compared with conventional continuation strategy, and has a significant cost saving effect.

TKI therapy is an important backbone in the management of locally advanced or metastatic RCC, with significant survival advantage. However, TKI therapy is associated with significant toxicities which often lead to dose reduction and/or discontinuation of treatment. In addition, TKI therapy comes with high costs. The multicentre, randomised, phase 2/3 STAR trial (EudraCT 2011-001098-16) was designed to determine if a TKI drug-free interval strategy (DFIS) was non-inferior to a conventional continuation strategy (CCS) in the first-line treatment of advanced RCC. Outcomes were overall survival (OS) and Quality Adjusted Life Years (QALYs). Both co-primary endpoints (OS and QALYs) had to demonstrate pre-defined non-inferiority (≤7.5% for OS; ≤10% for QALYs) in intention-to-treat and per-protocol analyses for non-inferiority to be concluded. Prof. Janet Brown (University of Sheffield, UK) presented the first results of the STAR trial [1].

A total of 920 patients with newly diagnosed metastatic RCC who started treatment with sunitinib or pazopanib were 1:1 randomised to DFIS or CCS. Overall, 488 (53.0%) patients (CCS, n=240; DFIS, n=248) continued on trial post-week 24. Intention-to-treat and per-protocol analyses included 461 versus 458 patients and 453 versus 418 patients, respectively.

After 24 weeks of treatment, DFIS patients took a treatment break until disease progression, with additional breaks dependent on disease response and patient/clinician choice. Trial strategy continued until intolerance, progression on treatment, or death. At least one treatment break was mandated, with a median treatment break length of 87 days; 27% of patients had 3 or more treatment breaks.

For OS, in the intention-to-treat population, HR was 0.97 (95% CI 0.83–1.12), whereas in the per-protocol population, HR was 0.94 (95% CI 0.80–1.09). With a non-inferiority margin of 95% CI ≥0.812, this meant DFIS in the per-protocol population could not be regarded as non-inferior to CCS. However, consistent non-inferiority in both populations was demonstrated for QALYs. At 2 years, DFIS was associated with cost savings (£6,954 per-participant).

"Although OS just fell short of predefined non-inferiority, probably due to fewer than expected events, non-inferiority of DFIS for QALYs was demonstrated. DFIS also appeared to be highly cost-effective compared to CCS. In addition, DFIS was seen to be acceptable to patients and clinicians," summarised Prof. Brown.

1. Brown JE, et al. STAR: A randomised multi-stage phase II/III trial of standard first-line therapy (sunitinib or pazopanib) comparing temporary cessation with allowing continuation, in the treatment of locally advanced and/or metastatic renal Cancer (RCC). Abstract LBA28, ESMO Congress 2021, 16–21 September.

Modified ipilimumab schedule reduces risk of grade 3/4 adverse events

First results of the randomised, phase 2 PRISM trial showed that ipilimumab every 12 weeks, instead of every 3 weeks, in combination with first-line nivolumab significantly reduced rates of grade 3/4 adverse events in patients with advanced renal cell carcinoma (RCC).

Ipilimumab/nivolumab is an approved and standard first-line treatment for patients with intermediate and poor-risk advanced RCC. Ipilimumab/nivolumab has proven to significantly increase overall survival (OS) versus sunitinib in patients with intermediate or poor risk advanced RCC [1]. However, grade 3/4 treatment-related adverse events are relatively common during the initial combination period. Therefore, the randomised, phase 2 PRISM trial (EudraCT 2017-001476-33) aimed to determine whether modified scheduling of ipilimumab, in combination with nivolumab, is associated with improved tolerability, whilst maintaining treatment efficacy in line with previous comparative studies with sunitinib. Dr Naveen Vasudev (St James University Hospital, UK) presented the first results of PRISM [2].

A total of 192 patients (69.8% intermediate/poor-risk) were randomised 1:2 to receive 4 doses of ipilimumab (1 mg/kg)

every 3 weeks (conventional) or every 12 weeks (modified), in combination with nivolumab (3 mg/kg), until disease progression or unacceptable toxicity.

The primary endpoint was the proportion of patients with a grade 3/4 treatment-related adverse events within 12 months of initiating treatment. Secondary endpoints included progression-free survival (PFS) at 12 months – tested against historical PFS associated with sunitinib – and objective response rate (ORR). The primary endpoint was met: significantly fewer grade 3/4 adverse events occurred in the modified arm than in the conventional arm (32.8% vs 53.1%; OR 0.43; P=0.0075). In particular, arthralgia and colitis were less observed in the modified arm. Also, discontinuation due to adverse events was reduced in the modified arm (22.7% vs 39.1%).

PFS rate at 12 months was 46.1% versus 39.7% in the historical control. Kaplan-Meier PFS- and OS-curves were comparable in the modified and conventional arms. "Giving ipilimumab every 12 instead of every 3 weeks led to a significant reduction in grade 3/4 treatment-related events and therefore supports further exploration of different ipilimumab/nivolumab regimens," concluded Dr Vasudev.

1. Motzer RJ, et al. N Engl J Med. 2018;378:1277–1290.
2. Vasudev NS, et al. Nivolumab in combination with alternatively scheduled ipilimumab in first-line treatment of patients with advanced renal cell carcinoma: A randomized phase II trial (PRISM). Abstract LBA29, ESMO Congress 2021, 16–21 September.

Optimal neoadjuvant dose ipilimumab/ nivolumab in stage III urothelial cancer

Neoadjuvant high-dose ipilimumab plus low-dose nivolumab is more efficacious than low-dose ipilimumab plus high-dose nivolumab in patients with stage III urothelial cancer, results from the NABUCCO cohort 2 showed.

Standard treatment for patients with stage III (cT3-4aN0M0 or cT1-4aN1-3M0) urothelial cancer is cisplatin-based chemotherapy followed by radical surgery. However, a substantial number of patients is unfit for cisplatin-based chemotherapy. Results from NABUCCO cohort 1 (NCT03387761) showed promising efficacy (46% pathological complete response) of neoadjuvant immunotherapy with ipilimumab/nivolumab [1]. Dosing in this cohort was: ipilimumab 3 mg/kg at day 1 and day 22, and nivolumab 3 mg/kg at day 43. Recent data in pre-operative trials for other cancer types suggests that a lower dose of ipilimumab has equal activity and is better tolerated [2]. NABUCCO cohort 2 compared efficacy and safety of alternative adjuvant dosing regimens. Patients in cohort 2A (n=15) were treated with ipilimumab 3 mg/kg and nivolumab 1 mg/kg at day 1 and day 22, and nivolumab 3 mg/kg at day 43. Patients in cohort 2B (n=15) were treated with ipilimumab 1 mg/kg and nivolumab 3 mg/kg at day 1 and day 22, and nivolumab 3 mg/kg at day 43. Primary endpoint was pathologic complete response (pCR) rate. Secondary endpoints included feasibility (resection within 12 weeks) and grade 3/4 immune-related adverse events. Dr Jeroen van Dorp (Netherlands Cancer Institute, Netherlands) presented the first results [3].

