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PEER-REVIEWED CONFERENCE REPORT

Interim Results from KEYNOTE-522

The first phase 3 trial of immunotherapy in early breast cancer revealed that immunotherapy added to chemotherapy improves pathological complete response in patients with early triple-negative breast cancer.

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PARP Inhibition in PROfound Trial

Olaparib delayed cancer progression by 4 months compared with new hormonal agents in patients with metastatic, pre-treated prostate cancer characterised by faulty DNA repair.

read more on PAGE 17

DNA Profiling of CUP

New research in carcinoma of unknown primary (CUP) showed that 1 in 3 patients may be suitable for matched targeted treatment or immunotherapy based on DNA changes in their tumour.

read more on PAGE 24

MEDICOM MEDICAL PUBLISHERS

Editor Dr Stefan Rauh, Centre Hospitalier Emile Mayrisch, Luxembourg

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Letter from the Editor

Stefan Rauh

Dear Reader,

Welcome to Medicom's report of this year's ESMO Annual Congress!

Again, as in previous years: quite some practice changing studies.
Remarkably, in the field of ovarian cancer, there are three parallel studies providing evidence for clinically relevant benefit of targeted agents (PARP inhibitors) – as well as the predictive factors: BRCA as an already established – and HRD, a "BRCA-ness" predictive factor well established through the 3 studies, broadening the patient group identifiable as the most benefitting.

Read the exciting results presented by Julien Taieb: are we getting closer to a true predictive marker in stage II colorectal cancer in detecting circulating tumor DNA after primary surgery? Can we stratify adjuvant treatment according to ctDNA?

Will we eventually treat all our patients with advanced non-small cell lung cancer without chemotherapy?

…just some examples. I'll stop here and let you have a closer look at our report.

Medical Oncology – truly evolving!

Yours, sincerely
Stefan Rauh

Biography

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

Conflict of Interest Statement:
Nothing to declare.

Breast Cancer

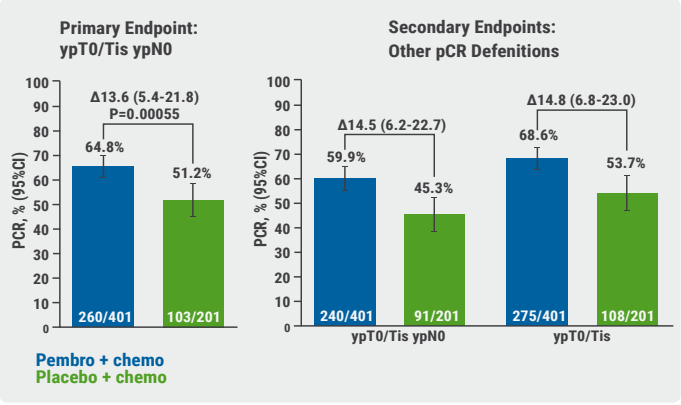
Triple-negative breast cancer gets positive news: KEYNOTE-522 interim results

Immunotherapy added to chemotherapy improves pathological complete response in patients with early triple-negative breast cancer, according to late-breaking results from the KEYNOTE-522 trial presented by Prof. Peter Schmid (Queen Mary University of London, UK) [1]. Interim results from the study, which is the first phase 3 trial of immunotherapy in early breast cancer, also indicated a non-significant trend of improvement in event-free survival.

KEYNOTE-522 investigated whether adding immunotherapy to chemotherapy prior to surgery could improve pathological complete response and event-free survival in women with early triple-negative breast cancer. A total of 1,174 patients were randomly allocated at a 2:1 ratio to pembrolizumab or placebo, both added to preoperative chemotherapy with anthracyclines, taxanes, and platinum for 5-6 months. After surgery, patients continued their allocated treatment of pembrolizumab or placebo for 9 cycles.

The analysis presented was performed after a median follow-up of 15.5 months. Pathological complete response, assessed in the first 602 patients, significantly improved from 51.2% (95% CI 44.1–58.3) in the placebo group to 64.8% (95% CI 59.9–69.5) in the pembrolizumab group (P=0.00055; see Figure).

Figure. Pathological complete response (pCR) at KEYNOTE-522 interim analysis



© Peter Schmid (provided by ESMO).

Because triple-negative breast cancer is aggressive and recurrences often occur early on, the investigators conducted an interim analysis of event-free survival. There was a favourable trend for the pembrolizumab group with a hazard ratio of 0.63 (95% CI 0.43–0.93), Prof. Schmid said. "These are preliminary data, but they provide a strong sign that the addition of immunotherapy to neoadjuvant chemotherapy prevents breast cancer recurrence. If we prevent recurrence, we cure more patients, but we need longer-term data for confirmation."

Grade 3 or higher treatment-related adverse events occurred in 78.0% and 73.0% of the pembrolizumab and placebo groups, respectively. Prof. Schmid noted that many of the side-effects were driven by the intensive chemotherapy regimen. Side-effects with a potential link to immunotherapy occurred in 42% of study participants taking pembrolizumab vs 21% on placebo. No new safety signals were identified.

1. Schmid P et al. ESMO Congress 2019. Abstract LBA8_PR.

CDK4/6 inhibitors change landscape of breast cancer treatment: 2 studies

New data from 2 studies has shown that treatment with a CDK4/6 inhibitor plus fulvestrant improves overall survival in women with hormone receptor-positive (HR+), human epidermal growth factor 2-negative (HER2-) advanced breast cancer [1,2].

The 2 studies included different patient populations as well as different CDK4/6 inhibitors used in different lines of therapy: Monarch 2 evaluated abemaciclib plus fulvestrant in patients with advanced breast cancer after failure of endocrine therapy and regardless the menopausal status; the Monaleesa-3 study investigated ribociclib plus fulvestrant as first- or second-line combination therapy only in postmenopausal patients.

Results of the Monaleesa-3 [1] trial have shown that first-line as well as second-line treatment with the CDK4/6 inhibitor ribociclib plus fulvestrant significantly improves overall survival in postmenopausal patients with HR+, HER2- advanced breast cancer. The benefits with ribociclib plus fulvestrant were seen in women not previously treated with hormonal therapy as well as in those who had become resistant to endocrine therapy.

"This is a significant, practice-changing report, in that we are now saying that patients with advanced breast cancer will have an overall survival benefit if they get the CDK4/6 inhibitor ribociclib upfront at the time of their recurrence, even if they have not had any prior endocrine therapy at the time of presenting with metastatic disease," said presenting author Prof. Dennis Slamon (University of California Los Angeles, USA).

"The argument has always been by some experts that you should first treat with endocrine therapy alone and then if patients recur, you would add something like a CDK4/6 inhibitor. In other words, you get what you can out of endocrine therapy alone, and save a CDK4/6 inhibitor until the subsequent recurrence. The data from Monaleesa-3 clearly show that if postmenopausal patients receive this right up front there is a very significant benefit, not only in progression-free survival –which had already been published– but now with this new report in overall survival, which is the hardest endpoint to reach and the most important one in terms of making an impact on the disease," Prof. Slamon explained.

The same session featured another trial, Monarch 2, which showed statistically and clinically meaningful improvement in overall survival with the CDK4/6 inhibitor abemaciclib plus fulvestrant in pre- and peri- as well as in postmenopausal women with HR+, HER2- advanced breast cancer resistant to hormonal therapy [2].

"Results from the Monarch 2 study presented two years ago [3] showed significant improvement in progression-free survival for patients treated with the combination of abemaciclib plus fulvestrant compared with fulvestrant alone. Now, with further follow-up we have overall survival data showing a statistically significant and clinically meaningful improvement in overall survival with the combination," said study first author Prof. George Sledge (Stanford University School of Medicine, USA).

Prof. Nadia Harbeck (University of Munich, Germany) commented on the relevance of the new studies, "The results of Monarch 2 nicely complement those reported in Monaleesa-3. Abemaciclib is the third CDK4/6 inhibitor to show an overall survival benefit in advanced HR+, HER2- breast cancer. Together with the data we have seen before with palbociclib [4] and ribociclib, these new data strengthen the argument that we should start treatment in the metastatic setting with a CDK4/6 inhibitor plus endocrine therapy because these drugs substantially improve patient outcomes compared with anti-hormonal treatment alone."

Considering possible limitations of the studies, Prof. Harbeck said, "All three of the CDK4/6 inhibitors powered their studies for progression-free survival and not for overall survival. Nevertheless, I think the data are strong enough, taken together, to give us certainty that this is really the way forward in this disease; to go for endocrine-based therapy plus CDK4/6 inhibition and not just endocrine therapy alone." She added that she would like to see detailed quality of life data from Monarch 2 to accompany the survival data and hoped this will be made available in the future. Moreover, she stated that these results make the doctors and patients hopeful for the results of the CDK4/6 inhibitor studies in early breast cancer, the first ones of which will be reported in the near future.

1. Slamon D et al. ESMO Congress 2019. Abstract LBA7_PR.
2. Sledge GW et al. ESMO Congress 2019. Abstract LBA6_PR.
3. Sledge GW et al. J Clin Oncol 2017; 35: 2875-2884.
4. Turner N et al. N Engl J Med 2018; 379:1926-1936.

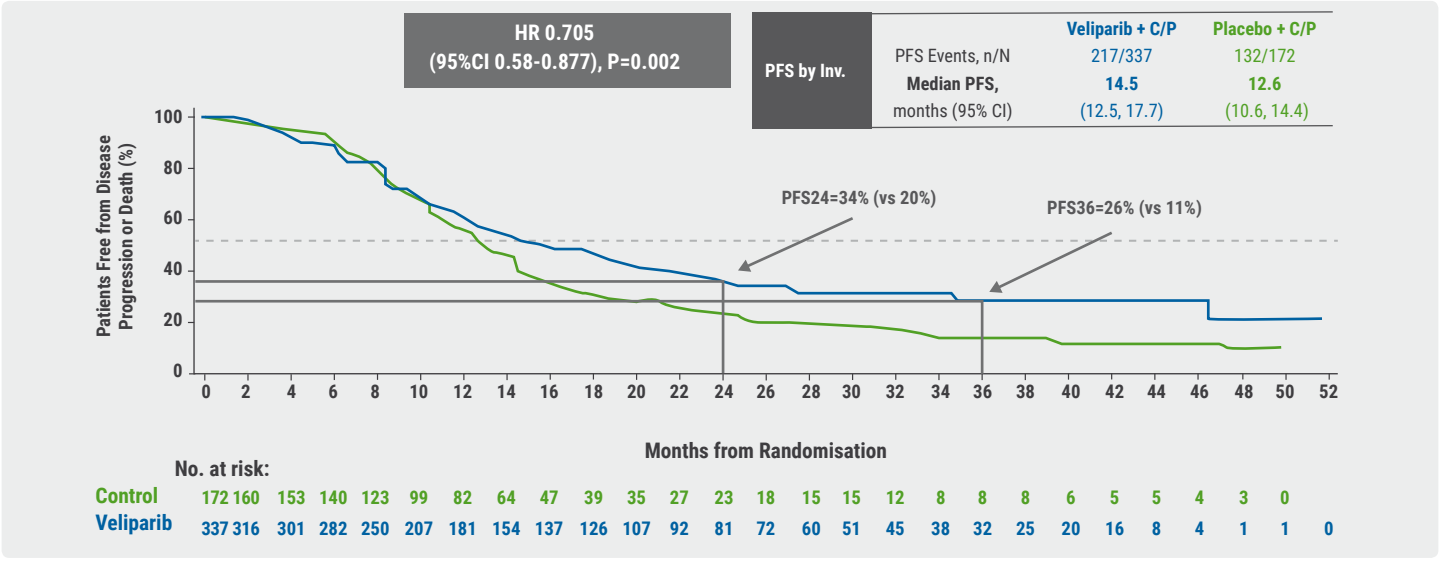
Veliparib-chemo combo prolongs survival without disease progression in some advanced breast cancer patients

The double blind, placebo-controlled, phase 3 BROCADE3 trial showed that veliparib in combination with chemo-therapy significantly prolongs progression-free survival (PFS) in women with metastatic HER2-negative breast cancer with *BRCA* mutations, compared with women on chemotherapy alone. Results were presented by Veronique Diéras (Centre Eugène Marquis, Rennes, France) [1].

The rationale behind the trial rose from the fact that *BRCA*-mutated tumours are deficient in homologous recombination that occurs during DNA repair, making them susceptible to both platinum and PARP inhibitors, such as veliparib. Patients were randomised 2:1 to receive oral veliparib at 120 mg twice daily or placebo on days 2 to 5, administered with carboplatin AUC 6 on day 1 and weekly paclitaxel at 80 mg/m^2 on days 1, 8, and 15 in 21-day cycles. Patients discontinuing both carboplatin and paclitaxel without disease progression received blinded single agent veliparib at 300 to 400 mg twice daily or placebo. All patients had germline *BRCA*1/2 mutations and had previously received ≤2 lines of cytotoxic therapy for metastatic breast cancer. Investigator-assessed PFS served as the primary endpoint and secondary endpoints included overall survival (OS), clinical benefit rate (CBR), objective response rate (ORR), and PFS2.

