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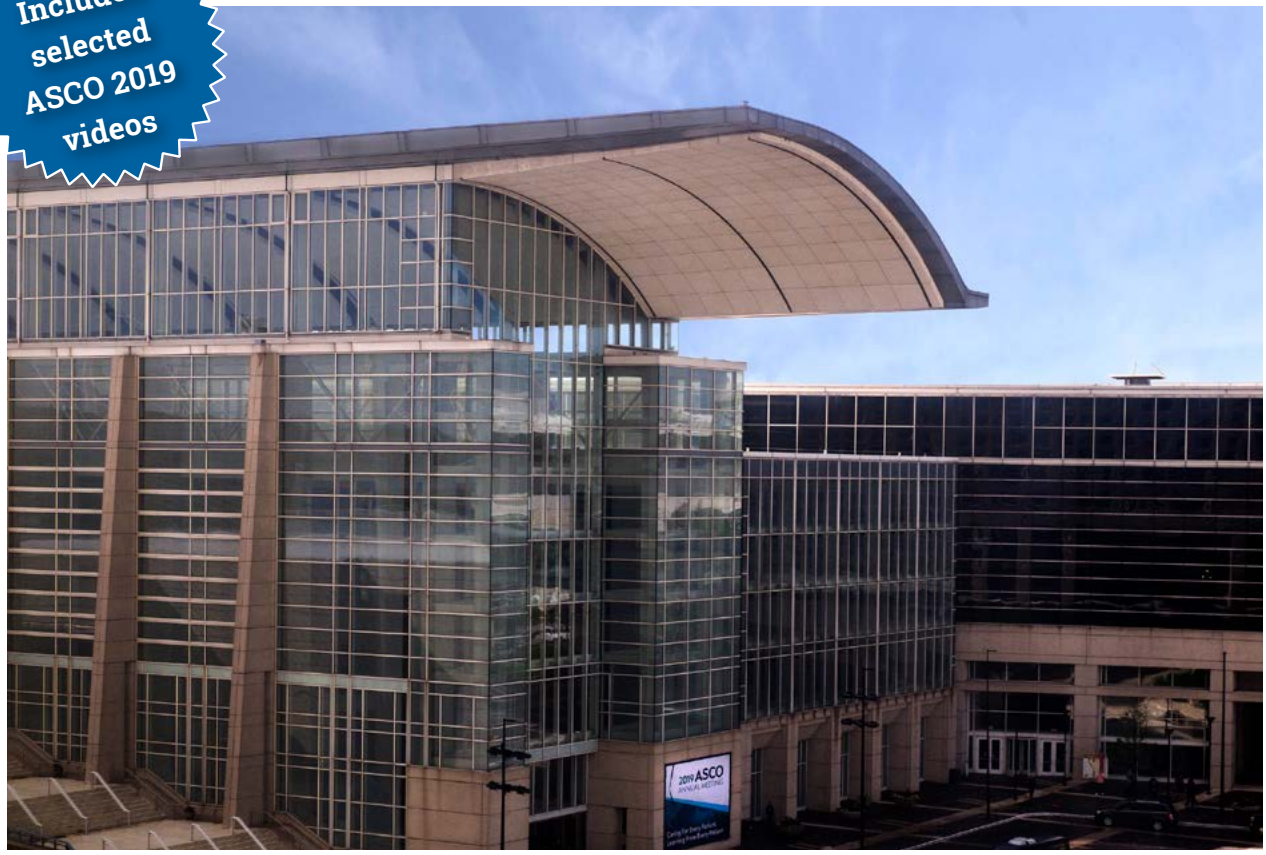

Breast Cancer

Longer overall survival in women treated with endocrine therapy plus ribociclib, compared with women treated with endocrine therapy alone, in the phase III MONALEE-SA-7 trial of premenopausal women with HR+/HER2-negative advanced breast cancer

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Colorectal Cancer

Neoadjuvant chemotherapy results in histologic regression and down-staging and decreased the rate of incomplete resections among patients with operable colon cancer: results of the FOxTROT trial

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Pediatric Cancers

Entrectinib is well tolerated and produced rapid and durable responses in children with refractory CNS and solid tumors harboring *NTRK1/2/3*, *ROS1*, and *ALK* fusions, as well as in a patient with *ALK*-mutated neuroblastoma

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MEDICOM MEDICAL PUBLISHERS

Editors Dr Sant P. Chawla, Sarcoma Oncology Research Center, CA, USA
Dr Erlinda Maria Gordon, Sarcoma Oncology Research Center, CA, USA

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Biography

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Biography

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Conflict of Interest Statement:
"Dr Gordon is PI of an Investigator Initiated Research study funded by BMS."

Letter from the Editors

Dear Readers,

""*Caring for every cancer patient & learning from every cancer patient*" — a far-reaching theme of the 2019 ASCO Annual Meeting — inspires both clinical oncologists and physician/scientists to value the importance of each cancer patient encounter. While phase 3 clinical trials are vital to the evidence-based FDA-approval process, it is the oncologist at the bedside who makes the ultimate decisions on how, and with precisely what drugs, an individual patient will be treated. Thus, contemporary oncologists assume responsibilities for continuing education and clinical research in this *Age of Precision Medicine and Tumor-Targeted Cancer Gene Therapy*. The ASCO annual meetings are valuable in this regard; for it is within these topical meetings that medical oncologists gather from around the world to share clinical experiences, exchange clinical insights, and introduce innovative therapies. In such networking, medical and scientific visions are broadly shared and ultimately translated into the safe and effective medicines of the future. Indeed, the promise of Precision Medicine has come of age with the development of *tumor-targeted viral vectors, genetic profiling, next generation sequencing, and complementary biomarkers*.

Sincerely,

Dr Erlinda M. Gordon and Dr Sant P. Chawla

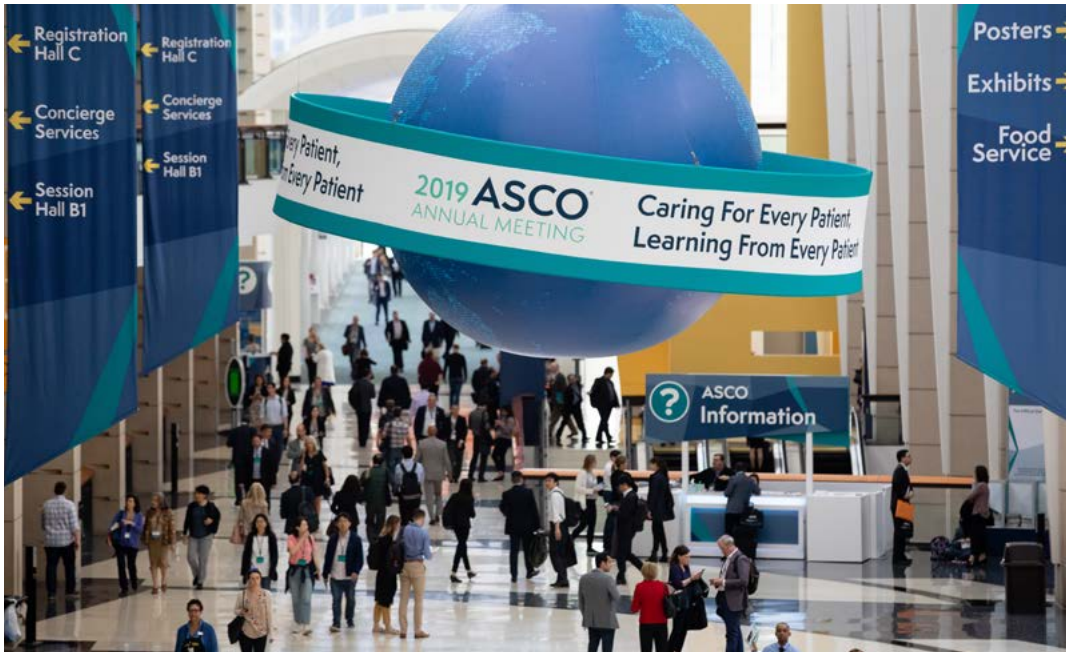

Photo by © ASCO/Todd Buchanan

Breast Cancer

Featured video: Phase III MONALEESA-7 trial of premenopausal patients with HR+/HER2– advanced breast cancer (ABC) treated with endocrine therapy ± ribociclib: Overall survival (OS) results. watch the video

Endocrine therapy plus ribociclib yields overall survival advantage in HR+/HER2-negative breast cancer

Medical writer: Jasenka Piljac Žegarac, PhD

Significantly longer overall survival (OS) was observed in women treated with endocrine therapy (ET) plus ribociclib, compared with women treated with ET alone, in the phase III MONALEESA-7 trial of premenopausal women with HR+/HER2-negative advanced breast cancer (ABC). This is the first study demonstrating significantly longer OS in patients treated with a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor plus ET combination, compared to ET alone, as initial endocrine-based therapy.

"MONALEESA-7 was the first phase III trial with a CDK4/6 inhibitor [conducted] exclusively in premenopausal patients," said Sara A. Hurvitz, MD, of the University of California, Los Angeles, Jonsson Comprehensive Cancer Centre, on June 4 (Abstract LBA1008).

A total of 672 premenopausal women with HR+/HER2-negative ABC who had not received ET for metastatic disease or who had received up to one prior line of chemotherapy were randomly assigned 1:1 to either 600 mg/day ribociclib plus goserelin (335) or placebo plus goserelin (337), with either a nonsteroidal aromatase inhibitor (letrozole or anastrozole) or tamoxifen. All women were younger than age 59, and the average age in both arms was comparable (age 43 years in the ribociclib plus ET arm and age 45 years in the placebo plus ET arm). The dosing regimen was 3 weeks on, followed by 1 week off treatment.

"The primary endpoint was progression-free survival (PFS), locally assessed, and our key secondary endpoint was OS," Dr Hurvitz said. OS was assessed using the Kaplan-Meier method and was compared by a one-sided stratified log-rank test, with superior efficacy defined as P≤0.01018.

Median follow-up was 34.6 months. At interim analysis data cut off (November 2018), treatment was ongoing in 35% of patients in the ribociclib arm and 17% of patients in the placebo arm. Dr Hurvitz said that the majority of patients who ended treatment did so because of disease progression.

Patients receiving ribociclib plus ET had a significantly longer median OS than patients receiving placebo plus ET (not reached vs 40.9 months, 95% CI [37.80 months, not evaluable]; HR = 0.712 95% CI [0.54, 0.95]; P=0.00973). OS analysis showed that "there was a 29% relative reduction in risk of death [in patients in the ribociclib arm]," Dr Hurvitz said. "The median OS was not met in the ribociclib arm and was 40.9 months in the placebo arm," she said. She added that "there was a consistent OS benefit seen across the subgroups."

According to Dr Hurvitz, "The benefit of ribociclib extended beyond the initial treatment based on the time-to-subsequent chemotherapy and PFS-2." PFS-2 was defined as time from random selection to progression on the next line of therapy or death. The prespecified stopping boundary for superior efficacy was reached, with a p value of 0.00973.

In presenting safety data, Dr Hurvitz noted that after 15 months of follow up, the adverse event profile for the ribociclib arm remained consistent with the known safety profile. Grade 3/4 events of special interest in the ribociclib and placebo arms were neutropenia (63.5% ribociclib and 4.5% placebo), hepatobiliary toxicity (11.0% ribociclib and 6.8% placebo), and prolonged QT interval (1.8% ribociclib and 1.2% placebo).

In the discussion that followed, Angelo Di Leo, MD, PhD, of the Hospital of Prato, Instituto Toscano Tumouri, Italy, said that the "MONALEESA-7 results are now setting a new standard of care for patients who are endocrine-therapy naive. I think that this is now a population where we should consider combination of a CDK4/6 inhibitor plus endocrine therapy as a new standard of care.

"My personal opinion is that this result should be expanded also to the menopausal population," he continued, and he noted that the "endocrine-sensitive population is the population who relapsed after at least 1 year from the end of adjuvant endocrine therapy."

Biomarker analysis predicts response to adjuvant trastuzumab, pertuzumab in HER2+ breast cancer

Medical writer: Leah Lawrence

A comprehensive genomic analysis of women with HER2-positive breast cancer enrolled in the APHINITY trial revealed several markers that may be associated with better prognosis and increased benefit from treatment with trastuzumab and pertuzumab (Abstract 1012).

Ian E. Krop, MD, PhD, of the Dana-Farber Cancer Institute, presented results of the analysis, which included DNA sequencing, RNA sequencing, tumor-infiltrating lymphocyte (TIL) analysis, and HER2 immunohistochemistry and FISH, during the "Targeting Breast Cancer: Breaking the Code" Clinical Science Symposium held June 1.

APHINITY was a phase III study investigating the benefit of adjuvant therapy with pertuzumab when added to trastuzumab and chemotherapy in women with HER2-positive early-stage breast cancer. The trial demonstrated an invasive disease-free survival benefit to adding pertuzumab, but the overall magnitude was relatively small at only 1.7% difference at 4 years, Dr Krop said.

In high-risk populations, such as patients with node-positive or hormone receptor–negative disease, the benefit was somewhat greater, but Dr Krop and colleagues wanted to elucidate biomarkers to identify subgroups of patients that might benefit even more from the added treatment.

The DNA and RNA testing occurred within a nested case control study including 299 patients with an invasive disease-free survival event who were matched 1:3 with an event-free control group of 1,023 patients. TIL analysis occurred in 4,313 patients, and HER2 analysis occurred in 4,804 patients of the intention-to-treat population from the APHINITY trial.

The DNA analysis revealed that PI3K pathway alterations (i.e., *PI3K/PTEN/AKT* alterations) occurred in 37% of patients and was associated with a worse outcome (HR 1.35, 95% CI [1.01, 1.79]; P=0.04). According to Dr Krop, there was a modest trend toward decreased benefit of pertuzumab seen in patients with PI3K pathway alterations, but it was not statistically significant.

MYC (HR 1.61, 95% CI [1.16, 2.23]; P=0.00) and *ZNF703* (HR 1.62, 95% CI [1.07, 2.47]; P=0.02) amplification was associated with worse prognosis. In contrast, *TOP2A* amplification (HR 0.49, 95% CI [0.32, 0.74]; P=0.00) was associated with a better prognosis, independent of anthracycline use.

RNA sequencing showed the luminal A subtype was associated with better outcomes, particularly compared with patients with basal subtype (HR 3.11, 95% CI [1.44, 6.6]; P=0.003). There was no significant interaction observed between PAM50 subtype and pertuzumab benefit.

High levels of certain immune markers were also associated with favorable prognosis and predicted pertuzumab benefit. A three-gene T-cell immune signature consisting of *IFNG, PD-L1*, and *CXCL9* (HR 0.68, 95% CI [0.52, 0.89]; P=0.005) and its individual components appeared to be associated with favorable outcomes. No link between the T-cell immune signature and pertuzumab benefit was found; however, higher levels of the individual component genes appeared to predict greater benefit of the drug (*CXCL9* > 75%, P=0.05; *IFNG* > 75%, P=0.03). Higher TIL levels, taken as a continuous variable, were also associated with favorable outcomes in a prognostic analysis (HR 0.91, 95% CI [0.86, 0.96]; P=0.001). Patients with TIL levels in the highest quartile appeared to also derive benefit from pertuzumab in a predictive analysis (HR 0.35, 95% CI [0.19, 0.65]; P=0.003).

Finally, the HER2 analyses showed that cancers with high HER2 copy number (≥ 6) had better prognosis (HR 0.68, 95% CI [0.50, 0.91]; P=0.01) and may be predictive of greater benefit with pertuzumab (HR 0.75, 95% CI [0.60, 0.93]; P=0.04).