A total of 26/30 (87%) patients received all 3 treatment cycles; these 26 patients underwent radical surgery, 24 within 12 weeks after start of treatment. Four patients missed one or more cycles of therapy due to immune-related adverse events. Response was evaluable in 28 patients. In cohort 2A, 6/14 (43%) patients had a pCR; 8/14 (57%) had a pCR or ypTisN0. In cohort 2B, 1/14 (7%) had a pCR whereas 3/14 (21%) had a pCR or ypTisN0. Grade 3/4 immune-related adverse events were observed in 5/15 (33%) patients in cohort 2A, and in 3/15 (20%) patients in cohort 2B.

"In contrast to what was observed in other malignancies, neoadjuvant ipilimumab 1 mg/kg and nivolumab 3 mg/kg was less efficacious than ipilimumab 3 mg/kg and nivolumab 1 mg/kg," concluded Dr van Dorp. Further translational work is currently ongoing.

1. Van Dijk N, et al. Nat Med. 2020;26:1839–1844.
2. Rozeman EA, et al. Lancet Oncol. 2019;20:948–960.
3. Van Dorp J, et al. High- vs low-dose pre-operative ipilimumab and nivolumab in locoregionally advanced urothelial cancer (NABUCCO cohort 2). Abstract LBA31, ESMO Congress 2021, 16–21 September.

Better survival with neoadjuvant dose-dense MVAC regimen in MIBC

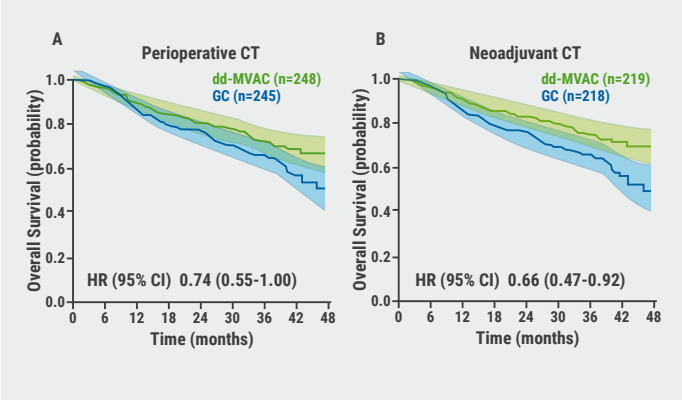
Dose-dense MVAC outperforms gemcitabine/cisplatin as neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer (MIBC), result from the phase 3 VESPER trial showed.

The optimal neoadjuvant chemotherapy regimen for patients with MIBC is not defined. Therefore, the VESPER trial (NCT01812369) randomised 493 MIBC patient 1:1 to either 4 cycles of gemcitabine/cisplatin every 3 weeks or 6 cycles of dose-dense methotrexate/vinblastine/doxorubicin/cisplatin (dd-MVAC) every 2 weeks, before surgery. Primary endpoint was progression-free survival (PFS) at 3 years. Dr Christian

Pfister (Rouen University Hospital, France) presented the results [1].

A total of 437 patients (88%) received neoadjuvant chemotherapy, 56 patients (12%) received adjuvant chemotherapy; 60% patients received all planned 6 cycles in the dd-MVAC arm and 84% received all 4 cycles in the gemcitabine/cisplatin arm. Thereafter, 91% and 90% of patients underwent surgery, respectively. Organ-confined response (<ypT3N0) was observed more frequently in the dd-MVAC arm (77% vs 63%; P=0.001). PFS rate at 3 years was improved in the neoadjuvant dd-MVAC arm (66% vs 56%; HR 0.70; P=0.025). In addition, both time to progression and overall survival were improved in the neoadjuvant dd-MVAC arm (HR 0.62 and 0.66 vs gemcitabine/cisplatin, respectively; see Figure). Results of the adjuvant arm were inconclusive due to the limited number of patients included.

Figure: Overall survival with dd-MVAC in VESPER [1]



"These results suggest dd-MVAC should become the gold standard for neoadjuvant chemotherapy because of higher local control and a significant improvement in 3-year PFS," concluded Dr Pfister.

1. Pfister C, et al. Dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (dd-MVAC) or gemcitabine and cisplatin (GC) as perioperative chemotherapy for patients with muscle-invasive bladder cancer (MIBC): Results of the GETUG/AFU VESPER V05 phase III trial. Abstract 652O, ESMO Congress 2021, 16–21 September.

PARP inhibitor rechallenge improves PFS in ovarian cancer

Results from the phase 3 OReO/ENGOT Ov-38 trial demonstrated that rechallenge with maintenance olaparib significantly prolonged progression-free survival (PFS) compared with placebo in both *BRCA1/2*-mutated and non-*BRCA1/2*-mutated disease.

Although most patients achieve a long-term response, most ultimately progress on PARP inhibitor maintenance therapy. The randomised, double-blind, phase 3 OReO/ENGOT Ov-38 study (NCT03106987) evaluated PARP inhibitor maintenance re-treatment in this setting. Dr Eric Pujade-Lauraine (Université Paris Descartes, France) presented the results [1].

A total of 112 patients were *BRCA1/2* mutated (BRCAm) and 108 patients were non-*BRCA* mutated (non-BRCAm). Patients were heavily pre-treated, with 93% (BRCAm) and 86% (non-BRCAm) receiving ≥3 prior lines of any chemotherapy. In the BRCAm cohort, >90% of patients had olaparib as first PARP inhibitor; in the non-BRCAm cohort, >50% of patients had niraparib as first PARP inhibitor. Both cohorts randomised patients 2:1 to olaparib tablets (300 mg twice daily) or placebo until progression. Primary endpoint was investigator-assessed PFS.

In the BRCAm cohort, median PFS was 4.3 months for olaparib versus 2.8 months for placebo (HR 0.57; P=0.022). PFS rates were 35% versus 13% at 6 months and 19% versus 0% at 12 months. In the non-BRCAm cohort, median PFS was 5.3 months for olaparib versus 2.8 months for placebo (HR 0.43; P=0.002). PFS rates in the non-BRCAm cohort were 30% versus 7% at 6 months and 14% versus 0% at 12 months. In an exploratory analysis, benefit in the non-BRCAm cohort appeared consistent irrespectively of HRD status. No new safety signals were observed and discontinuations due to adverse events were low.

