# ASCO17 Report
# Important Considerations for Decision-Makers

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# PLENARY SESSIONS- JUNE 4, 2017

## Overall survival results of a randomized trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment.

Ethan M. Basch University of North Carolina at Chapel Hill

Overall survival results of a randomized trial assessing PROs for symptom monitoring during routine cancer treatment was presented by Ethan M. Basch, MD, MSc, FASCO, of The University of North Carolina at Chapel Hill.

The protocol-specified primary outcome was change in health-related quality of life at 6 months compared with enrolment and was the basis of the sample size determination. Significant benefits in quality of life as well as secondary outcomes of 1-year quality-adjusted survival, duration of chemotherapy, and emergency department use were found and previously reported.

766 patients initiating routine chemotherapy for metastatic solid tumours at Memorial Sloan Kettering Cancer Centre between September 2007 and January 2011 were randomly assigned to either the usual care group of the PRO group, in which patients self-reported 12 common symptoms from the National Cancer Institute's Common Terminology Criteria for Adverse Events via a web-based PRO questionnaire platform. Participation was continuous until cessation of cancer treatment, voluntary withdrawal from the trial, transition to hospice care, or death.

When the PRO group participants reported a severe or worsening symptom, an email alert was triggered to a clinical nurse responsible for the care of that patient. A report profiling each participant's symptom burden history was generated at clinic visits for the treating oncologist.

Overall survival was assessed in June 2016. Integration of PROs into the routine care of patients with metastatic cancer was associated with increased survival compared with usual care.

One potential mechanism of action is early responsiveness to patient symptoms preventing adverse downstream consequences. Another potential mechanism is that patients in the intervention group were able to tolerate continuation of chemotherapy longer than usual care. Median overall survival was 31.2 months in the PRO group and 26.0 months in the usual care group.

Electronic patient-reported symptom monitoring may be considered for implementation as a part of high-quality cancer care.

These single-centre results are being further evaluated in a national multi-centre implementation trial. Clinical trial information: NCT00578006

## Risk-Based Approach to Chemotherapy Duration Recommended for Stage III Colon Cancer

June 4, 2017 Dr. Qian Shi, PhD, Mayo Clinic Cancer Center and Cathy Eng, MD, FACP, of The University of Texas MD Anderson Cancer Center

In patients with stage III colon cancer, a 3-month course of chemotherapy was almost as effective as a standard 6-month course—with a difference in disease-free survival (DFS) of less than 1%—while reducing the risk of neurotoxicity and other adverse events. A subgroup analysis further showed that the 3-month course was most appropriate for low-risk patients.

Investigators in the IDEA collaboration reached a clinical consensus to recommend a risk-based approach to selecting adjuvant chemotherapy for stage III colon cancer. Recommending 3 months of adjuvant chemotherapy for patients with low-risk disease, defined as T1-3N1 tumours (approximately 60% of stage III patients). For high-risk patients, defined as patients with T4 or N2 tumours, decisions on use of the shorter course should be based on an individual assessment of tolerability, risk, and choice of regimen.

The rationale for the collaboration was to determine whether the standard 6 months of oxaliplatin-based chemotherapy is necessary. Six phase III trials were conducted in 12 countries and included more than 12,000 patients to determine the noninferiority of 3 versus 6 months of treatment. In each trial, patients were randomly assigned to 3 or 6 months of treatment.

The primary endpoint was DFS, defined as the earliest date of relapse, secondary colorectal primary tumour, or death due to all causes. To demonstrate non-inferiority, investigators reached consensus that a 12% relative risk increase in DFS in the 3-month arm compared with the 6-month arm was acceptable. The estimated 3-year DFS in the 3-month arm was lower than that in the 6-month arm by 0.9%. Non-inferiority was not established.

Adverse events were lower in the 3-month arm compared with the 6-month arm. Grade 2 or higher neurotoxicity was especially notable; the rate in the 6-month arm was about triple that observed in the 3-month arm.

When high- and low-risk groups were analyzed, 3 months of treatment was non-inferior to 6 months of treatment for low-risk patients. For high-risk patients, 3 months of treatment was clearly inferior to 6 months. The IDEA collaborative advises to consider the tradeoff between loss of DFS benefit and reduced neurotoxicity in clinical decision-making regarding treatment duration. Longer-term data are needed to show the robustness of these results.

***Conclusions:*** Six months of oxaliplatin-based chemotherapy for stage III colon cancer remains the standard of care, however, few patients are able to receive all 6 months of oxaliplatin-based

chemotherapy due to treatment-related serious adverse events. Longer-term data are needed to show the robustness of these results. Investigators allowed their individual data to be pooled for the common objective of reducing toxicity for patients.

## Olaparib Improves Outcomes in BRCA-Mutated Metastatic Breast Cancer

June 4, 2017 Mark E. Robson, MD, of Memorial Sloan Kettering Cancer Center

Olaparib tablet monotherapy yielded improved progression-free survival compared with standard-of-care chemotherapy among women with HER2-negative metastatic breast cancer and a germline BRCA mutation, according to results of a phase III trial. Inhibition of poly (ADP-ribose) polymerase (PARP) when BRCA1/2 mutations are not present to aid in DNA damage repair can induce "synthetic lethality" in cancer cells, and some small studies suggested that PARP inhibition could be effective in patients with breast cancer when BRCA mutations are present.

OLYMPIAD study included 302 patients with HER2-negative metastatic breast cancer with a confirmed or suspected deleterious germline BRCA mutation.

The study met its primary endpoint of progression-free survival (PFS), patients treated with olaparib had a median PFS of 7.0 months compared with 4.2 months with chemotherapy. The overall survival (OS) data are not yet mature, but an interim analysis demonstrated a median OS of 19.3 months with olaparib and 19.6 months with chemotherapy.

Time to second progression or death based on investigator assessment was similar between groups. The median was 13.2 months with olaparib compared with 9.3 months with chemotherapy.

In the olaparib group, 60% of patients achieved a complete response compared with 29% of chemotherapy recipients; partial responses were seen in 9% and 2%, respectively. The median time to response was similar, at 47 days with olaparib and 45 days with chemotherapy, as was the median duration of response, at 6.2 months and 7.1 months, respectively.

Subgroup analyses showed that olaparib may be more effective specifically in TNBC.

Grade 3 or higher adverse events (AEs) occurred in 36.6% of patients treated with olaparib and in 50.5% of patients treated with chemotherapy. The median duration of treatment was 8.2 months with olaparib and 3.4 months with chemotherapy. There was one death due to an AE in each group. Among the AEs of any grade that occurred more frequently with olaparib were nausea, anemia, vomiting, and fatigue. Grade 3 or higher anemia was more common with olaparib, whereas grade 3 or higher neutropenia was more frequently seen in patients receiving chemotherapy.

An analysis of quality of life using the EORTC QLQ-C30 instrument showed an adjusted mean change with olaparib of 3.9 compared with -3.6 with chemotherapy. This yielded an estimated difference between the two of 7.5, which would be considered clinically significant according to investigators.

***Conclusions:*** Olympiad is the first phase III study in patients with metastatic breast cancer demonstrating benefit for a PARP inhibitor over an active comparator, olaparib could be an effective treatment option, importantly, in women with BRCA mutations and triple-negative disease. This likely represents only a first step in this field, and there may be potential to add PARP inhibition to chemotherapy and perhaps move the therapy to the earlier metastatic setting or adjuvant setting.