"While we identified a number of predictive markers, none were so strong that we could use them in clinic to say which patients would benefit from pertuzumab and which would not, but we certainly identified some directions worth exploring," Dr Krop said. Discussant Matthew P. Goetz, MD, of Mayo Clinic, congratulated the authors on the important study, calling it a "tour de force."

"This study is incredibly important because it is a large international study, but also because the researchers were able to get biomarker analyses for over 1,000 patients, which, as far as I know, is certainly one of the largest analyses in the adjuvant HER2 setting," Dr Goetz told *ASCO Daily News*.

The path forward for optimization of HER2-targeted therapies, according to Dr Goetz, is clinical research focusing on using tissue and imaging biomarkers, de-escalation of therapy when possible to reduce chemotherapy without altering efficacy, and escalation of therapy based on biology and initial response to anti-HER2–based therapy.

ImPassion130 brings breast cancer into the immunotherapy era

Medical writer: Dr Giuseppe Curigliano

2018 was a pivotal year in breast cancer research, with the phase III ImPassion130 trial bringing breast cancer into the immunotherapy era. Schmid et al.demonstrated a substantial overall survival (OS) benefit in patients with PD-L1–positive metastatic triple-negative breast cancer (TNBC) by the addition of the anti–PD-L1 agent atezolizumab to first-line chemotherapy with nab-paclitaxel [1].

At median follow-up of 12.9 months, the median progression-free survival (PFS) in the ITT population was significantly improved with the addition of atezolizumab (5.5 vs 7.2 months; HR 0.80, 95% CI [0.69, 0.92]; P=0.002). A PFS benefit with atezolizumab was also observed in the PD-L1–positive population (5.0 vs 7.5 months; HR 0.62, 95% CI [0.49, 0.78]; P<0.001). An interim OS analysis was performed, and the OS difference was not statistically significant in the ITT population (median OS, 17.6 to 21.3 months; HR 0.84, 95% CI [0.69, 1.02]; P=0.08). However, an impressive median OS increase of 9.5 months was observed with the addition of atezolizumab in the PD-L1–positive population (15.5 vs 25.0 months; HR 0.62, 95% CI [0.45, 0.86]).
According to these data, is immunotherapy transformative for metastatic TNBC? Many open questions can be raised from the current trial. What is the best way to test the tumor for PD-L1 expression since this subgroup of patients derived benefit from atezolizumab? Is nab-paclitaxel the ideal partner for an immune checkpoint inhibitor? Did we miss an atezolizumab monotherapy arm that might be a good option for certain subset of patients? Should we be more focused on OS rather than PFS? What can we learn from the neoadjuvant setting?

The positive result in the PD-L1–positive subgroup suggests that we need to enrich the study population. Therefore, we need to define the immunogram of patients with breast cancer who are most likely to respond to immune checkpoint inhibitors. The objective response rate (per RECIST) was numerically higher with the addition of atezolizumab in the ITT population (56% vs 46% without atezolizumab) and PD-L1–positive population (59% vs 43% without atezolizumab), and more complete responses were observed with atezolizumab than without (ITT: 7% vs 2%; PD-L1–positive group: 10% vs 1%). A companion diagnostic test assessed PD-L1 expressed only on immune cells.

Conclusion

It is an exciting time in the treatment of TNBC. The multiple ongoing trials may shed light on breast cancer immune response biomarkers and determine whether a multidimensional immunogram could predict efficacy better than the current PD-L1–based unidimensional immunogram.

Reference

1. Schmid P, et al. *New Engl J Med*. 2018;379:2108-21

Melanoma

Nivolumab-mediated adverse events are independent of efficacy in resected advanced melanoma

Medical writer: Dr Rachel H. Giles

Prof. Mario Mandalà (Papa Giovanni XXIII Cancer Centre Hospital, Bergamo, Italy) provided data from CheckMate 238 plotting treatment-related adverse events (TRAEs) for nivolumab (NIVO) in patients with resected stage IIIB/C or IV melanoma against recurrence-free survival (RFS). His comprehensive analysis demonstrated a safety profile consistent with the other nivolumab studies. The majority of TRAEs with adjuvant NIVO occurred early during treatment, and patients had a reduced frequency of TRAEs after the treatment course. Most TRAEs resolved within 3 months [1].

CheckMate 238 demonstrated that adjuvant treatment with nivolumab significantly improved RFS for patients with stage III/IV melanoma with pathologic involvement of regional lymph nodes >1 mm who have undergone complete resection including total lymphadenectomy, reducing the risk of recurrence or death by 35% compared with ipilimumab

(HR, 0.65; 97.56% CI, 0.53-0.80; P<0.001). Besides showing clear benefit under the nivolumab arm, initial results also showed significantly less toxicity, although it was unclear if toxicity related to efficacy. The proportion of patients under nivolumab arms who had to stop therapy from TRAE's was 8% compared >30% of those who were on the ipilimumab arms.

In the current study, Prof Mandalà and colleagues performed a subgroup analysis of CheckMate 238 patients (n=453) using discrete follow-up intervals and interrogated a putative association of these AEs with efficacy (RFS). The primary endpoint was RFS. Patients were followed for safety for up to 100 days following their last dose; as of the previous 18-month database lock, all patients had been off study drug for > 100 days. Safety data were analysed within the pre-defined time intervals: 0–3 months of treatment, 3–12 months of treatment, and from the last dose to 100+ days after the last dose.

The incidence of the first onset of TRAEs reported in ≥5% of patients was highest in the 0–3 month time frame; the most common TRAEs with nivolumab were fatigue (28% for 0–3 months vs 6% for 3–12 months vs 2% for +100 days post-last dose), pruritus (16% vs 7% vs 1%, respectively), and diarrhoea (15% vs 7% vs 2%, respectively). Most TRAEs with nivolumab resolved within 3 months of occurrence, except for endocrine AEs, which could have required hormone supplementation, and skin AEs (median overall resolution time of 48 and 22 weeks, respectively). The authors concluded that there was no correlation between TRAE's and RFS.

Reference

1. Mandalà M et al. Abstract 9584. An analysis of nivolumab-mediated adverse events and association with clinical efficacy in resected stage III or IV melanoma (CheckMate 238). ASCO 2019, 31 May-4 June, Chicago, USA.

Long term quality of life with nivolumab, or in combination (ipilimumab) in advanced melanoma

Medical writer: Dr Rachel H. Giles

Two new analyses of CheckMate 067 data determined that quality of life (QoL) was maintained throughout the course of treatment (either nivolumab alone or with ipilimumab), on long-term (4 year) follow-up and, importantly, that these benefits persisted when the patients were off therapy [1,2]. The phase 3 CheckMate 067 was a Phase 3, double-blind, randomized trial that evaluated the combination of nivolumab plus ipilimumab (n=314) or nivolumab monotherapy (n=316) vs ipilimumab monotherapy (n=315) in a total of 945 patients with previously untreated advanced melanoma.

An analysis exploring long-term quality of life (QoL) and symptom burden found that QoL was maintained during the treatment-free interval (TFI) – the period where a patient is off study treatment and free of subsequent therapy – in patients with previously untreated unresectable or metastatic melanoma following discontinuation of therapy with nivolumab or nivolumab plus ipilimumab. Patient reported outcome (PRO) scores were maintained from last on-treatment visit to follow-up 1 (30 days after the last dose) or follow-up 2 (84 days after follow-up 1) for patients who discontinued treatment. PRO scores remained stable beyond follow-up 2 for the EQ-5D-3L (measures of mobility, self-care, usual activities, pain/discomfort and anxiety/depression), which were collected at survival follow-up visits every three months in the first year and then every six months.

Finally, a four-year analysis from the CheckMate 067 study of nivolumab and ipilimumab, alone or in combination, in patients with previously untreated unresectable or metastatic melanoma, showed that patient reported QoL and symptoms were maintained from baseline during extended treatment. Of 813 patients included in the PRO analysis population, QoL – including an assessment of functioning and symptom burden – was maintained for the duration of treatment and in follow-up, with no sustained clinically meaningful deterioration in any treatment arm.

References

1. Schadendorf et al. Abstract 9551. Patient-reported quality of life (QoL) of advanced melanoma patients in a Phase 3 study of nivolumab (NIVO) with or without ipilimumab (IPI) vs. IPI: CheckMate 067 4-year data. ASCO 2019, 31 May-4 June, Chicago, USA.
2. Taylor et al. Abstract 9568. Quality of life (QoL) and symptom burden in patients (pts) with advanced melanoma during the treatment-free interval (TFI) after discontinuation of nivolumab (NIVO) or NIVO plus ipilimumab (IPI). ASCO 2019, 31 May-4 June, Chicago, USA.

Kidney Cancer

Classification of metastatic renal cell carcinoma patients in immunotherapy era and positive responses for sarcomatoid tumors

Medical writer: Dr Rachel H. Giles

Prof. Bernhard Escudier (Gustave Roussy Cancer Campus, Paris, France) presented a post-hoc analysis of CheckMate 214, concluding that the IMDC prognostic criteria, based on anti-VEGF treatment outcomes, may not be as relevant for immunotherapy treatment outcomes in metastatic renal cell carcinoma [1]. Prof. D. McDermott (Dana-Farber, Harvard Cancer Centre, USA) presented a subgroup analysis demonstrating that the ipilimumab + nivolumab arm provided improved efficacy and prolonged survival vs sunitinib, with consistent safety, in previously untreated, intermediate/poor-risk, advanced clear-cell RCC with sarcomatoid features [2].

The randomized controlled trial CheckMate 214 (ipilimumab + nivolumab vs sunitinib in 1st line metastatic renal cell carcinoma) demonstrated a complete response rate of 16% in patients with intermediate- and poor-risk features whose tumor tested positive for PD-L1. The key take-home message was that this combination resulted in an overall survival advantage, but those data were mainly driven by the patients who were defined as intermediate- or poor-risk at the outset of the study by the IMDC prognostic criteria. The study was ended prematurely after the first interim analysis because the results on overall survival were clearly in favour of the immunotherapy combination; the survival advantage was even more pronounced in patients with higher risk scores.

Prof. Escudier and colleagues compared efficacy with nivolumab + ipilimumab vs sunitinib by number of IMDC risk factors present in 1096 intent-to-treat patients in both arms: 21%, 61%, and 18% had favourable, intermediate, or poor-risk, respectively. Of intermediate-risk patients, 58% had 1 factor; and 42% had 2 factors. Of poor-risk patients, 58% had 3 factors, 29% had 4 factors, and few had 5 (10%) or 6 (3%) factors. Due to small numbers, pts with 4–6 factors were pooled. At 30-months minimum follow-up, RECIST v1.1-confirmed objective response rate and complete response rate per investigator remained consistently higher with nivolumab + ipilimumab vs sunitinib across pts with 1–4 factors, although with sunitinib, ORR decreased with increasing number of factors. The authors conclude that nivolumab + ipilimumab showed consistent efficacy across number of IMDC risk factors, while sunitinib decreased in efficacy with increasing number of factors. These results show a need for improved prognostic models for immunotherapies in aRCC.

Professor McDermott's paper addressed the unmet need of patients with advanced renal cell carcinoma with sarcomatoid features (sRCC), who have poor prognosis with anti-VEGF targeted therapy. They performed a post-hoc exploratory analysis of 112 CheckMate 214 randomized sRCC patients with pathologically confirmed sRCC (nivolumab + ipilimumab, n=60; sunitinib, n=52). In descriptive analyses performed at a minimum follow-up of 30 months, confirmed overall response rate and complete response rate per investigator (RECIST v1.1), overall survival, and progression-free survival per investigator were improved with nivolumab + ipilimumab vs sunitinib in intermediate/poor-risk patients with sRCC.

There were two additional presentations assessing the response rates of patients with intermediate/poor risk features or sarcomatoid histologies to checkpoint inhibitor therapies [3-4]. These two abstracts similarly describe treatment of patients bearing sarcomatoid tumors with pembrolizumab plus axitinib, or atezolizumab plus bevacizumab, respectively. Presence of sarcomatoid cells in a tumor is typically associated with a worse prognosis, and patients with sarcomatoid tumors do not respond as well to targeted drugs like sunitinib or pazopanib. However, sarcomatoid tumors typically harbor more immune cells, and we see in each of the first three abstracts that patients with sarcomatoid kidney tumors respond to combinations including IO agents considerably better than to sunitinib alone, with complete disappearance of disease in a small but significant percentage of cases. These findings collectively open a therapeutic option for patients that in the past did not have any good treatment options.

References

1. Escudier B et al. Abstract 4575. Consistent efficacy of nivolumab plus ipilimumab across number of International Metastatic Database Consortium (IMDC) risk factors in CheckMate 214. ASCO 2019, 31 May-4 June, Chicago, USA.
2. McDermott D et al. Abstract 4513. CheckMate 214 post-hoc analyses of nivolumab plus ipilimumab or sunitinib in IMDC intermediate/poor risk patients with previously untreated advanced renal cell carcinoma with sarcomatoid features. ASCO 2019, 31 May-4 June, Chicago, USA.

3. Rini B et al. Abstract 4500. Pembrolizumab (pembro) plus axitinib (axi) vs. sunitinib as first-line therapy for metastatic renal cell carcinoma (mRCC): Outcomes in the combined IMDC intermediate/poor risk and sarcomatoid subgroups of the phase 3 KEYNOTE-426 study. ASCO 2019, 31 May-4 June, Chicago, USA.

4. Rini et al. Abstract 4512. Atezolizumab (atezo) + bevacizumab (bev) vs. sunitinib (sun) in pts with untreated metastatic renal cell carcinoma (mRCC) and sarcomatoid (sarc) histology: IMmotion151 subgroup analysis. ASCO 2019, 31 May-4 June, Chicago, USA.

Sarcoma

Featured video: A randomized, placebo (PBO)-controlled, double-blind, phase (Ph) III trial of doxorubicin (dox) + olaratumab versus dox + PBO in patients (pts) with advanced soft tissue sarcomas (STS). watch the video

Olaratumab trial in soft tissue sarcoma fails to meet overall survival endpoint

Medical writer: Tim Donald, ELS

The ANNOUNCE trial, assessing the overall survival (OS) benefit of olaratumab in patients with advanced soft tissue sarcoma (STS), failed to meet its dual primary endpoint of OS in all STS histologies or in a subset of patients with leiomyosarcoma (LMS), according to a Late-Breaking Abstract (Abstract LBA3) presented at the June 2 Plenary Session. William D. Tap, MD, of Memorial Sloan Kettering Cancer Centre, presented the study data.

Dr Tap explained that, after the data readout from this study, the trial sponsor and global regulatory agencies recommended that no new patients be started on olaratumab. Withdrawal of the drug from the market is in progress. Patients who are currently receiving treatment with olaratumab with apparent benefit may continue to be treated with the drug.

"ANNOUNCE was a well-controlled and conducted phase III trial, which failed to meet its overall survival primary endpoint in all STS histologies or the LMS population," he said, adding that the trial did not confirm the benefit seen in an earlier trial.

In that previous phase Ib/II clinical trial in patients with advanced STS, a regimen of doxorubicin plus olaratumab improved progression-free survival (PFS) and OS in comparison with doxorubicin alone. After that trial, the U.S. Food and Drug Administration granted accelerated approval to olaratumab, conditional on the performance of a follow-up study; ANNOUNCE was that study.

Possible confounding factors in the phase Ib/II study, Dr Tap said, included that the trial was unblinded; that there was a large discrepancy between results in OS and PFS, the study's primary endpoint; and that the drug had an unknown mechanism of action in sarcoma subtypes.