Median PFS per investigator in 337 patients treated with veliparib plus chemotherapy was 14.5 months (95% CI 12.5–17.7)

Figure. BROCADE3 primary endpoint: PFS by Investigator Assessment



compared with 12.6 months (95% CI 10.6-14.4) in 172 patients receiving placebo plus chemotherapy (HR 0.71; 95% CI 0.57-0.88; P=0.002: see Figure). Duration of response was longer at 19.3 (95% CI 16.5- 23.3) months compared with 13.5 (95% CI 12.5-16.3) months, respectively (HR 0.70; 95% CI 0.54-0.90). PFS at 3 years was doubled with veliparib; the respective cohorts demonstrated 3-year PFS rates of 26% vs 11%.

Median OS at 24 weeks was unchanged; 33.5 (95% CI 27.6-37.9) months with veliparib/chemotherapy compared with 28.2 (95% CI 24.7-35.2) months with placebo/chemotherapy (HR 0.95; 95% CI 0.73-1.2; P=0.67). Likewise, CBR (90.7% vs 93.2%) and ORR (75.8% vs 74.1%) were similar between arms. However, prolonged PFS2 was seen with veliparib (21.3 months; 95% CI 19.8-25.1) vs placebo (17.4 months; 95% CI 16.0-20.0) HR 0.76.

Importantly, the addition of veliparib did not substantially alter the toxicity profile of chemotherapy. The most common ≥grade 3 adverse event occurring ≥20% of patients in the respective arms were anaemia (27% vs 17%), neutropenia (52% vs 50%), and thrombocytopenia (25% vs 15%).

1. Diéras VC et al. ESMO Congress 2019. Abstract LBA9.

Lung Cancer

Improved response rates without survival benefit with pembrolizumab in pretreated mesothelioma

Results from the PROMISE-meso study showed better response rates but no survival benefit in pretreated mesothelioma patients treated with pembrolizumab monotherapy compared with chemotherapy. Nonetheless, current results are encouraging and the results of investigations of checkpoint inhibitor treatments in earlier stage mesothelioma are eagerly awaited [1].

PROMISE-meso randomised 144 patients with advanced pre-treated mesothelioma to either immune checkpoint inhibitor pembrolizumab (200 mg every 3 weeks) or to investigators' choice of standard chemotherapy (gemcitabine or vinorelbine). Patients in the control group were able to cross over to pembrolizumab at progression. Nearly 4 times more patients responded to immunotherapy. The objective response rate was 22% in patients with pembrolizumab compared with 6% with chemotherapy (P=0.004). Median progression-free survival was 2.5 months (95% CI 2.1 to 4.2)

and 3.4 months (95% CI 2.2 to 4.3) respectively (P=0.76). Median overall survival was 10.7 months for pembrolizumab vs 11.7 months for chemotherapy (P=0.85). Treatment-related adverse events grade ≥3 were experienced by 19% of patients in the pembrolizumab group and 24% in the chemotherapy group, with 1 fatal adverse event in each group.

"In PROMISE-meso, significantly more patients responded to immunotherapy than to standard chemotherapy, but unfortunately these responses did not delay progression or improve survival. These findings are disappointing but, as in previous studies, some patients benefitted from immunotherapy for long periods. If we can find out how this happens, we will have a better idea of which patients should preferentially receive this treatment over chemotherapy," said study author Dr Sanjay Popat (Royal Marsden Hospital NHS Foundation Trust, UK). "Nevertheless, whilst pembrolizumab was not superior to chemotherapy, survival was similar, and so pembrolizumab may represent an alternative."

1. Popat S et al. ESMO Congress 2019. Abstract LBA91_PR.

Frontline ipilimumab/nivolumab improves OS in advanced NCLSC

The first-line combination of ipilimumab plus nivolumab provided clinically meaningful improvement in overall survival (OS) compared with chemotherapy in patients with advanced non–small cell lung cancer (NSCLC), regardless of PD-L1 expression, according to a final analysis of part 1 of the phase 3 CheckMate-227 trial [1].

The open-label CheckMate-227 trial is a multi-cohort study in treatment-naïve patients with stage IV or recurrent NSCLC. In part 1 of the trial, presented by Prof. Solange Peters (Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland), there were 2 cohorts: patients whose tumours expressed ≥1% PD-L1 (part 1a) and those whose PD-L1 expression was <1% (part 1b). In part 1a, 1,189 patients were randomised 1:1:1 to receive either chemotherapy, nivolumab monotherapy, or nivolumab plus low-dose ipilimumab. In part 1b, 550 patients were randomised 1:1:1 to nivolumab/low-dose ipilimumab, chemotherapy, or nivolumab/chemotherapy.

The independent co-primary endpoints of the study were progression-free survival (PFS) in a high tumour mutational burden (TMB) population and OS in the PD-L1 ≥1% population. Secondary endpoints included PFS and OS with nivolumab/chemotherapy vs chemotherapy in the PD-L1 <1% subgroup, and OS with nivolumab vs chemotherapy in patients with PD-L1 expression ≥50%. The minimum follow-up for the primary endpoint was 29 months.

In patients with tumours expressing PD-L1 ≥1% the median OS with nivolumab plus ipilimumab compared with chemotherapy was 17.1 months vs 14.9 months, respectively (HR 0.79; 97.72% CI 0.65-0.96; P=0.007). Moreover, the median OS was 17.1 months with the combination and 13.9 months with chemotherapy in patients regardless of PD-L1 expression (HR 0.73; 95% CI 0.64-0.84). The 1- and 2-year OS rates were 63% and 40% with nivolumab/ipilimumab and 56% and 33% with chemotherapy, respectively. The median duration of response by blinded independent central review was 23.2 months, 15.5 months, and 6.2 months for nivolumab/ipilimumab, nivolumab, and chemotherapy, respectively. Objective response rates (ORR) at 1 year were 64%, 63%, and 28%, respectively; the rates of those in response at 2 years were 49%, 40%, and 11%, respectively. Notably, patients with tumours expressing PD-L1 ≥50% benefitted the most from nivolumab/ipilimumab combination therapy.

In part 1b, patients whose tumours had <1% PD-L1 expression had a median OS of 17.2 months, 15.2 months, and 12.2 months with nivolumab/ipilimumab, nivolumab/chemotherapy, and chemotherapy, respectively (HR for nivolumab/ipilimumab vs chemotherapy 0.62; 95% CI 0.48-0.78; HR for nivolumab/chemotherapy vs chemotherapy 0.78; 95% CI 0.60-1.02) The 1-year OS rates with nivolumab/ipilimumab, nivolumab/chemotherapy, and chemotherapy were 60%, 59%, and 51%, respectively; the 2-year OS rates were 40%, 35%, and 23%, respectively.

For all randomised patients, regardless of PD-L1 expression, the 1-year OS rates with nivolumab/ipilimumab and chemotherapy were 62% and 54%, respectively; the 2-year OS rates were 40% and 30%, respectively.

Additionally, no new safety findings of the combination were reported with longer follow-up. Grade 3/4 treatment-related adverse events were reported in 33%, 19%, and 36% of patients in the nivolumab/ipilimumab, single-agent nivolumab, and chemotherapy arms, respectively.

One limitation of this study was that it compared nivolumab/ipilimumab with nivolumab monotherapy as a second immunotherapy option (which has not shown benefit in the first-line setting in PD-L1 expressing patients). In the treatment group expressing PD-L1, the main response seems to have been driven by the high PD-L1 expressing tumours, with an overall response similar to other checkpoint inhibitor monotherapy in

other studies, but higher toxicity. In tumours not expressing PD-L1, the response rate was significantly higher as compared with platinum doublet chemotherapy. This did however not translate in a survival benefit and came with notable toxicity.

1. Peters S, et al. ESMO Congress 2019. Abstract LBA4.
2. Hellmann MD et al. N Eng J Med. doi: 10.1056/NEJMoa1910231.

First-line osimertinib significantly lengthens OS in NSCLC

Prof. Suresh Ramalingam (Emory University, Atlanta, USA) presented the final overall survival (OS) data of the FLAURA trial in the first Presidential Symposium. First-line osimertinib significantly lengthened overall survival compared with first generation EGFR TKIs (gefitinib or erlotinib) in patients with advanced non–small cell lung cancer (NSCLC) harbouring Ex19del/L858R *EGFR* mutation [1].

The primary endpoint of progression free survival (PFS) was previously reported [2]. Final overall survival results were presented (58% maturity): the median OS with osimertinib was 38.6 months vs 31.8 months with first generation EGFR TKIs, with a hazard ratio of 0.799 (P=0.0462; see Table). More than half (54%) of patients in the osimertinib group were alive at 3 years compared with 44% in the standard care group.

Table. Efficacy results of the FLAURA trial

Efficacy output	Osimertinib n=279	Comparator EGFR-TKI n=277
OS hazard ratio (95.05% CI)	0.799 (0.641, 0.997); P=0.0462	
Median OS, months (95.05% CI)	38.6 (34.5, 41.8)	31.8 (26.6, 36.0)
Deaths, total pts (%)	155 (56)	166 (60)
Median follow-up for OS in all pts, months	35.8	27.0
Median follow-up for OS in censored pts, months	43.1	43.1
12-months survival rate, % (95.05% CI)	89 (85, 92)	83 (77, 87)
24-months survival rate, % (95.05% CI)	74 (69, 79)	59 (53, 65)
36-months survival rate, % (95.05% CI)	54 (48, 60)	44 (38, 50)

Prof. Ramalingam noted that after disease progression, 31% of patients in the control group crossed over to the osimertinib arm, representing 47% of patients in the control group that received post-study therapy. He concluded: "FLAURA met both its primary and key secondary endpoints and showed a favourable safety profile for osimertinib. The results further reinforce the clinical utility and superiority of osimertinib in the front-line setting. Based on these data, osimertinib should be the preferred front-line therapy for *EGFR*-mutated lung cancer patients."

1. Ramalingam SS. ESMO Congress 2019. Abstract LBA5_PR.
2. Soria JC, et al. N Engl J Med. 2018;378:113–125.

Liquid biopsy to decide the best treatment for NSCLC

In the BFAST analysis, over 2,000 patients with untreated non-small cell lung cancer (NSCLC) had liquid biopsies (blood tests) using state-of-the-art technology to check for multiple driver genetic mutations. Approximately 1 in 20 were found to have tumour DNA showing a rearrangement in the *ALK* gene. In patients treated with alectinib, a cancer treatment that targets the *ALK* mutation, over three quarters showed no signs of disease progression in the subsequent 12 months.

New data from the BFAST trial presented by Dr Shirish Gadgeel (University of Michigan, USA) have shown that the test can be used successfully to identify complex DNA mutations in the cells of patients with (NSCLC) suitable for the latest targeted medicines [1]. The sensitive technique detects tumour DNA that is shed from cancer cells into the blood.

In the phase 2/3 BFAST trial, 2,219 patients with stage IIIB/IV untreated NSCLC had blood-based next generation sequencing (NGS) of actionable genetic alterations and results were obtained in 2,188 patients. Overall, 119 patients (5.4%) had *ALK*+ disease and 87 of these were enrolled to receive alectinib. Median follow-up was 12.6 months. Confirmed objective response rate reported by investigators was 87.4% (95% CI 78.5-93.5) and 12-month duration of response was 75.9% (95% CI 63.6-88.2). Median progression-free survival (PFS) was not reached but 12-month PFS reported by investigators was 78.4% (95% CI 69.1-87.7). Safety data were consistent with the known safety profile of alectinib.
The results are encouraging, as a growing number of patients with advanced lung cancer could be offered a liquid biopsy in complement or instead of tissue biopsy in order to identify their disease mutation and decide the best treatment.

Invited discussant Prof. Alberto Bardelli, (University of Turin, Italy) said: "Rearrangement in the *ALK* gene described in the BFAST study is typically difficult to detect so it is an important advance to have shown that it can be detected in the blood and used to guide ALK inhibitor treatment, which has then been demonstrated to be effective in patients with this mutation."

1. Gadgeel S et al. ESMO Congress 2019. Abstract LBA81_PR.

Melanoma

Long-term data from CheckMate 067

Prof. James Larkin (Royal Marsden NHS Foundation Trust, London, UK) presented the 5-year analysis of CheckMate 067, which represents the longest phase 3 follow-up for checkpoint inhibitor combination therapy and demonstrated long-term survival with both nivolumab-containing arms vs ipilimumab. In descriptive analyses, nivolumab plus ipilimumab was associated with improved survival and a higher likelihood of being alive and treatment-free compared with nivolumab alone, both without loss of quality-of-life.

The 5-year analysis is the longest phase 3 follow-up for checkpoint inhibitor combination therapy. A total of 945 patients with previously untreated stage III or IV melanoma were randomly allocated in a 1:1:1 ratio to 1) nivolumab plus ipilimumab; 2) nivolumab plus placebo; or 3) ipilimumab plus placebo until progression or unacceptable toxicity. Each nivolumab arm was compared with ipilimumab monotherapy.
The 5-year overall survival rates were 52% for nivolumab plus ipilimumab, 44% for nivolumab, and 26% for ipilimumab (see Table). The median time from randomisation to subsequent therapy was 8 months with ipilimumab monotherapy, 25.2 months with nivolumab monotherapy, and as yet unreached with combination immunotherapy. The proportion of patients alive and free from subsequent therapy at 5 years was 45% with ipilimumab, 58% with nivolumab, and 74% with combination therapy. Quality of life was preserved in both nivolumab arms. Prof. Larkin said there is currently no method to predict which patients are most likely to benefit from combination immunotherapy.