Despite improvement with olaparib, their is a clear need to understand acquired resistance mechanisms. Discussants believed these results are practice-changing, although several outstanding questions remain, including how olaparib would compare with anthracyclines and taxanes, which are more commonly used as first-line therapies rather than the chemotherapies in this study.

## ADT Plus Abiraterone Improves Survival in Hormone-Sensitive Advanced Prostate Cancer

June 4, 2017 Nicholas D. James, BSc, MBBS, PhD, Queen Elizabeth Hospital and the University of Birmingham and Karim Fizazi, MD, PhD

Adding abiraterone to androgen-deprivation therapy (ADT) increased overall survival (OS) among men with locally advanced or hormone-sensitive metastatic prostate cancer, and the therapy was well tolerated, according to results presented from the LATITUDE (Abstract LBA3) and STAMPEDE trials (Abstract LBA5003).

Historically, ADT has been the standard of care for patients with hormone-sensitive, locally advanced or metastatic disease, and in the past several years docetaxel has been added to that therapy for patients with high metastatic burden. Abiraterone acetate plus prednisolone should be part of the standard of care for men starting long-term ADT.

LATITUDE is a phase III, double-blind, randomized trial of androgen deprivation therapy with abiraterone acetate plus prednisone or placebos in newly diagnosed high-risk metastatic hormone-naive prostate cancer.

The LATITUDE trial randomly assigned 1,199 patients with newly diagnosed, high-risk, hormone-sensitive metastatic prostate cancer to receive ADT plus placebo (602 patients) or ADT plus abiraterone and prednisone (597 patients). High-risk was defined as two of three factors including a Gleason score of at least 8, the presence of three or more lesions on a bone scan, and evidence of measurable visceral lesions. The study was conducted across 235 sites in 34

countries. The co-primary endpoints were OS and radiologic PFS (rPFS), and the secondary endpoints included pain progression, PSA progression, next symptomatic skeletal event, chemotherapy, and subsequent prostate cancer treatment.

After a median follow-up of 30.4 months, the OS endpoint was met, with a significant reduction in the risk of death with abiraterone and prednisone. The median OS with ADT and placebo was 34.7 months, but was not yet reached in the abiraterone group. The OS rate at 3 years was 66% with abiraterone and prednisone, and 49% without.

rPFS improved with abiraterone as well. The median rPFS in the control group was 14.8 months compared with 33.0 months with abiraterone.

All secondary endpoints of the trial were also met. The addition of abiraterone improved time to PSA progression; time to pain progression; time to next symptomatic skeletal event; time to chemotherapy; and time to subsequent prostate cancer therapy.

It was also noted that survival benefit seen with abiraterone plus prednisone is related to the study drug rather than to drugs used after progression.

The safety profile of ADT with the abiraterone plus prednisone combination was similar to what was previously reported. Grade 3/4 hypertension was more common with abiraterone (20% vs. 10.2%), as was hypokalemia (10.8% vs. 1.2%), and increased alanine transaminase (5.3% vs. 1.0%). Adverse events leading to treatment discontinuation were relatively infrequent, at 12% with abiraterone and 10% in the control group; only two patients discontinued abiraterone because of hypokalemia.

***Conclusions:*** The findings presented support the fact that adding abiraterone and prednisone to castration should now be considered as the new standard of care for these men with high-risk, newly diagnosed metastatic prostate cancer

Early use of AA+P added to ADT in patients with high-risk mHNPC yielded significantly improved OS, rPFS, and all secondary end points vs ADT+PBOs alone. ADT+AA+P had a favourable risk/benefit ratio and supports early intervention with AA+P in newly diagnosed, high-risk mHNPC. Clinical trial information: NCT01715285

STAMPEDE is a randomized controlled trial using a multi-arm multi-stage platform design, recruiting patients with high-risk locally advanced or metastatic PCa starting long-term ADT.

The STAMPEDE trial began in 2005 and is the largest randomized clinical trial of treatments for prostate cancer. This ongoing study has a multistage, multi-arm design to allow adaption and addition of new therapies. An abiraterone comparison arm was opened in 2011 and closed January 2014. Enrolled patients included those with high-risk locally advanced or metastatic

prostate cancer that was newly diagnosed or relapsed after radical prostatectomy or radiation therapy and who were starting ADT.

In the abiraterone group, OS was improved by 37% compared with the standard-of-care group. Early addition of abiraterone and prednisolone improved OS by 37% and FFS by 71%, and reduced symptomatic skeletal events by 55%. The benefit in FFS was pronounced. Time to failure improved by 71% in the abiraterone group.
Regarding safety, the number of grade 3 to 5 adverse events was similar in most categories, although the abiraterone group reported more cardiovascular disorders than the standard-of-care group (10% vs. 4%, respectively) and more hepatic disorders (7% vs. 1%, respectively).

The results show a clinically and statistically significant effect on overall survival & failure-free survival from adding abiraterone at start of ADT with a manageable increase in toxicity. ADT (+/- RT) + abiraterone is a new standard of care for this group.

Clinical trial information: NCT00268476

***Conclusions:*** Abiraterone brings the same or greater level of effectiveness against prostate cancer with far fewer side effects than chemotherapy. Data should immediately reshape treatment algorithms for prostate cancer, and abiraterone with conventional hormone therapy should become a new standard of care for men with high-risk metastatic prostate cancer.

Results of both STAMPEDE and LATITUDE were published immediately following the Plenary Session in the New England Journal of Medicine.

# ECONOMICS OF CANCER CARE I BIOSIMILARS

## Biomarkers for Checkpoint Inhibition

June 3, 2017 Jeffrey S. Weber, MD, PhD, Laura and Isaac Perlmutter Cancer Center, NYU Langone Medical Center

The most critical question in the field of cancer immunotherapy is whether biomarkers can be defined that predict benefit from the use of these drugs and allow oncologists to choose patients most likely to respond to them. In melanoma and non–small cell lung cancer (NSCLC), a variety of studies have suggested that tumours have three potential immune profiles: (1) those that are infiltrated with T cells and express an "inflammatory" signature of genes, which could be amenable to checkpoint inhibition; (2) tumours that are devoid of any T-cell or inflammatory infiltrate on histologic examination and have a noninflamed, or "cold" gene expression profile and could be amenable to adoptive cell therapy; (3) and tumours that have T cells and other

immune cells present, but only at the periphery or within the stromal tissue and not within the tumour itself and might be amenable to antiangiogenic therapy.

The number of CD8 T-cells infiltrating the tumour microenvironment and expressing PD-1 and/or CTLA-4 appears to be a key indicator of success with checkpoint inhibition. The nature of the tumour microenvironment also plays an important role in resistance or susceptibility to checkpoint inhibition.

There is also an association between tumour activation of the WNT/β-catenin signaling pathway and absence of a T-cell gene expression signature, which leads to deficiencies of infiltrating dendritic cells and a "cold" tumour microenvironment.

When tumours become resistant to PD-1 blockade after an initial response, exhibiting adaptive resistance to therapy, the induction of tumour *JAK1* and *JAK2* mutations, or deletion of beta 2-microglobulin may be responsible, leading to impaired T-cell immunity and inability to detect tumour antigens.

The definition of serum biomarkers associated with the benefit of PD-1 blockade is still immature.

There is a long history of work suggesting that the composition of the host microbiota in mice is associated with a favourable outcome with immunotherapy and checkpoint blockade, and recent data suggest that both clinical outcome and the immune-related adverse events often seen with checkpoint blockade may be associated with specific microbial taxa.