ANNOUNCE enrolled adult patients with unresectable locally advanced or metastatic STS, with ECOG status 0 or 1, and with any number of previous treatments but no anthracycline. Patients were randomly assigned 1:1 to olaratumab 20 mg/kg for cycle 1, then olaratumab 15 mg/kg for cycles 2 through 8, or placebo, on days 1 to 8 of each 21-day cycle. Patients in both arms received doxorubicin 75 mg/m^2 on day 1 for up to eight cycles. After eight cycles, patients with disease control continued on olaratumab or placebo as monotherapy until progression or toxicity. Treatment with dexrazoxane was allowed to mitigate doxorubicin-related cardiotoxicity.

Randomization was stratified by number of previous treatments, histology, and ECOG status. The primary endpoint was OS by intent-to-treat in the total STS and the LMS populations, and the study was designed to be positive if either population, or both, had a statistically significant improvement in OS. The secondary endpoints were PFS, safety, pharmacokinetics, objective response rate, and patient-reported outcomes. A total of 509 patients randomly assigned, 258 were in the investigational regimen and 251 in the control arm. Baseline characteristics were well balanced.

In the total STS population, median OS was 20.4 months in the investigational arm and 19.7 months in the control arm (HR 1.05, 95% CI [0.84, 1.30]; P=0.6945). In the LMS population, median OS was 21.6 months in the investigational vs. 21.9 months in the control arm (HR 0.95, 95% CI [0.69, 1.31]; P=0.7618).

Why was the study negative? Dr Tap listed several possible reasons, including that olaratumab is not effective in combination with doxorubicin in STS, or that olaratumab has some activity in

STS, but it was masked by heterogeneity of the study populations within and between studies or by differences in study designs.

Another consideration is that patients in the control arm in ANNOUNCE performed better than expected. "Median OS in the doxorubicin and placebo arm was 19.7 months," Dr Tap said. "This is the highest survival rate described to date in any phase III sarcoma study."

In light of the large number of subtypes, Dr Verweij questioned the predictive value of phase II randomized studies investigating the addition of drugs to doxorubicin for STS. Several randomized phase II studies in STS to date have overestimated PFS and OS benefits in comparison to subsequent phase III studies of the same drug combinations, he said.

When STS subtypes are lumped together in phase II studies, even when those studies are randomized, they can provide misleading results, Dr Verweij said. Phase II studies should be considered a screening tool, and they always need confirmation in a phase III trial, even when activity data in phase II are compelling.

He suggested that phase II studies in specific STS subtypes could yield better predictions of outcomes for subsequent phase III studies. Global collaboration now allows the performance of rapidly accruing clinical studies in STS, and investigators should favour subtype-specific, biomarker-driven studies whenever possible.

Gastrointestinal Cancers

Featured video: Pembrolizumab with or without chemotherapy versus chemotherapy for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: The phase III KEYNOTE-062 study watch the video

Featured video: Olaparib as maintenance treatment following first-line platinum-based chemotherapy (PBC) in patients (pts) with a germline BRCA mutation and metastatic pancreatic cancer (mPC): Phase III POLO trial. watch the video

FOLFOXIRI plus bevacizumab an option for patients with mCRC and poor prognosis

Medical writer: Debra Gordon

FOLFOXIRI plus bevacizumab improves progression-free survival (PFS) by about 3 months compared to FOLFOX plus bevacizumab in patients with first-line metastatic colorectal cancer (mCRC) and a poor prognosis, albeit with a higher rate of serious side effects, according to the results of the phase III VISNU-1 trial (Abstract 3507) reported during the Gastrointestinal (Colorectal) Cancer Oral Abstract Session on June 1. VISNU-1 is the first mCRC study performed in a population selected by baseline circulating tumor cell (CTC) count.

Although FOLFOXIRI plus bevacizumab has a demonstrated PFS and overall survival (OS) benefit compared with FOLFOX plus bevacizumab, this schedule is not routinely recommended in all patient groups because of toxicity, lead author Javier Sastre, MD, PhD, of Hospital Clínico San Carlos, Spain, said.

"We considered that it would be of interest to explore the role of this combination in a subgroup of patients with poor prognostic factors," he said, specifically patients with CTCs greater than or equal to three. Higher CTC levels have been shown to be a poor prognostic factor for survival [1].

VISNU-1 is an open, multicentre, randomized phase III trial. Investigators screened 1,252 patients, enrolling 349 patients younger than age 70 with an ECOG score of 0 to 1.
After accrual of 63 patients, the protocol was changed to recommend the use of prophylactic GCSF in the FOLFOXIRI arm due to a high rate of neutropenia, Dr Sastre said.

There was a significant difference in PFS between the two arms, with a PFS of 12.4 months in the FOLFOXIRI arm compared with 9.3 months in the FOLFOX arm (HR 0.64, 95% CI [0.49, 0.82]; P=0.0006). A subgroup analysis showed that most subgroups would benefit from the FOLFOXIRI

combination, except patients with a *P13K* mutation. These data also suggested a greater benefit for those with a primary tumor located on the left side and with a wild-type *RAS/BRAF* tumor, Dr Sastre said.

The multivariate analysis demonstrated that *BRAF* and *RAS* status, CTCs greater than 20, and an ECOG score of 1 were independent predictors for PFS, he said.

Although the OS was not statistically significant at a median follow-up of 50.7 months, "these are not final results," Dr Sastre said. Additional data should be available by the end of the year.

There was no statistically significant difference between the two arms in objective response rate (ORR) or duration of response in the intent-to-treat analysis. However, there were statistically significant differences in ORR in the overall population (57% for FOLFOX compared with 69% for FOLFOXIRI; HR 0.61, 95% CI [0.38, 0.97]; P=0.0381).
Overall, there were 133 grade 3 or higher toxicities in the FOLFOXIRI arm vs 119 in the FOLFOX arm (P=0.022).

"This study suggests that FOLFOXIRI plus bevacizumab could be considered an adequate treatment option for patients with mCRC and three or more CTCs," Dr Sastre said, although further studies evaluating the role of CTCs as a predictive factor are needed.

"To what extent can we generalize these trials to the patient sitting in front of us?" asked Discussant Hanna K. Sanoff, MD, MPH, of the University of North Carolina Lineberger Comprehensive Centre. Although the subgroup analyses are based on small numbers of patients, "to me, the lack of a consistent pattern is reassuring that there isn't any particular subgroup for which FOLFOXIRI won't work," she said.
Nonetheless, she said, "I don't feel comfortable generalizing the results to patients older than 70 or those with a poor performance status," because neither were represented in the study.

She also questioned the effect of FOLFOXIRI on the patient experience and whether the additional toxicity was worth the survival benefit. "The bottom line is that we have no systematically collected patient-related outcomes data to know how the [toxicities] relate to the patient experience vs chemotherapy," she said.

Reference

1. Sastre J, et al. *Oncologist*. 2012;17:947-55.

KEYNOTE-062: Pembrolizumab combination fails to improve survival in gastric/GEJ cancer

Medical Writer: Muriel Cunningham

Pembrolizumab plus chemotherapy failed to prolong overall survival (OS) and progression-free survival (PFS) among patients with PD-L1–positive gastric and gastroesophageal cancers, according to results from the phase III KEYNOTE-062 trial (Abstract LBA4007). Pembrolizumab monotherapy improved OS among patients with high PD-L1 expression but not PFS.

The objective of the KEYNOTE-062 trial (NCT02494583) was to determine the safety and efficacy of first-line treatment with pembrolizumab with and without chemotherapy in patients with gastric or gastroesophageal cancer. This study was conducted in patients with HER2-negative, advanced gastric or gastroesophageal cancer who had a PD-L1 combined positive score (CPS) of 1 or higher. Josep Tabernero, MD, PhD, of Vall d'Hebron University Hospital, Spain, presented the study results.

Patients who met eligibility criteria were randomly selected 1:1:1 to one of the following three groups: pembrolizumab 200 mg every 3 weeks (Q3W) for up to 2 years; pembrolizumab 200 mg Q3W plus chemotherapy (cisplatin 80 mg/m^2 + 5-fluorouracil [5-FU] 800 mg/m^2/day for 5 days Q3W or capecitabine 1,000 mg/m^2 twice daily on days 1 to 14 Q3W according to local guidelines); or placebo Q3W plus chemotherapy. Patients were stratified by region, disease status, and fluoropyrimidine treatment. The primary endpoints were (1) OS in patients with CPS 1 or higher and patients with CPS 10 or higher for pembrolizumab plus chemotherapy vs chemotherapy alone and pembrolizumab vs chemotherapy alone; and (2) PFS using RECIST version 1.1 with central review in patients with a CPS of 1 or higher for pembrolizumab plus chemotherapy vs chemotherapy alone. The secondary endpoint was the overall response rate (ORR) using RECIST version 1.1 with central review in patients with CPS 1 or higher for pembrolizumab plus chemotherapy vs chemotherapy alone. The prespecified analysis plan allowed alpha passing from successful hypotheses.

A total of 763 patients were randomly assigned: 257 (33.7%) to pembrolizumab plus chemotherapy, 256 (33.6%) to pembrolizumab alone, and 250 (32.8%) to chemotherapy alone. The demographic characteristics were well balanced among the treatment groups. The median age was 62, and the majority of patients (> 95%) had metastatic disease.

The presented efficacy results are summarized in the Table. Pembrolizumab was noninferior to chemotherapy for OS in patients with CPS 1 or higher. Clinically meaningful improvement in OS was observed with pembrolizumab vs chemotherapy in CPS 10 or higher (median OS=17.4 vs 10.8 months; HR 0.69, 95% CI [0.49, 0.97]). No significant differences were seen in subgroup analyses. Pembrolizumab plus chemotherapy was not superior to chemotherapy for OS in patients with CPS 1 or higher (HR 0.85; P=0.046) or CPS 10 or higher (HR 0.85; P=0.158) per prespecified boundaries. A modest benefit in PFS and ORR was seen with pembrolizumab plus chemotherapy vs chemotherapy alone.

The incidence of any-grade treatment-related adverse events was lower with pembrolizumab (54% pembrolizumab vs 92% chemotherapy) as were grade 3/4 events (16% pembrolizumab vs 68% chemotherapy). The safety profile of pembrolizumab plus chemotherapy was comparable to chemotherapy alone. "Patients receiving pembrolizumab had a better tolerability profile than those who received chemotherapy. There was a modest additional benefit of pembrolizumab plus chemotherapy vs chemotherapy, and the safety profile of this combination was manageable as well," Dr Tabernero said.

Discussant Ian Chau, MD, of The Royal Marsden Hospital, United Kingdom, gave an overview of possible reasons why pembrolizumab combined with chemotherapy did not improve survival in patients with gastric cancer. Dr Chau reviewed data from other studies and discussed the following elements: the combination of anti–PD-1 with chemotherapy, the chemotherapy backbone, whether gastric cancer is optimal for this combination, the choice of biomarker, and study design. He specifically noted the multiple endpoints, treatment groups, and populations of KEYNOTE-062, and referred to a recent review on multiplicity in clinical trials [1].

"There are many, many different facets in this clinical trial," Dr Chau said. These results and design considerations may have implications for future studies.

Reference

1. Dmitrienko A, et al. *N Engl J Med*. 2018;378:2115-22.

Neoadjuvant chemotherapy as a potential treatment option in colon cancer

Medical writer: Muriel Cunningham

Neoadjuvant chemotherapy (NAC) resulted in histologic regression and downstaging and decreased the rate of incomplete resections among patients with operable colon cancer, according to results of the FOxTROT trial presented by Matthew T. Seymour, MD, of the National Institute for Health Research Clinical Research Network, on June 1.

The objectives of FOxTROT were to determine if NAC administration prior to surgery improves disease-free survival among patients with colon cancer. In addition, a substudy evaluated whether adding panitumumab to preoperative NAC for patients whose disease harbored wildtype KRAS would increase NAC anti-tumor activity (Abstract 3504).

Patients with operable, nonobstructed, radiologically staged T3 or T4 (N0-2) colon cancer without metastases were randomly assigned 2:1 to either the NAC group or the control group. Patients in the NAC group received 6 weeks of FOLFOX followed by surgery and then another 18 weeks of FOLFOX, whereas the control group underwent surgery and then received postoperative FOLFOX for 24 weeks.

Patients with wildtype *KRAS* tumors assigned to the NAC group had the option to be randomly assigned 1:1 to receive panitumumab during 6 weeks of NAC treatment. The protocol allowed for two other options: a total chemotherapy duration of 12 weeks instead of 24 weeks, or treatment with oxaliplatin and capecitabine (OxCap) instead of FOLFOX for patients who were not in the panitumumab substudy. The primary endpoint was 2-year freedom from recurrent or persistent disease. Secondary outcomes included downstaging, tumor regression, R0 resection rate, and perioperative safety.

A total of 1,052 patients were randomly assigned (698 to the NAC group and 354 to the control group). The overall median age was 65, and 64% of patients were male. The baseline characteristics of both treatment arms were well balanced. Surgery was performed in the majority of patients (98% in both groups). In both arms, 28% were to receive OxCap and 6% were to receive 12 weeks of postoperative chemotherapy. A significantly greater proportion of patients in the control group did not receive chemotherapy compared with the NAC group (27% vs 4%; P<0.0001) because their tumor was low risk (16%) or they were too ill/declined chemotherapy (11%).

There were no unexpected findings of chemotherapy-associated toxicity. Significantly more patients in the control arm experienced complications that necessitated additional surgery compared with patients receiving NAC (7.1% vs 4.3%; P=0.05). Higher numbers of patients in the control group also experienced anastomotic leak or intra-abdominal abscess

compared with those in the NAC group (7.4% vs 4.7%) or a complication prolonging their hospital stay (14.3% vs 11.6%), but these data did not reach statistical significance.

"Preoperative chemotherapy did not increase surgical morbidity; in fact, there were fewer major surgical complications," Dr Seymour said.

The 2-year failure rate improved but was not statistically significant, with rates of 13.6% in the NAC group compared with 17.2% in the control group (HR 0.75, 95% CI [0.55, 1.04]; P=0.08). The control recurrence rate of 17.2% was much lower than the estimates used when powering the study (25% to 32%).

Other outcomes favoured NAC: risk of undergoing surgery without achieving R0, tumor stage/size at surgery, nodal stage at surgery, and tumor regression grade at surgery (all; $P < 0.001$). Results from a sensitivity analysis indicated that the observed rate of tumor regression was not driven by the addition of panitumumab.

"We feel this approach can be considered a new therapeutic option for locally advanced operable colon cancer," Dr Seymour said.

Discussant Jordan Berlin, MD, FASCO, of Vanderbilt University, thought the study results were promising. The safety data from FOxTROT support moving chemotherapy prior to surgery in patients with resectable colon cancer, with positive effects on complication and R1 resection rates, but the tradeoff is that some patients may be over treated.

"This is not practice changing in terms of standard of care, but it gives us a new option when we are thinking about our patients," Dr Berlin said.

Laparascopic surgery: less morbidity, same survival benefits as open surgery in colorectal cancer with liver metastases

Medical writer: Dr Rachel H. Giles

The randomized OSLO-COMET trial found that laparoscopic surgery did not change chances of survival, when compared to open surgery, to remove metastases that had spread to the liver in patients with colorectal cancer. Overall, patients lived more than 6.5 years after surgery, regardless of whether it was laparoscopic or open [1].

"Laparoscopic liver surgery not only had a lower rate of post-operative complications, an improved quality of life, and was cost-effective, compared to open liver surgery, it also had life expectancies that are similar to open surgery," explained presenting author Åsmund Avdem Fretland (Oslo University Hospital, Norway).