Based on these results, Dr Pujade-Lauraine concluded that "in a heavily pre-treated ovarian cancer population, rechallenge with maintenance following response to platinum-based chemotherapy provided a statistically significant improvement of PFS compared with placebo, irrespectively of *BRCA*-mutation status. A proportion of patients derived clinically relevant long-term benefit."

1. Pujade-Lauraine E, et al. Maintenance olaparib rechallenge in patients (pts) with ovarian carcinoma (OC) previously treated with a PARP inhibitor (PARPi): Phase IIIb OReO/ENGOT Ov-38 trial. Abstract LBA33, ESMO Congress 2021, 16–21 September.

Pembrolizumab prolongs survival in persistent, recurrent, or metastatic cervical cancer

First results from KEYNOTE-826 showed that addition of pembrolizumab to chemotherapy ± bevacizumab significantly improved survival in patients with persistent, recurrent, or metastatic cervical cancer, regardless of PD-L1 expression.

Standard treatment for persistent, recurrent, or metastatic cervical cancer is platinum-based chemotherapy, with platinum, paclitaxel, and bevacizumab as a preferred regimen [1]. PD-L1 inhibitors have shown efficacy as monotherapy in previously treated patients with cervical cancer [2,3].

KEYNOTE-826 (NCT03635567) evaluated the efficacy and safety of pembrolizumab plus chemotherapy (plus bevacizumab at the investigators' and patients' discretion). Eligible patients had persistent, recurrent, or metastatic cervical cancer, were not amenable to curative treatment, and had not previously been treated with systemic chemotherapy (unless as part of chemoradiotherapy).

A total of 617 patients were randomised 1:1 to pembrolizumab (200 mg every 3 weeks for ≤35 cycles) or placebo added to 6 cycles of chemotherapy (paclitaxel plus cisplatin or carboplatin) ± bevacizumab (15 mg/kg every 3 weeks). Patients were stratified by metastatic status at diagnosis, planned bevacizumab use, and PD-L1 combined positive score (CPS). Of all patients enrolled, 51% were CPS ≥10, 38% were CPS 1-10, and 11% were CPS <1. Dual primary endpoints were progression-free survival (PFS) and overall survival (OS). First results of KEYNOTE-826 were presented by Prof. Nicoletta Colombo (Istituto Europeo di Oncologia, Italy) [4].

Addition of pembrolizumab to chemotherapy (± bevacizumab) significantly improved PFS and OS in the CPS ≥1, all-comer, and CPS ≥10 population. Median PFS was 10.4 months versus 8.2 months (CPS ≥1), 10.4 months versus 8.1 months (CPS ≥10), and 10.4 months versus 8.1 months (all-comers), compared with placebo. Median OS was not reached versus 16.3 months (CPS ≥1), not reached versus 16.4 months (CPS ≥10), and 24.4 months versus 16.5 months (all-comers), compared with placebo. The pembrolizumab benefit was seen regardless of bevacizumab use. Grade ≥3 adverse events incidence was 81.8% in the pembrolizumab plus chemotherapy arm and 75.1% in the placebo plus chemotherapy arm.

Based on these results, Prof. Colombo concluded that "pembrolizumab plus chemotherapy provided statistically significant and clinically meaningful improvement of both PFS and OS in patients with persistent, recurrent, or metastatic cervical cancer. Along with a manageable safety profile, these data suggest pembrolizumab plus chemotherapy may be a new standard of care for this population."

1. Tewari KS, et al. N Engl J Med. 2014;370:734-743.
2. Chung HC, et al. J Clin Oncol. 2019;3:1470-1478.
3. Tewari KS, et al. EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9: Interim analysis of phase III trial of cemiplimab vs. investigator's choice (IC) chemotherapy (chemo) in recurrent/metastatic (R/M) cervical carcinoma. Abstract VP4-202, ESMO Congress 2021, 16–21 September.
4. Colombo N, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for persistent, recurrent, or metastatic cervical cancer: randomized, double-blind, phase 3 KEYNOTE-826 study. Abstract LBA2, ESMO Congress 2021, 16–21 September.

Pembrolizumab has durable effect in previously treated MSI-H/dMMR advanced endometrial cancer

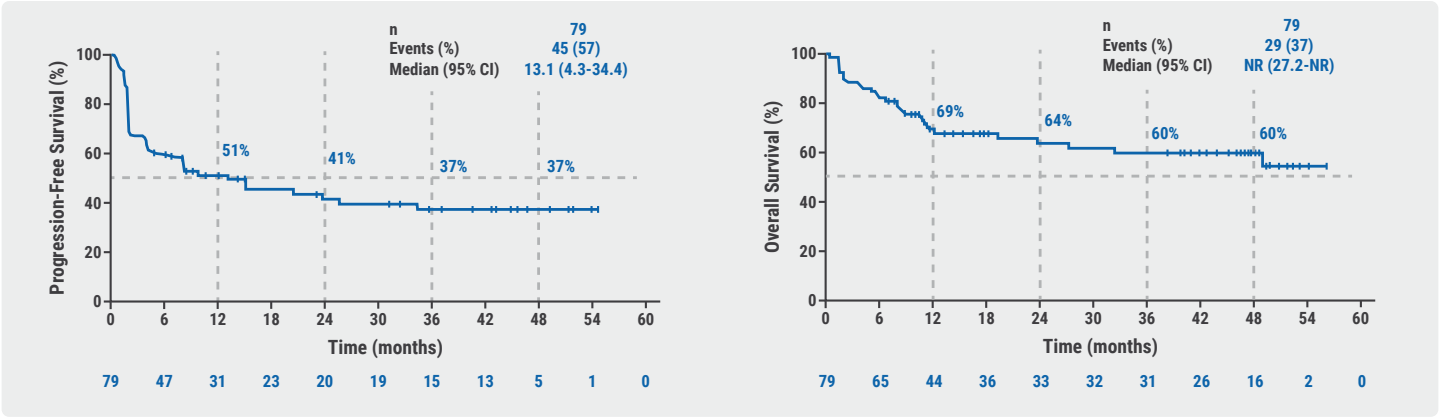
Longer follow-up from the phase 2 KEYNOTE-158 trial showed pembrolizumab to have promising and long-standing efficacy in patients with previously treated MSI-H/dMMR advanced endometrial cancer.