***Conclusion***: There is no clear-cut and clinically useful single biomarker associated with the benefit of checkpoint blockade, or which could be used to select patients that would not benefit from this treatment. Current efforts in which peripheral blood cells, tumour and serum, as well as microbiome specimens are routinely collected in patients before and after treatment with checkpoint inhibition will be critical to research in defining biomarkers of response and resistance to immunotherapies.

## Biosimilars in the Changing Cancer Care Landscape

June 3, 2017 Gary H. Lyman, MD, MPH, FASCO

The rapid increase in health care costs—most notably in cancer care and the price of cancer drugs in the United States—has prompted increasing consideration of strategies for containing the cost of cancer care.

Despite considerable enthusiasm about the rapid advances in our understanding of cancer biology and the identification of critical molecular targets for potentially less toxic and more precise biologic therapies, nowhere has the increase in the cost of cancer care been more apparent than in the costs associated with such products. Clearly, the continuing rise in the cost

of cancer care has substantially affected providers and practices, payers, and the larger health system resulting in concerns about patient access and equity of care because of the financial burden imposed on the healthcare system and cancer care.

Available data from Europe has not suggested that switching a reference product to a corresponding biosimilar leads to any safety or efficacy concerns. The Biologics Price Competition and Innovation Act of 2009 provides a framework by which biosimilars may be evaluated, including the distinction of interchangeability whereby the product may be substituted for the reference drug and alternating between the two products would be considered safe and effective.

Currently, there are no biosimilars in the United States approved by the FDA as interchangeable biologics. In early 2017, the FDA issued guidance on demonstrating interchangeability of a biosimilar with a reference product. This draft guidance encourages further studies to gather evidence to substantiate interchangeability when the biologic product has been developed in the United States. However, the final regulatory criteria for successfully demonstrating interchangeability, including multi-switch clinical data, await final FDA guidance.

**In the end, the appropriate biologic product prescribed should be determined by the patient and treating oncologist.**

Although biosimilars have already been approved in Europe and now in the United States, a number of biosimilars with potential use in oncology are ready for FDA review and approval as patents of originator biologics expire. However, there remain challenges concerning the uptake and utilization of biosimilars in the United States and the overall impact on health care costs.

The FDA approval process for biosimilars makes it less likely that large phase III trials will be undertaken for all approved indications for originator use, the driving potential for cost reduction would not likely be realized if these were required. Therefore, approval of the biosimilar for other indications must largely be based on extrapolation, and the appropriate incorporation of biosimilars into practice is left largely to clinical experience and judgment.

The complexity of manufacturing and the extensive preclinical analytic structural and functional studies necessary result in biosimilars requiring a considerably longer period of time to develop and test at costs that will likely be 100-fold greater than the development of traditional generics. The impact of biosimilars on health care costs, therefore, is likely to be proportionately less dramatic than that experienced with the introduction of generics.

A number of additional challenges to the forthcoming oncology biosimilar marketplace include nomenclature and tracking, pricing, coverage determinations, and the impact of new payment models.

Despite a slow start compared with Europe–where 21 biosimilars have been approved, including 10 for treating or supporting patients with cancer–a wave of biosimilars is expected in the United States (and Canada), with cancer treatments likely to make up a significant proportion of these. Confusion persists related to extrapolation, switching or automatic substitution, interchangeability, the naming and labeling of biosimilars, the value of biosimilars, issues related to coverage and reimbursement, and when and how biosimilars should be incorporated into standard clinical practice and guidelines.

In response to growing concern about the adequacy and appropriateness of regulation state legislation related to biosimilars in an effort to prevent automatic substitution as with generic drugs and ensure proper patient and physician notification, an ASCO policy initiative has begun to specifically address both the opportunities and the challenges confronting oncologists regarding the use of biosimilars in the cancer setting. A working group has been established to review all available evidence and regulatory information and to develop a formal ASCO Policy Statement on Biosimilars in Oncology. (CONECTed along with pCODR has also started to undertake such conversations to identify the challenges and opportunities and to collaborate with all stakeholders to identify best practices as these become available in Canada- report available at conected.saveyourskin.ca).

In 2015, ASCO issued a policy brief on biosimilars to provide guidance to its members and to policymakers on the evolving regulatory landscape of biosimilars. The policy brief articulated the following principles:

- Biosimilar clinical trials should demonstrate efficacy and safety, including lack of immunogenicity.
- The FDA should establish a transparent regulatory pathway for approval of biosimilars.
- Physician choice between biologic products in the best interest of patients should not be restricted.
- Approved biosimilars should be subject to careful post-market safety surveillance.
- Interchangeability should be established by clinical trials that are adequately designed and performed to support substitution.
- Congress should ensure adequate FDA funding to meet new demands.

## Biosimilars Reported Safe, Effective for Breast Cancer Therapy

June 4, 2017 The safety and efficacy of trastuzumab (TRZ) biosimilars for neoadjuvant breast cancer therapy demonstrated comparable safety and efficacy, according to two studies presented.

*Biosimilar SB3 Compared With Trastuzumab*
Xavier B. Pivot, University Hospital Jean Minjoz, (France)

A randomized, double-blind phase III trial compared the biosimilar SB3 to TRZ (Abstract 509). The objective of the trial was to demonstrate comparable clinical efficacy of neoadjuvant SB3 and TRZ in HER2-positive, early-stage or locally advanced breast cancer. The trial substantiates the biosimilarity of SB3 to TRZ, and thoroughly demonstrates the evaluation of a biosimilar based on the 'totality of evidence' approach, with comprehensive assessments including clinical efficacy, safety, pharmacokinetics, and immunogenicity.

Patients received a loading dose of 8 mg/kg of either SB3 or TRZ followed by a maintenance dose of 6 mg/kg every 3 weeks prior to surgery. All patients also received four cycles of docetaxel and four cycles of 5-fluorouracil, epirubicin, and cyclophosphamide (FEC). The primary endpoint was breast pathologic complete response (pCR), which was evaluated at the time of surgery. After surgery, the two groups received 10 cycles of SB3 or TRZ.

Safety and immunogenicity were comparable between the groups, with neutropenia, alopecia, and nausea being the most commonly reported adverse events. The pharmacokinetics of the two drugs was also similar. Equivalence was demonstrated between SB3 and TRZ based on the ratio of breast pCR rates in patients treated with neoadjuvant therapy for HER2-positive, early-stage breast cancer.

Overall safety was similar between the two drugs In the SB3 group, there were 42 treatment-emergent adverse events compared with 47 in the TRZ group. There were 46 serious treatment-emergent adverse events in the SB3 group compared with 47 in the TRZ group. Treatment-emergent adverse events of special interest included congestive heart failure and left ventricular systolic dysfunction; the most common were infusion-related reactions, with 36 in the SB3 group and 44 in the TRZ group. Treatment-emergent adverse events with incidence of at least 15% included alopecia, neutropenia, nausea, leukopenia, diarrhea, increased alanine aminotransferase, anemia, and fatigue.

Biosimilar CT-P6 Compared With Trastuzumab
Justin Stebbing, MD, PhD, Imperial College Healthcare NHS Trust (United Kingdom)

Results from another randomized, double-blind phase III study, which compared the efficacy and safety of another TRZ biosimilar, were also reported (Abstract 510). The comparison of biosimilar CT-P6 to TRZ also demonstrated similar efficacy when used as neoadjuvant therapy in HER2-positive, early-stage breast cancer.

Patients received CT-P6 therapy as an 8 mg/kg loading dose and then 6 mg/kg every 3 weeks or an 8 mg/kg loading dose of TRZ followed by 6 mg/kg every 3 weeks for eight cycles. The therapy was given in conjunction with neoadjuvant docetaxel during cycles one through four and FEC during cycles five through eight.