From February 2012 to January 2016 the investigators randomly assigned 280 colorectal cancer patients with liver metastases to either laparoscopic surgery or open surgery. The operations were performed with a liver-sparing technique, which means that the surgeons removed only the tumors and a minimal amount of surrounding liver tissue. One-hundred and thirty-three people received laparoscopic surgery, while 147 people had open surgery. About half of the patients received chemotherapy before or after their surgery, following standard Norwegian guidelines, which included the use of chemotherapy medicines 5-fluorouracil plus leucovorin (folinic acid) and oxaliplatin.

Based on ongoing outcomes (patients who were enrolled in 2015-2016 have not yet been observed for 5 years), the researchers found the following comparable, non-statistically significant results:

- People who had the laparoscopic procedure lived a median of 80 months after surgery compared to 81 months for those who had open surgery.
- For people who had a laparoscopic procedure, median recurrence-free survival was 19 months compared to 16 months for those who had open surgery.
- After a minimum of 3 years of follow-up (the last patients were enrolled in early 2016), the researchers were able to estimate that 56% of people who had open surgery would be alive 5 years after their procedure compared to 57% of those who had a laparoscopic procedure.
- An estimated 31% of people who had open surgery would have no recurrence of disease 5 years later compared to 30% of those who had laparoscopy.

When looking solely at the surgical process, there was no difference between the groups in terms of the rate of complete tumor removal, or the amount of tissue removed beyond the observable tumor. Patients reported improved health-related quality of life after laparoscopy, which also had less post-operative complications (19% with laparoscopy vs 31% with open surgery). The researchers found that the monetary costs for either type of surgery were comparable, however, differences in costs may vary in other countries.

Dr Fretland and colleagues are now using artificial intelligence, genetic, and digital-image analyses to parse results from the study so that they can improve the diagnosis and treatment of future patients. They plan to explore new aspects of minimally invasive liver surgery, including enrolling patients in multicentre randomized trials to examine other types of liver operations. The researchers are also exploring thermoablation of liver tumors to kill cancer cells.

Reference

1. Fretland A et al. Abstract LBA3516. Long-term survival after laparoscopic vs. open resection for colorectal liver metastases. ASCO 2019, 31 May-4 June, Chicago, USA.

Maintenance olaparib improved PFS in patients with BRCA+ pancreatic cancer

Medical writer: Tim Donald, ELS

Maintenance therapy with olaparib prolonged progression-free survival (PFS) of metastatic pancreatic cancer (MPC) with a germline *BRCA* mutation in the randomized, phase III POLO trial. Olaparib, which was administered following first-line treatment with platinum-based chemotherapy, was well tolerated, and health-related quality of life (HRQOL) was preserved compared with placebo. Hedy L. Kindler, MD, FASCO, of The University of Chicago, presented these results (Abstract LBA4) during the June 2 Plenary Session.

"Our results are the first from a phase III trial to validate a targeted treatment in a biomarker-selected population of patients with pancreatic cancer, highlighting the importance of germline *BRCA* mutation testing in this setting," Dr Kindler said. "We conclude that a strategic approach of first-line platinum-based chemotherapy followed by olaparib treatment should become a new standard of care for patients with MPC who have a germline *BRCA* mutation." No targeted treatment for MPC in a biomarker-selected population has been validated in a phase III trial, Dr Kindler noted. Approximately 4% to 7% of patients with MPC have a *BRCA1* and/or *BRCA2* mutation.

"This is a huge step forward for patients with MPC," ASCO Expert Suzanne Cole, MD, of The University of Texas Southwestern Medical Centre, said during a press briefing earlier in the day. "This is the first time that a targeted medication has been successful at stopping the growth of MPC in people who carry the *BRCA* mutation. More patients with MPC who also have a *BRCA* mutation saw their disease go dormant when they received olaparib." Dr Cole further noted that "at 2 years, 20% of patients were still alive, with excellent disease control, because they were taking olaparib." Dr Cole said "it is now our duty" to search for this mutation in all patients with MPC, in order to identify those who can benefit from treatment with this oral agent.

The international, double-blind POLO trial enrolled patients with a germline *BRCA* mutation and metastatic pancreatic adenocarcinoma who had received 16 weeks or more of first-line platinum-based chemotherapy without progression. Of 3,315 patients screened for the study, 247 (7.5%) were identified to have a germline *BRCA* mutation. Of those, 154 patients were randomly assigned 3:2 to receive maintenance oral olaparib (300 mg twice daily; 92 patients assigned, 90 treated) or placebo (62 patients assigned, 61 treated). Maintenance was continued until disease progression or unacceptable toxicity. Patient characteristics were well balanced between arms.

The primary endpoint was PFS by blinded independent central review using modified RECIST version 1.1 criteria. Secondary endpoints included time to second progression, objective response rate, HRQOL, safety and tolerability, and overall survival (OS). With 104 events recorded, PFS was significantly improved with olaparib compared with placebo (HR 0.53, 95% CI [0.35, 0.82]; P=0.0038) with a median of 7.4 months in the olaparib arm and 3.8 months in the placebo arm. "This represents a 47% decrease in the risk of progression or death," Dr Kindler said.

At the data cut off of January 15, 2019, 30 patients receiving olaparib (32.6%) and 12 patients receiving placebo (19.4%) were progression-free. From 6 months onward, more than twice as many patients in the olaparib arm progression-free, compared with the placebo arm, Dr Kindler said.

At the interim OS analysis, the median OS was 18.9 months in the olaparib arm and 18.1 months in the placebo arm (HR 0.91, 95% CI [0.56, 1.46]; P=0.68). The OS data were at 46% maturity, with the final OS analysis planned at 106 events.
Objective response was seen in 23.1% of patients in the olaparib arm and 11.5% in the placebo arm. Two patients in the olaparib arm had a complete response, both of which were ongoing at data cut off, Dr Kindler said.

"What is truly remarkable is that the median duration of response to olaparib in these patients who had MPC was more than 2 years," she said. Specifically, median duration

of response was 24.9 months in the olaparib arm and 3.7 months in the placebo arm. The effect size for the primary endpoint of PFS in the trial was "impressive," Dr Messersmith said, especially in the setting of pancreatic cancer. Side effects in the study were manageable, especially compared to those with cytotoxic agents, and adverse events were similar to those seen in other trials of PARP inhibitors.

The POLO trial accomplishes several "firsts" in pancreatic cancer, he said. POLO is the first successful biomarker-driven trial with a germline mutation, and the first successful maintenance trial design—an approach that is rare with MPC. One important implication of the study, Dr Messersmith said, is that molecular testing should be standard for patients with advanced pancreatic cancer.

Hematologic Malignancies

Daratumumab a promising treatment option for transplant-eligible multiple myeloma

Medical writer: Emily Kuhl, PhD

Primary analyses are complete from the first phase III clinical trial to investigate whether transplant-eligible patients with newly diagnosed multiple myeloma (MM) benefit from the addition of daratumumab (DARA) to standard pretransplant treatment. The findings, presented on June 2 (Abstract 8003), suggest that induction and consolidation treatment with the anti-CD38 monoclonal antibody DARA improves response rates without compromising safety.

"This is the largest phase III trial to look at the path of DARA for MM patients," said study investigator and presenter Philippe Moreau, MD, of the University Hospital Hôtel-Dieu, France.

Previous trials have supported the efficacy of DARA for significantly reducing risk of disease progression and death and improving complete remission (CR) and minimal residual disease–negative rates in relapsed/refractory MM or transplant-ineligible, newly diagnosed MM. DARA in combination with bortezomib/thalidomide/dexamethasone (VTd) is also an approved approach for patients with newly diagnosed MM who are not candidates for autologous stem cell transplant. But until now, the effects of this combination as an induction and consolidation treatment in those who are suitable candidates have been unclear in terms of possibly conferring an additional benefit on response and survival.

The CASSIOPEIA trial (NCT02541383), conducted in two parts, was designed to assess this question. In Part 1, patients with newly diagnosed MM who were candidates for transplant (1,085 patients) were randomly assigned to receive VTd with or without DARA before and after transplant. The primary endpoint was stringent CR (sCR), assessed post-transplant. Safety endpoints were also examined.

The study found that post consolidation sCR was significantly greater among patients receiving combination DARA/VTd compared with VTd alone (29% vs 20%, odds ratio 1.6; P=0.001).

"One could comment that the sCR is not that high," Dr Moreau said. "But we used a strict method to define sCR, and all of the [inclusion] data were required. If any [single] data [point] was missing, the patient was downgraded to very good partial response. So, clearly, DARA improved the depth of the response."

Examination of long-term follow-up outcomes (median 18.8 months from first randomization) again revealed a benefit of the combination treatment over VTd (P<0.0001), including progression-free survival (93% in the DARA/VTd arm vs 85% in the VTd arm). This led to a 53% reduction in risk of disease progression or death in the combination arm. Minimal residual disease negativity (64% in the DARA/VTd arm vs 44% in the VTd arm; P<0.0001) similarly favoured the combination drug. "Overall survival was immature, but there is already a trend in favor of the DARA arm of the study," Dr Moreau said. "The hazard ratio is more than 0.4, and the 24-month overall survival rate is 97% in the DARA arm of study. These are the best ever reported in the setting of stem cell transplantation."

In addition to efficacy, investigators looked at safety and tolerability. The most common grade 3/4 treatment-emergent adverse events included neutropenia, lymphopenia, stomatitis, and thrombocytopenia. A little over one-third of patients in the combination arm (35%) experienced infusion-related reactions.

Discussant Faith Davies, MD, MRCP, MRCPath, FRCPath, of New York University Langone Health, noted that, although the presented data "clearly demonstrate that these drugs are effective in the newly diagnosed patient group," questions about patient-reported outcomes are also clinically meaningful.

"We know that many of the side effects of the data in VTd were related to neurotoxicity," she said. "And now that we have patients with longer survival, we need to think about how we actively manage these side effects or stop them from happening so that patients can have a really good quality of life."
Data from Part 2 of the trial, in which patients will receive either DARA monotherapy or observation, are currently unavailable but may shed additional light on the clinical benefits of DARA in the transplant-eligible population.

Rituximab/lenalidomide regimen shows clinical benefit in non-hodgkin lymphoma trials

Medical writer: Tim Donald, ELS

Rituximab plus lenalidomide (R^2) demonstrated significant clinical benefit in two trials in patients with indolent non-Hodgkin lymphoma (iNHL), according to abstracts to be presented during a Poster Session on June 3.

David Jacob Andorsky, MD, of Rocky Mountain Cancer Centres, US Oncology Research, will present interim analyses of the MAGNIFY trial (Abstract 7513). John G. Gribben, MD, Dsc, FRCP, FRCPath, FMedSci, of the Centre for Haemato-Oncology, Barts Cancer Institute, Queen Mary University of London, will present analyses of results from the AUGMENT trial (Abstract 7514).
Both trials included patients with previously treated follicular lymphoma (FL) and previously treated marginal zone lymphoma (MZL). The presentations are timely, as the U.S. Food and Drug Administration approved the use of lenalidomide in combination with rituximab for previously treated FL and previously treated MZL in the week before the ASCO Annual Meeting.

In an interview before the Annual Meeting, the discussant of the two presentations, Carla Casulo, MD, of the University of Rochester, Wilmot Cancer Institute, said the results "add value to the trajectory of treatment for FL." With the approval of the R^2regimen for this indication, she said, "we now have effective, durable, and well-tolerated treatment alternatives for patients with previously treated disease."
MAGNIFY is a multicentre non-registrational phase IIIb trial in patients with relapsed or refractory FL, grade 1 to 3a, and MZL, designed to determine the optimal duration of lenalidomide. All patients received R^2, consisting of lenalidomide 20 mg/d for days 1 to 21 of 28, plus rituximab 375 mg/m^2 per week for one cycle and every 8 weeks for three cycles and above for 12 cycles. After this induction phase, patients with stable disease or better were randomly assigned 1:1 to continued R^2 vs rituximab maintenance. The primary endpoint was overall response rate (ORR) for induction R^2 in efficacy-evaluable patients receiving one or more treatments. Baseline and post-baseline assessments were conducted.

With a median 16.7 months follow-up, 370 patients (80% with FL and 20% with MZL) were enrolled. Median age was 66, and 83% of patients had stage III or stage IV disease and a median of two prior therapies, 95% of which included rituximab. Efficacy-evaluable patients showed a 73% ORR, and 45% showed a complete response (CR). Median time to relapse was 2.7 months, and median progression-free survival (PFS) was 36.0 months.

In an exploratory analysis, Dr Andorsky explained, response rate was stratified by several risk factors known to be associated with adverse outcomes for FL. These included rituximab-refractory status, double-refractory (refractory to both rituximab and an alkylating agent) status, and early relapse. "There was significant clinical benefit [in response rate], even in patients with rituximab-refractory disease, the patients with double-refractory disease, and the patients who experience early relapse," Dr Andorsky said. "The study supports that, even in those high-risk populations, this is a beneficial therapy and one that's well tolerated."

AUGMENT was a phase III study evaluating patients with relapsed or refractory FL grade 1 to grade 3a (82%) and MZL (18%) after one or more prior systemic therapy. In one difference from MAGNIFY, patients with rituximab-refractory disease were not included. Patients were randomly assigned 1:1 to R^2 or to rituximab/placebo (R/placebo) with the same dosing schedule. The primary endpoint was PFS. Secondary and exploratory analyses included time to next anti-lymphoma or chemotherapy treatment (TTNLT/TTNCT) and response to next treatment.
Median PFS was superior for R^2 over R/placebo (39.4 vs 14.1 months; HR 0.46; P<0.0001). As of June 2018, median TTNLT, TTNCT, and progression after next line of therapy (PFS2) were not reached for R^2 and were significantly longer for R^2 than for R/placebo (HR 0.54, 0.50, and 0.52, respectively). For 49 of 178 (28%) R^2 and 80 of 180 (44%) R/placebo patients receiving next anti-lymphoma therapy, response was generally higher with R^2 (57% ORR; 31% CR) than with R/placebo (36% ORR; 16% CR).

The AUGMENT investigators concluded that R^2 prolonged time to subsequent treatment compared with R/placebo, and that R^2 was associated with longer PFS2, enabling greater response to next therapy.

"What I find most interesting about these abstracts," Dr Casulo said, "is that we see efficacy in high-risk subgroups (as reported in MAGNIFY) such as patients with early relapsing FL and double-refractory FL, populations that historically have poor outcomes. In the AUGMENT secondary and exploratory endpoints reported in this abstract [7514], we see that lenalidomide and rituximab have a longer time to next treatment and longer PFS2 after next treatment. This is an important contribution since historically, response rates and duration of response decrease with subsequent therapies in FL. It suggests that lenalidomide and rituximab could render patients more sensitive to subsequent therapies (compared with R/placebo), although since the numbers are small and some of these were exploratory objectives, results should be interpreted with caution."

Pediatric Oncology

Entrectinib produces rapid and durable responses in children with refractory CNS and solid tumors

Medical Writers: Jasenka Piljac Žegarac, PhD

Entrectinib, an oral inhibitor of TRKA/B/C, ROS1, and ALK tyrosine kinases and a central nervous system (CNS)–penetrant, was well tolerated and produced rapid and durable responses in patients with refractory CNS and solid tumors harboring *NTRK1/2/3, ROS1,* and *ALK* fusions, as well as in a patient with *ALK*-mutated neuroblastoma (Abstract 10009).
"Entrectinib is extremely promising in its anti-tumor activity and progression-free survival, and, because there were no responses in nontarget patients, this study now remains open but only for patients with target gene fusions," Giles W. Robinson, MD, of St. Jude Children's Research Hospital, said during an Oral Abstract Session on June 2.