Treatment options for previously treated, advanced, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumours are limited. Pembrolizumab showed a durable and clinically meaningful benefit in previously treated, advanced MSI-H/dMMR tumours – including endometrial cancer – in the non-randomised, open-label, phase 2 KEYNOTE-158 study (NCT02628067) [1]. Prof. David O'Malley (Ohio State University, USA) presented longer follow-up data in 90 patients with previously treated, advanced, MSI-H/dMMR endometrial cancer [2].

Patients received pembrolizumab (200 mg every 3 weeks) for up to 35 cycles. Primary endpoint was overall response rate (ORR); secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety.

At data cut-off, 18/90 patients (20%) had completed 35 cycles of pembrolizumab and 52 patients (58%) had discontinued treatment. In the efficacy population (n=79), median time from first dose to data cut-off was 42.6 month. ORR was 48%, with DOR ≥3 years in 68 patients. Median PFS was 13.1 months, PFS rates at 24, 36, and 48 months were 41%, 37%, and 37%. Median OS was not reached, OS rates at 24, 36, and 48 months were 64%, 60%, and 60% (see Figure).

Figure: PFS and OS results from KEYNOTE-158 [2]



Treatment-related adverse events were observed in 68/90 patients (76%). Immune-mediated adverse events and infusion reactions were observed in 25 patients (28%).

Based on these results, Prof. O'Malley concluded that "pembrolizumab monotherapy represents a promising treatment option for patients with previously treated, MSI-H/dMMR, advanced endometrial cancer."

1. Marabelle A, et al. J Clin Oncol. 2020;38:1-10.
2. O'Malley DM. Et al. Pembrolizumab (pembro) in patients (pts) with microsatellite instability-high (MSI-H) advanced endometrial cancer (EC): Updated results from KEYNOTE-158. Abstract 795MO, ESMO Congress 2021, 16–21 September.

HRR mutational status is prognostic and predictive biomarker olaparib activity

Homologous recombination repair (HRR) mutation status in patients with recurrent, platinum-sensitive ovarian cancer is prognostic for progression-free survival (PFS) and predictive for activity of olaparib compared with chemotherapy, results from pre-planned exploratory analysis of the NRG-GY004 trial showed.

Homologous recombination deficiency (HRD) is associated with improved efficacy of PARP inhibitors in patients with (recurrent) platinum-sensitive ovarian cancer, but interaction between HRD and combined anti-angiogenics and PARP inhibitors is unclear. Previously presented results from the randomised phase 3 NRG-GY004 trial (NCT02446600) did not show an improved PFS or overall response rate (ORR) of the combination cediranib/olaparib compared with platinum-based chemotherapy [1]. Assessment of outcomes by HRD status was a pre-planned translational endpoint. Results were presented by Dr Joyce Liu (Dana-Farber Cancer Institute, MA, USA) [2].

Associations between clinical outcomes, HRR mutation status, and loss of heterozygosity (LOH) in 470 patients were evaluated. Core HRR genes were wildtype (HRRwt) in 323 patients, mutant (HRRmt) in 147, and not assessable (NA) in 21. Over 90% of HRRmt were *BRCA*-mutated. LOH was low in 147 patients, high in 79, and NA in 265, mostly due to inadequate tumour content. Across all patients, HRRmt was prognostic for a longer PFS versus HRRwt (median PFS 13.7 vs 8.3 months; HR 0.41: P<0.0001). In patients with HRRmt, median PFS was 12.3, 13.1, and 20.4 months for chemotherapy, olaparib, and cediranib/olaparib, respectively. In patients with HRRwt, median PFS was 9.0, 6.4, and 8.5 months for chemotherapy, olaparib, and cediranib/olaparib. So, HRR status predicted olaparib response versus chemotherapy (P=0.0176) but not cediranib/olaparib response versus chemotherapy (P=0.1009). LOH was not an independently prognostic and/or predictive biomarker for activity versus chemotherapy.

"In NRG-GY004 patients, HRR mutational status, but not LOH, was prognostic for PFS and predictive for activity of olaparib compared with chemotherapy," summarised Dr Liu.

1. Liu JF, et al. J Clin Oncol 38: 2020 (suppl; abstr 6003).
2. Liu JF, et al. Association of homologous recombination deficiency (HRD) with clinical outcomes in a phase III study of olaparib or cediranib and olaparib compared to platinum-based chemotherapy in recurrent platinum-sensitive ovarian cancer (PSOC): Biomarker analyses from NRG-GY004. Abstract LBA34, ESMO Congress 2021, 16–21 September.

Mutational analyses are predictive in malignant lymphomas

Mutational profiles are predictive for transformation in patients with follicular lymphoma and for overall survival in patients with gastrointestinal diffuse large B-cell lymphoma (DLBCL), 2 presentations showed.

Follicular lymphoma is an indolent but mainly incurable disease. Histological transformation to DLBCL is associated with rapid progression, treatment resistance, and poor prognosis. Prior research showed a prognostic signature for transformation [1]. Dr Ismael Fernández-Miranda (Institute of Sanitary Investigation Puerta de Hierro, Spain) now reported on the validation of a previously identified, prognostic, genetic signature (*DTX1*, *HIST1H1E*, *UBE2A*, *NOTCH2*) [2].

A targeted massive parallel sequencing was performed on new diagnostic samples from 21 pre-transformed and 30 non-transformed patients. Additionally, the previously published cohort of 42 samples (22 pre-transformed and 20 non-transformed patients) was included to enable risk analysis. In this validation sample, the detection of mutations in *HIST1H1E*, *NOTCH2*, *UBE2A*, and *IRF8* were statistically ($P<0.05$) associated with transformation by the multivariate Cox analysis. Inclusion of the Follicular Lymphoma International Prognostic Index (FLIPI) with alterations in *HIST1H1E*, *NOTCH2*, *UBE2A*, and *IRF8* into the multivariate Cox model rendered a classification of the samples into 3 risk groups, with distinct transformation probabilities at 5 years ($P<0.0001$).

"Genomic analysis on follicular lymphoma samples have enabled the association of mutated genes with higher risk of transformation," concluded Dr Fernández-Miranda. "Integration of the mutational status with clinical risk factors into a predictive model improves the risk stratification and could be useful for identifying patients at higher risk of transformation."