Randomization was stratified by clinical stage, hormone receptor status, and country. Among the 781 patients who were screened, 549 were randomly assigned, with 271 given CT-P6 therapy and 278 given TRZ.

Surgery was followed by an adjuvant treatment period of up to 1 year, and long-term safety and efficacy was monitored for 3 years from the last enrolment. The primary efficacy endpoint was pCR, which was assessed through specimens obtained during surgery and analyzed by a central review of local histopathology reports. In the per-protocol population, which included 248 patients treated with CT-P6 and 256 treated with the reference drug, a similar proportion achieved pCR (46.8% vs. 50.4%, respectively).

Serious treatment-emergent adverse events were reported by 6.6% of the 271 patients in the CT-P6 group and 7.6% in the reference product group. Serious adverse events of grade 3 or higher that were considered related to treatment occurred in 8.6% of the patients in the CT-P6 group compared with 10.1% in the reference drug group; neutropenia was the most frequently reported hematologic adverse event. Median left ventricular ejection fraction (LVEF) at baseline was 66.0%, and the median lowest LVEF was 62% with CT-P6 and 62.8% with the reference drug.

The availability of TRZ biosimilars could increase access to this targeted therapy for HER2-positive, early-stage cancer with savings for health care systems around the world.

Five proposed TRZ biosimilars have shown positive phase III results in equivalence studies, two for metastatic disease, and three, including CT-P6 and SB3, in the neoadjuvant setting.

The primary patent for Herceptin (TRZ) expired in Europe in 2014 and is set to expire in the United States in 2019. The potential cost savings of a biosimilar, anticipated to be about 30% of the cost of the brand name drug, could be substantial, given that the brand name drug's worldwide sales are about $6.7 billion.

# BREAST CANCER

## Shorter Duration of Trastuzumab May Reduce Cardiac Toxicity, Costs

June 5, 2017 Dr. Pier F. Conte, Istituto Oncologico Veneto IRCCS and Dr. Carey K. Anders The University of North Carolina at Chapel Hill Lineberger Comprehensive Cancer Center

A randomized phase III trial comparing two different regimens of combination chemotherapy given together with trastuzumab to see how well they work in treating women with HER2-positive stage I, stage II, or stage III breast cancer was presented by Pier Franco Conte from the Instituto Oncologico Veneto IRCCS. Results from the Short-HER study suggest a shorter course may reduce the rate of severe cardiac toxicity.

Patients were randomly selected to receive 1 year of trastuzumab plus chemotherapy ("long" group) or 9 weeks of trastuzumab plus chemotherapy ("short" group). Primary endpoints were disease-free survival (DFS) and overall survival (OS). Secondary endpoints included failure rate at 2 years and the incidence of cardiac events. Primary endpoints were analyzed after 198 events or at a median follow-up of 5 years.

From December 2007 to October 2013, the study enrolled 1,253 patients; there were 189 DFS events reported over a median of 5.2 years.
There were 89 DFS events in the long group (627 patients) and 100 in the short group (626 patient). The 5-year DFS did not achieve non-inferiority in the frequentist analysis (87.5% vs. 85.4% in the long and short groups.. There were 37 OS events in the long group and 38 in the short group. The 5-year OS was virtually identical between the two arms (95.1% vs. 95.0% in the long and short groups.

According to the results of the Short-HER study there may be a protective effect from a shorter duration of trastuzumab therapy against cardiac toxicity.

There was no difference in OS at 5 years, and the smaller subset analysis found that patients with stage III disease with multiple positive lymph nodes "appeared to derive greater benefit from the longer duration of trastuzumab.

From a financial perspective 1 year of trastuzumab is about $55,000, based on Medicare estimates (in the US).

Savings were close to $50,000 for 9 weeks of therapy compared to 1 year when compared, these estimates to commonly accepted additions to adjuvant therapy, 10 years versus 5 years of letrozole adds approximately $15,000, while the addition of paclitaxel to [doxorubicin and cyclophosphamide] is about $12,500. For select patients who cannot tolerate 12 months of trastuzumab therapy, the shorter duration "may be reasonable."

Clinical trial information: NCT00629278

## Significant Increase in PFS With Abemaciclib Plus Fulvestrant in Metastatic Breast Cancer

June 3, 2017 George W. Sledge Jr., MD, FASCO, Stanford University

The CDK4/6 inhibitor abemaciclib combined with the estrogen inhibitor fulvestrant may significantly reduce the risk of disease progression and increase the objective response rate in women with metastatic breast cancer, according to the results of the MONARCH 2 study presented during the Breast Cancer–Metastatic Oral Abstract Session on June 3 (Abstract 1000).

The combination protocol reduced the risk of disease progression by 45% with a tolerable side effect profile.

The **MONARCH 2** study was a double-blind, phase III trial involving 669 women with hormone receptor–positive, HER2-negative advanced breast cancer resistant to endocrine therapy. The initial dose of 200 mg twice daily of abemaciclib was reduced to 150 mg twice daily because of diarrhea after 178 patients enrolled. The fulvestrant dose was 500 mg twice daily. The dose reduction did not change study results.

At the median follow-up of 19.5 months, the median progression-free survival (PFS) in the combination treatment arm was 16.4 months compared with 9.3 months in the placebo arm in all patient subgroups.
Patients with measurable disease receiving combination treatment achieved a twofold higher objective response rate compared with those receiving fulvestrant alone (48.1%, 95% CI [42.6%, 53.6%] for abemaciclib vs. 21.3%, 95% CI [15.1%, 27.6%] for placebo).

Response rate is the highest recorded in an endocrine-resistant population. The median duration of response has not yet been reached in the combination group but is 25.6 months in the placebo cohort.

The most common treatment-related adverse events in the combination arm compared with the placebo arm were diarrhea (86.4% vs. 24.7%) and neutropenia (46.0% vs. 4.0%). Grade 3/4 neutropenia occurred in 26.5% of the combination treatment arm compared with 1.7% in the placebo arm with few instances of febrile neutropenia, and grade 3/4 diarrhea in 13.4% compared with 0.4% of patients, respectively.

It was suggested that clinicians choose from two management scenarios based on data from MONARCH 2, as well as other studies on the CDK4/6 inhibitors palbociclib and ribociclib, which all have similar PFS rates (Table).

**Table. Treatment Scenarios Using CDK4/6 Inhibitors**

| | Scenario 1 | | Scenario 2 | |
|---|---|---|---|---|
| First-line treatment | AI | 15 months | CDK4/6 inhibitor + AI | 25 months |
| Second-line treatment | CDK4/6 inhibitor + fulvestrant | 18 months | Fulvestrant | 4 months |
| Third-line treatment | mTOR inhibitor + AI | 8 months | mTOR inhibitor + AI | 8 months |
| **Total PFS** | | **40 months** | | **37 months** |

Given the expense of these treatments, clinicians should be making their treatment choices for patients based on biology.

Scenario 1 is likely best for patients with a long disease-free interval who have acquired estrogen therapy resistance, she said, while scenario 2 appears most appropriate for patients with primary estrogen therapy resistance. Those patients are unlikely to experience long-term response with an aromatase inhibitor alone.

# GI CANCERS

## Adjuvant capecitabine for biliary tract cancer: The BILCAP randomized study

June 4, 2017 John N. Primrose, MD, University of Southampton (United Kingdom)

In a study of 447 patients with biliary tract cancers, capecitabine improved overall survival (OS) when used after surgery and should become the standard of care. Currently the only curative treatment is surgical resection, but only 15% to 20% of patients are eligible. Of those, there is a 15% 5-year survival rate.