Entrectinib has shown efficacy in several prior phase I (STARTRK-1 and ALKA-372-001) and phase II (STARTRK-2) trials of patients with *NTRK* fusion–positive solid tumors. In May 2017, it was granted a Breakthrough Therapy Designation by the U.S. Food and Drug Administration for use in adult and pediatric patients with *NTRK*-positive solid tumors who have either progressed following prior therapies or who are left with no other treatment options.

Dr Robinson presented the results of a phase I/Ib trial of the agent, which enrolled 29 pediatric patients, age 20 or younger, with recurrent/refractory solid or CNS tumors—16 in the dose-finding phase and 13 in phase Ib who received 550 mg/m^2entrectinib daily. The median age of enrolled patients was 7 (range 0-20), and 51.7% (15) were male. Sixteen patients had neuroblastoma, six had sarcoma, five had high-grade glioma, and one had melanoma or CNS embryonal tumor, respectively.
"About half of the population had fusions and alterations, and about half of the population did not," Dr Robinson said, adding that "these are heavily pre-treated patients who have received chemotherapy, radiation therapy, and a variety of other therapies, even immunotherapy and some targeted therapy."
Patient responses were evaluated according to the response assessment in neuro-oncology (RANO) criteria for CNS tumors, RECIST for solid tumors, and Curie score for neuroblastoma. October 31, 2018, was the data cut off.
Measurable and durable responses were attained in both extracranial solid and CNS tumors. The main takeaway of the trial, Dr Robinson said, was that "if you have a fusion, then you are likely to respond," and "once [the patients have] responded, they continued to maintain that response for long periods of time afterward." He also noted that "75% of these patients still continue therapy and still continue to derive a benefit."

Dr Robinson specifically emphasized the responses achieved in five patients with high-grade glioma who were enrolled in the study because they had different *NTRK1* and *ROS1* fusions.
"What I hope you can see is that the burden of disease starts very high at baseline and then decreases over time, and then, in certain patients, it actually disappears over time," he said. "These patients [had] high-grade gliomas, and high-grade gliomas at relapse are universally fatal.

"The median duration of response was 56 days for the patients who did not respond and 281 days and counting for the patients who did respond," he continued, noting that entrectinib was very well tolerated overall. Dose-limiting toxicities included elevated blood creatinine, dysgeusia, and pulmonary edema, which were reversible upon dose interruption and/or reduction, he said, adding that "there were no deaths related to this drug." According to Dr Robinson, weight gain was an interesting treatment-related adverse event and the most common reason for dose reduction.

Daniel A. Morgenstern, MBBChir, PhD, of the University College London, United Kingdom, was the discussant for the abstract. Despite very promising results outlined by Dr Robinson, he noted that many questions remain regarding the use of TRK inhibitors, such as entrectinib and larotrectinib.

"One of the key questions is how we are actually going to identify patients to treat with these inhibitors," he said. The other unanswered questions Dr Morgenstern raised related to the duration of treatment after achieving a complete response, the drug's long-term effects, especially on neurodevelopment, and the potential incorporation of TRK inhibitors into the upfront treatment.

"Clearly there are more data that we need to collect about the potential long-term toxicity of these agents, even though the short-term toxicity, so far, looks very good," he said.

Head and Neck Cancer

Ado-trastuzumab emtansine a potential new treatment option for HER2-amplified advanced salivary gland cancer

Medical writer: Kara Nyberg, PhD

Ado-trastuzumab emtansine, the antibody-drug conjugate more commonly known as T-DM1, demonstrated robust activity in *HER2*-amplified salivary gland cancer (SGC) within a phase II basket trial, warranting further investigation in this disease (Abstract 6001). Among the 10 patients with SGC treated with T-DM1, nine obtained an objective response, six of which were complete responses. The median duration of response and median progression-free survival have yet to be reached despite a median follow-up of 12 months (range: 4 to 20 months). To gain ground in this rare malignancy, researchers are capitalizing on the targetable mutations offered up by the diverse molecular landscape of SGC. *HER2*gene amplification identified through next-generation sequencing (NGS) occurs in 8% of patients with SGC and approximately 30% of patients with the aggressive salivary duct carcinoma histologic subtype [1]. Based on this information, lead investigator Bob T. Li, MD, MPH, of Memorial Sloan Kettering Cancer Centre, and colleagues hypothesized that patients with SGC found to be *HER2* positive by molecular testing would benefit from T-DM1, which delivers a highly potent maytansine-derived antimitotic agent directly to HER2-bearing cells.

To test this hypothesis, patients with SGC participated in a single-arm basket trial that included several cohorts of patients with *HER2*-amplified advanced solid cancers. *HER2* amplification was defined as a 2-fold or greater increase in *HER2*gene copy number using the Memorial Sloan Kettering IMPACT platform or another validated NGS platform, or a *HER2/CEP17* FISH ratio of at least 2.0. All patients received treatment with 3.6 mg/kg of intravenous T-DM1 every 3 weeks—the standard dosing regimen—until disease progression or unacceptable toxicity occurred. Responses were determined using the RECIST version 1.1 or the PET Response Criteria in Solid Tumors (PERCIST).

The 10 participants with SGC had a median age of 65 and 90% were male. Notably, these patients had already received a median of two prior systemic therapy regimens, which included HER2-targeted therapy for two patients and anti-androgen therapy for five patients. Discussant Vanita Noronha, MD, of the Tata Memorial Centre, India, said that T-DM1 holds the potential to change clinical practice. "Ado-trastuzumab emtansine appears to be a good treatment option in patients with *HER2*-amplified salivary gland tumors," and she believes the agent fulfills an unmet need.

SGC accounts for only 0.8% of all cancers. Diseases arising in the salivary ducts portend a particularly poor prognosis given its tendency to metastasize and the fact that no approved therapies exist for metastatic SGC.

Because NGS was used to screen patients for study entry, Dr Li and colleagues felt it important to correlate *HER2* gene amplification using this less conventional approach with the more standard FISH and immunohistochemistry (IHC) techniques. They found excellent concordance between the biomarker measures. Among the 10 patients with NGS-identified *HER2* amplification (fold-change: 2.8 to s22.8), all eight patients tested had a FISH *HER2/CEP17* ratio of at least 2.0, and all 10 patients had a HER2 IHC score of 3+.

The SGC cohort tolerated T-DM1 fairly well. Adverse events included thrombocytopenia (70%), transaminitis (60%), anaemia (20%), maculopapular rash (20%), and anorexia (10%), and all of these events were grade 1 or 2 in severity except for one case of grade 3 thrombocytopenia.

The plan now is to enroll 14 additional patients with SGC to expand the T-DM1 dataset, according to Dr Li. "There are patients in need of this treatment. That is certainly the priority—to further accrue patients, complete the trial, publish the data, and hopefully have this treatment approved to benefit all patients," he said.

Both Dr Li and Dr Noronha acknowledged that it would be nearly impossible to conduct a randomized controlled trial of T-DM1 given the rarity of SGC. Dr Li said it took 2 years to enroll 10 patients with SGC in the basket trial, so a larger undertaking beyond the plan to enroll 24 total patients would prove challenging. He feels that T-DM1 will still be approved based on this small sample size, as has occurred with other agents in rare diseases.

Reference

1. Zehir A, et al. *Nat Med*. 2017;23:703-13.

Sentinel lymph node biopsy shows promise for early oral cancer

Medical writer: Michelle Dalton, ELS

Sentinel lymph node biopsy (SNB)–navigated neck dissection (ND) could replace elective ND without survival disadvantage and reduce postoperative disability of the neck in patients with early-stage oral cancer, according to results from a Japanese study (Abstract 6007).

During his presentation, Yasuhisa Hasegawa, MD, PhD, of Asahi University Hospital, in Japan, said that another recent study identified a survival benefit with prophylactic ND at the time of primary surgery compared with a "wait and see" approach followed by therapeutic ND for nodal relapse in patients with early-stage oral squamous cell carcinoma.

In this trial, the eligibility criteria included histologically confirmed squamous cell carcinoma in the oral cavity that were classified as clinical categories T1 and T2, N0M0 by the Union for International Cancer Control (UICC) TNM classification 7th edition. The clinical depth of invasion of T1 disease was > 4 mm (defined as late T1), and tumors were previously untreated. The primary endpoint was 3-year overall survival (OS), with secondary endpoints including 3-year disease-free survival (DFS), as well as postoperative functional disabilities of the neck and neck complications.

A radioisotope method was used to detect sentinel nodes (SNs), and they were examined with multi-slice frozen section analysis intraoperatively, after hematoxylin and eosin and cytokeratin stain for a final postoperative diagnosis. One-stage or backup neck discussion procedures were used for patients with positive SNs.

Study Results

From November 2011 through January 2016, the researchers identified 275 oral cancers with late T1 or T2N0. There were 137 patients in the ND group and 134 patients in the SNB group who comprised the full analysis set. (Baseline characteristics of the two groups were evenly matched.) In the SNB group, pathologic positive nodal status was 34% (45/134), while in the ND group, the pathologic positive nodal status was 25% (34/137).

Overall, there were 93 patients (34%) who did not undergo neck dissection, 168 patients (62%) who underwent unilateral dissection, and 10 (4%) who underwent bilateral dissection. Postoperatively, 258 patients (95%) did not have any additional therapy (128 patients in the ND group and 130 patients in the SNB group). A total of 10 patients (4%) required radiation/chemoradiation (six patients in the ND group and four patients in the SNB group). The median follow-up was 37 months (interquartile range 36 to 39).

The 3-year OS in SNB group was 88% (95% CI [0.8106, 0.9243]), which was noninferior to the OS in ND group (87%, 95% CI [0.7955, 0.9133]). The 3-year DFS was 79% (95% CI [0.7063, 0.8476]) in SNB group and 81% (95% CI [0.7364, 0.8699]) in the ND group. "Functionally, the patients who had SNB had better outcomes at 1 and 3 months," Dr Hasegawa said. Discussant Maie A. St. John, MD, PhD, of the David Geffen School of Medicine, University of California, Los Angeles, said there is level 1 evidence from earlier studies that elective treatment offers a survival advantage, but as metastatic disease occurs in only 20% to 30% of patients, "how do you avoid overtreating the remaining 70%?" she asked.

"If no imaging tests are accurate enough to predict the presence of metastatic disease in the neck, SNB should be considered as an alternative to elective ND," Dr St. John said. However, there are several reasons why SNB has not "caught on," she said, including a concern that it may miss 10% to 15% of occult metastatic disease and that head and neck surgeons are comfortable performing elective NDs.

Genitourinary Cancer- Prostate Cancer

Featured video: Overall survival (OS) results of a phase III randomized trial of standard-of-care therapy with or without enzalutamide for metastatic hormone-sensitive prostate cancer (mHSPC): ENZAMET (ANZUP 1304), an ANZUP-led international cooperative group trial. watch the video

Featured video: EV-201: Results of enfortumab vedotin monotherapy for locally advanced or metastatic urothelial cancer previously treated with platinum and immune checkpoint inhibitors. watch the video

Enzalutamide offers survival advantage over other NSAAs in mHSPC

Medical writer: Dave Levitan

Enzalutamide and testosterone suppression significantly prolonged overall survival compared with other nonsteroidal anti-androgens (NSAAs) and testosterone suppression in men with metastatic hormone-sensitive prostate cancer (mHSPC), according to the interim analysis from the phase III ENZAMET trial (Abstract LBA2).

Enzalutamide is a potent direct inhibitor of the androgen receptor (AR), with established benefit in castration-resistant prostate cancer. ENZAMET randomly assigned 1,125 men with mHSPC to either testosterone suppression and other NSAAs, including bicalutamide, nilutamide, or flutamide (562 patients), or testosterone suppression and enzalutamide (563 patients).

On May 31, results of the TITAN study (Abstract 5006) were presented, showing that the addition of another AR inhibitor, apalutamide, can significantly improve survival when added to androgen-deprivation therapy; this was regardless of prior docetaxel use. ENZAMET adds to that body of evidence, although it is the first trial to examine the use of enzalutamide with or without concurrent docetaxel; 45% of patients in the enzalutamide group and 44% in the NSAA group received docetaxel, and 61% of those patients had a high volume of metastases. The men were followed for a median of 34 months.

Christopher Sweeney, MBBS, of the Dana-Farber Cancer Institute, discussed results from an interim analysis of the trial during a press briefing on June 2; the study was also presented during the Plenary Session. Patient characteristics were similar between the two groups, with a median age of approximately 69. Most of the study was conducted in Australia, New Zealand, Canada, the United Kingdom, Ireland, and the United States.
At 36 months, 80% of the enzalutamide group remained alive, compared with 72% of the NSAA group (HR 0.67, 95% CI [0.52, 0.86]; P=0.002). Enzalutamide also resulted in a significant increase in the time to prostate-specific antigen rise, clinical progression, or death (HR 0.39, 95% CI [0.33, 0.47]; P < 0.001). The same was true for a delay in the time to clinical progression, based on imaging, worsening of symptoms, change of therapy, or death (HR 0.40, 95% CI [0.33, 0.49]; P<0.001).

The overall survival difference was seen specifically in men who did not receive docetaxel, but there was no significant difference among those who did. The 3-year overall survival rate in those who did receive docetaxel was 74% with enzalutamide and 75% with other NSAAs; in those who did not receive docetaxel, those rates were 83% with enzalutamide and 70% without it. Of the 588 patients with a high volume of metastases, 61% received docetaxel; Dr Sweeney pointed out that in other studies the survival outcomes for patients with a high volume is poorer than for those with lower volume.

Dr Sweeney said the toxicity profile was similar to previous reports with enzalutamide. The rate of serious adverse events per year of therapy exposure was similar between the groups.

There was more grade 3 fatigue with enzalutamide vs NSAA (6% vs 1%, respectively), as well as more grade 3 syncope (4% vs 1%, respectively) and grade 3 hypertension (8% vs 4%, respectively). Seven patients in the enzalutamide group experienced seizures (1%), compared to none in the NSAA group. "Enzalutamide added to testosterone suppression represents an appropriate option for men with metastatic prostate cancer commencing testosterone suppression," Dr Sweeney said. "The benefits are clear in patients with both low and high volume of metastases."

ASCO Expert Neeraj Agarwal, MD, of the Huntsman Cancer Institute, called the overall survival difference "remarkable" and said during a press briefing on June 2 that the study increases his confidence that targeting AR is likely the best approach in this setting. "In my view, using enzalutamide early on will allow our patients to avoid chemotherapy and steroids for many years, thus hopefully improving their quality of life," he said.

Tanya B. Dorff, MD, of City of Hope, was the discussant for the abstract during the Plenary. She said that these results continue a "revolution" that began in 2015 with the data from the CHAARTED trial, when it began to become clear that intensified up-front treatment is beneficial. "With ENZAMET, the trend of increased benefit with intensified treatment upfront was validated," she said.

There are trade-offs with the use of agents like enzalutamide or abiraterone, she noted, with the potential for added toxicity and the need to take the agents over an extended period of time; however, docetaxel requires a shorter course of treatment but potentially more debilitating side effects.
"We anticipate that upfront trials will continue to yield major advances, especially as molecular stratification and novel agents are added into the paradigm," Dr Dorff said.