About 10% of DLBCL cases primarily occur in the gastrointestinal tract. Previous reports have revealed that primary gastrointestinal DLBCL harbours different genetic mutations from other nodal or extranodal DLBCL [3]. However, the exonic mutation profile of primary gastrointestinal DLBCL has not been fully addressed. Therefore, Chinese investigators now performed whole-exome sequencing of 53 matched tumour and normal samples from primary gastrointestinal DLBCL patients. Dr Shan-Shan Li (Hospital of Sun Yat-sen University, China) presented the results [4]. A total of 6,848 protein-altering events were found in the primary gastrointestinal DLBCL cohort, and among these mutations, the 5 most frequent mutated genes were *IGLL5* (47%), *TP53* (42%), *BTG2* (28%), *IGHV2-70* (26%), and *P2RY5* (26%). Compared with the nodal DLBCL, significantly less mutations were found within *MYD88* (0%), *EZH2* (0%), or *BCL2* (2%) genes in primary gastrointestinal DLBCL. The top 50 mutated genes of primary gastrointestinal DLBCL were mostly enriched in pathways related to complement activation, immunoglobulin receptor binding, and positive regulation of B-cell activation. Moreover, the nucleotide mutational signature analysis revealed that the primary gastrointestinal DLBCL mutation pattern was fitted with COSMIC signature 3, which has been implicated with the activation-induced cytidine deaminase during the pathogenesis of chronic lymphocytic leukaemia. In addition, survival analysis demonstrated that primary gastrointestinal DLBCL patients with wildtype *P2RY8* gene, an orphan Gα13-coupled receptor promoting the clustering of activated B cells, had a significantly longer overall survival time compared with those harbouring its mutation after receiving tumour resection surgery plus rituximab-based therapy.

"Our study provides a comprehensive view of the exonic mutational landscape of primary gastrointestinal DLBCL, within which a specific gene cluster was mutated relating to humoral immunity activation and *P2RY8* mutation was associated with patient prognosis," concluded Dr Li.

1. González-Rincón J, et al. PLoS One. 2019;14(2):e0212813.
2. Fernandez-Miranda I, et al. A gene signature to predict risk of transformation in patients with follicular lymphoma. Abstract 829MO, ESMO Congress 2021, 16–21 September.
3. Ye H, et al. Int J Clin Exp Pathol. 2015;8(10):13043–13050.
4. Li S, et al. Exonic mutation profile of primary gastrointestinal diffuse large B-cell lymphoma. Abstract 828MO, ESMO Congress 2021, 16–21 September.

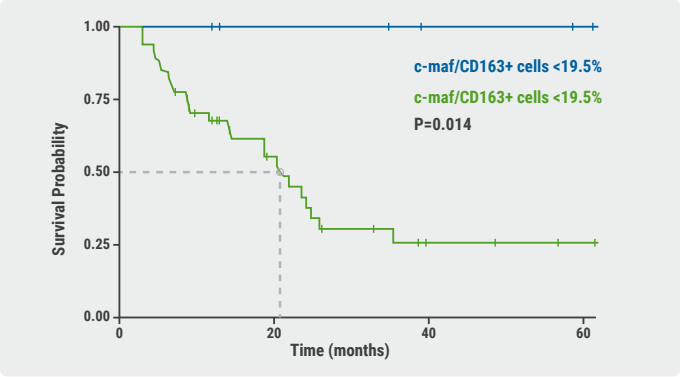
Low numbers of M2 macrophages in tumour microenvironment associated with superior response to immunotherapy in Hodgkin lymphoma

A low baseline number of M2 macrophages in Hodgkin lymphoma patients treated with nivolumab was associated with complete remission and high progression-free survival (PFS), Russian investigators showed.

One of the explanations for the depressed anti-tumour response in classical Hodgkin lymphoma is hyperexpression of inhibitory immune checkpoint receptors on T cells as well as increased proportion of M2 macrophages in the tumour microenvironment. The presence of high number of M2 has been demonstrated to worsen the prognosis of patients treated with standard chemotherapy, while data regarding the prognostic value of tumour microenvironment features in patients treated with PD-1 inhibitors is limited.

A retrospective study included 61 primary tumour samples from patients with relapsed/refractory Hodgkin lymphoma treated with nivolumab, and 15 repeated samples were obtained during relapse or progression of disease after immunotherapy [1]. The tumour microenvironment was characterised by the proportion of cells positive for CD68, CD163, PD-1, LAG-3, TIM-3, CTLA-4, TIGIT, c-MAF present in the samples. The antibody combination CD163/c-MAF was used for identification of M2, the anti-inflammatory-like macrophages. Dr Liudmila Fedorova (Pavlov University, Russia) presented the results [1].

Figure: Presence of tumour-associated macrophages predicts PFS outcome of nivolumab treatment [1]



Both a relatively low presence of CD163-positive cells (P=0.0086) and CD68-positive cells (P=0.037) at baseline appeared to be associated with an inferior 4-year PFS after treatment with nivolumab, whereas a relatively low presence of CD163/c-MAF-positive (i.e. M2) cells was associated with a superior 4-year PFS (P=0.014; see Figure). In addition, an association was observed between complete remission achievement to nivolumab and a lower level of M2 in primary biopsies (P=0.047). In the analysis of sequential samples, an increase of PD-1-positive and LAG-3-positive T cells and depletion of CD68-positive and CD163-positive cells was observed after nivolumab treatment.

"We found that low numbers of M2 macrophages in primary samples were associated with achievement of complete response and higher PFS," concluded Dr Fedorova.

1. Fedorova L, et al. Immune microenvironment in classical Hodgkin lymphoma: Composition and dynamics in patients with relapsed/refractory disease. Abstract 832MO, ESMO Congress 2021, 16–21 September.

COVID-19

Adequate response to SARS-CoV-2 vaccine in cancer patients

Results from both the VOICE and CAPTURE study showed that cancer patients in general have an adequate response to SARS-CoV-2 infection and/or SARS-CoV-2 vaccination.

Patients with cancer have an increased risk of complications from SARS-CoV-2 infection [1]. Vaccination is recommended, but the impact of chemotherapy and immunotherapy on immunogenicity and safety is still unclear [2]. The prospective, multicentre, non-inferiority VOICE trial (NCT04715438) aimed to assess the impact of immunotherapy, chemotherapy, and chemo-immunotherapy on immunogenicity and safety of SARS-CoV-2 vaccination in patients treated for a solid tumour [3].

VOICE compared 4 cohorts: individuals without cancer (A) and patients with solid tumours who were treated with immunotherapy (B), chemotherapy (C), or chemo-immunotherapy (D). Participants received 2 mRNA-1273 vaccinations 28 days apart. The primary endpoint was SARS-CoV-2 Spike S1-specific IgG serum antibody response, defined as >10 binding antibody units (BAU)/mL, 28 days after the second vaccination. An adequate response was defined as a cut-off level of 300 BAU/mL based on the neutralising capacity of vaccine-induced antibodies. First results were presented by Dr Sjoukje Oosting (University Medical Center Groningen, The Netherlands).