The BILCAP randomized study (Abstract 4006) examined a cancer type for which outcomes are poor—1- and 5-year survival rates are 22% and 9%, respectively. In the two-arm, open-label, controlled study, patients were randomly assigned after surgery to observation or to capecitabine (1,250 mg/m2) twice daily for eight cycles; the primary outcome was OS (by the intent-to-treat [ITT] population). Secondary outcomes were relapse-free survival (RFS), toxicity, quality of life, and health economics (the latter of which was not presented).

In the ITT population, the median OS in the capecitabine group was 51.1 months (95% CI [34.6, 59.1]) and 36.4 months in the observation group (95% CI [29.7, 44.5]). The 15-month difference was not statistically significant. However, when analyzed by the per-protocol population, the difference became significant, with median OS at 52.7 months in the capecitabine group (95% CI [40.3, not reported]) and was 36.1 months in the observation group (95% CI [29.6, 44.2]).

The RFS times were also statistically significant in favour of capecitabine in the ITT group (24.6 vs. 17.6 months) and the per-protocol group (25.9 vs. 17.6 months).

The effect does seem higher in men, but no real differences were noted in tumour site and quality of life is undiminished by the use of capecitabine. Capecitabine should be both the control arm in future adjuvant trials in patients with biliary tract cancers and the standard of care for treatment of biliary tract cancers.

Biliary tract cancers are extremely heterogeneous, and the widely varying median OS can range from 8 to 79 months in gall bladder cancer and is around 36 months in perihilar cancers.

The National Comprehensive Cancer Network guidelines are all over the place, mainly because of the lack of phase III trials and a paucity of well-controlled data during the past decade. The 15-month improvement seen in the BILCAP study is highly relevant even if not statistically significant.

***Conclusions:*** Adjuvant capecitabine improves OS in biliary tract cancers and should be the new standard of care.

# GYNECOLOGICAL CANCERS

## The State of the Art in High-Grade Serous Ovarian Cancer

The introduction of PARP inhibitors revolutionized the treatment of ovarian cancer, providing much-needed therapeutic options. However, clinical challenges remain as many patients are not candidates for PARP inhibitors and responses are often short-lived. Furthermore, biomarkers have not been established to definitively match patients with the most appropriate therapies.

Despite these challenges, ovarian cancer experts say it is an encouraging and exciting time in the field, with a multitude of combination approaches being investigated to enhance responses to therapy and identify relevant biomarkers.

*Two-Tiered Classification System*
Elise C. Kohn, MD, National Cancer Institute
In 2014 the World Health Organization and the International Federation of Gynaecology and Obstetrics (FIGO) published revised staging classification criteria categorizing serous adenocarcinoma (SOC) into two grades—low and high—that differ in their histology and molecular characteristics. It is important for clinicians to recognize this distinction, as high- and low-grade SOC respond differently to chemotherapy and thus may require different treatment approaches. High-grade SOC is considered to be highly chemosensitive, though low-grade SOC can still respond to chemotherapy. Given the clinical significance of the classification criteria, It is very important that clinicians are all on the same page that separate into high-grade and low-grade. p53 immunostaining may help differentiate between the two subgroups.

High-grade SOC is associated with null or over-expressed p53, whereas p53 expression is sporadic in low-grade SOC. A morphologic assessment can also provide useful information.

For patients with high-grade SOC, treatment may include chemotherapy, antiangiogenic therapy, DNA repair inhibition therapy, and radiation therapy. For low-grade SOC and all other subtypes (clear-cell, endometrial, and mucinous ovarian cancer), no validated type-specific treatment has been established.

The Gynecologic Cancer InterGroup (GCIG) recently published primary treatment recommendations for these patients. The consensus document notes that primary debulking surgery remains an important first-line intervention in high-grade SOC, with a goal of R0 resection. Neoadjuvant therapy may be considered for patients in whom R0 resection is not feasible; these patients should be considered for clinical trials. The standard chemotherapy regimen for high-grade SOC is intravenous carboplatin/paclitaxel administered every 3 weeks, although certain variations on this are acceptable.

Over the past year, a number of clinical trials have been presented or published evaluating different strategies in ovarian cancer treatment. The **GOG-0262** trial reported no difference with the use of weekly compared with every-3-week paclitaxel except for a subset of patients who were not also receiving bevacizumab.

For patients with aysmptomatic CA125 relapse, GCIG guidelines note there is no proven effective therapy. For patients with platinum-sensitive recurrent disease, guidelines recommend a platinum combination with or without an antiangiogenic agent, or a platinum combination followed by a PARP inhibitor.

Results were published from the **GOG-0213** trial, which showed a nonsignificant small but persistent trend toward improved overall survival with the addition of bevacizumab to paclitaxel/carboplatin in patients with recurrent platinum-sensitive ovarian cancer. Bevacizumab received U.S. Food and Drug Administration approval for use in patients with platinum-sensitive recurrent ovarian cancer in late 2016.

PARP maintenance therapy has also been evaluated as a strategy for improving outcomes in recurrent ovarian cancer.

In the randomized, double-blind, phase III **NOVA** trial, niraparib maintenance therapy was associated with a significant improvement in progression-free survival (PFS) regardless of patients' germline *BRCA* mutation. Results of the randomized, phase III **SOLO2** trial were recently presented showing a significant improvement in median PFS with olaparib maintenance compared with placebo in patients with platinum-sensitive ovarian cancer with germline *BRCA* mutations.

Finally, in the **AURELIA** study, the addition of bevacizumab to chemotherapy was associated with a significant improvement in PFS in patients with platinum-resistant ovarian cancer. Interestingly, bevacizumab and weekly paclitaxel were driving these results and researchers agreed that this needs to be considered.

For patients with platinum-resistant ovarian cancer, surgery is used only for organ protection, and standards of care for treatment include various chemotherapy regimens with or without bevacizumab.

The frontier of ovarian cancer therapy should emphasize leveraging the DNA damage response to improve responses to therapy. One option is through epigenetic generation of homologous recombination deficiency (HRD). Research has shown the importance of hypoxia, generated locally through the use of angiogenesis inhibitors, which can modulate the DNA damage response.

Based on this scientific rationale, the combination of a PARP inhibitor and a VEGFR inhibitor could be fruitful. Data from a phase II study suggested that a combination of olaparib and the antiangiogenic agent cediranib could be more effective than olaparib alone for patients with recurrent platinum-sensitive ovarian cancer. Early-phase trials in other cancers are now underway.

A variety of other combination strategies are being evaluated to leverage the DNA damage response of PARP inhibitors, including the addition of cell cycle inhibitors, other DNA repair-targeting agents, and immunotherapeutics. Although these approaches are still early in development, there is a lot of optimism about the future.

The importance of a combination approach to the treatment of ovarian cancer encompassing all therapeutic modalities would be needed to fulfill the promise of targeted therapy. Efforts are underway to develop rational combinations by studying how tumour cells act in response to targeted therapy and employing appropriate targeted therapies to account for both adaptive responses and genomic resistance.

Another key line of inquiry in ovarian cancer research relates to the identification of biomarkers to appropriately select treatments for individual patients based on molecular factors. With the explosion of combinations to explore in ovarian cancer, and the work to be done in establishing biomarkers, many clinical trials can be expected on the horizon.