Benefits seen with apalutamide plus ADT in metastatic castration-sensitive prostate cancer

Medical writer: Tim Donald, ELS

The addition of apalutamide to androgen-deprivation therapy (ADT) significantly improved radiographic progression-free survival (rPFS) and overall survival (OS) in patients with metastatic castration-sensitive prostate cancer (mCSPC) in the TITAN trial, according to a presentation on May 31 during a Genitourinary (Prostate) Cancer Oral Abstract Session (Abstract 5006). The safety profile of the regimen was tolerable in the trial, according to presenter Kim N. Chi, MD, FRCPC, of BC Cancer Agency, Canada.

"These results support the addition of apalutamide to ADT for a broad range of patients with mCSPC, such as those in the TITAN study, which included patients with high- and low-volume disease, with prior docetaxel treatment, those who had metastatic disease at diagnosis or relapsed metastatic disease, and those who had received prior treatment for localized disease," Dr Chi said.

The results he presented were based on a final analysis of rPFS and, coincidentally, the first planned interim analysis of OS in the trial. Based on results of the analysis, in January the trial's independent data monitoring committee recommended unblinding and amending the study protocol to allow crossover of patients receiving placebo to receive apalutamide. "For the dual primary endpoint, apalutamide significantly reduced the risk of radiographic progression or death by 52%," Dr Chi said. "At 2 years, there was an absolute 20% difference in the rate of rPFS, with 68% of patients on the apalutamide arm remaining free of progression, vs 48% of patients on the placebo arm. The rPFS benefit from apalutamide was consistent across subgroups."

Apalutamide also significantly reduced the risk of death in the study by 33%, with 82% OS at 2 years in the apalutamide arm compared with 74% in the placebo arm. The OS benefit was also consistent across subgroups.

TITAN (NCT02489318) was designed to evaluate apalutamide, an androgen-receptor inhibitor, vs. placebo in a broad population of patients with mCSPC who would also receive continuous ADT. The trial tested the proposition that direct inhibition of androgen receptors may provide a more complete reduction of androgen signaling than ADT alone, leading to improved clinical outcomes.

The randomized, double-masked, phase III study included patients with mCSPC regardless of extent of disease, randomly assigned 1:1 to apalutamide 240 mg/d or placebo, added to continuous ADT, in 28-day cycles. The study's dual primary endpoints were rPFS and OS.

Secondary endpoints in TITAN included time to initiation of cytotoxic chemotherapy, time to pain progression, time to chronic opioid use, and time to skeletal-related event. Exploratory endpoints included time to prostate-specific

antigen (PSA) progression, second PFS (PFS2), and time to symptomatic progression. Results for secondary and exploratory endpoints also favoured apalutamide.

Regarding the exploratory endpoint of time to PFS2, defined as the time from randomization to progression on next subsequent treatment, Dr Chi commented that the difference favoring apalutamide (HR 0.66, 95% CI [0.50, 0.87]; P=0.0026) "supports the earlier use of apalutamide." Treatment with apalutamide was tolerable, and the safety profile was consistent with the known side effects of the drug, Dr Chi said. Health-related quality of life was maintained and not different from placebo.

Discussant Michael A. Carducci, MD, FASCO, of the Sidney Kimmel Cancer Centre at Johns Hopkins, noted that the OS benefit was not consistent in all subgroups, notably in patients with prior docetaxel use (about 10% of the study population), patients over age 75, and those with low disease volume.

It will be important, he said, in deciding which drug is appropriate for which patient, to consider these factors. There is a clear benefit in OS with apalutamide in patients with high-volume disease, "but there may be these subpopulations that may not derive benefit," he said.

Enfortumab vedotin highly active in previously treated advanced urothelial carcinoma

Medical writer: Kara Nyberg, PhD

Enfortumab vedotin, a novel antibody-drug conjugate (ADC), demonstrated pronounced activity in patients with advanced urothelial carcinoma who experienced progression after prior treatment with platinum chemotherapy and an immune checkpoint inhibitor. Results from the pivotal phase II EV-201 study conducted in the United States and Japan showed that single-agent enfortumab vedotin yielded an objective response rate (ORR) of 44%, far surpassing the typical ORR of approximately 11% observed with single-agent chemotherapy in the second- and third-line settings (Abstract LBA4505).

Objective responses to enfortumab vedotin were seen in all patient subgroups evaluated (range, 33% to 60%), even those with poor prognostic features indicative of aggressive disease. Most notably, strong responses emerged regardless of whether patients did or did not have liver metastases (38% and 48%, respectively) and whether they did or did not respond to prior anti–PD-1/PD-L1 therapy (56% and 41%, respectively).

"If approved, enfortumab vedotin may have the potential to become a new standard of care in patients who have [experienced progression] after platinum-based chemotherapy as well as PD-1/PD-L1 inhibitors"—patients who otherwise face a dearth of therapeutic options, concluded Daniel P. Petrylak, MD, of the Yale School of Medicine, who presented the EV-201 findings.

The phase II results are highly consistent with data from the dose-finding phase I study of enfortumab vedotin, which demonstrated an ORR of 42% among patients with advanced urothelial cancer who previously received treatment with a PD-1/PD-L1 inhibitor [1]. The U.S. Food and Drug Administration (FDA) granted enfortumab vedotin a breakthrough therapy designation on the basis of phase I data. Now, with the EV-201 data, plans are underway to seek FDA approval of enfortumab vedotin later this year.

Enfortumab vedotin works by targeting nectin-4, a cell adhesion molecule highly expressed in urothelial cancers and other solid tumors. After binding to nectin-4 on the cell surface, enfortumab vedotin becomes internalized and processed by lysosomes, which liberate the drug's cytotoxic payload, monomethyl auristatin E. Then, monomethyl auristatin E disrupts microtubule assembly, leading to cell cycle arrest and apoptosis.

The EV-201 trial features a single treatment arm in which 1.25 mg/kg of intravenous enfortumab vedotin is administered on days 1, 8, and 15 of each 28-day cycle and includes two patient cohorts. Dr Petrylak presented the results for the 125 patients in cohort 1, all of whom previously received platinum-based therapy as well as a PD-1/PD-L1 inhibitor. Enrollment is ongoing for cohort 2, which comprises platinum-naive, cisplatin-ineligible patients previously treated with a PD-1/PD-L1 inhibitor.

The 44% ORR observed with enfortumab vedotin in cohort 1 was based on blinded independent central review and consisted of both complete responses (12%) and partial responses (32%). Overall, 84% of evaluable patients showed some degree of tumor shrinkage. Objective responses occurred quickly, at a median of 1.8 months after treatment initiation, and lasted for a median of 7.6 months. With single-agent enfortumab vedotin, the median progression-free survival reached 5.8 months, and the median overall survival was 11.7 months.

The toxicity associated with enfortumab vedotin was manageable. Neutropenia (8%), anaemia (7%), and fatigue (6%) were some of the most common grade 3/4 treatment-related adverse events (TRAEs), as categorized by preferred term. Grade 3/4 TRAEs of special interest, as categorized by the medical dictionary for regulatory activities term, included rash (12%), hyperglycemia (6%), and peripheral neuropathy (3%). Overall, 12% of patients discontinued therapy because of TRAEs, the most common of which was peripheral sensory neuropathy (6%). Of note, one patient in the study died of interstitial lung disease—an event deemed related to enfortumab vedotin therapy but that was confounded by the use of high-dose corticosteroids for a suspected pulmonary infection.

To confirm the findings of EV-201, the global, randomized, controlled, phase III EV-301 trial (NCT03474107), which opened recently, will compare enfortumab vedotin against standard single-agent chemotherapy in patients with locally advanced or metastatic urothelial cancer previously treated with platinum chemotherapy and a PD-1/PD-L1 inhibitor.

Discussant Andrea Necchi, MD, of the Fondazione IRCCS Istituto Nazionale dei Tumouri, Italy, commented that the enfortumab vedotin data are "so clear, so good." However, verification of the results in the phase III setting will be critical, as will identification of a biomarker to detect those patients most likely to respond to the ADC. Dr Necchi also questioned whether the favorable outcomes of EV-201 are specific to enfortumab vedotin or are common to other ADCs, such as sacituzumab govitecan, which recently demonstrated similar positive findings in heavily pre-treated urothelial cancer [2].

Despite these uncertainties, Dr Necchi thinks that ADCs are best positioned as the standard of care in metastatic urothelial carcinoma after progression occurs during treatment with a checkpoint inhibitor because of the cumulative efficacy with this sequence of compounds observed to date.

References
1. Rosenberg JE, et al. *J Clin Oncol*. 2019;37(suppl; abstr 377).
2. Tagawa ST, et al. *J Clin Oncol*. 2019;37(suppl; abstr 354).

Multiple Myeloma

Featured video: Insurance status and survival of multiple myeloma (MM) patients. watch the video

Anti-CD38 antibody isatuximab improves treatment response, PFS in R/R multiple myeloma

Medical writer: Emily Kuhl, PhD

A novel anti-CD38 monoclonal antibody, isatuximab, may be a key player in improving progression-free survival (PFS) and treatment response among patients with relapsed/refractory multiple myeloma (RRMM).

"Isatuximab has become a breakthrough target in multiple myeloma therapy and is an important new treatment option for patients with RRMM," co-investigator Paul G. Richardson, MD, of the Dana-Farber Cancer Institute and Harvard Medical School, said during his presentation on June 2 (Abstract 8004). A previous phase Ib study showed that isatuximab combined with pomalidomide and dexamethasone was safe and effective for RRMM. Based on this, ICARIA-MM, a phase III, randomized, open-label, multicentre trial (NCT02990338), was initiated to examine the combination of isatuximab plus pomalidomide vs pomalidomide alone. This was the first randomized phase III study to investigate the addition of an anti-CD38 antibody to pomalidomide. The primary endpoint was PFS, and key secondary endpoints were overall response rate and overall survival.

"These patients represented a true real-world analysis," Dr Richardson said. "We included a broad age range, a median time since initial diagnosis that was about 4 years, and, importantly, a number of older patients, patients with chronic obstructive pulmonary disease, and also patients with renal dysfunction and those at high cytogenic risk."

Patients with RRMM who had received at least two prior lines of therapy with lenalidomide and a proteasome inhibitor (307 patients) were randomly assigned to isatuximab plus pomalidomide or pomalidomide alone.

At a median follow-up of 11.6 months, the median PFS was significantly longer in the isatuximab plus pomalidomide arm compared with the pomalidomide arm (11.5 vs 6.5 months; HR 0.59, 95% CI [0.44, 0.81]; P=0.001). ORR also was favorable in the combination group (60.4% vs 35.3%; P < 0.0001). Very good partial response rate or better was 31.8% for isatuximab plus pomalidomide but only 8.5% for pomalidomide alone, and minimal residual disease negativity at 10-5 was 5.2% in the isatuximab plus pomalidomide group compared with 0% in the pomalidomide group. Median OS was not reached in either arm; however, a clinically meaningful trend toward improvement was observed with combination therapy (72% vs 63%).

Even though the addition of isatuximab to pomalidomide increased rates of grade 3 or higher treatment-emergent adverse events (TEAEs; 86.8% in isatuximab plus pomalidomide vs 70.5% in pomalidomide) and serious TEAEs (61.8% in isatuximab plus pomalidomide vs 53.7% in pomalidomide), its safety profile was generally manageable. Fatal events and TEAEs leading to treatment discontinuation were statistically similar between the two groups. All-grade infusion reactions were reported in 38.2% of isatuximab plus pomalidomide treatment, including 2.6% with grade 3/4. Anaemia and thrombocytopenia also were similar, but grade 4 neutropenia was more common in the combination therapy arm. However, this did not appear to detrimentally impact the patients' quality of life (QOL).

"When we looked at QOL, we were encouraged by the results," Dr Richardson said. "The QOL was maintained with the three drugs, vs the two, with remarkable consistency."
Discussant Faith Davies, MD, MRCP, MRCPATH, FRCPath, of NYU Langone Health, said that although "the data look fantastic," they do raise important questions about how oncologists contend with having another clinical tool in their armamentarium.

"We now have three different drug combinations," she said. "Which triplet combination do we use, and how do we choose that combination? Is it possible to have just one pathway for our patients with myeloma? I would argue that it's not; we should treat them as individuals and look at the therapy they had before and their responses and side effects, and then choose the best treatment moving forward."

Lung Cancer

Featured video: Impact of broadening clinical trial eligibility criteria for advanced non-small cell lung cancer patients: Real-world analysis. watch the video

Neoadjuvant nivolumab/ipilimumab shows promise in resectable NSCLC

Medical writer: Dave Levitan

Neoadjuvant nivolumab plus ipilimumab offered a promising rate of major pathologic response (MPR) in patients with untreated, resectable non–small cell lung cancer (NSCLC), according to a phase II study (Abstract 8504). Nivolumab monotherapy also yielded some MPRs, although not at the prespecified threshold for efficacy.

"More than 50% of patients with stage I to III resectable NSCLC will relapse if treated with surgery alone," said Tina Cascone, MD, PhD, of The University of Texas MD Anderson Cancer Centre, during an Oral Abstract Session on June 1. Because tumor upregulation of PD-L1 is critical for the spread and survival of metastases in mouse models, anti–PD-1 therapy is being tested in the neoadjuvant setting to prime an anti-tumor response and eradicate micrometastases.

The phase II NEOSTAR study included 44 patients with stage I to IIIA NSCLC who were considered surgical candidates; they were randomly selected to receive either nivolumab (Arm A; 23 patients) or nivolumab plus ipilimumab (Arm B; 21 patients). Thirty-nine of those patients eventually underwent surgery with curative intent. The median age in the full cohort was 65.6 years, and 64% of patients were male; 84% were white, and 82% were current or former smokers. Most patients had adenocarcinoma (59%), followed by squamous cell histology (39%) and adenosquamous histology (2%). Overall, 93% of patients completed the course of neoadjuvant therapy.

In the full intention-to-treat cohort, 11 patients (25%) achieved the primary endpoint of an MPR (≤ 10% viable tumor). This was achieved in 17% of patients receiving nivolumab and

33% of those receiving the combination regimen; only the combination therapy group achieved the pre-specified trial efficacy boundary of at least six MPRs. When only the 37 patients who underwent resection on trial were considered, the overall MPR rate was 30% (19% with nivolumab and 44% with the combination).

A total of 11% of patients had the appearance of radiographic progression after the treatment, but a pathologic assessment revealed granulomas but no evidence of tumor. The investigators termed this as "nodal immune flare," and Dr Cascone said it is critical because distinguishing it from true disease progression could allow some patients to avoid curative surgery.

With regard to radiographic responses, there was one complete response (CR) in the combination group (5%); five patients in Arm A and three in Arm B achieved a partial response (PR), for an overall response rate of 18% (22% in Arm A, 14% in Arm B). In total, 64% of the cohort had stable disease, and 14% had progressive disease (one patient was not evaluable). There was a correlation between MPR and radiographic response: 78% of those with an MPR achieved either a CR or a PR, compared with only 22% of those with no MPR (P<0.001). Elevated levels of PD-L1 expression at baseline were associated with both radiographic and pathologic responses.

The most common grade 1 to 2 treatment-related adverse events (TRAEs) included rash in the nivolumab plus ipilimumab group (52%) and fatigue in the nivolumab monotherapy group (35%). Grade 3 to 5 TRAEs included hypermagnesemia, hypoxia, pneumonia, and pneumonitis (4% each) in the nivolumab group, and diarrhea and hyponatremia (4% each) in the combination group.

Dr Cascone noted the combination of nivolumab and ipilimumab was associated with increased T-cell infiltration, diversity, and reactivity. She said the MPR rate in the study supports further evaluation of the combination approach in this setting.