In total, 743 of 791 enrolled participants were antibody-negative at baseline, received 2 mRNA-1273 vaccinations 28 days apart, and completed assessments on day 28 after the second vaccination (per protocol population). The primary endpoint was achieved in 100%, 99.3%, 97.4%, and 100% of the participants in cohorts A, B, C, and D. The antibody response was considered adequate after the second vaccination in respectively 99.6%, 93.1%, 83.8%, and 88.8% in cohorts A, B, C, and D. Moreover, spike-specific T cell responses were detected in 46.7% of suboptimal and non-responders. No new safety signals were observed.

"These data show that vaccination with mRNA-1273 is safe in patients receiving immunotherapy, chemotherapy, or chemo-immunotherapy for a solid tumour," concluded Dr Oosting. "Seroconversion rate is very high after 2 vaccinations and non-inferior to controls. However, a significant minority of patients does not develop an adequate antibody response. An additional booster may turn inadequate into adequate responders. In addition, longer follow-up will indicate if there is a difference in the duration of immune response between patients and controls."

In line with these results, results from CAPTURE (NCT03226886), presented by Dr Scott Shepherd (Royal Marsden NHS Foundation Trust, UK) [4], showed that infection with SARS-CoV-2 induces durable immune responses in cancer patients. However, haematological malignancy patients had impaired immune responses that were disease and treatment-specific (anti-CD20), but with evidence suggestive of compensation from T cells. In addition, neutralising responses to Beta and Delta variants are reduced when compared with wildtype SARS-CoV-2. CAPTURE also showed a diminished serological response to vaccination in patients with haematological malignancies, in particular a diminished serological response to Delta variant. However, prior SARS-CoV-2 infection booster vaccines induced responses. "These results lend support to prioritisation of all cancer patients for further booster vaccination," concluded Dr Shepherd.

1. Venkatesulu BP, et al. JNCI Cancer Spectr. 2021; 5(2):pkaa102.
2. Garassino MC, et al. Ann Oncol. 2021;32:579–581.
3. Oosting S, et al. Vaccination against SARS-CoV-2 in patients receiving chemotherapy, immunotherapy, or chemo-immunotherapy for solid tumors. Abstract LBA8, ESMO Congress 2021, 16–21 September.
4. Shepherd STC, et al. Adaptive immunity to SARS-CoV-2 infection and vaccination in cancer patients: The CAPTURE Study. Abstract 1557O, ESMO Congress 2021, 16–21 September.

Cancer patients more likely to die from COVID-19 when hospital admittance is required

Results from prospective data of >20,000 hospitalised patients with (a history of) cancer and COVID-19 show that these patients are more likely to die from COVID-19 than non-cancer patients with COVID-19.

To evaluate the influence of (a history of) cancer on the in-hospital outcomes of patients with COVID-19, the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) WHO Clinical Characterisation Protocol (CCP) UK (ISRCTN66726260) has collected complete data from 195,000 COVID-19 patients in the UK from 17 January 2020 to 12 August 2021. A total of 15,250 of these patients had a history of cancer and 5,357 were on active treatment for cancer. In-hospital outcomes of patients with (a history of) cancer were compared to those patients with no history of cancer. Dr Tom Drake (University of Edinburgh, UK) presented the results [1].

Relative mortality was increased in both patients with a history of cancer and patients on active treatment for cancer compared with non-cancer patients (38.9% and 37.6% vs 23.6%). Although patients with a history of cancer were older than non-cancer patients (77.5 vs 67.0 years), patients on active treatment were not (69.8 years). In addition, no differences in comorbidity could explain the difference in relative mortality. Relative mortality was particularly increased in younger cancer patients and diminished with age. Patients with (a history of) cancer were significantly less likely to be admitted to the critical care unit, compared with non-cancer patients. In addition, where relative mortality in non-cancer patients gradually decreased during the pandemic, no reduction in relative mortality over time was observed in cancer patients with COVID-19. In contrast, relative mortality for COVID-19 hospitalised cancer patients spiked in August 2020 and May 2021.

"At the moment, it is unclear what is driving poorer outcomes and lack of improvement in outcome over time," said Dr Drake. "A data linkage program is ongoing to explore this question."

1. Drake TM, et al. Prospective data of >20,000 hospitalised patients with Cancer and COVID 19 derived from the COVID 19 Clinical Information Network and international Severe Acute Respiratory and Emerging Infections Consortium WHO Coronavirus Clinical Characterisation Consortium. Abstract LBA60, ESMO Congress 2021, 16–21 September.

Third global survey of the ESMO Resilience Task Force

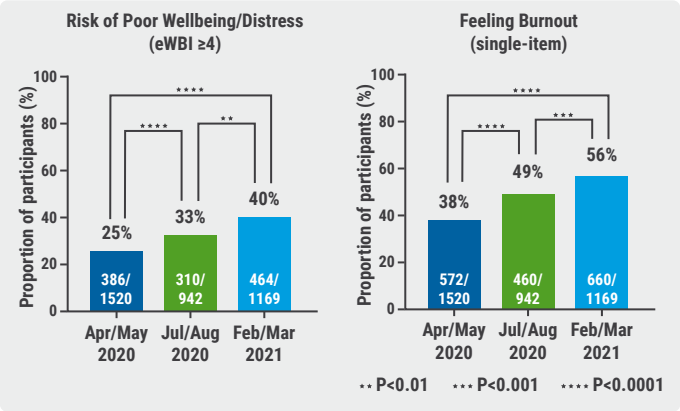
Risk of poor wellbeing/distress and feeling burned out for oncology professionals has increased during the COVID-19 pandemic, results from the third global survey of the ESMO Resilience Task Force show.

From 9 February to 3 March 2021, the ESMO Resilience Task Force did a third global survey on the wellbeing and professional performance of oncology professionals. Dr Jonathan Lim (Imperial College London, UK) presented the results [1]. A total of 1,269 participants responded to the survey (54% aged >40 years, 55% female, 69% white ethnicity, 51% general hospital, 37% cancer centre, 73% medical oncologist, 22% trainees).