# HEMATOLOGICAL CANCERS

## Durable remissions with BCMA specific chimeric antigen receptor (CAR)-modified T cells in patients with refractory/ relapsed multiple myeloma

June 5, 2017 Wanhong Zhao, MD, PhD, The Second Affiliated Hospital of Xi'an Jiaotong University in Xi'an (China)

Chimeric antigen receptor engineered T cell (CAR-T) is a novel immunotherapeutic approach for cancer treatment and has been clinically validated in the treatment of acute lymphoblastic leukaemia (ALL). report an encouraging breakthrough of treating multiple myeloma (MM) using a CAR-T designated LCAR-B38M CAR-T, which targets principally BCMA.

A single arm clinical trial was conducted to assess safety and efficacy of this approach. A total of 19 patients with refractory/relapsed multiple myeloma were included in the trial. The median number of infused cells was 4.7 (0.6 ~ 7.0) × 10e6/ kg. The median follow-up times was 208 (62 ~ 321) days.

Among the 19 patients who completed the infusion, 7 patients were monitored for a period of more than 6 months. Six out of the 7 achieved complete remission (CR) and minimal residual disease (MRD)-negative status. The 12 patients who were followed up for less than 6 months met near CR criteria of modified EBMT criteria for various degrees of positive immunofixation. All these effects were observed with a progressive decrease of M-protein and thus expected to eventually meet CR criteria. In the most recent follow-up examination, all 18 survived patients were determined to be free of myeloma-related biochemical and hematologic abnormalities.

One of the most common adverse event of CAR-T therapy is acute cytokine release syndrome (CRS). This was observed in 14 (74%) patients who received treatment.

***Conclusion:*** A 100% objective response rate (ORR) to LCAR-B38M CAR-T cells was observed in refractory/relapsed myeloma patients. 18 out of 19 (95%) patients reached CR or near CR status without a single event of relapse in a median follow-up of 6 months. The majority (14) of the patients experienced mild or manageable CRS, and the rest (5) were even free of diagnosable CRS.

**Based on the encouraging safety and efficacy outcomes, it is believed that **LCAR-B38M** CAR-T cell therapy is an innovative and highly effective treatment for multiple myeloma.*

# IMMUNOTHERAPY

## History of Immunotherapy

June 3, 2017 James P. Allison, PhD, of The University of Texas MD Anderson Cancer Center, and Suzanne L. Topalian, MD, of the Bloomberg-Kimmel Institute for Cancer Immunotherapy,

James P. Allison, PhD, of The University of Texas MD Anderson Cancer Center, and Suzanne L. Topalian, MD, of the Bloomberg-Kimmel Institute for Cancer Immunotherapy, highlighted the transformative nature of immune checkpoint inhibitors on cancer treatment and outlined a roadmap for future research. Jim Allison was the first to identify the co-stimulatory proteins required to trigger the T-cell proliferation that begins the immune response.

To date, the U.S. Food and Drug Administration (FDA) has approved six immune checkpoint inhibitors for more than nine cancers, including one approved on the basis of a tumor's genetic makeup rather than the tumour type. (pembrolizumab was approved by the FDA for MSI-H/ dMMR solid tumours on May 23, 2017).

One unique aspect of checkpoint inhibitors is that their benefits continue for years as a result of the continued antitumour activity of T cells. 10 years after enrolling in the original clinical trial for ipilimumab, approximately 20% of patients are still alive, providing hope that at least a fraction of patients can be cured.

In 2001, Dr. Allison and others identified the PD-1/PD-L1 immune checkpoint pathway. Clinical trials for the first approved PD-1 inhibitor, nivolumab, showed that blocking PD-1 could cause regression of several cancers. Since nivolumab's approval in 2014, one other PD-1 inhibitor, pembrolizumab, and three PD-L1 inhibitors, atezolizumab, avelumab, and durvalumab, have been approved.(USA)

Like ipilimumab, patients experience long-lasting responses to PD-1 and PD-L1 inhibitors, with one-third of patients with metastatic melanoma who received nivolumab still alive after 5 years. In lung cancer, data show that 16% of patients were still alive after 5 years. Historically, only about 4% would be expected to be alive.

PD-1 inhibitors have now been approved for several indications, demonstrating that anti–PD-1 therapy can be a common denominator for anticancer therapy, with one treatment approach applied to many disease settings.

One challenge noted by Dr. Allison is the clinical studies are outstripping our knowledge. There are more than 250 presentations at the 2017 ASCO Annual Meeting this year involving checkpoint inhibitors, with more than 1,000 studies underway. Mechanistic insight is needed to rationally select the most appropriate combinations.  There is also a need for reverse translation–

using clinical outcomes to drive basic science research, something that is necessary, but underappreciated, and underfunded.

The side effect profile of this class is also a concern particularly immune-related effects. Although the therapies release the brakes on anti-tumour immune response, this can sometimes have a spillover effect, leading to an inflammatory response in normal tissue. The incidence of such effects is much higher when two checkpoint inhibitors are used together. Making it even more important than ever to find biomarkers to identify which patients should receive the combination and which don't need to.

The underlying biologic processes that lead to the side effects seen with checkpoint inhibitors is a very active area of research. Interestingly, patients who experience immune-related side effects are more likely to exhibit tumour regression. In one study of patients with advanced melanoma treated with an anti–PD-1 therapy, the overall response rate was about 31%, but patients with three or more immune-related side effects had a response rate of more than 80%.

Researchers stressed the importance of identifying biomarkers for efficacy. One such biomarker already in use is PD-L1, with studies finding high expression associated with a greater likelihood of response. However, the response differs across tumours.

There is the possibility that cancer genetics could guide immunotherapy, as mutational load correlates with responsiveness to immune checkpoint blockade. Indeed, cancers that are most responsive to PD-1/PD-L1 inhibitors tend to have the greatest number of mutations. However, there are exceptions on both sides.

Tumours with microsatellite instability resulting from mismatch repair deficiency have a particularly strong response to PD-1 inhibitors regardless of cancer type. This finding led the FDA to approve pembrolizumab in May as a second-line therapy for patients with nonresectable or metastatic microsatellite instability–high solid tumours or those with mismatch repair deficiency, regardless of tumour type.

Other areas of intense research include the role of viruses in checkpoint inhibitor response; the effect of the T-cell repertoire and functional state on response; and the effect of other cells in the tumour environment.

# What Has the Checkpoint Inhibitor Experience in Melanoma Taught Us About Immunotherapy for Other Cancers?

June 3, 2017 Jeffrey Webber, Laura and Isaac Perlmutter Cancer Center and a professor of medicine at the NYU-Langone Medical Center in New York.

Since the checkpoint inhibitors ipilimumab and tremelimumab were first tested in patients with melanoma in 2002, the field of immunotherapy for cancer has exploded with hundreds of new trials and an increasing presence in the developmental therapeutics oncology field. Ipilimumab, nivolumab, and pembrolizumab have become mainstays of treatment for metastatic melanoma, but a far more important clinical development is the U.S. Food and Drug Administration (FDA) approval of three different anti–PD-1/–PD-L1 agents for non–small cell lung, renal cell, head and neck, and bladder cancers, as well as Hodgkin lymphoma. Additional approvals in different tumour types are not far off, and numerous combination trials are underway in an effort to optimize the use of checkpoint inhibition. Lessons learned from patients with melanoma will undoubtedly help accelerate the development of checkpoint inhibition for other cancers and may suggest new strategies for treating patients with immunotherapy-resistant cancers, such as prostate, pancreatic, and non–microsatellite instability high colon cancers.