Table. Summary of key results from CheckMate-067

	NIVO+IPI (n=314)	NIVO (n=316)	IPI (n=315)
Objective response rate, % (95%CI)	58 (53-64)	45 (39-50)	19 (15-24)
Median duration response rate, mo (95% CI)	NR	NR (50.4-NR)	14.44 (8.3-53.6)
Median PFS, mo (95% CI)	11.5 (8.7-19.3)	6.9 (5.1-10.2)	2.9 (2.8-3.2)
5-year PFS rate, % (95% CI)	36 (31-42)	29 (24-35)	8 (5-12)
Median OS, mo (95% CI)	NR (38.2-NR)	39 (28.2-58.7)	19.9 (16.8-24.6)
5-year OS, mo (95% CI)	52 (46-57)	44 (39-50)	26 (22-31)
BRAF mutant	60 (50-69)	46 (36-56)	30 (21-39)
BRAF wild-type	48 (41-54)	43 (37-50)	25 (19-31)
PD-L1 <5%	51 (44-57)	43(36-50)	24 (18-30)
PD-L1 ≥5%	57 (44-68)	51 (40-62)	33 (23-44)
Median time from randomisation to subsequent systemic therapy, mo (95% CI)	NR (59.6-NR)	25.2 (16.0-43.2)	8.0 (6.5-8.7)
Patients alive and free from subsequent therapy, n/N (%)	112/151 (74)	75/130 (58)	30/67 (45)

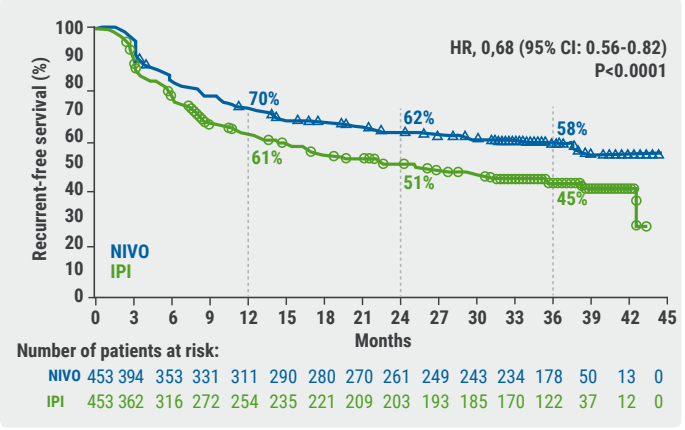
NR, not reached.

Adjuvant nivolumab provides benefit

Patients with melanoma who have successfully undergone resection but who are at high risk for relapse have substantially better outcomes with adjuvant nivolumab than the current standard-of-care ipilimumab [1].

The new results, presented by Prof. Jeffrey S. Weber (NYU Langone Medical Center, New York City, USA), come from the phase 3 CheckMate 238 trial, which was stopped early owing to benefit. The primary endpoint was recurrence-free survival (RFS) in the intention-to-treat population, with overall survival, safety, side-effect profiles, and RFS relative to tumour PD-L1 expression. Adjuvant nivolumab increased RFS by a significant 35% compared with adjuvant ipilimumab while also reducing the rate of grade ≥3 adverse effects by approximately a third (see Figure).

Figure. Sustained long-term improvement in recurrence-free survival with nivolumab vs ipilimumab as adjuvant treatment for resected stage IIIB/IIIC or IV melanoma



© Jeffrey S. Weber (provided by ESMO).

CheckMate 238 was a randomised, double-blind, phase 3 trial that included 906 patients who had undergone complete resection for stage IIIB, IIIC, or IV melanoma, who were randomly allocated to receive either nivolumab 3 mg/kg (n=453) every 3 weeks for 4 doses or ipilimumab 10 mg/kg every 3 weeks for 4 doses and then once every 12 weeks (n=453). At 3 years of follow-up, nivolumab continued to demonstrate superior RFS compared with ipilimumab, the active control, with RFS rates of 58% and 45%, respectively (HR 0.68; 95% CI 0.56–0.82; P<0.0001). Distant-metastasis-free survival also continued to be significantly longer for nivolumab, with 36-month rates of 66% and 58%, respectively (HR 0.78; 95% CI 0.62–0.99; P=0.044). Both

RFS and distant-metastasis-free survival benefit continued to be observed across key subgroups, including disease stages, *BRAF* mutation status and PD-L1 expression. No new safety data were generated as part of the 36-month analysis.

1. Weber J et al. ESMO Congress 2019. Abstract 1310O.

Nivolumab+ipilimumab superior to monotherapy for melanoma brain metastases

Prof. Georgina Long (Melanoma Institute Australia, Sydney, Australia) reported that melanoma patients with brain metastases receiving the combination therapy of ipilimumab plus nivolumab had the best intracranial response and also better survival rates [1].

Prof. Long's data were from an independent, investigator-driven ABC (Anti-PD-1 Brain Collaboration) trial, which compared the combination of ipilimumab and nivolumab with nivolumab alone in melanoma patients with brain metastases. The ABC trialists from Australia and New Zealand enrolled 60 patients who received no treatment for asymptomatic brain metastases to receive the combination of ipilimumab and nivolumab (n=35) or nivolumab alone (n=25).

Rates of complete (CR) and partial (PR) responses were also higher for patients receiving the combination. CR and PR were 26% and 26%, respectively, for patients who received the combination compared with 16% and 4%, respectively for patients who received nivolumab.
Best extracranial responses were also higher for patients receiving the combination (57% vs 29% for nivolumab alone). Three-year intracranial PFS was 43% for patients on the combination and 15% for patients on nivolumab alone. Three-year OS was 49% for patients receiving the combination and 42% for patients receiving nivolumab alone.

Prof. Long reported that there were no unexpected toxicities and that the quality of life was maintained across the study groups.

1. Long GV et al. ESMO Congress 2019. Abstract 1311O.

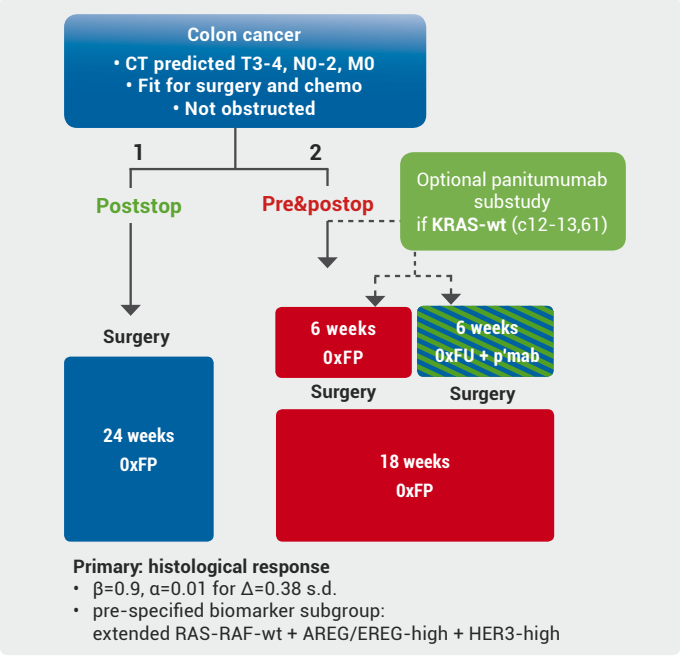
Gastrointestinal Cancers

Preoperative chemotherapy for colon cancer

Prof. Dion Morton (University of Birmingham, UK) presented the new results of the FOxTROT trial. The study compared outcomes with a 6-month course of postoperative oxaliplatin-based chemotherapy vs 6 weeks of neoadjuvant therapy, followed by surgery and an additional 18 weeks of adjuvant chemotherapy. Neoadjuvant chemotherapy led to a non-significant reduction in recurrence rate, but it was associated with significantly fewer surgical complications and improved surgical outcomes (R0 resections) vs adjuvant therapy [1].

The primary endpoint was the frequency of relapse during the first 2 years post-surgery. Investigators assumed a 2-year treatment failure rate of 25%-32% for the control arm and hypothesised that neoadjuvant therapy would reduce the rate by 25%. On that basis, they enrolled and randomised 1,052 patients 2:1 to pre- and postoperative therapy or to adjuvant therapy only (see Figure).

Figure. Study design for FOxTROT



0xFP, oxaliplatin/fluoropyrimidine.

Patients who received chemotherapy before surgery had a 2-year recurrence rate of 13.6% vs 17.2% for patients receiving adjuvant chemotherapy. The difference met the prespecified reduction in the hazard ratio (0.75), but the confidence interval crossed 1.0 (95% CI 0.55-1.04, P=0.08) and consequently did not achieve statistical significance because of a lower-than-expected event rate in the control arm. The 5-year recurrence rates were 27% for the control arm and 21% for the neoadjuvant arm.

Attempted curative surgery was successful in 98% of patients in both treatment groups. Significantly, more patients in the control arm did not receive planned chemotherapy (27% vs 4%; P<0.0001), either because the patient was too sick or refused treatment (11%) or the tumour was considered low risk (16%).

Fewer patients receiving preoperative chemotherapy went to surgery but had no resection (0.3% vs 1.1%), leading to a higher rate of microscopically complete surgical resection (93.1% vs 88.4%). Collectively, the differences resulted in a significant advantage for the neoadjuvant group (P=0.001).
Neoadjuvant therapy led to substantial tumour downstaging, including more patients with pT0 (4.1% vs 0%) and pT1/pT2 (11.7% vs 5.8%) at surgery and fewer patients with pT4 disease (20.5% vs 29.8%). These differences were significantly in favour of neoadjuvant chemotherapy (P<0.0001). Nodal stage at surgery was also lower in the neoadjuvant chemotherapy group (P<0.0001), including half as many patients with positive apical nodes (3.8% vs 7.5%, P=0.013). Fewer patients had macroscopically incomplete surgery (0.3% vs 1.1%), or had microscopically incomplete surgery (4.2% vs 8.8%). Interestingly, there was no benefit observed in tumours deficient in DNA mismatch repair.
Patients receiving neoadjuvant treatment had lower perio-perative morbidity rates: anastomotic leaks (3.6% vs 8.0%); complications prolonging hospital stay and re-operations (4.3% vs 6.7%). The 30-day postoperative mortality was 0.4% after neoadjuvant therapy vs 0.6% in the control arm.

While the observed differences did not translate into a significant overall or progression-free survival benefit, FOxTROT has shown the feasibility of a neoadjuvant approach, which seems non-inferior to today's standard approach (and reminds of initial studies in breast cancer). It opens the way for future studies exploring a higher number of neoadjuvant treatment cycles or a more intensive treatment approach.

1. Morton D et al. ESMO Congress 2019. Abstract 523O.

Nivolumab improves OS in advanced oesophageal cancer

Positive results from the phase 3 ATTRACTION-3 trial, evaluating nivolumab vs chemotherapy (docetaxel or paclitaxel) for the second-line treatment of patients with unresectable advanced or recurrent oesophageal squamous cell carcinoma (ESCC) refractory or intolerant to combination therapy with fluoropyrimidine and platinum-based drugs, were presented by Prof. Byoung Chul Cho (Yonsei University College of Medicine, South Korea), in the Presidential Symposium [1] and simultaneously published in The Lancet Oncology [2].

ATTRACTION-3 is a phase 3, multicentre, randomised, open-label global study, although 96% of patients in both treatment arms were from Asia. Patients were treated until disease progression or unacceptable toxicity. A total of 419 patients were enrolled: 210 were allocated to nivolumab and 209 to chemotherapy.

For the primary endpoint of overall survival (OS), nivolumab demonstrated a statistically significant improvement over chemotherapy (see Table), with a 23% reduction in risk of death (HR 0.77; 95% CI 0.62-0.96; P=0.019) and a 2.5-month improvement in median OS (10.9 months; 95% CI 9.2-13.3) compared with patients treated with chemotherapy (8.4 months; 95% CI 7.2-9.9). The safety profile of nivolumab in this trial was consistent with previously reported studies in ESCC and other solid tumours.

Table. Results from the ATTRACTION-3 trial, which demonstrated superior OS and a favourable safety profile vs CT in pts with previously treated advanced ESCC, with survival benefit observed regardless of tumour PD-L1 expression

Efficacy (all randomised patients)	nivolumab (n=210)	chemotherapy (n=209)
Median OS, mo (95% CI)	10.9 (9.2-13.3)	8.4 (7.2-9.9)
HR (95% CI; P-value)	0.77 (0.62-0.96; P=0.02)	
12-mo rate, % (95% CI)	47 (40-54)	34 (28-41)
18-mo rate, % (95% CI)	31 (24-37)	21 (15-27)
ORR, n (%; 95% CI)	33 (19; 14-26)	34 (22; 15-29)
Median DOR, mo (95% CI)	6.9 (5.4-11.1)	3.9 (2.8-4.2)
Median PFS, mo (95% CI)	1.7 (1.5-2.7)	3.4 (3.0-4.2)
HR (95% CI)	1.08 (0.87-1.34)	
6-mo rate, % (95% CI)	24 (19-30)	17 (12-23)
12-mo rate, % (95% CI)	12 (8-17)	7 (4-12)
Safety (all treated patients)	n=2019	n=208
Patients with TRAEs, n (%)	137 (66)	198 (95)
Grade 3-4 TRAEs, n (%)	38 (18)	131 (63)
Patients with serious TRAEs, n (%)	33 (16)	47 (23)
Patients with TRAEs leading to discontinuation, n (%)	18 (9)	19 (9)

Table provided by ESMO

Patients treated in the nivolumab arm showed 12- and 18-month OS rates of 47% (95% CI 40-54) and 31% (95% CI 24-37), respectively, vs 34% (95% CI 28-41) and 21% (95% CI 15-27) among patients in the chemotherapy arm. Survival benefit with nivolumab was observed regardless of tumour PD-L1 expression levels. An exploratory analysis of patient-reported outcomes showed significant overall improvement in quality of life with nivolumab vs chemotherapy.