Discussant Maximilian Diehn, MD, PhD, of the Stanford Cancer Institute, Stanford School of Medicine, noted that the use of MPR as a surrogate endpoint has promise thanks to research suggesting an association with overall survival, and because there is strong inter-observer agreement between experienced pathologists. It is not currently accepted as a validated surrogate endpoint, however, meaning it cannot yet be used for drug approvals.

Dr Diehn said that the results of this study, along with other new research, suggest that combining immunotherapy and chemotherapy may offer the best activity, as it has in the advanced NSCLC setting. He also stressed that patient selection remains a challenge. "We have a major unmet need for developing biomarkers for personalizing treatment in this area," he said. He noted that PD-L1, tumor mutation burden, and circulating tumor DNA may still prove useful as biomarkers for these patients.

Overcoming the challenges of immunotherapy in non–small cell lung cancer

Medical writer: Jasenka Piljac Žegarac, PhD

Several experts discussed the current challenges in the use of immunotherapy in non–small cell lung cancer (NSCLC)—the most common type of lung cancer—as well as strategies to overcome them, in the Interactive Case-Based Session "Challenges in Use of Immunotherapy in NSCLC: Where the Rubber Meets the Road," held May 31. The session was chaired by Jyoti D. Patel, MD, FASCO, of the University of Chicago Medical Centre.

"The objectives are to understand the factors that affect the risk/benefit ratio of treatment with immune checkpoint inhibitors (ICIs) in patients with advanced NSCLC and to understand what challenges this poses in patients with dysregulated immunity, chiefly those with autoimmune diseases," Dr Patel said.

She further noted that it is important to understand:

1) how the data hold up in patients encountered in the clinic and not just those enrolled in clinical trials;
2) which patients are too high risk for ICIs;
3) what the boundaries are, if any, beyond which it is no longer safe to treat patients with ICIs; and
4) which clinicians need to be part of the care team for high-risk patients.

Immunotherapy in Patients with Underlying Autoimmune Disease

Sarah B. Goldberg, MD, of the Yale University School of Medicine, presented the first case: a 55-year-old man with a history of ulcerative colitis (UC) and smoking who was diagnosed with stage IV NSCLC. He had an ECOG performance status of 1. She asked the attendees how likely they were to treat this patient with immunotherapy as part of first-line therapy. The informal survey showed that the majority of respondents (approximately 56%) selected pembrolizumab alone as their therapy of choice, followed by carboplatin/pemetrexed/pembrolizumab (approximately 28%).

Dr Goldberg said that it was "very reasonable to consider pembrolizumab as part of first-line treatment" in this patient because his UC was fairly mild and had been well controlled on sulfasalazine, but noted that there "should be a discussion with the patient about the risks and benefits of immunotherapy and the possibility of worsening UC."

She summarized the data from the KEYNOTE-024 and KEYNOTE-189 trials, which demonstrated that pembrolizumab alone and pembrolizumab in combination with chemotherapy improved survival in patients with a PD-L1 tumor proportion score greater than or equal to 50% and any PD-L1 status, respectively [1,2].

She continued by presenting the data on the prevalence of ADs in patients with lung cancer and noted that ADs are fairly common in this patient population. A total of 13.5% of patients in one study reported having any AD [3].
"If you treat patients with lung cancer, then you will see patients with ADs," she said. "The most common is rheumatoid arthritis at about 6%."

Psoriasis (2.8%) was the second most common autoimmune comorbidity, followed by polymyalgia rheumatica (1.8%), Addison disease (1.0%), and systemic lupus erythematosus (0.9%) [3].

Immunotherapy in patients with renal insufficiency

Melissa Lynne Johnson, MD, of the Sarah Cannon Research Institute, presented the second case: a 59-year-old female with a history of smoking, non–insulin-dependent diabetes mellitus, gastroesophageal reflux disease (GERD), and hypertension who was diagnosed with metastatic adenocarcinoma with confirmed liver lesions. She was treated with four cycles of carboplatin/pemetrexed/pembrolizumab, during which time her creatinine increased from 0.85 to 1.33. On the third cycle of maintenance pemetrexed/pembrolizumab, the patient's creatinine had increased to 2.5.

Dr Johnson noted that this patient had additional risk factors for developing acute kidney injury (AKI) beyond use of immunotherapy, which included a history of diabetes and hypertension that were moderately well controlled, as well as a history of GERD for which she was treated with proton pump inhibitors (PPIs). She outlined several important aspects that clinicians need to consider in patients on chemotherapy/immunotherapy combinations with worsening AKI, including ruling out alternative causes of AKI, grading the severity of kidney injury, and seeking an early nephrology consultation.

Immunotherapy for Patients with Poor Performance Status Stage III Disease

The third case was presented by Alexander Chi, MD, of West Virginia University. He discussed the treatment approach in an 84-year-old female with underlying chronic obstructive pulmonary disease and poor pulmonary function tests who was diagnosed with stage IIIb NSCLC. The patient's MRI was negative for metastatic disease. Dr Chi said that, aside from the PACIFIC trial, "there is not a lot of data guiding the utilization of immunotherapy, mainly ICIs, in the stage III setting."

In reflecting on the prevalence of pulmonary toxicity in NSCLC trials to date, he noted that the incidence of severe radiation pneumonitis was fairly low with concurrent chemotherapy with intensity-modulated radiation therapy (RTOG 0617 trial) [4] —only 3.5%—and that it was less than 5% with chemoradiation plus durvalumab combination therapy (PACIFIC trial) [5]. However, he also emphasized that the patients included in these trials are not necessarily representative of the patients encountered in the clinics because, in addition to having an excellent functional performance status, most of them had no prior autoimmune disease, no immunodeficiency of immunosuppression, and no primary cancer within 3 to 5 years.

References
1. Reck M, et al. *N Engl J Med*. 2016;375:1823-33.
2. Gandhi L, et al. *N Engl J Med*. 2018;378:2078-92.
3. Khan SA, et al. *JAMA Oncology*. 2016;2:1507-08.
4. Bradley JD, et al. *Lancet Oncol*. 2015;15:16:187-99.
5. Antonia SJ, et al. *N Engl J Med*. 2018;379:2342-50.

Repotrectinib shows encouraging safety, efficacy for patients with ROS1+ NSCLC

Medical writer: Emily Kuhl, PhD

Early results from the first-in-human phase I/II clinical trial of the tyrosine kinase inhibitor (TKI) repotrectinib, presented May 31 (Abstract 9011), suggest that the novel drug is both well tolerated and efficacious for patients with advanced *ROS1* fusion–positive non–small cell lung cancer (NSCLC). These findings are important because TKIs, like all targeted therapies, are limited by drug resistance; however, repotrectinib was developed to overcome treatment-resistant mutations. Study investigator Byoung Chul Cho, MD, PhD, of Yonsei Cancer Centre, Yonsei University College of Medicine, South Korea, presented the preliminary analyses.

Repotrectinib is a next-generation, macrocyclic TKI designed for potent selectivity against tumors with ROS1, tropomyosin

receptor kinase (TRK), and ALK rearrangements. Preclinical studies thus far appear to support the robust activity of repotrectinib against *ROS1* fusion–positive resistance mutations—including G2032R, the most common *ROS1* solvent-front mutation. However, until now, it has been unclear whether or not preclinical findings are generalizable to humans with *ROS1* fusion–positive NSCLC.

In an effort to tackle this issue, Dr Cho and colleagues are currently conducting a phase I/II dose-escalation trial (TRIDENT-1; NCT03093116) of repotrectinib for patients with advanced *ROS1/NTRK1-3/ALK*–positive solid tumors that are TKI naive or TKI refractory. The primary endpoints include determining the maximum tolerated dose, the recommended phase II dose, and overall response rate (ORR).

Dr Cho shared results from the phase I safety analysis, conducted for all 83 patients with solid tumors, and the efficacy analysis, which included the 33 patients with *ROS1*-positive NSCLC. All patients received repotrectinib at dose levels from 40 mg daily to 200 mg twice daily.

The overall confirmed ORR of the 11 evaluable patients with *ROS1*-positive NSCLC whose disease was TKI-naive was 82%, and the ORR for 160 mg daily or higher doses was 83%. "Intracranial response rate was 100%, and the clinical benefit rate was 100%," Dr Cho said. "This is exciting because this is the most promising data presented so far on a ROS1 TKI in a TKI naive population."

Patients with TKI-refractory disease experienced similarly positive outcomes. Three of four patients treated with more than one prior TKI experienced tumor regression from baseline. Among 18 patients pre-treated with only one prior TKI, the confirmed ORR was 39%, and the ORR for doses of 160 mg daily or higher was 55%. The intracranial response rate was 75%, and the clinical benefit response rate was 78%. Interestingly, five patients who underwent prior crizotinib also had the G2032R mutation—and all five experienced tumor regression with repotrectinib.

Most adverse events were manageable and minor (grade 1-2). Four dose-limiting toxicities (grade 3 dyspnea/hypoxia and grade 2 or 3 dizziness) occurred, and 12 treatment-related adverse events were observed that required dose modifications. The maximum tolerated dose is still unknown.
"Time to response was rapid, usually within 2 months following treatment," Dr Cho said. "Dose escalation was preceded in 11 patients. And, interestingly, dose escalation was well tolerated and allowed for treatment continuation for several months."

Further data are still needed, such as progression-free survival. To meet this goal, discussant Benjamin Besse, MD, PhD, of Paris-Sud University, Orsay, and Gustave Roussy, France, emphasized the importance of recruiting patients with ROS1-positive NSCLC for trials going forward.

"One of my concerns is, since we have such a potent drug, are we sure it is being tested adequately? Are we sure we are testing [for] *ROS1*?" Dr Besse said. "Roughly a third of patients with NSCLC are not tested for *ROS1*. So, there might be a little bit of a concern here if we don't adequately test these patients." Building on these optimistic outcomes, the phase II portion of TRIDENT-1 is projected to begin the second half of 2019.

Pembrolizumab monotherapy leads to 5-year survival in some patients with NSCLC

Medical writer: Jasenka Piljac Žegarac, PhD

Pembrolizumab monotherapy induces a durable anti-tumor response in patients with advanced non–small cell lung cancer (NSCLC), according to 5-year data from KEYNOTE-001—the first clinical trial evaluating pembrolizumab in advanced NSCLC (Abstract LBA9015).

"This is the longest follow-up for a large population of treatment-naive and previously treated patients with NSCLC treated with an inhibitor of the PD-1 immune checkpoint," lead author Edward B. Garon, MD, MS, of the David Geffen School of Medicine, University of California/TRIO-US Network, said. "Not only were we able to induce durable responses, but now we have 5-year follow-up for this patient population."

KEYNOTE-001 is a phase Ib, randomized, open-label study evaluating pembrolizumab in several different types of locally advanced or metastatic cancers. Cohorts C and F aimed to assess the safety, tolerability, and efficacy of pembrolizumab in patients with locally advanced or metastatic NSCLC. It enrolled 101 treatment-naive and 449 previously treated patients whose -s were subjected to PD-L1 evaluation by immunohistochemistry. Patients received pembrolizumab according to one of three dosing schedules: 2 mg/kg every 3 weeks or 10 mg/kg every 2 weeks or every 3 weeks. Objective response rate (ORR) served as the primary endpoint, and overall survival (OS) was the secondary endpoint.

At the data cut off, the median follow-up was 60.6 (51.8 to 77.9) months, and 82% of patients (450/550) had died. Estimated 5-year survival was 15.5% for previously treated patients and 23.2% for treatment-naive patients. ORR (by investigator per Independent Regulatory Review Commission) was 23% (95% CI [19, 27]) for previously treated patients and 42% (95% CI [32, 52]) for treatment-naive patients. Median duration of response was 38.9 and 16.8 months in the two patient groups, respectively.

"At the beginning of my career in 2006, the estimated 5-year survival of a patient with metastatic NSCLC was considered to be less than 1%," Dr Garon said. "Back in the spring of 2012 when we started the first lung cancer cohort in KEYNOTE-001, it would have been hard for us to believe that we would have more than 15% of pre-treated patients, and close to a quarter of treatment-naive patients, alive 5 years out. [This is] very exciting for our field."

At the 5-year mark, 17% of patients reported immune-mediated adverse events (AEs), which was similar to the AE incidence reported at the 3-year follow-up. "We now have patients who have been on pembrolizumab for almost 7 years, and what is reassuring is that there does not appear to be a significant increase in AEs over time," Dr Garon said. "The optimal duration of therapy is something that is still being explored."

Novel RET inhibitor BLU-667 offers promise for RET+ advanced NSCLC

Medical writer: Dave Levitan

The novel selective RET inhibitor BLU-667 demonstrated promising anti-tumor activity and was well tolerated in patients with *RET*fusion–positive advanced non–small cell lung cancer (NSCLC), according to a study presented on June 3 (Abstract 9008).

Approximately 1% to 2% of patients with NSCLC have tumors harboring *RET* fusions. "In contrast to other oncogenic fusions in NSCLC, such as ALK…there are currently no [U.S. Food and Drug Administration (FDA)]–approved selective RET inhibitors to date," Justin F. Gainor, MD, of Massachusetts General Hospital, said, during the presentation of the results of the ongoing ARROW phase I dose-escalation and expansion study.

Patients with NSCLC have had low response rates to chemotherapy and immune checkpoint inhibition, and multikinase inhibitors have demonstrated low activity and high levels of off-target toxicity. BLU-667 potently and selectively inhibits RET with alterations and resistance mutants, according to preclinical research.

Dr Gainor reported results from 120 patients with *RET* fusion–positive NSCLC who were treated with the dose that was established during the dose-escalation phase, 400 mg once daily; 91 of those patients had received prior platinum-based therapy. The most common *RET* fusion partner was *KIF5B* (66%), followed by *CCDC6* (13%); 19% had an unknown fusion partner. The median age in the full cohort was 60, 49% of patients were male, and 40% had brain metastases.

The agent was reasonably well tolerated, and treatment-related toxicities were generally low-grade and reversible. The most common treatment-related toxicities of any grade included neutropenia (26%), increased aspartate aminotransferase (20%), and constipation (17%). The most common grade 3 or higher treatment-related adverse events included neutropenia (13%), hypertension (10%), and anaemia (4%). A total of 7% of the cohort discontinued BLU-667 due to treatment-related toxicities (pneumonitis, respiratory distress/hypoxemia, mucositis/colitis, and others).

A total of 48 patients were evaluable for response; they had enrolled as of November 2018 and had a scan for response evaluation as of April 2019. There was one complete response and 27 partial responses among those patients, for an objective response rate of 58%; 18 patients had stable disease, for a disease control rate of 96%. Among the 35 evaluable patients who had received prior platinum therapy, there was one complete response and 20 partial responses, for an objective response rate of 60%. In addition, there were 14 patients with stable disease, which resulted in a disease control rate of 100%. Five of seven patients who were treatment-naive had a confirmed partial response.

The responses were rapid in onset, with most occurring at the first scan at week 8. Most of the responding patients (82%) remained on treatment at the time of data cut off, and the median duration of response was not yet reached. The agent was active across *RET* fusion genotypes and regardless of prior checkpoint inhibition therapy. It was also active regardless of central nervous system involvement, and appeared to be active against intracranial metastases, with seven of nine patients (78%) experiencing shrinkage of measurable brain metastases. Dr Gainor said that the two without such shrinkage had an unknown *RET* fusion partner.

"BLU-667 demonstrates broad and durable anti-tumor activity in patients with *RET*fusion–positive advanced NSCLC," Dr Gainor said, adding that the agent has been granted breakthrough therapy designation by the FDA. "Data support expansion of the ARROW trial in treatment-naive NSCLC patients and continued enrollment of other *RET*-altered solid tumor groups."