Early in the development of checkpoint inhibitors for melanoma, their unique kinetics of response became apparent. Patterns of response included slow regression over 6 to 12 months, mixed responses with subsequent regression, and progression followed by regression. Although these unusual patterns were observed in up to 10% of patients, they raised the issue of how long to keep treating after what seemed like RECIST progression of disease, or whether to keep treating in the face of a mixed response.

A key issue in the cancer immunotherapy field is how long to treat patients with checkpoint inhibitors. Early trials in melanoma allowed treatment until progression; then, 2 years was the maximal duration, and several reports have examined the outcome in patients who achieved a response and stopped therapy after 2 to 3 years. In most cases, patients who achieved a complete response and subsequently stopped therapy maintained their remission, and many of those who did not achieve a complete response and whose disease progressed were able to respond to further immunotherapy*. Similar data have been observed for those who achieved a partial remission. The existence of the “tail on the curve” of survival in melanoma, and now other cancers, suggests that many responders to checkpoint inhibition may be cured or at least have long-term freedom from progression of their disease and do not need to be treated until progression.

*A duration of not less than 1 year and not more than 2 years seems reasonable.

The unique pattern of side effects observed with ipilimumab and noted with PD-1/PD-L1 inhibitors presents a challenge for physicians who are inexperienced with the use of these drugs.

Algorithms have been established for the successful management of these immune-related adverse events, which are mechanism related and directly tied to breaking tolerance as a mode of action of checkpoint inhibition.

Key lessons to take away are:

- that clinicians must have a low threshold for ruling out endocrinopathies with non-specific symptoms of fatigue,
- that patients may benefit from the occasional use of short steroid regimens to manage grade 2 side effects,
- and that clinicians must be aware of the need for longer-term steroid regimens to manage grade 3 to 4 immune-related side effects.

The most vexing question in the field of checkpoint inhibition is whether biomarkers can be defined that predict regression from the use of these drugs and that allow practitioners to choose patients who are most likely to respond to them. In patients with melanoma or non–small cell lung cancer, there have been a number of studies suggesting that tumours can be divided into three categories: those that are infiltrated with T cells and tend to have an "inflammatory" or "hot" profile of tumour gene expression, tumours that are devoid of any T cell or inflammatory infiltrate on histology and have a non-inflamed or "cold" profile, and tumours that have T cells and other immune cells at the periphery but not within the tumour. The "hot" tumours are the ones most likely to respond to PD-1/PD-L1 blockade and have been primed but have T cells with high levels of PD-1. Many studies have evaluated the role of PD-L1 tumour and/or immune cell immunohistochemical staining and its association with outcome with PD-1/PD-L1 blockade.

***Conclusion:*** Although most studies are in agreement that the higher the level of membranous tumour PD-L1 the better the outcome with PD-1/PD-L1 blockade, it is clear that patients whose tumours stain PD-L1 negative may still gain benefit from checkpoint inhibition. This negates the utility of PD-L1 to choose patients for therapy because it is unable to define those who should not be treated. The nature of the tumour microenvironment also plays an important role in resistance or susceptibility to checkpoint inhibition. There will, undoubtedly, be common pathways of innate and adaptive resistance to checkpoint protein inhibition across many different tumour types. Successful prediction of outcome to these drugs will require an amalgamated biomarker that combines tumour cell intrinsic and host T-cell–specific determinants.

# IMMUNOTHERAPY I LUNG CANCER

## Studies Explore Targeted Therapies in Lung Cancer

June 6, 2017

Researchers presented results of four studies evaluating new approaches to targeted therapies for patients with lung cancer, including metastatic non–small cell lung cancer (NSCLC). For these less common genetic alterations, researchers emphasized the importance of collaboration to continue progress.

## T-DM1 in HER2-Overexpressing NSCLC

Thomas Stinchcombe, MD, Duke University

Results of a phase II trial evaluating T-DM1 in patients with HER2 immunohistochemistry (IHC) 2+/3+ metastatic NSCLC previously treated with chemotherapy was presented. Alterations in HER2, including over-expression and gene amplifications and mutations, have been detected in a subset of patients with NSCLC. In contrast to breast cancer, HER2 amplification in NSCLC does not always correlate with HER2 over-expression. However, HER2 over-expression is associated with poor prognosis. In general, HER2 amplifications and mutations are mutually exclusive in NSCLC.

The frequency of HER2 alterations in NSCLC varies based on the tools and criteria used for assessment; up to 6% of patients exhibit IHC 3+ over-expression, or gene amplification or mutations.

The low frequency of HER alterations, as well as the need to separate out HER2 over-expression and gene amplification and mutations, has made it more challenging to select the patients most likely to benefit from HER2-targeted therapy.

An exploratory biomarker analysis suggested that responses may be more likely in patients with both HER2 IHC 3+ and HER amplification by next-generation sequencing. Of five patients meeting these criteria, two had objective responses to T-DM1. Dr. Stinchcombe concluded that additional research is needed to identify the patients mostly likely to benefit from T-DM1.

Abstract 8509

## T-DM1 in *HER2*-Mutated Lung Cancer

Bob T. Li, MD, MPH, FRACP, Memorial Sloan Kettering Cancer Center

Partial results from a phase II basket trial of T-DM1 in patients with HER2-amplified or mutant advanced solid tumour cancers was reported. The current analysis focused specifically on the

population with HER2 mutations; this included 18 patients who had received a median of two prior lines of therapy. The majority of patients (72%) were female and 39% were never-smokers. In this cohort, T-DM1 administered at the standard dose was associated with an ORR of 44% and a median PFS of 4 months. The median response duration was 5 months, though some responses did not occur until 3 to 4 months into treatment.

***Conclusion:*** Although 50% of patients who experience a response had received prior HER2-targeted therapy, there was no association between prior anti-HER2 therapy and response. Safety outcomes were as expected, aside from a higher rate of infusion reactions that were manageable. Correlative studies suggested that high levels of HER2 protein expression were not required for responses.
These patients do not have an approved targeted therapy; a confirmatory multi-centre study of T-DM1 is warranted. A durable PFS benefit is necessary for a targeted therapy of any kind, and that isn't seen that here.

## MET Inhibitors in *MET*-Mutated NSCLC

Mark M. Awad, MD, PhD, of the Dana-Farber Cancer Institute

A retrospective analysis on the effect of MET inhibitors on survival in patients with MET exon 14–mutated NSCLC was presented. To attempt to gauge the effects of MET tyrosine-kinase inhibitors (TKIs) on survival in this population, Dr. Awad and colleagues retrospectively evaluated clinical outcomes in 61 patients with MET exon 14–mutated, stage IV NSCLC, including 34 who had not received a MET TKI and 27 patients who had received a MET TKI. The TKIs included crizotinib (administered to 20 patients off-label and four patients on a trial), glesatinib (four patients), and capmatinib (three patients); some patients had received multiple TKIs. The researchers reported a substantial survival advantage among patients who had received a MET TKI, with a median OS from the date of stage IV diagnosis of 24.6 months compared with 8.1 months in patients who had never received a MET TKI. Findings were similar in the subset of patients who received crizotinib, in whom the median OS was 20.5 months. The median PFS with crizotinib was 7.4 months. In a subset analysis, the researchers found that patients who had received a MET TKI had also received significantly more lines of systemic therapy in general than those who had not received a MET TKI. Patients who were treated with a MET TKI were also significantly more likely to have received a PD-1 inhibitor than those not treated with a MET TKI (37% vs. 9%).

The significance of these findings—whether they reflect a more indolent disease course, differences in treatment decisions, or other patient-related differences—is unknown. The imbalance in the lines of treatment between cohorts raises some concern regarding the analysis.