The objective response rates between the two arms were comparable at 19% (95% CI 14-26) among patients receiving nivolumab vs 22% (95% CI 15-29) among those receiving chemotherapy. However, the study showed nivolumab substantially increased the median duration of response for patients (6.9 months; 95% CI 5.4-11.1) vs 3.9 months (95% CI 2.8-4.2). In total, 7 patients in the nivolumab arm had ongoing responses at data cut-off compared with 2 patients in the chemotherapy arm. An overall HR of 1.08 (95% CI 0.87-1.34) suggested no meaningful difference in progression-free survival between the nivolumab and chemotherapy arms.

Fewer treatment-related adverse events (AEs) were reported with nivolumab vs chemotherapy, with a rate of 66% of any grade treatment-related AEs for patients receiving nivolumab compared with 95% for patients receiving chemotherapy. Patients in the nivolumab arm also experienced a lower incidence of grade 3 or 4 treatment-related AEs compared with those in the chemotherapy arm (18% vs 63%), and the percentage of patients experiencing treatment-related AEs leading to discontinuation was the same in both arms (9%).

"The significant survival benefit coupled with the favourable safety profile and patient-reported outcomes observed in this trial suggest nivolumab has the potential to represent an important new second-line treatment option for patients with advanced oesophageal squamous cell carcinoma, offering the possibility to extend their survival and improve their quality of life during treatment," said Prof. Cho.

1. Cho BC et al. ESMO Congress 2019. Abstract LBA 11.
2. Kato K et al. Lancet Oncol. 2019 Sep 27. pii: S1470-2045(19)30626-6.

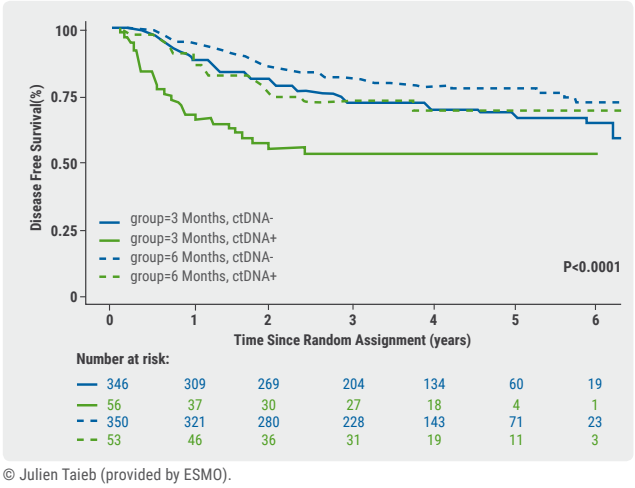
Liquid biopsy identifies relapse in patients with colorectal cancer after surgery

In a landmark trial, Prof. Julien Taieb (Hopital European Georges Pompidou, France) presented the phase 3 IDEA-FRANCE trial, in which 805 stage 3 colorectal cancer (CRC) patients were prospectively enrolled to have a liquid biopsy 4 weeks post-surgery and prior to adjuvant chemotherapy. Of these patients, 109 (13.5%) had circulating tumour DNA (ctDNA) in their blood. In this group, 2-year disease-free survival (DFS) was 64%, compared with 82% in those who were ctDNA-negative [1]. The study not only confirmed ctDNA to be an important independent prognostic marker. Although not designed nor powered to provide clear predictive evidence (patients where not randomised to receive either 3 or 6 months of treatment according to their ctDNA status), patients with ctDNA fared significantly worse when treated with 3 months chemotherapy as compared to 6 months.

A substantial number (30-50%) of patients with localised CRC relapse, despite primary optimal therapy. This study aimed to analyse the role of liquid biopsy in identifying patients with CRC who are likely to relapse after surgery. "In this large prospective trial, we confirmed that ctDNA is an independent prognostic factor in colorectal cancer and that approximately 6 out of 10 patients who are ctDNA-positive will remain disease-free 2 years after standard adjuvant chemotherapy, compared with 8 out of 10 of those who are ctDNA-negative," said Prof. Taieb.

IDEA-FRANCE also showed that 6 months of adjuvant treatment was superior to 3 months in both ctDNA-positive and -negative patients (see Figure). Furthermore, ctDNA-positive patients treated for 6 months had a similar prognosis to ctDNA-negative patients treated for 3 months. Adjuvant therapy was FOLFOX (folinic acid, fluorouracil, and oxaliplatin) in 90% of cases.

Figure. ctDNA and treatment arm



"ctDNA testing did not predict which patients should have 3 or 6 months of adjuvant chemotherapy and there is continuing debate over the optimal type and duration of treatment

for patients who are ctDNA-positive, but we do now know that ctDNA is a major prognostic factor which will be very useful in stratifying patients and driving future trials of CRC," said Prof. Taieb. "In all subgroups, ctDNA-positive patients who only had 3 months of adjuvant therapy had the worst prognosis," he added.

1. Taieb J et al. ESMO Congress 2019. Abstract LBA30_PR.

In hepatocellular carcinoma, CheckMate 459 misses OS endpoint, but some interesting trends emerge

CheckMate 459 in patients with advanced hepatocellular carcinoma (HCC) did not meet its prespecified primary endpoint for improved overall survival (OS), despite showing a trend towards clinically meaningful improvements in survival and response rates and a favourable safety profile with first-line immunotherapy agent nivolumab compared with current standard treatment, sorafenib [1].

The data, reported by Dr Thomas Yau (University of Hong Kong, China) originated from the phase 3 CheckMate 459 study, which randomised 743 patients with advanced HCC to receive nivolumab every 2 weeks or oral sorafenib twice daily as first-line treatment. Median OS was 16.4 months for nivolumab and 14.7 months for sorafenib (HR 0.85; 95% CI 0.72-1.02; P=0.0752; see Table). This did not meet the predefined threshold of statistical significance. However, clinical benefit was observed across predefined subgroups of patients, including those with hepatitis infection and those with vascular invasion and/or extrahepatic spread. The overall response rate was 15% for nivolumab (including 14 patients with complete response) and 7% for sorafenib (5 patients with complete response). Grade 3/4 treatment-related adverse events were reported in 22% of patients in the nivolumab arm (81 patients) and in 49% of those given sorafenib (179 patients). Adverse events led to discontinuation in 4% (n=16) and 8% (n=29) of the patients, respectively.

Dr Yau said, "the primary analysis demonstrated a non-significant trend towards clinically meaningful OS benefit. Importantly, there was also a higher complete response rate with nivolumab compared with sorafenib." He added that the patient-reported findings suggested that patients in the nivolumab arm experienced better quality of life and further supported clinical data that demonstrated a treatment benefit for nivolumab vs sorafenib in advanced HCC. Invited discussant Dr Arndt Vogel (Hannover Medical School, Germany) noted that regorafenib, lenvatinib, cabozantinib, and ramucirumab are other tyrosine kinase inhibitors in the second-line setting of advanced HCC that may account for some of the results.

Table. Results from 743 patients with advanced HCC were randomised to nivolumab or sorafenib with minimum follow-up of 22.8 months at data cut-off

	nivolumab (n=371)	sorafenib (n=372)
Median OS, mo (95% CI)	16.4 (13.9-18.4)	14.7 (11.9-17.2)
12-mo OS rate, % (95% CI)	59.7 (5.4-64.6)	55.1 (49.8-60.1)
24-mo OS rate, % (95% CI)	36.8 (31.8-41.8)	33.1 (28.3-38.0)
Median PFS, mo (95% CI)	3.7 (3.1-3.9)	3.8 (3.7-4.5)
ORR, n (%)	57 (15)	26 (7)
BOR, n (%)		
Complete response	14 (4)	5 (1)
Partial response	43 (12)	21 (6)
ORR by baseline PD-L1 expression, n/N (%)		
PD-L1 <1%	36/295 (12)	20/300 (7)
PD-L1 ≥1%	20/71 (28)	6/64 (9)

BOR, best overall response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

Two possible limitations were mentioned, namely the unselected population and the predefined threshold of statistical significance. Results suggested patients with high PD-L1 had an increased response rate only in the nivolumab arm suggesting its potential role as a predictor biomarker, but preselection of patients based on PD-L1 will require another study.

1. Yau T et al. ESMO Congress 2019. Abstract LBA38_PR.

Heavily pre-treated GIST: ripretinib improves PFS

In the double-blinded phase 3 INVICTUS trial, ripretinib (a novel KIT and PDGFRA inhibitor) demonstrated a dramatic improvement in progression-free survival (PFS) compared with placebo in heavily pre-treated patients with heavily advanced gastrointestinal stromal tumours (GIST).

Primary mutations in *KIT* and *PDGFRA* drive GIST in approximately 85% of cases, according to presenting author Prof. Margaret von Mehren (Fox Chase Cancer Center, USA) [1]. Ripretinib works as an inhibitor of KIT and PDGFRA.

The INVICTUS trial randomised patients to receive ripretinib at 150 mg daily (n=85) or placebo (n=44). The median age of patients was 60 years, with more aged 75 or more in the

placebo group (9% for ripretinib vs 23% for placebo). Two-thirds of patients had received 3 prior therapies, and a third had received more than 4 (range, 4-7). The most common mutation was at *KIT* exon 11 (58%) followed by *KIT* exon 9 (16%).

In the study, the median PFS was 6.3 months with ripretinib compared with 1.0 months for placebo, amounting to a 85% reduction in the risk of progression or death (HR 0.15; 95% CI 0.09-0.25; P<0.0001). Additionally, the secondary endpoint of median overall survival was 15.1 for ripretinib vs 6.6 months for placebo (HR 0.36; 95% CI 0.20-0.63; P=0.0004), representing a 64% reduction in the risk of death. However, the hierarchical testing procedures utilised for the study prevented a conclusive establishment of statistical significance for OS.

The 6-month PFS rate was 51.0% (95% CI 39.4%-61.4%) for ripretinib compared with 3.2% for placebo (95% CI 0.2%-13.8%). PFS benefit was observed across all assessed patient subgroups. In those treated with 3 therapies, the HR for PFS was 0.15, in favour of ripretinib (95% CI 0.08-0.29). In those treated with ≥4 therapies, the HR was 0.24, also in favour of ripretinib (95% CI, 0.12-0.51).

"Ripretinib represents a potential new standard of care with broad activity in fourth-line GIST, a patient population with advanced refractory disease and no other approved options," said Prof. von Mehren.

1. von Mehren M et al. ESMO Congress 2019. Abstract LBA87.

FGFR2+ cholangiocarcinoma: pemigatinib active as second-line treatment

More than one-third of patients with previously treated locally advanced or metastatic cholangiocarcinoma (CCA) with an *FGFR2* rearrangement or fusion had durable objective responses to treatment with pemigatinib, a selective oral inhibitor of FGFR1, 2, and 3, according to findings from an open-label, single-arm phase 2 clinical trial [1].

Results from FIGHT-202, a phase 2 study of pemigatinib as a second-line treatment for patients with advanced/metastatic or surgically unresectable CCA, were presented by Prof. Antoine Hollebecque (Gustave Roussy Cancer Center, France). Eligible patients had locally advanced or metastatic CCA despite at least 1 line of prior therapy and had their *FGF/FGFR* status centrally confirmed. Adequate renal function was required.

A total of 1,206 patients were screened to find 127 with *FGFR2* alterations; 107 patients with *FGFR2* fusions/rearrangements (cohort A), 20 patients with other *FGF/FGFR* genetic alterations (cohort B). An additional 18 patients were enrolled with no *FGF/FGFR* alterations (cohort C). Among the 107 patients in cohort A, there were 92 fusions and 15 rearrangements discovered. A total of 56 unique fusion partners were identified, the most common of which was *BICC1*, which occurred in 29%. Median age of the entire 146 patients enrolled was 59 years, but those in cohort A tended to be younger, said Prof. Hollebecque, with 77% being younger than 65 years, compared with 50% in cohort B and 39% in cohort C. Some 58% of patients were women (61% in cohort A), and 61% were enrolled in North America, 24% in Western Europe, and 15% in the rest of the world.

Patients in the 3 cohorts were treated with oral pemigatinib (13.5 mg) using a 2 weeks on/1 week off schedule. The study was not designed to make statistical comparisons between the 3 cohorts. The primary endpoint was the confirmed ORR in cohort A by independent central review.