Christine M. Lovly, MD, PhD, of Vanderbilt University Medical Centre, was the Discussant for the abstract. "ASCO 2019 has brought us hope for some of these elusive targets," she said, noting that RET's function in NSCLC has been known since the mid-1980s, though targeting it has proven extremely difficult in the past.

Dr Lovly said questions remain regarding the best sequencing of this or other selective RET inhibitors, and whether they should be sequenced with multi-kinase inhibitors, checkpoint inhibitors, or chemotherapy. Importantly, she also said that encouraging genetic testing in NSCLC is crucial. "Thirty-three percent of patients [in this study] had a history of tobacco use," she said. "Testing is not just for never-smokers; it should be broad-based in lung cancer."

Lurbinectedin shows promise as second-line therapy for SCLC

Medical writer: Tim Donald, ELS

Lurbinectedin, an inhibitor of activated transcription, showed notable anti-tumor activity as a second-line treatment in small cell lung cancer (SCLC) in a phase II clinical trial, according to a June 1 presentation (Abstract 8506).

"Lurbinectedin is an active single agent in second-line SCLC," said presenter Luis G. Paz-Ares, MD, PhD, of Hospital Universitario 12 de Octubre, CNIO, and Universidad Complutense and Ciberonc, Spain. "Anti-tumor activity has been observed in sensitive patients, with an overall response rate [ORR] of 45%. But also, in a setting where we have very few opportunities for treatment, in the setting of resistance, with ORR of 22.2%."

In addition, the safety profile was favorable, and side effects were easily managed, he said. There were low percentages of treatment-related serious adverse events (SAEs) and of discontinuation due to adverse events (AEs), and there were no toxic deaths. "With these data, we may conclude that lurbinectedin is emerging as a potential new [second-line] treatment alternative for SCLC," he said.

Lurbinectedin's anti-tumor activity in SCLC was first observed in a phase I/II study in combination with doxorubicin. The study Dr Paz-Ares presented is a phase II basket trial assessing the efficacy of lurbinectedin in several cancer types, including SCLC. The primary endpoint was ORR by RECIST V.1.1. For the SCLC cohort, a target ORR of 30% or greater was set.

Patients included had at least one prior chemotherapy line and adequate organ function. Patients with prior immunotherapy could be included. Patients with central nervous system metastasis were excluded. Patients received lurbinectedin 3.2 mg/m^2 as a 1-hour intravenous infusion on day 1 every 3 weeks.

In addition to assessing the total population, investigators stratified patients into resistant (chemotherapy-free interval [CTFI] < 90 days) and sensitive (CTFI ≥ 90 days) groups. In the total population (105 patients), ORR was 35.2% (95% CI [26.2, 45.2]). Median duration of response (mDoR) was 5.3 months (95% CI [4.1, 6.4]).

In resistant patients, ORR was 22.2% (95% CI [11.2, 37.1]), and mDoR was 4.7 months (95% CI [2.6, 5.6]). In sensitive patients, ORR was 45.0% (95% CI [32.1, 58.4]), and mDoR was 6.2 months (95% CI [3.5, 7.3]).

Median progression-free survival (PFS) in the total population was 3.9 months (95% CI [2.6, 4.6]). In the resistant population, PFS was 2.6 months (95% CI [1.3, 3.9]), and in the sensitive population, it was 4.6 months (95% CI [3.0, 6.5]).

Median overall survival (OS) in the total population was 9.3 months (95% CI [6.3, 11.8]). In the resistant population, OS was 5.0 months (95% CI [4.1, 6.3]), and in the sensitive population it was 11.9 months (95% CI [9.7, 16.2]).

Regarding safety, in the 105 patients, there were 11 SAEs (10.5%), with two (1.9%) leading to discontinuation. Most AEs were less than grade 3. Most grade 3/4 treatment-related AEs were hematologic. The most frequent nonhematologic AEs were grade 1/2 fatigue and nausea.

Discussant Anna F. Farago, MD, PhD, of Massachusetts General Hospital, thanked the study authors for "focusing on a disease where we still have tremendous unmet clinical need." She noted that, although cross-study comparisons have limited value, the ORR and median OS data in the lurbinectedin study compare well to recent randomized studies assessing topotecan and amrubicin.

Especially regarding the ORR of 35.2%, she said, "Here, lurbinectedin does stand out as being numerically higher than the responses we've seen in these other studies."

Regarding limitations of the study, Dr Farago said it is a single-arm phase II study, and the OS data are immature, as one-third of the patients are still in follow-up. In addition, she said there are questions about how the "shifting standards for first-line therapy"—with more patients receiving combined chemotherapy and immunotherapy—are affecting patient responses to second-line therapies.

Lurbinectedin has received orphan drug designation from the U.S. Food and Drug Administration, she noted, but phase III study data are needed. A 600-patient phase III study comparing doxorubicin plus lurbinectedin to either topotecan or cyclophosphamide/doxorubicin/vincristine, with a primary endpoint of OS, has completed enrolment.

Early results from TAK-788 in NSCLC with EGFR exon 20 insertions

Medical writer: Muriel Cunningham

TAK-788 is an investigational oral EGFR/HER2 inhibitor under development for the treatment of non–small cell lung cancer (NSCLC) with mutations, including patients with NSCLC *EGFR* exon 20 insertions. A phase I/II open-label study of TAK-788 enrolled patients with advanced, previously treated NSCLC from multiple centres (NCT02716116). In the phase I dose-escalation trial, TAK-788 doses ranged from 5 to 180 mg once a day (QD), with a recommended phase II dose (R2PD) of 160 mg QD. Results as of the data cut off (March 1, 2019) were presented by Gregory Riely, MD, PhD, of Memorial Sloan Kettering Cancer Centre during an Oral Abstract Session on June 3 (Abstract 9007).

Safety data were reported for the 137 patients who received any dose of TAK-788 and the subgroup of 72 patients treated with at least one dose of TAK-788 at 160 mg QD. Ninety-five percent of patients at any dose or at the R2PD dose experienced a treatment-emergent adverse event (TEAE). The rates of TEAEs grade 3 or higher were 61% overall and 63% for patients taking 160 mg QD. Approximately 50% of all patients and 50% of those taking 160 mg QD required a dose interruption due to TEAEs. Ten patients (14%) receiving 160 mg QD and 18 patients overall (13%) discontinued treatment due to TEAEs. The most frequently reported TEAEs at the 160 mg QD dose were diarrhea (85%), nausea (43%), rash (36%), vomiting (29%), and decreased appetite (25%).

Efficacy data were presented for the 28 patients with *EGFR* exon 20 insertions who received at least one dose of TAK-788 160 mg QD (six patients in dose escalation and 22 in expansion cohort 1). As of the data cut off, 14 of 28 patients (50%) remained in the study and the other 14 (50%) had discontinued (seven patients due to disease progression, three due to TEAEs, and three as a result of physician decision; one patient died). The prespecified eligibility criteria for efficacy included at least one prior regimen of systemic therapy (history of prior tyrosine kinase inhibitor [TKI] therapy allowed if no response) and excluded patients with active and measurable brain metastases. Efficacy data are provided in the table. Lower response rates and shorter median progression-free survival were seen in the patients with baseline brain metastases. "TAK-788 demonstrates responses in patients with diverse *EGFR* exon 20 insertion variants. The TAK788 safety management profile was manageable and consistent with that of other EGFR TKIs," Dr Riely said.

Table Efficacy results from patients with NSCLC *EGFR* Exon 20 insertions treated with ≥ 1 dose of TAK-788 160 mg QD

	All patients (28)	Patients with CNS Metastases as baseline[b] (12)	Patients without CNS Metastases as baseline (16)
Best response (confirmed)[a], n (%)			
Partial response	12 (43)	3 (25)	9 (56)
Stable disease[c]	12 (43)	5 (42)	7 (44)
Progressive disease	2 (7)	2 (18)	0
Not evaluable	2 (7)	2 (18)	0
Confirmed objective response, n (%), 95% CI	12 (43), 24-63	3 (25), 5-57	9 (56), 30-80
Disease control n (%), 95% CI	24 (86), 67-96	8 (67), 35-90	16 (100), 79-100
Median PFS in months, 95% CI	7.3, 4.4-NR	3.7, 1.8-NR	8.1, 5.6NR

Abbreviations: CI, confidence interval, CNS, central nervous system; NSCLC, non-small cell lungcancer; NR, not reached; PFS, progressionfree survival; QD, once a day.

[a]Response by RECIST v1.1. Median time to response among confirmed responders was 1.8 months. At data cutoff, 12/15 responses were confirmed, with three partial responses unconfirmed at 160 mg QD.

[b]Seven of 12 patients (58%) had active brain metastases at baseline.

[c]Stable disease observed ≥ 6 weeks after first study drug administration.

"We enthusiastically look forward to additional data with this drug," said Discussant Christine M. Lovly, MD, PhD, of Vanderbilt University, but she called attention to the rates of overall TEAEs and those grades 3 and higher. Dr Lovly encouraged clinicians to expand the reach of precision medicine by improving the uptake and utilization of tumor biomarker testing.

Developmental Therapeutics-Immunotherapy

IL-6 and C-reactive protein as potential biomarkers for checkpoint inhibition

Medical writer: Muriel Cunningham

Elevations of C-reactive protein (CRP) and interleukin-6 (IL-6) are associated with poor outcomes in cancers such as melanoma, lung, colorectal, and breast. CRP is synthesized in the liver in response to different stimuli, including IL-6. To further explore the associations between IL-6, CRP, and patient outcomes, an investigation was conducted using samples from patients with melanoma enrolled in three studies of checkpoint inhibitors. Jeffrey S. Weber, MD, PhD, of the Laura and Isaac Perlmutter Cancer Centre, NYU Langone Medical Centre, presented the results of this study (Abstract 100).

Pretreatment and on-treatment serum samples from patients with melanoma enrolled in the following three studies were analysed: CheckMate-064 (140 patients; NCT01783938), CheckMate-066 (418 patients; NCT01721772), and CheckMate-067 (945 patients; NCT01844505). Levels of CRP and IL-6 were measured using Luminex multiplex panels. Analyses of the associations between CRP and IL-6 levels and patient response or survival were determined using Kaplan-Meier analysis.

In the initial analyses of CheckMate-064, modest associations between IL-6 and best overall response (BOR) were seen at baseline and on treatment. Higher baseline levels of IL-6 were seen in patients with a BOR of stable disease/progressive disease/not evaluable compared with patients who had a BOR of complete response or partial response in both cohorts at week 13, when the planned switch occurred.

Additional analyses of the associations of IL-6 with survival in CheckMate-064 were subsequently performed, which found that high baseline or on-treatment levels of IL-6 were associated with poor survival. Similar results were seen when samples from the two larger trials were tested. "This is not a predictive marker; this is a baseline prognostic marker," Dr Weber said. Associations were also seen with CRP in all three studies, with high CRP levels leading to shorter overall survival. *In vitro* experiments were conducted to determine why CRP might be associated with poor survival. Treating cells isolated from patients with melanoma with CRP indicated that CRP suppressed T-cell and dendritic cell function, decreased the generation of antigen-specific T cells, and inhibited calcium influx in T cells. "If you treat the dendritic cells, [CRP] suppresses antigen presentation. Treat the T cells, it suppresses T-cell aggregation. Treat both and combine them in an ex vivo assay, [and] you basically abrogate completely the ability to generate T-cell reactivity," Dr Weber said. A prospective clinical study to follow up on the IL-6 and CRP findings is planned.

Discussant Charles G. Drake, MD, PhD, of Herbert Irving Comprehensive Cancer Centre, agreed that the data indicate that IL-6 and CRP are prognostic biomarkers in melanoma and may be able to aid in patient selection. He noted that a key development advantage is that CRP is already a widely available, validated test approved by the U.S. Food and Drug Administration. Using the medians as cut points is appropriate for the early stages of biomarker development, but these parameters should be further refined. "There could be additional work to look at cut points and power calculations including positive and negative predictive value," Dr Drake said.

First-in-human study shows IL1RAP-targeting drug safe in solid tumors

Medical writer: Leah Lawrence

The interleukin-1 (IL-1) receptor accessory protein (IL1RAP)-targeting CAN04 (nidanilimab) was well tolerated, with infusion-related reactions as the most common treatment-related adverse events occurring in a first-in-human study (Abstract 2504) presented on June 2.

"IL1RAP is required in order to activate IL-1 receptor signaling," which is critical in solid tumors, presenter Ahmad Awada, MD, PhD, of Institut Jules Bordet, Belgium, said. Chronic tumor IL-1 signaling is involved in resistance to cancer therapies, immune evasion, and metastases. CAN04 is a humanized and antibody-dependent cellular cytotoxicity (ADCC)-enhanced IgG1 antibody targeting IL1RAP with two modes of action: blocking IL-1 alpha and beta signaling and triggering ADCC.

This study included 22 patients with non–small cell lung cancer (NSCLC; four patients), pancreatic ductal adenocarcinoma (six patients), or colorectal cancer (12 patients). In a 3+3 design, patients were assigned to CAN04 at doses ranging from 1 to 10 mg/kg. The average age of patients was 62 years, and they had undergone a median of three prior lines of therapy.

No grade 4/5 adverse events occurred, and 55 documented adverse events were potentially related to the study drug. Ten infusion-related reactions occurred in nine patients. Most of the infusion-related reactions occurred after the first drug dose and were resolved within a few hours, Dr Awada said. To mitigate these reactions for the first dose, the researchers administered premedication with paracetamol, antihistamines, and corticosteroids, used a priming dose, and prolonged the infusion time from 1 to 2 hours.

Dr Awada noted that one reversible dose-limiting toxicity occurred. One patient on the 6 mg/kg dose had leukopenia/neutropenia. Three grade 3 events occurred: an infusion-related reaction (3 mg/kg), hypokalemia (6 mg/kg), and leukopenia/neutropenia (6 mg/kg).

Serious adverse events occurred in nine patients; five of the 20 events were considered treatment related. These included one patient with grade 3 leukopenia, three grade 1/2 infusion-related reactions, and one patient with grade 2 embolism.

Dr Awada said there was a linear increase in area under the curve and Cmax (1 to 10 mg/kg). Initial data suggest that the drug half-life is longer than 2 weeks.

All but one patient had pre- and post-treatment imaging used for evaluation of efficacy. The best overall response was stable disease in nine of 21 patients: three of four patients with NSCLC, four of 11 patients with colorectal cancer, and two of six patients with pancreatic cancer. No complete responses or partial responses occurred.

Dr Awada discussed two patients with durable responses. One patient with NSCLC had 7-month progression-free survival and one patient with pancreatic cancer had a 5-month progression-free survival.

The 10 mg/kg dose was selected as the recommended phase II dose. The phase IIa study will look at CAN04 monotherapy, in combination with cisplatin and gemcitabine for NSCLC, and in combination with gemcitabine/nab-paclitaxel in pancreatic cancer, with expansion of the most promising subgroup.

Discussant Benjamin G. Vincent, MD, of the UNC Lineberger Comprehensive Cancer Centre, said this research is based on compelling preclinical data in multiple murine models showing that knockout or inhibition of IL-1 signaling leads to improved survival and delayed tumor growth, and that this is also additive with anti–PD-1 inhibition.

"However, there are some caveats, in that IL-1 receptor knockout or IL-1 signaling inhibition may differentially affect tumor cells in different subsets of tumor-associated leukocytes or leukocytes residing in lymphatics or circulation," Dr Vincent said.

Going forward, studying the IL-1 axis will require very careful and robust studies of different subsets of tumor-associated leukocytes, as well as gut microbiome composition, to parse these differential effects and understand that they can be separated from one another.