Compared with the first (April-May 2020, n=1,520) and second survey (July-August 2020, n=942), scores for risk of poor wellbeing/distress (40%), and feeling burned out (56%) were increased in the third survey. However, job performance score improved since the first survey (see Figure). In particular, young participants (≤40 years) and female participants appeared at significantly higher risk of poor wellbeing/distress (49% and 45%, respectively) and feeling burned out (61% and 63%, respectively). In addition, job demands had steadily increased. Significant increases were reported in feeling overwhelmed with workload, COVID-19-related clinical and research work, out-of-hours work, shift work, and overall working hours, and inadequate time for personal/family life. There were also concerns about the negative impact of the pandemic on career development/training, job security, and international fellowship opportunities. Overall, less than half of the participants felt supported by their work management, professional societies or government, and/or had access to wellbeing support services. One in four participants were considering changing their future career.

"There is a real threat of potential attrition in the current workforce. National and international stakeholders must act together to ensure robust recovery plans as we emerge from the COVID-19 crisis," concluded Dr Lim.

Figure: Comparison of survey results over time during the COVID-19 pandemic [1]



1. Lim J, et al. The future of the oncology workforce since COVID-19: Results of the ESMO Resilience Task Force survey series. Abstract 1561O, ESMO Congress 2021, 16–21 September.

High COVID-19 mortality in Swiss cancer patients

Final results of a national registry on COVID-19 in Switzerland showed a high mortality (21.5%) in cancer patients. Age and disease setting were independent predictors for death.

Cancer patients are at an increased risk of unfavourable outcome of COVID-19 infection. Dr Markus Joerger (Cantonal Hospital St Gallen, Switzerland) presented final results of a national registry on COVID-19 in Switzerland [1].

Data was collected on 501 symptomatic COVID-19-infected cancer patients from 23 Swiss sites, starting 1 March 2020. At data cut-off date of 15 March 2021, 455 patients were included into the final analysis. Most frequent malignancies were breast cancer (14%), lung cancer (10%), prostate cancer (6%), and myeloma (4%); 205 patients (45%) had non-curative disease. Systemic treatment within 3 months prior to COVID-19 diagnosis included chemotherapy (21.8%), targeted therapy (20.7%), steroids (11.6%), and checkpoint inhibitors (7.3%).

A total of 285 patients (62.6%) were hospitalised for COVID-19, 213 (46.8%) required oxygen, 43 (9.5%) invasive ventilation, 62 (13.6%) were admitted to the ICU. Death from COVID-19 infection occurred in 98 patients, resulting in a mortality rate of 21.5%. Age ≥65 versus <65 (OR 3.22; P=0.001), non-

curative versus curative disease (OR 2.34; P=0.008), ICU admission (OR 4.36; P<0.001), and oxygen requirement (OR 22.37; P<0.001) were independently associated with increased mortality. Neither male versus female gender (OR 1.28; P=0.43), haematological versus solid malignancy (OR 0.921; P=0.80), pulmonary comorbidity (OR 0.96; P=0.93), cardiovascular comorbidity (OR 1.11; P=0.75), chemotherapy (OR 1.52; P=0.22), or checkpoint inhibitors (OR 2.81; P=0.082) were significant risk factors for death.

"COVID-19 mortality in Swiss cancer patients is high, 21.5%, for the first wave of the pandemic in a country with a decentralised, high-quality healthcare system with universal access," concluded Dr Joerger.

1. Joerger M, et al. Outcome and prognostic factors of COVID-19 infection in cancer patients: Final results of SAKK 80/20. Abstract 1570P, ESMO Congress 2021, 16–21 September.

Basic Science & Translational Research

Neutrophils negatively correlate with response to anti-PD-1 monotherapy in dMMR tumours

Responses to treatment with anti-PD-(L)1 therapy vary across different mismatch repair deficient (dMMR) tumours. Local inhibitory effects of neutrophils were associated with a poor response.

Clinical studies have highlighted the efficacy of anti-PD-(L)1 treatment in patients with hypermutated microsatellite instability-high (MSI-H) or dMMR tumours. However, the responsiveness of MSI-H/dMMR tumours to anti-PD-(L)1 treatment is variable. To get more insight in the cause of this variability of response, investigators of Institute Gustave Roussy (Paris, France) generated two mouse tumour cell lines inactivated for *MSH2* ($4T1^{MSH2-/-}$ and $CT26^{MSH2-/-}$) to recapitulate the MSI-H/dMMR phenotype. Dr Laetitia Nebot-Bral (Gustave Roussy, France) presented the first results [1].

While anti-PD-1 treatment was effective in the CT26 model, no efficacy was observed in the 4T1 model, even in ultra-mutated 4T1 tumours (>280 mutations/Mb). Unlike the CT26 model, the 4T1 model is characterised by an accumulation of neutrophils. In addition, neutrophil depletion with the antibody αLy6G restored the response of 4T1 tumours to anti-PD-1. The combination of anti-PD-1 and anti-CTLA-4 was also able to restore the response to immunotherapy in the 4T1 model.

"Given that the combination treatment was accompanied by a decrease in neutrophils, it is likely that CTLA-4 blockade may hamper the accumulation of neutrophils," suggested Dr Nebot-Bral.

Based on these results, Dr Nebot-Bral concluded that "accumulation of neutrophils is associated with resistance to anti-PD-(L)1 monotherapy in MSI-H/dMMR tumours. We propose that anti-PD-1 plus anti-CTLA-4 combination therapy may represent an effective strategy in patients with abnormal neutrophil accumulation."

1. Nebot-Bral L, et al. Neutrophils are associated with resistance to anti-PD-1 monotherapy in mismatch repair-deficient tumors. Abstract 1801MO, ESMO Congress 2021, 16–21 September.

Tetraspecific ANKETs harnesses innate immunity in cancer therapies

Tetraspecific, artificial molecules that recognise both tumour antigens and natural killer cell receptors harness the innate immune response to tumours, both *in vitro* and *in vivo*, French investigators showed.

Natural killer (NK) cells are able to kill tumour cells directly and to stimulate anti-tumour T-cell responses indirectly. ANKETs (antibody-based NK cell Engager Therapeutics) are artificial molecules that recognise both tumour antigens and NK cell receptors. Previously, trispecific ANKETs were designed, recognising a tumour antigen as well as CD16 and NKp46, both NK-expressed antigens. Now, Prof. Eric Vivier (University Hospital Marseille, France) presented a tetraspecific ANKET [1]. In addition to NKp46 and CD16, the tetraspecific ANKET also binds to the IL-2 receptor on NK cells.

In vitro, this tetraspecific ANKET promoted IL-2R signalling preferentially in NK cells, inducing primary human NK cell

proliferation and cytolytic activity, and the secretion of cytokines and chemokines only after binding to the tumour target. In mouse models of both invasive and solid tumours, the tetraspecific ANKET induced NK cell proliferation and accumulation at the tumour bed, and had a higher anti-tumour efficacy than approved therapeutic antibodies like obinutuzumab, targeting the same tumour antigen. In non-human primates, CD20-directed tetraspecific ANKETs resulted in sustained CD20-positive B-cell depletion with minimal systemic cytokine release and no clinical sign of toxicity.