Results demonstrated an objective response rate (ORR) in cohort A of 35.5% and the median duration of response was 7.5 months. In contrast, there were no responses observed in cohort B or C. The higher ORR translated into a longer median progression-free survival (PFS) in cohort A. Median PFS was 6.9 months in cohort A compared with 2.1 months in cohort B and 1.7 months in cohort C.

Overall survival (OS) data were not yet mature at the time of data cut-off (March 22, 2019), but with a median follow-up of 15.4 months and a median duration of treatment of 7.2 months, the median OS was 21.1 months in cohort A, whereas median OS was only 6.7 months in cohort B after a median follow-up of 19.9 months, and only 4.0 months in cohort C after a median follow-up of 24.2 months.
In cohort A, the 35.5% ORR consisted of 3 (2.8%) complete responses, 35 (32.7%) partial responses, and 50 (46.7%) patients with stable disease, for a disease control rate of 82%. The ORR was consistent across subgroups, including when stratified by the number of prior lines of therapy and by *FGFR2* rearrangement partner.

Adverse events (AEs) were manageable and consistent with the mechanism of action of pemigatinib. The most common AE was hyperphosphatemia, which occurred in 60% of patients but no grade ≥3 cases were encountered.

Based on the results of FIGHT-202, a phase 3 study evaluating first line pemigatinib compared with standard chemotherapy (gemcitabine plus cisplatin) in patients with CCA and *FGFR2* fusions/rearrangements is ongoing.

1. Vogel A et al. ESMO Congress 2019. Abstract LBA40.

IDH1+ cholangiocarcinoma: phase 3 results show improved PFS

New data have shown for the first time that targeted therapy can improve the outcome of patients diagnosed with advanced cholangiocarcinoma.

Results of the ClarIDHy phase 3 trial have shown that ivosidenib, an oral drug targeting the *IDH1* mutation to inhibit the production of a metabolite (D-2-hydroxyglutarate) that promotes oncogenesis -expected in around 15% of advanced cholangiocarcinoma patients- significantly improved progression-free survival (PFS) with a trend to improved overall survival compared with placebo [1].

The study randomised 185 patients with advanced cholangiocarcinoma and *IDH1* mutations to ivosidenib or matched placebo. Patients could crossover from placebo to ivosidenib when their disease progressed.

Median PFS was 2.7 months for patients treated with ivosidenib compared with 1.4 months with placebo (HR 0.37; 95% CI 0.25 to 0.54; P<0.001). The median PFS rate at 6 months was 32.0% with ivosidenib, while no patients randomised to placebo were free from progression.
Results showed a favourable trend in overall survival with ivosidenib. Median overall survival was 10.8 months for ivosidenib and 9.7 months for placebo (HR 0.69; one-sided P=0.06). Adjusting the overall survival results to take account of 57% of placebo patients crossing over to ivosidenib gave an adjusted overall survival of 6 months for placebo, which was significantly shorter than with ivosidenib (HR 0.46; P=0.0008). Ivosidenib was generally well tolerated, with grade 3 or higher adverse events reported in 46% of patients on the targeted agent and 36% of those on placebo. There were no treatment-related deaths.

"The ClarIDHy study demonstrates for the first time the feasibility and clinical benefit of targeting a molecularly defined subgroup in cholangiocarcinoma. It shows that targeting mutated *IDH1* with ivosidenib significantly improves PFS and gives a favourable trend in overall survival in patients with advanced *IDH1*-mutated cholangiocarcinoma," said presenting author Dr Ghassan Abou-Alfa (Memorial Sloan-Kettering Cancer Center, New York, USA).

Commenting on the relevance of the new data, Dr Chris Verslype (University Hospital Leuven, Belgium) said: "What we see in this study is really unprecedented. We previously had no options for patients with cholangiocarcinoma who failed systemic therapy, and they had very limited survival. These are important data. There is a gain in PFS with ivosidenib that is clinically relevant for this patient population."

Dr Verslype considered there were few limitations. Patients selected for the study had to have good performance status after previous chemotherapy, so results may not be representative of patients whose disease progresses rapidly on chemotherapy. "But it is still a strong study because of the randomisation to placebo. It showed a real effect." The study had a high crossover rate from placebo to ivosidenib, making the overall survival endpoint difficult to assess, but he pointed out that allowing patients to crossover was important from an ethical perspective. "Additional analysis suggested a benefit in overall survival if there had been no crossover."

1. Abou-Alfa G et al. ESMO Congress 2019. Abstract LBA10_PR.

Advanced colorectal cancer and *BRAF* mutations: triplet combination improves survival

The three-drug combination of encorafenib, binimetinib, and cetuximab significantly improved overall survival (OS) in patients with *BRAF*-mutated metastatic colorectal cancer (mCRC), according to results of the BEACON CRC phase 3 clinical trial [1,2].

Prof. Scott Kopetz (MD Anderson Cancer Center, Houston, USA) presented the international collaboration, which included >200 centres worldwide in this open label, three-arm randomised clinical trial. A total of 665 patients with *BRAF* V600E-mutant mCRC who had progressed after one or two prior regimens in the metastatic setting were randomised to receive triplet therapy, doublet therapy (encorafenib and cetuximab), or the investigator's choice of irinotecan or folinic acid, fluoruracil and irinotecan (FOLFIRI) and cetuximab [1]. *BRAF* mutations are estimated to occur in up to 15% of patients with mCRC, with V600E being the most common mutation and representing a poor prognosis for these patients.

The treatment combination resulted in median OS of 9 months (95% CI 8-11.4) for the triplet combination therapy compared with 5.4 months (95% CI 4.8-6.6) for current standard-of-care (HR 0.52; 95% CI 0.39-0.7, P<0.0001). Objective response rate (ORR) for the triplet-targeted therapy was 26% (95% CI 18-35) compared with just 2% (95% CI 0-7; P<0.0001) for standard therapy.

Median OS for the doublet combination was 8.4 months (95% CI 7.5-11) compared with standard therapy (HR 0.6; 95% CI 0.45-0.79; P<0.0003). The study was not powered to compare triplet and doublet therapies, but future analyses will explore which patients are most likely to benefit from triplet vs doublet combinations.

BRAF V600E targeted treatment was well tolerated, with grade 3 or higher adverse events seen in 58% of patients on triplet treatment, 50% of those in the doublet group, and 61% of those in the standard therapy group.

In conclusion, BEACON CRC is the first and only phase 3 trial designed to test BRAF/MEK combination targeted therapies in patients with mCRC and the *BRAF* V600E mutation, and the study reported clinical benefit for those selected patients. An ongoing study (ANCHOR-CRC) is evaluating the effect of triplet therapy in *BRAF*-mutant mCRC.

1. Kopetz S et al. ESMO Congress 2019. Abstract LBA006.
2. Kopetz S et al, N Engl J Med. 2019 Oct 24;381(17):1632-1643.

Genitourinary Cancers

25% reduction in the risk of death in patients with nmCRPC treated with apalutamide

The second interim analysis of the randomised, phase 3 SPARTAN trial showed that apalutamide continued to offer a metastasis-free survival (MFS) benefit over placebo for patients with non-metastatic (M0) castration-resistant prostate cancer (CRPC) with higher risk (PSA doubling time ≤10 months prior to trial entry), and reduced the risk of death by 25% [1]. These findings were simultaneously published in the Annals of Oncology [2].

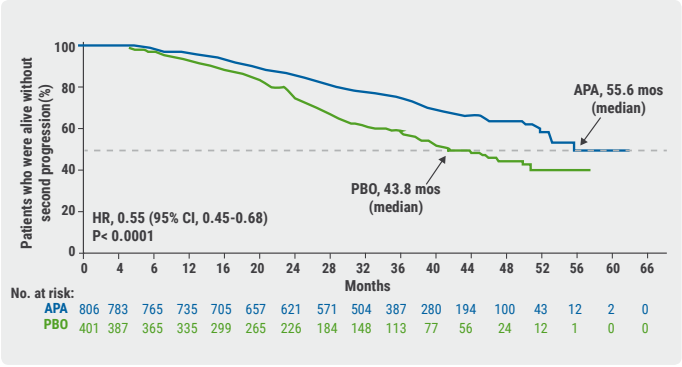
Prof. Matthew Smith (Massachusetts General Hospital, Boston, USA) presented the final MFS analysis and the second interim analysis for overall survival. Not surprisingly, the MFS benefit was sustained. The fist interim analysis was reported last year at ESMO 2018. In this year's longer median follow-up of 41 months, 4-year overall survival (OS) rates were 72.1% for patients treated with apalutamide and 64.7% for patients treated with placebo, but this was not quite significant. Overall, a 25% reduction in the risk of death was observed for patients receiving apalutamide compared with placebo (HR 0.75; 95% CI 0.59-0.96; P=0.0197; to reach statistical significance in their model, a P-value of P<0.0121 was predetermined as the the O'Brien-Fleming boundary). The OS benefit of apalutamide was consistent across baseline subgroups, including race, prior treatments, baseline PSA and performance status.

This current interim analysis took place when 67% of the required OS events had been observed, as opposed to last year when only 24% of required OS events had occurred (HR 0.70; 95% CI 0.47-1.04; P=0.07). After unblinding of the study and prior to the second interim analysis, 76 non-progressing patients in the placebo group (19% of the placebo arm) crossed over to open-label apalutamide; the OS rates in the placebo group included those patients who crossed-over to apalutamide treatment. The third and final OS analysis will occur in 2022 at 427 (100%) events.

The rates of treatment-emergent adverse events for apalutamide at the second interim analysis were consistent with rates previously reported. The most common adverse events (≥10%) were fatigue, hypertension, rash, diarrhoea, nausea, weight loss, arthralgia, falls, hot flush, decreased appetite, fracture, and peripheral oedema.

The exploratory progression-free survival 2 (PFS2) analysis, where patients were followed from randomisation beyond the initial progression on either apalutamide or placebo until the second progression, confirmed a clinical benefit (HR 0.55; 95% CI 0.45-0.68; P<0.0001, see Figure).

Figure. Results of time to second objective disease progression (PFS2) from the SPARTAN study.



(provided by ESMO)

In summary, although the OS data is still not statistically significant at this time, the study will continue to follow the patients on the trial. Regardless of the ultimate results from the future final OS analysis, this data supports treating patients with high risk M0 CRPC with apalutamide, given the confirmed MFS benefit from the primary endpoint analysis.

1. Smith MR et al. ESMO Congress 2019. Abstract 8430.
2. Small EJ et al. Ann Oncol. 2019 Sep 27.

Enfortumab vedotin and pembrolizumab in advanced bladder cancer: initial results

Initial results from the phase 1 EV-103 study, combining enfortumab vedotin with pembrolizumab as a first-line treatment for advanced urothelial cancer, showed that the study met outcome measures for safety and exhibited encouraging clinical activity for this platinum-free combination. Results were presented by Prof. Christopher Hoimes (Case Comprehensive Cancer Center, Cleveland, USA) [1].

EV-103 is an ongoing, multicohort, open-label, multicentre phase 1 trial of investigational drug enfortumab vedotin alone or in combination with a different drug, evaluating safety, tolerability, and efficacy in muscle-invasive, locally advanced, and first- and second-line metastatic urothelial cancer. Enfortumab vedotin is a first-in-class antibody-drug conjugate designed to target nectin-4, a protein present on almost all urothelial tumour cells, coupled to the microtubule disrupting agent monomethyl auristatin E. This initial analysis reported on 45 patients (5 from the dose-escalation cohort and 40 from the dose-expansion cohort A) with locally advanced and/or metastatic urothelial cancer who were ineligible for treatment with cisplatin-based chemotherapy, who had been treated with enfortumab vedotin (1.25 mg/kg) plus pembrolizumab in the first-line setting.

The primary outcome measure of the cohorts was safety. Secondary outcomes included objective response rate (ORR), disease control rate (DCR), duration of response (DOR), and overall survival (OS). DOR and OS were not mature at the time of analysis.

Half of patients (23/45) had an adverse event greater than or equal to grade 3. Among these events, an increase in lipase was the most frequent (13%; 6/45). In total, 4 patients (9%) discontinued treatment due to treatment-related adverse events, most commonly peripheral sensory neuropathy. There was 1 death deemed to be treatment-related by the investigator, attributed to multiple organ dysfunction syndrome. Treatment-related adverse events of clinical interest that were greater than or equal to grade 3 were rash (11%; 5/45), hyperglycaemia (7%; 3/45), and peripheral neuropathy (4%; 2/45); these rates were similar to those observed with enfortumab vedotin monotherapy. One in ten (5/45) of patients had treatment-related immune-mediated adverse events of clinical interest greater than or equal to grade 3 that required the use of systemic steroids (one event each of pneumonitis, dermatitis bullous, hyperglycaemia, tubulointerstitial nephritis, myasthenia gravis). None of the adverse events of clinical interest were grade 5.

The data demonstrated the combination of enfortumab vedotin plus pembrolizumab reduced tumours, resulting in an ORR of 71% (32/45; 95% CI 55.7-83.6). The complete response rate was 13% (6/45), 58% (26/45) of patients had a partial response, and 22% (10/45) had stable disease. Almost all (91%) responses were observed at the first assessment.

1. Hoimes C et al. ESMO Congress 2019. Abstract 901O.

PFS extension with immunotherapy + chemotherapy in urothelial cancer

Patients with metastatic urothelial cancer had longer progression-free survival (PFS) when treated with first-line immunotherapy and chemotherapy instead of chemotherapy alone, according to late-breaking results of the IMvigor130 trial [1].

IMvigor130 randomly allocated 1,213 patients with metastatic urothelial cancer from 35 countries in a 1:1:1 ratio

to atezolizumab plus platinum-based chemotherapy (Arm A), atezolizumab alone (Arm B), or placebo plus platinum-based chemotherapy (Arm C). IMvigor130 is the first trial to test the combination of chemotherapy and immunotherapy in patients eligible and ineligible for chemotherapy.

The coprimary efficacy endpoints were investigator-assessed PFS and overall survival (Arm A vs C) and overall survival (Arm B vs C). After a median follow-up of 11.8 months, median PFS was 8.2 months in Arm A and 6.3 months in Arm C. This corresponded to a statistically significant HR of 0.82 (95% CI 0.70–0.96; P=0.007).
In an interim analysis, median overall survival was 16.0 vs 13.4 months in Arms A and C, respectively (HR 0.83; 95% CI 0.69–1.00; P=0.027) and 15.7 vs 13.1 months in Arms B and C, respectively (HR 1.02; 95% CI 0.83–1.24).
Objective response rates were 47%, 23%, and 44% in Arms A, B, and C, respectively; complete response rates were 13%, 6%, and 7%. Adverse events leading to treatment withdrawal occurred in 34%, 6%, and 34% of patients in Arms A, B, and C, respectively.

Compared with chemotherapy alone, chemotherapy plus atezolizumab improved the median time to progression of metastatic tumours by 2 months. Patients receiving the combination had an 18% reduced likelihood of progression. Interim analysis of overall survival showed a trend for improvement with the combination, but it was not statistically significant. There was also a trend for improved survival in patients with overexpression of PD-L1 who were treated with atezolizumab alone compared with chemotherapy.

Presenting author Dr Enrique Grande (MD Anderson Cancer Centre Madrid, Spain), said the adverse effects from combined chemotherapy and immunotherapy were consistent with studies in other solid tumours. "This is a new option for the upfront treatment of patients with metastatic urothelial cancer. Longer follow-up is needed on overall survival and we will continue to search for biomarkers to identify which patients respond best to this therapy."

Commenting on the results, Dr Ignacio Durán (Hospital Universitario Marques de Valdecilla-IDIVAL, Spain) cautioned that this improvement in PFS may be insufficient for regulatory approval at this stage, but said the data look promising. Dr Durán also noted that the observed complete responses were around twice as likely with the combination compared with chemotherapy or immunotherapy alone. "This is remarkable. We are now eager to see if patients receiving the two therapies together live longer, and with a similar quality of life, compared with those receiving chemotherapy and immunotherapy alone or sequentially. The interim analysis of overall survival seems to be promising, but data are immature: overall survival data are needed to consider the combination of chemotherapy and immunotherapy as a new standard of care," he said.

1. Grande E et al. ESMO Congress 2019. Abstract LBA14_PR.

PARP inhibition in selected patients slows progression on advanced prostate cancer

Data from the phase 3 PROfound trial, presented by Prof. Maha Hussain (Northwestern University, Chicago, USA) showed that olaparib delayed cancer progression by about 4 months compared with new hormonal agents (enzalutamide or abiraterone acetate) in patients with metastatic, pre-treated prostate cancer (mCRPC) whose cancer cells had faulty DNA repair genes. Preliminary data showed that treatment also prolonged overall survival by over 3 months [1].

The PROfound trial compared the efficacy of the poly-ADP ribose polymerase (PARP) inhibitor olaparib with the physician's choice of new hormonal agent treatment with enzalutamide or abiraterone. Cohort A patients had alterations in *BRCA1*, *BRCA2*, or *ATM* genes while those in Cohort B had alterations in any of 12 other genes known to be involved in DNA repair. Targeting DNA repair pathways in cancer cells is already used to treat breast and ovarian cancer in patients with mistakes in two DNA repair genes, *BRCA1* and *BRCA2*. Changes in other genes that are involved in DNA repair, such as *ATM*, can also make cancer cells more susceptible to PARP inhibitors.

In Cohort A, median progression-free survival was 7.39 months with olaparib compared with 3.55 months for hormonal treatment (HR 0.34; P<0.0001). In the overall population (Cohort A+B), median progression-free survival was 5.82 vs 3.52 months respectively (HR 0.49; P<0.0001).
Although insufficient deaths had occurred for a conclusive result, interim overall survival analysis in Cohort A showed that median overall survival was 18.5 months with olaparib compared with 15.1 with hormonal treatment (HR 0.64; P=0.0173). Median overall survival in the overall population (Cohort A+B) was 17.5 vs 14.3 months (HR 0.67; P=0.0063) with olaparib vs hormonal treatment respectively. Adverse events were more common with olaparib than with hormonal treatment, though median treatment duration was longer

with olaparib (7.4 months) than with hormone treatment (3.9 months). In the olaparib group, 16.4% of patients discontinued treatment due to adverse events, compared with 8.5% on hormonal treatment.

Commenting on the PROfound data, Dr Eleni Efstathiou (MD Anderson Cancer Center, Houston, USA) said: "This is a landmark trial, as it is the first phase 3 trial looking specifically at tumours harbouring a targetable molecular alteration. In patients with such tumours, treatment with olaparib resulted in a 66% greater delay in progression than the new hormonal agents which were used in PROfound. This is impressive because it is considerably higher than the 35-40% improvements with which we have been very satisfied in previous prostate cancer studies, in this more advanced disease setting. There is a trend towards improved survival, but we need to wait for the final analysis."

1. Hussain M et al. ESMO Congress 2019. Abstract LBA12_PR.

Third-line in mCRPC: CARD trial

Cabazitaxel third-line treatment offered statistically significant radiologic progression-free survival benefit over alternative anti-androgen therapy in pretreated castration-resistant prostate cancer (mCRPC) patients [1]. The data were simultaneously published in *The New England Journal of Medicine* [2].

Several agents are available for mCRPC patients with overall survival benefit, including abiraterone, cabazitaxel, docetaxel, enzalutamide, radium-223, and sipuleucel-T. However, due to a lack of head-to-head trials, the optimal sequence as to when to give these medications is unclear. Of note, a clear-cut third-line agent has not been approved, and the best treatment option after docetaxel and one of the novel endocrine agents is unknown, representing an unmet clinical need.

To address this unmet need, Prof. Ronald De Wit (Erasmus University Rotterdam, the Netherlands) presented results from the CARD trial, an open label investigation of men with mCRPC who progressed 12 months on either abiraterone or enzalutamide and were then randomised to either cabazitaxel or the other anti-androgen therapy. The "European" dose of 25 mg/m2 of cabazitaxel with G-CSF prophylaxis was given, as opposed to the FDA-approved dose of 20 mg/m2. The primary endpoint was radiographic progression-free survival (PFS). Secondary endpoints were overall survival, PFS, and tumour response.

A median of 22 weeks or 7 cycles of cabazitaxel were administered, as opposed to 12.5 weeks of alternative anti-androgen. About 20% of patients in the cabazitaxel arm discontinued treatment due to treatment-related side effects, which was attributed to the total number of cumulative chemotherapy doses. More patients discontinued therapy in the alternative anti-androgen arm due to disease progression. Side effects were generally balanced between groups. Febrile neutropenia was only noted in 3.2% of patients.

The primary outcome was met, as cabazitaxel treatment offered statistically significant radiographic PFS benefit over alternative anti-androgen therapy (HR 0.54; P<0.001). Pre-planned subgroup analysis showed statistically significant benefit with cabazitaxel in almost all subgroups, and if not significant, data suggested a trend towards benefit with cabazitaxel.
Overall survival data also suggests a benefit for cabazitaxel. A benefit for other secondary outcomes such as PSA, pain response, and tumour size were also seen. Importantly, in a post-hoc analysis, the authors showed that regardless of which anti-androgen is administered first, the second anti-androgen has minimal efficacy, especially relative to cabazitaxel.

In summary, this study suggests that cabazitaxel should be a standard third line of care for patients who have received one of either abiraterone or enzalutamide and docetaxel chemotherapy.

Invited discussant Dr Silke Gillessen (Kantonsspital St. Gallen, Switzerland) pointed out that we still do not know what the impact of docetaxel in the castration-sensitive setting vs the castration-resistant setting is.

1. de Wit, R et al. ESMO Congress 2019. Abstract LBA13.
2. de Wit, R et al. 2019. New Engl J Med. doi:10.1056/nejmoa1911206.

Prostate cancer: spare radiotherapy after surgery

Men with prostate cancer can be spared radiotherapy after surgery, according to late breaking results of the RADICALS-RT trial presented by Prof. Chris Parker (The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, UK), as well as a supportive meta-analysis of 3 trials [1,2].

The study answered a longstanding question about whether the benefits of radiotherapy after surgery outweigh the side-effects. RADICALS-RT enrolled 1,396 patients after surgery for prostate cancer from the UK, Denmark, Canada, and Ireland. Men were randomly allocated to postoperative

radiotherapy or the standard approach of observation only, with radiotherapy kept as an option if the disease recurred.

At a median follow-up of 5 years, progression-free survival was 85% in the radiotherapy group and 88% in the standard care group (HR 1.10; 95% CI 0.81–1.49; P=0.56). Self-reported urinary incontinence was worse at 1 year in 5.3% of patients receiving radiotherapy compared with 2.7% who had standard care (P=0.008). Radiation Therapy Oncology Group (RTOG) grade 3/4 urethral stricture was reported at any time in 8% vs 5% of the radiotherapy and standard care groups, respectively (P=0.03). Longer follow-up is needed to report on survival and on the primary outcome of freedom from distant metastases at 10 years.

The findings were confirmed in a collaborative meta-analysis, presented by Dr Claire Vale (University College London, UK) [2]. The ARTISTIC collaboration meta-analysis included 3 randomised trials comparing adjuvant radiotherapy with early salvage radiotherapy following prostatectomy for men with localised prostate cancer: RADICALS, GETUG-AFU 17, and RAVES. The analysis was planned before the results of the trials were known.

The results are based on all 2,151 men included in the 3 trials, of whom 1,074 were randomised to adjuvant radiotherapy and 1,077 men were randomised to early salvage radiotherapy – of those, 395 men (37%) have commenced salvage treatment to date.
The analysis found no evidence that adjuvant radiotherapy improves event-free survival compared with early salvage radiotherapy (HR 1.09; 95% CI 0.86–1.39; P=0.47). Based on these results, the difference in 5-year event-free survival is likely only to be around 1%.

1. Parker C et al. ESMO Congress 2019. Abstract LBA49_PR.
2. Vale CL et al. ESMO Congress 2019. Abstract LBA48_PR.

Novel mode of action for kidney cancer treatment

Prof. Eric Jonasch (MD Anderson Cancer Center, Houston, USA) presented the first-in-human phase 1/2 trial data of investigational drug PT2977 (MK-6482) for the treatment of advanced clear cell renal cell carcinoma (RCC) [1]. PT2977 has a favourable safety profile and at a median follow-up of 13 months, the clinical activity of PT2977 shows promise for the treatment of heavily pre-treated RCC.

Hypoxia-inducible factor (HIF)-2α is a key oncogenic driver in RCC attributed, in 80-90% of patients, to the underlying protein product of von Hippel-Lindau (VHL) tumour suppressor gene deficiency. PT2977 is a potent and selective small molecule HIF-2α inhibitor. The objective of the current study was to evaluate the efficacy and safety of PT2977 (recently renamed MK-6482) for the treatment of advanced clear cell RCC.

In this study, patients with advanced solid tumours were treated with PT2977 in a dose-escalation design to determine the recommended phase 2 dose. Patients with advanced clear cell RCC who had received at least 1 prior therapy were enrolled in an expansion cohort at the recommended phase 2 dose of 120 mg orally once daily. A total of 55 RCC patients were treated with PT2977 120 mg (3 in dose escalation; 52 in expansion). The median number of prior therapies was 3 (range 1-9), 73% of patients were intermediate risk and 18% were poor risk by IMDC criteria.

As of May 15, 2019, the most common all-grade, all-cause adverse events (AEs) >25% were anaemia (75%), fatigue (67%), dyspnoea (47%), nausea (33%), peripheral oedema (29%), and cough (31%). Anaemia (26%) and hypoxia (15%) were the most common grade 3 AEs and on-target effects of HIF2α inhibition. Discontinuation due to a treatment-related AE was reported in 2 patients (4%).

There were 13 patients (24%) who experienced a confirmed partial response and 31 patients (56%) had stable disease, with a clinical benefit rate of 80%. Remarkably, approximately half (49%) of these very heavily pre-treated patients with metastatic RCC were alive and progression-free at 1 year. The median duration of response was not reached and 81.4% of patients experienced response ≥6 months; 16 (29%) of patients continued treatment beyond 12 months. The median progression-free survival was 11 months (95% CI 6-17), and the 12-month progression-free survival rate was 49%.

In summary, oral PT2977 demonstrated good tolerability and had a confirmed response rate of 24%, with 81.4% of patients with response 6 months. A PT2977 monotherapy phase 3 trial in previously treated advanced RCC patients is planned.