"Tetraspecific ANKETs constitute a synthetic technological platform combining the induction of NK cell proliferation and effector functions without toxicity, supporting their clinical development for next-generation cancer immunotherapies," concluded Prof. Vivier.

1. Vivier E, et al. Harnessing innate immunity in cancer therapies: The example of natural killer cell engagers. Abstract 1O. ESMO Congress 2021, 16–21 September.

Early ctDNA reduction in metastatic uveal melanoma correlates better with OS than RECIST response

An early reduction in circulating tumour (ct)DNA after second-line tebentafusp treatment in patients with metastatic uveal melanoma is associated with overall survival (OS), regardless of RECIST response, results from the IMCgp100-202 trial showed.

Treatment with tebentafusp, a novel bispecific fusion protein that targets gp100 and activates T cells, has been shown to reduces the risk of death from metastatic uveal melanoma at 14 months by half, compared with available treatments [1]. However, OS was improved in patients regardless of RECIST best response, suggesting better surrogate efficacy endpoints are needed.

In the IMCgp100-202 trial (NCT02570308), 127 patients with metastatic uveal melanoma were treated weekly with tebentafusp in second line. RECIST was assessed and serum samples (n=118) collected at baseline, week 5, and week 9 were analysed for ctDNA. Dr Alexander Shoushtari (Memorial Sloan Kettering Cancer Center, NY, USA) presented the results [2].

Levels of ctDNA were associated with tumour burden at baseline. At 9 weeks, ctDNA was reduced in 70% of patients on tebentafusp, despite a RECIST response rate of only <10%. ctDNA reduction was strongly associated with improved OS, even in patients with RECIST progressive disease or stable disease. OS rate at 1 year was 100% for patients with ctDNA clearance (n=14) versus 57% for patients with ctDNA not cleared. Best overall response among those with ctDNA clearance was progressive disease in 4 (29%), stable disease in 8 (57%), and partial response in 1 (7%); 1 patient was not evaluable.

Dr Shoushtari concluded that "early ctDNA reduction may be a better surrogate of tebentafusp efficacy than RECIST objective response in patients with metastatic uveal melanoma."

1. Piperno-Neumann S, et al. Cancer Res 2021; 81 (Suppl), CT002.
2. Shoushtari AN, et al. Early reduction in ctDNA, regardless of best RECIST response, is associated with overall survival (OS) on tebentafusp in previously treated metastatic uveal melanoma (mUM) patients. Abstract 1757O, ESMO Congress 2021, 16–21 September.

Gut microbiota as a potential predictive biomarker

The diversity of gut microbiota just before treatment with a checkpoint inhibitor is of predictive value for response and progression-free survival (PFS), first results of the Japanese MONSTAR-SCREEN trial suggest. In addition, sarcopenia in cancer patients appears to be associated with the composition of the gut microbiome.

Immune checkpoint inhibitors (ICIs) have shown promising anti-tumour activity in a variety of cancer types, and gut microbiota have been shown to modulate efficacy of ICIs [1]. For example, *Bifidobacterium longum*, *Dorea formicigenerans*, and *Enterococcus faecium* are associated with good response of ICIs, whereas *Prevotella histocola,* and *Bacteroidales* are associated with poor response of ICIs. In addition, the diversity of the gut microbiome is regarded as predictive for favourable responses to ICIs.

MONSTAR-SCREEN is a nationwide cancer genome-screening project that prospectively assesses gut microbiota and circulating tumour (ct)DNA in 2,000 patients with advanced solid tumours, at 31 Japanese institutions. Dr Kentaro Sawada (Kushiro Rosai Hospital, Japan) reported results from an initial analysis of MONSTAR-SCREEN [2].

16S ribosomal RNA-sequencing was conducted to assess the alpha diversity index (ADI) of faecal microbiome, which was represented as an operational taxonomic unit (OTU)

score (OTU-high was defined as a score >240). Microsatellite instability (MSI) and blood tumour mutational burden (TMB) status were measured at the same timepoints as the faeces collection. In addition, tissue TMB was measured using pre-treatment tissue samples. Primary endpoints of MONSTAR-SCREEN are the association between OTU status, MSI status, blood TMB, and tissue TMB status, as well as response rate (ORR) and PFS on ICIs.

A total of 167 patients were included. Most common cancer types were head and neck cancer (n=43), malignant melanoma (n=26), and gastric cancer (n=25). Of these, 136 (81%) patients received ICI alone, while 31 (19%) received ICI and chemotherapy combination. The ORR in OTU-high patients (n=52) was 35%, while that in OTU-low patients (n=115) was 17% (P=0.01). MSI status, blood TMB status, and tissue TMB status were not associated with ORR. In addition, OTU-high patients had a significantly longer PFS on ICIs than OTU-low patients (8.6 vs 2.6 months; HR 0.48; P=0.002).

"Although this was a preliminary analysis, diversity in gut microbiota just before treatment with ICIs was significantly associated with higher response and longer PFS in patients with advanced solid tumours," concluded Dr Sawada. "These results indicate the potential of OTU as a predictive tumour-agnostic biomarker for the efficacy of ICIs." Further study with shotgun and single cell metagenome analyses are ongoing.

In addition, Dr Zeynep Zengin (City of Hope Comprehensive Cancer Center, CA, USA) presented results of a study exploring the association between stool microbiome and sarcopenia in patients with metastatic renal cell cancer (mRCC) or metastatic breast cancer (mBC) [3]. In 82 patients (62 mRCC, 20 mBC; 37 sarcopenic, 45 non-sarcopenic) the microbiome was analysed. Species that were differentially abundant were *Alistipes putredinis* and *Dialister sp*. CAG 357 in patients with sarcopenia, and *Collinsella aerofaciens* in patients without sarcopenia. "More studies are needed to determine if there is a causal interplay," concluded Dr Zengin

.

1. Helmink BA, et al. Nat Med 2019;25:377–388.
2. Sawada K, et al. Gut microbiota and efficacy of immune-checkpoint inhibitors (ICIs) in patients (pts) with advanced solid tumor: SCRUM-Japan MONSTAR-SCREEN. Abstract 60MO, ESMO Congress 2021, 16–21 September.
3. Zengin Z, et al. Associations between sarcopenia and gut microbiota in patients with metastatic renal cell carcinoma and breast cancer. Abstract 1759MO, ESMO Congress 2021, 16–21 September.

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