1. Jonasch E et al. ESMO Congress 2019. Abstract 911PD.

Gynaecological Cancers

Ovarian cancer patients benefit from combined maintenance therapy

Prof. Isabelle Ray-Coquard (Université Claude Bernard, Lyon, France) presented the late-breaking results of the PAOLA-1/ENGOT-ov25 trial showing a benefit in progression-free survival when adding the PARP inhibitor olaparib to bevacizumab treatment, in an all-comers ovarian cancer population, irrespective of *BRCA* mutation [1].

PAOLA-1/ENGOT-ov25 is the first phase 3 trial to examine the efficacy and safety of a pharmacological inhibitor of the enzyme poly-ADP ribose polymerase (PARP) with bevacizumab as first-line maintenance therapy in patients in women with newly-diagnosed advanced ovarian cancer who had a complete or partial response to first-line treatment with platinum-based chemotherapy and bevacizumab, with and without a *BRCA* mutation. This international, academic-led trial enrolled 806 patients. After completing first-line chemotherapy, patients were randomly allocated 2:1 to olaparib or placebo, in addition to the standard of care, bevacizumab monotherapy. They received olaparib for up to 24 months and bevacizumab for 15 months in total. The primary outcome was investigator-assessed progression-free survival.

The median follow-up was 24 months in the olaparib arm and 22.7 months in the placebo arm. Median progression-free survival was 22.1 months in the olaparib group and 16.6 months in the placebo group (HR 0.59; 95% CI 0.49-0.72; P<0.0001). In prespecified subgroup analyses, the progression-free survival benefit of olaparib vs placebo was even more pronounced in patients with a *BRCA* mutation and in those with homologous recombination deficiency (HRD), with hazard ratios of 0.31 and 0.33, respectively. Median progression-free survival with olaparib reached 37.2 months in patients with a *BRCA* mutation and in patients with HRD. Prof. Ray-Coquard noted that randomisation in PAOLA-1/ENGOT-ov25 started a median 6 weeks after the last cycle of chemotherapy, whereas most previous trials started randomisation with the first cycle of chemotherapy. "It is an important point to consider when comparing the results to other data," she said.

1. Ray-Coquard IL et al. ESMO Congress 2019. Abstract LBA2

Combination of PARP inhibition plus chemotherapy in ovarian cancer

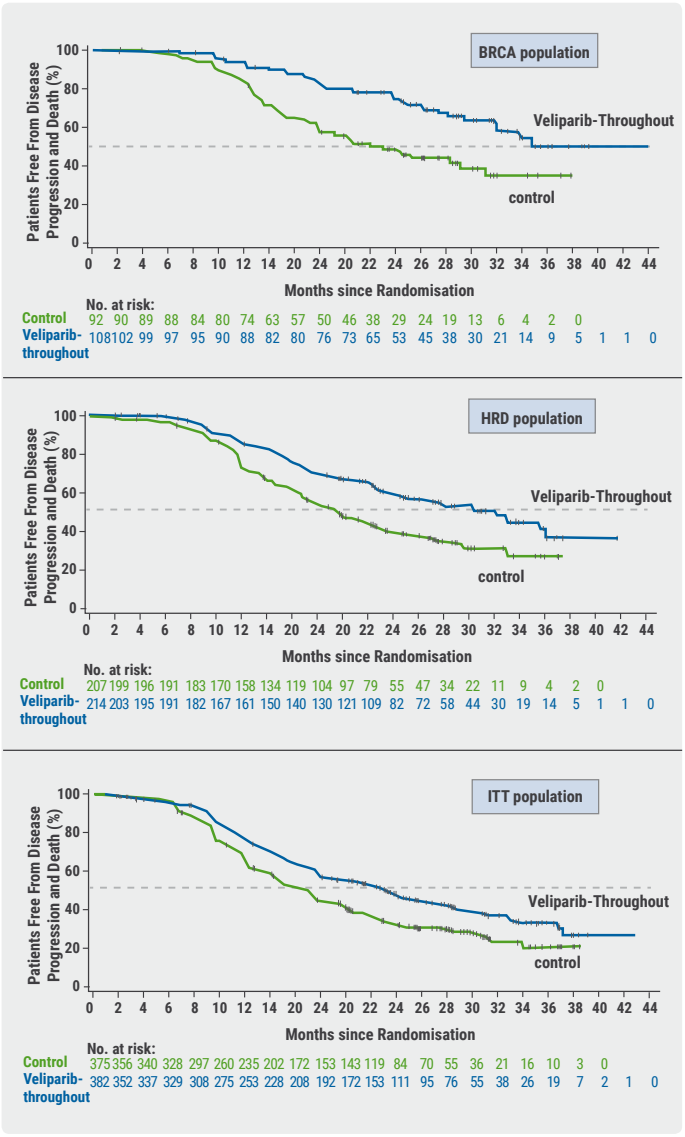
Patients with high-grade serous ovarian cancer experienced a 32% reduction in the risk of progression or death with frontline combination veliparib plus carboplatin and paclitaxel followed by veliparib maintenance, according to the phase 3 VELIA trial study, presented by Robert Coleman (University of Texas, MD Anderson Cancer Center, Houston, USA) [1].

The VELIA study evaluated the efficacy of veliparib plus first-line induction chemotherapy with carboplatin and paclitaxel and continued as maintenance monotherapy in newly diagnosed high grade serous ovarian carcinoma. A total of 1,140 patients were randomised in a 1:1:1 ratio to chemotherapy plus placebo followed by placebo maintenance (Arm 1); chemotherapy plus veliparib followed by placebo maintenance (Arm 2); and chemotherapy plus veliparib followed by veliparib maintenance (Arm 3). Combination chemotherapy was administered for 6 cycles and maintenance therapy was administered for 30 additional cycles. The patients were stratified by stage (III vs IV), residual disease and regimen, region, and germline *BRCA* status.

The primary endpoint was investigator-assessed progression-free survival (PFS) in Arm 3 compared with Arm 1 using stratification by the presence germline *BRCA* mutations, and homologous recombination deficiency (HRD; see Figure). Secondary outcomes of overall survival and disease-related symptom scores have yet to be reported.
In patients with *BRCA* mutations, the median PFS was 34.7 months in Arm 3 compared with 22 months in Arm 1 (HR 0.44; 95% CI 0.28-0.68; P<0.001). In patients with HRD-tumours, the median PFS was 31.9 months vs 20.5 months, respectively (HR 0.57; 95% CI 0.43-0.76; P<0.001). In the intention-to-treat population, the median PFS was 23.5 months in Arm 3 compared with 17.3 months in Arm 1 (HR 0.68; 95% CI 0.56-0.83; P<0.001).

The investigators concluded that the addition of veliparib to front-line carboplatin and paclitaxel with continued veliparib monotherapy maintenance significantly improved PFS in all cohorts of women with newly diagnosed high-grade serous

Figure. Kaplan Meier curves of patients free from disease progression or death, stratified by the presence of *BRCA* mutations, or HRD mutation, or all data combined



carcinoma, including the overall population without selection for biomarkers, nor timing or outcome of cytoreductive surgery and in cohorts of patients with *BRCA* mutation or HRD. The study findings were simultaneously published in the *NEJM* [2].

Invited discussant Mansoor Raza Mirza (Copenhagen University Hospital, Denmark) said that VELIA demonstrated clinically significant benefit of the experimental arm combining chemotherapy plus veliparib followed by veliparib in maintenance in the population with *BRCA* mutation or HRD. VELIA is the first phase 3 study to assess impact of combination chemotherapy plus PARPi followed by PARPi. Addition to chemotherapy caused increased toxicity, reduced use of potentially curative chemotherapy, and did not provide a benefit over what is observed in other PARPi first-line trials (in which the PARPi was added as maintenance only). Absence of comparator arm with veliparib in maintenance phase only makes it unclear if addition of veliparib to chemotherapy is necessary to provide observed benefit.

1. Coleman RL, et al. ESMO Congress 2019. Abstract LBA3.
2. Coleman RL et al. N Engl J Med. 2019 Sep 28.

PFS benefit with niraparib as first-line maintenance in ovarian cancer

Niraparib significantly improved progression-free survival (PFS) in patients with newly diagnosed advanced ovarian cancer, including patients at high risk of progressive disease. Niraparib should be considered as a treatment option for patients with advanced ovarian cancer after completion of first-line chemotherapy.

Lead study author Prof. Antonio González Martín (Clinica Universidad de Navarra, Spain) presented the results from the phase 3 PRIMA/ENGOT-OV26/GOG-3012 study in the Presidential Symposium [1]. The study investigated the efficacy and safety of the oral poly-ADP ribose polymerase (PARP) inhibitor niraparib after response to platinum-based chemotherapy in patients with newly-diagnosed ovarian cancer, including those at high risk of relapse. Overall, niraparib treatment resulted in a 38% reduction in the risk of disease progression or death in the overall population (HR 0.62; 95% CI 0.50-0.75; P<0.001).

In particular, results of the trial demonstrated a clinically meaningful reduction in risk of progression in women across biomarker subgroups (see Table). For example, patients whose tumours harboured a *BRCA* mutation experienced a marked risk reduction of 60% (HR 0.40; 95% CI 0.27-0.62; P<0.001). Furthermore, *BRCA* wild-type tumours but with homologous recombination-deficiency had a risk reduction of 50% (HR 0.50; 95% CI 0.30-0.83; P=0.006). Homologous recombination-proficient tumours, however, had a risk reduction of 32% (HR 0.68; 95% CI 0.49-0.94; P=0.020).

Although median overall survival was not yet reached, a pre-planned interim analysis supported a trend in improved overall survival, favouring over placebo. In the overall population, niraparib showed 84% overall survival vs 77% from the placebo arm alive at 24 months. Patients with homologous recombination-deficient tumours had 91% overall survival vs 85%, and homologous recombination-proficient tumours were associated with 81% vs 59%.

No new safety signals were identified for niraparib, with the most common treatment-emergent adverse event being reversible myelosuppression, according to the study. Dr Gonzalez indicated that these data support niraparib monotherapy after first-line platinum-based chemotherapy as a new standard of care.

Table. Summary of results

	niraparib mPFS (95% CI)	placebo mPFS (95% CI)	HR (95% CI); P-value
HRDpos subgroup	21.9 (19.3-NE)	10.4 (8.1-12.1)	0.43 (0.31-0.59); P<0.0001
overall population	13.8 (11.5-14.9)	8.2 (7.3-8.5)	0.62 (0.5-0.75); P<0.0001

mPFS, Median progression free survival; placebo, PBO; CI, confidence interval, homologous recombination-deficient positive, HRDpos, NE not estimable.

1. González Martín et al. ESMO Congress 2019. Abstract LBA1.

CNS Tumours

Ceritinib in *ALK*+ NSCLC brain metastases

Oral ceritinib showed efficacy in patients with *ALK*-positive non-small cell lung cancer (NSCLC) that has metastasised to the brain, according to results from the phase 2 ASCEND-7 study presented by Dr Laura Quan Man Chow (University of Texas at Austin, USA) [1].

As the prognosis of patients with *ALK*-positive NSCLC improves, so does the likelihood of developing leptomeningeal disease; brain metastases occur in approximately 30% to 50% of patients with *ALK*-positive NSCLC and are associated with poor outcomes, according to Dr Chow. The phase 2 ASCEND-7 trial results demonstrated that ceritinib was effective in controlling leptomeningeal metastasis in patients with *ALK*-positive NSCLC.

The study treatment arms were divided based on prior treatment with radiotherapy and ALK inhibitors, with a primary endpoint of investigator-assessed whole body overall response rate (ORR) according to RECIST 1:1. Treatment arms included prior brain radiotherapy and prior ALK inhibitor (Arm 1), no prior brain radiotherapy and prior ALK inhibitor (Arm 2), prior brain radiotherapy and no prior ALK inhibitor (Arm 3), and no prior brain radiotherapy and no prior ALK inhibitor (Arm 4). Across all 4 arms, median follow-up was 5.49 months for a total of 138 patients. The main results are shown in the Table.

The safety profile in this population was consistent with the reported profile of ceritinib, with no new or unexpected safety signals observed in the study. Regardless of prior ALK inhibitor treatment, ceritinib activity was consistent with its known efficacy established in patients with *ALK*-positive NSCLC with or without brain metastases. Across all study arms, ceritinib achieved fast, high, and durable intracranial responses.

Dr Chow also noted that patients who were naïve to a previous ALK inhibitor had higher intracranial response and intracranial disease control rate was high across all arms.

1. Chow LQ et al. ESMO Congress 2019. Abstract 14780.

Table. Results of the ASCEND-7 trial

	ARM 1 (prior brain radiotherapy and prior ALKI) n=42	ARM 2 (no prior brain radiotherapy and prior ALKI) n=40	ARM 3 (prior brain radiotherapy and no prior ALKI) n=12	ARM 4 (no prior brain radiotherapy and no prior ALKI) n=44
Whole body efficacy (RECIST v1.1) ORR, % [95% CI] DCR, % [95% CI]	35.7 [21.6, 52.0] 66.7 [50.5, 80.4]	30.0 [16.6, 46.5] 82.5 [67.2, 92.7]	50.0 [21.1, 78.9] 66.7 [34.9, 90.1]	59.1 [43.2, 73.7] 70.5 [54.8, 83.2]
Whole body efficacy (RECIST v1.1) Median DOR, months, % [95% CI] Estimated 6 months event-free probability, % [95% CI]	L‡ - 15 10.8 [4.1, NE] 64.6 [34.7, 83.5]	L‡ - 12 12.8 [3.7, 17.3] 74.1 [39.1, 90.9]	L‡ - 6 NE [11.7, NE] 100 [100, 100]	L‡ - 26 9.2 [7.3, 23,9] 72.7 [51.1, 86.0]
Whole body efficacy (RECIST v1.1) Median PFS, months, % [95% CI] Estimated 6 months event-free probability, % [95% CI]	7.2 [3.3, 10.9] 58.7 [41.6, 72.4]	5.6 [3.6, 9.2] 44.7 [28.5, 59.5]	NE [1.0, NE] 66.7 [33.7, 86.0]	7.9 [5.5, 9.4] 63.4 [46.8, 76.1]
Intracranial response (modified RECIST v1.1) ORR, % [95% CI] DCR, % [95% CI]	M - 28 39.3 [21.5, 59.4] 75.0 [55.1, 89.3]	M - 29 27.6 [12.7, 47.2] 82.8 [64.2, 94.2]	M - 7 28.6 [3.7, 71.0] 85.7 [42.1, 99.6]	M - 33 51.5 [33.5, 69.2] 75.8 [57.5, 88.9]
Intracranial response (modified RECIST v1.1) Median DOR, months, % [95% CI] Estimated 6 months event-free probability, % [95% CI]	L‡ - 11 9.2 [3.7, NE] 66.7 [28.2, 87.8]	L‡ - 8 10.1 [3.8, 17.3] 62.5 [22.9, 86.1]	L‡ - 2 NE 100 [100, 100]	L‡ - 17 7.5 [5.6, 11.2] 70.6 [43.1, 86.6]
Extracranial response (RECIST v1.1) ORR, % [95% CI] DCR, % [95% CI]	31.0 [17.6, 47.1] 47.1 [52.9, 82.4]	42.5 [27.0, 59.1] 92.5 [79.6, 98.4]	41.7 [15.2, 72.3] 66.7 [34.9, 90.1]	61.4 [45.5, 75.6] 72.7 [57.2, 85.0]
Median OS, months, % [95% CI] Estimated 12 months event-free probability, % [95% CI]	24.0 [12.6, NE] 67.4 [50.4, 79.6]	NE [16.2, NE] 72.9 [55.5, 84.5]	NE [1.0, NE] 75.0 [40.8, 91.2]	NE [26.5, NE] 77.9 [61.8, 87.9]

‡L is the number of patients included in the duration of response analysis. M, number of patients with measurable brain metastases at baseline DCR, disease control rate; DOR, duration of response; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression free survival

Adding bevacizumab to temozolomide-based therapy in neuroblastoma

The addition of bevacizumab to temozolomide-based therapy was associated with an improvement in overall response (OR) in children with relapsed/refractory neuroblastoma enrolled in the phase 2 BEACON-Neuroblastoma clinical trial [1].

Patients with relapsed or refractory neuroblastoma aged 1-21 years were randomly assigned to receive treatment in 5 experimental arms: temozolomide-bevacizumab; irinotecan-temozolomide; irinotecan-temozolomide-bevacizumab; temozolomide-topotecan; and topotecan-temozolomide.

The primary end point for part 1 (n=106) of the study was best response, with at least 4 more responses in the bevacizumab plus chemotherapy arms compared with the chemotherapy alone arms set as the criterion for a positive result. In total, 17 of 52 patients (33%) receiving chemotherapy plus bevacizumab and 8 of 54 patients (15%) receiving chemotherapy alone had an objective response to treatment, meeting the criterion for a positive study.

The BEACON-Neuroblastoma clinical trial protocol was amended to include part 2 of the study, which enrolled an additional 40 patients and inclusion of a coprimary end point of progression-free survival. Available data again showed a positive result with respect to overall response, with responses observed in 21 of 77 patients (27%) and 13 of 77 (17%) of those patients receiving bevacizumab vs those who did not receive bevacizumab, respectively.

Longer follow-up is required to determine whether addition of bevacizumab to temozolomide-based therapy has an impact on progression-free or overall survival.

The rate of grade 3 or higher adverse events was 86% in patients receiving bevacizumab and 58% for patients who did not. A decrease in platelet count and anaemia were most common in patients treated with bevacizumab.

1. Moreno L et al. ESMO Congress 2019. Abstract LBA64.

Solid Tumours/Pan-Tumour Data

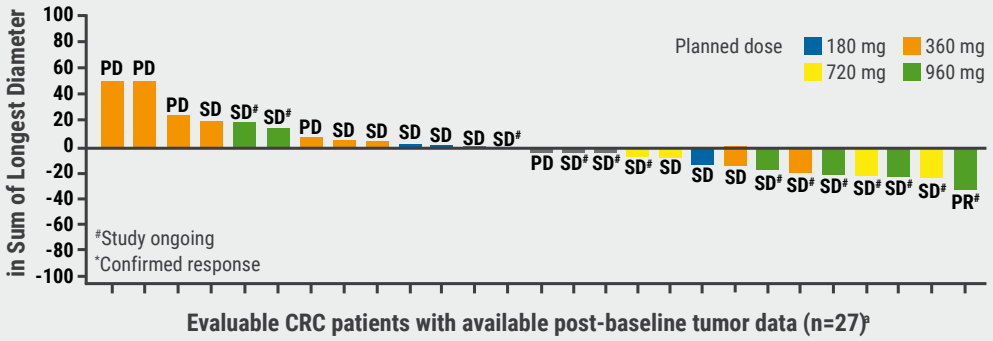
Mixed data: AMG 510 in tumours with KRAS^{G12C}

The ongoing phase 1 study evaluating investigative drug AMG 510 in patients with previously treated *KRAS* G12C-mutant solid tumours (KRAS^{G12C}) was presented by Prof. Ramaswamy Govindan (Washington University, St Louis, USA) [1]. The data include the first evidence of anti-tumour activity reported in patients with colorectal cancer (CRC) and appendiceal cancer, as well as previously presented non-small cell lung cancer (NSCLC) findings. AMG 510 continues to be well-tolerated with no dose-limiting toxicities.

This first-in-human, open-label, multicentre study enrolled 76 patients with KRAS^{G12C}-mutant solid tumours. Eligible patients were heavily pre-treated with at least two prior lines of treatment. The primary endpoint was safety, and key secondary endpoints include pharmacokinetics, objective response rate (assessed every 6 weeks), duration of response, and progression-free survival. Patients were enrolled in 4 dose cohorts: 180 mg, 360 mg, 720 mg, and 960 mg, taken orally once daily.

A subset of 55 evaluable patients as of the July 2019 data cut-off were presented, including CRC, appendiceal cancer, and NSCLC patients. Of these, 29 had CRC, 12 of whom received the target dose of 960 mg once daily (see Figure). Only 1 patient in this dose cohort experienced a partial response, and 10 had stable disease for a disease control rate of 92%. Of the evaluable patients with NSCLC, 13 received 960 mg, of which 7 (54%) achieved a partial response at one or more timepoints and 6 (46%) achieved stable disease, for a disease control rate of 100%. Data across dosing cohorts also showed tumour responses in 2 evaluable patients with appendiceal cancer with 1 partial response and 1 experiencing stable disease.

Figure. Change in colorectal (CRC) tumour burden after treatment with AMG 510



[a]2 patients-1 with SD, and 1 with PD-didn't have post-baseline tumour burden available and therefore, are not shown on the graph.
Evaluable patients: patients who had the first 6-week scan or early PD.

CRC: colorectal cancer; PR: partial response; SD: stable disease; PD: progressive disease.
Figure provided by ESMO.

Among the 76 patients enrolled across treatment groups, 52 remain on treatment. The majority of treatment-related adverse events (AEs) were grade 1 and 2. Only two treatment-related AEs were grade 3 (diarrhoea and anaemia). Thus, although the primary endpoint of safety was met, the single partial response in the CRC cohort was disappointing with regard to efficacy, despite better response in NSCLC.

1. Govindan R et al. ESMO Congress 2019. Abstract 446PD.

DNA profiling of carcinoma of unknown primary should inform treatment

New research showed that 1 in 3 patients with carcinoma of unknown primary (CUP; when no primary tumour site of origin can be found) may not be adequately treated with standard chemotherapy but may be suitable for matched targeted treatment or immunotherapy based on DNA changes in their tumour [1,2].

Looking for DNA changes in 303 CUP tissue samples collected in 2018, Prof. Jeffrey Ross (Upstate Medical University, Syracuse, USA) and colleagues used cutting edge technology to reveal that 32% of the tumours investigated could have been targeted by the latest medicines [1]. The same technology is now being used in the ongoing prospective CUPISCO trial. This current study is being followed up by one in which patients with CUP are being randomised to individualised targeted treatment or immunotherapy based on genetic alternations in their tumour, or to standard platinum-based chemotherapy. Initial results are expected within the next few years.

The need for a greater understanding of CUP tumour biology and a wider range of targeted therapies is reinforced by results of the also reported GEFCAPI 04 trial [2]. Started in 2012, this study used gene expression technology to identify the most likely primary tumour source in patients with CUP. However, best available targeted and other treatment tailored to primary tumours failed to improve disease progression or survival compared with standard platinum–based chemotherapy.

"The GEFCAPI 04 results are disappointing but many of the patients had pancreatic, biliary, and other kinds of cancer which are extremely difficult to treat and for which there are no targeted treatments. In a small number of patients who had suspected primary cancers unlikely to respond to empiric chemotherapy, molecular testing allowed use of a targeted agent or better tailored chemotherapy or immunotherapy. But there were probably not enough to make a difference to the overall results of the study," said presenting author Prof. Karim Fizazi (University of Paris Sud, France).

1. Ross J et al. ESMO Congress 2019. Abstract 1983PD_ PR.
2. Fizazi K et al. ESMO Congress 2019. Abstract LBA15_PR.

Larotrectinib: safe and effective in TRK fusion-positive tumours

Dr David Hyman (Memorial Sloan Kettering Cancer Center, New York, USA) reported an integrated analysis showing that the tropomyosin receptor kinase (TRK) inhibitor larotrectinib shows anti-tumour activity in tumours with *NTRK* gene fusions, agnostic of tumour type, including long-lasting objective responses and low toxicity [1].

Treatment with larotrectinib led to objective responses in 79% of 153 evaluable patients across 18 different tumour types. The overall response rate included complete responses in 24 (16%) patients. An additional 12% of patients had stable disease as best response, resulting in a clinical benefit rate of 91%. Invited discussant Dr Christian Dittrich (Vienna University School of Medicine, Austria) characterised the overall response rate as "sensational." He noted that the complete responses included 3 pathologic complete responses in patients with infantile fibrosarcoma.

In a subset of 108 patients with confirmed responses, the median duration of response was 35.2 months. "These data confirm the marked tissue-agnostic efficacy and long durability of response in patients with *TRK* fusion–positive cancer treated with larotrectinib," the investigators concluded. "Larotrectinib continued to demonstrate a favourable long-term safety profile. Screening patients for *NTRK* gene fusions should be actively considered."

The integrated analysis comprised the primary and supplementary cohorts enrolled in an adult phase 1 trial, the phase 1/2 SCOUT paediatric trial, and the phase 2 adult/adolescent NAVIGATE trial. The most common tumour types were infantile fibrosarcoma (18%), thyroid cancer (16%), salivary gland cancer (13%), lung cancer (8%), and a variety of other soft-tissue sarcomas (23%).
The analysis cohort consisted of 52 paediatric patients and 107 adults; 35 patients received larotrectinib as frontline treatment, whereas 48 patients had received 1 prior systemic therapy, 34 had received 2, and 42 patients had receive 3 or more prior lines. The gene fusions translocated *NTRK1* in 64 cases, *NTRK2* in 4 patients, *NTRK3* in 88 patients, and remained unconfirmed in 3 patients.

The 79% overall response rate in the integrated analysis was virtually identical to response rates observed in the primary (80%) and supplementary (79%) data sets. Among 12 evaluable patients with brain metastases, the overall response rate was 75% in the primary data set, while it was 83% in the supplementary data set. The median time to objective response was 1.8 months (0.9-6.1 months), and the median treatment duration was 8.0 months (0.03-47.2 months).
In addition to the 35.2-month median duration of response, landmark analyses showed that 75% of patients from the primary data set and 83% from the supplementary data set had responses lasting at least 12 months. The researchers observed a median progression-free survival of 28.3 months and a 12-month progression-free survival of 67%. Median overall survival was 44.4 months, and 12-month overall survival was 88%.

An expanded safety cohort of 260 patients treated with larotrectinib showed no new safety signals. The most common treatment-emergent adverse events (AEs, any grade) were fatigue (33%), increased alanine aminotransferase (ALT; 28%), cough (28%), constipation (27%), anaemia (27%), increased aspartate aminotransferase (AST; 27%), dizziness (25%), nausea (25%), vomiting (25%), diarrhoea (24%), and pyrexia (20%). The most common grade 3/4 treatment-emergent AE was anaemia (10%, all grade 3). No other grade 3/4 treatment-emergent AEs occurred in more than 5% of patients.

1. Hyman DM et al. ESMO Congress 2019. Abstract 445PD.