The researchers concluded that testing for MET exon 14 mutations should be performed up front in all patients with stage IV NSCLC, and prompt initiation of a MET inhibitor should be considered in patients with MET exon 14 mutations.

## Response to Immunotherapy in MET-Mutated NSCLC

Joshua K. Sabari, MD, of Memorial Sloan Kettering Cancer Center

Results of a retrospective study evaluating tumour characteristics and therapeutic outcomes in 81 patients with *MET* exon 14–altered NSCLC was presented. Investigators were specifically interested in responses to immune checkpoint inhibitors and the relevance of PD-L1 expression in these patients.

Of the 81 patients in the analysis, PD-L1 expression by IHC was performed on 54 specimens (67%). Nearly half of samples (46%) tested PD-L1–high, defined as at least 50% of cells expressing PD-L1. Another 19% had PD-L1 expression between 1% and 49%, and the remaining 35% were PD-L1–negative. No significant associations were found between PD-L1 expression and any clinical or molecular features.

Tumour mutational burden, which reflects the number of non-synonymous somatic mutations present per megabase of genome, has been identified as a potential biomarker of response to immunotherapy. Compared tumour mutational burden in 78 patients with *MET* exon 14-altered NSCLC against a large set of 1,769 NSCLC cases sequenced on the same platform at their institution.

They found that tumour mutational burden was significantly lower in patients with *MET* exon 14 alterations compared with the general NSCLC population, with a median of 3.8 mutations per megabase and 5.7 mutations per megabase, respectively. Researchers found no significant association between PD-L1 expression and total tumour burden.

A total of 15 patients with *MET* exon 14–altered NSCLC received an immune checkpoint inhibitor and were evaluable for response. Fourteen patients had received a PD-1– or PD-L1–targeting single agent, and the remaining patient had received a PD-1–targeting and CTLA-4–targeting combination therapy. A total of six patients had not received any prior therapy.

***Conclusion:*** In this cohort, responses to immunotherapy were poor, with an ORR of only 6.7%. PD-L1 expression did not appear to predict responses to immunotherapy in this cohort, and no responses were observed among the six patients with high PD-L1 expression. Tumour mutational burden was also not predictive of response to immunotherapy (no responses were observed in patients with high tumour mutation burden). Prompt initiation with a MET inhibitor in these

patients remains vital. Additional research is urgently needed regarding the interplay between *MET* exon 14 alterations and the immune checkpoint pathway.

* Researchers concluded that *MET* exon 14 should not be excluded at this time for immune-oncology therapy until further investigation.

Abstract 8512

## Second- or third-line nivolumab (Nivo) versus nivo plus ipilimumab (Ipi) in malignant pleural mesothelioma (MPM) patients: Results of the IFCT-1501 MAPS2 randomized phase II trial

June 5, 2017 Arnaud Scherpereel, MD, PhD, University Hospital of Lille (France)

Both nivolumab alone and in combination with ipilimumab resulted in a promising disease control rate in patients with relapsing malignant pleural mesothelioma (MPM), according to the results (Abstract LBA8507).

MPM is an aggressive and quite rare cancer without any validated curative treatment. Recent studies have shown that anti-angiogenic agents can improve results, but after chemotherapy failure there is no validated subsequent option and disease control rates (DCRs) are usually under 30%.

There is a strong rationale for the use of immune checkpoint inhibition in this malignancy. PD-L1 expression is associated with poor outcomes, and early trials had promising results with anti–PD-1/L1 agents with and without anti–CTLA-4 inhibition. MAPS-2 was a non-comparative phase II trial including 125 patients randomly assigned to receive either nivolumab monotherapy (63 patients) or nivolumab plus ipilimumab (62 patients, 61 received treatment). All patients had unresectable MPM with documented progression after one or two previous lines of chemotherapy, including a pemetrexed/platinum doublet.

The study met its primary endpoint of DCR, which was assessed after 12 weeks. In the first 108 eligible patients, the DCR with nivolumab was 44.4% (18.5% with an objective response, 25.9% with stable disease); with the combination regimen, it was 50.0% (25.9% with objective response, 24.1% with stable disease). In the full intention-to-treat (ITT) population, these rates were 39.7% and 51.6%, respectively.

After 10.4 months of follow-up, the ITT population's median progression-free survival was 4.0 months with nivolumab, and 5.6 months with nivolumab plus ipilimumab. The median overall survival was 10.4 months with nivolumab monotherapy, and has not been reached with the combination regimen.

In the nivolumab arm, 77.8% of patients experienced at least one drug-related adverse event (AE) of any grade; six patients (9.5%) had a grade 3/4 AE. Among patients in the nivolumab/ipilimumab group, 86.9% experienced an AE of any grade, and 11 patients (18.0%) had a grade 3/4 AE. There were three treatment-related deaths during the study, all in the combination group.

Both nivolumab alone and nivolumab plus ipilimumab reached their primary endpoint in second- and third-line MPM patients, increasing meaningfully the 12-week DCR.

Patients from both arms of this study seem to have prolonged median overall survival than all previous reports in this setting. Immunotherapy may provide new therapeutic options as second- and third-line treatment for patients with relapsing MPM. Approximately 30% of patients in each group did not reach the third cycle of therapy. It will be important to know whether this was because of clinical progression or toxicity.

Immune checkpoint inhibitors are likely to change the standard of care in mesothelioma, but the population that benefits the most still needs to be identified. This study suggests an improvement with the combined PD-1/CTLA-4 inhibition in spite of the lack of power to directly compare, but a trial making such a direct comparison is likely needed. Dual inhibition could be more beneficial in certain subgroups, and it may have higher efficacy in the front-line setting.

# DRUG DEVELOPMENT

## The Path Forward: Pathways and Practice Transformation

June 4, 2017 Dr. Robin Zon, Michiana Hematology Oncology

Oncology providers and patients are fortunate to experience the full potential of advancing research in treatments, including precision medicine and immunotherapy, resulting in meaningful increases in cancer survivors–15.1 million in 2016, with a prediction of more than 20 million in 2026. An unprecedented influx of patients with cancer, coupled with increased resource utilization characterized by soaring diagnostic and drug costs, has resulted in financial toxicity on the cancer care delivery system in its entirety, as well as an increasing financial strain to patients.

In an effort to manage patients' needs while improving the value of cancer care, payers and other stakeholders—including ASCO—are pursuing new payment and care delivery models that enhance quality while controlling spending. This movement has resulted in innovative, practice-changing payment models. The trigger for this transformation was the Centers for Medicare & Medicaid Services' (CMS) implementation of the Medicare Access and Chip Reauthorization Act (MACRA) of 2015, which encourages providers to participate in new payment models with increasing accountability in the delivery of high-quality care. This statutory program represents a paradigm shift away from volume-based, provider-centric reimbursement and toward patient-centric, value-based reimbursement to incentivize high-quality cancer care while controlling and/or reducing costs for the delivery of this care.

Clinical pathways are detailed, evidence-based protocols for delivering quality cancer care for patients with specific disease types and stages. Cancer specialists often lead the development of pathways, and many in the oncology field view pathways as a means to improve, not hinder, care. However, with increasing adoption of pathways, ASCO members, the State Affiliate Council, and the Clinical Practice Committee articulated concerns regarding the proliferation of pathways, lack of transparency in development and methodologies used, administrative burden, and other factors that could paradoxically hinder patient access, care quality, and parity.

In response to member concerns, ASCO established the Task Force on Clinical Pathways to examine these concerns and subsequently published a policy statement in March 2016 to guide future development and implementation of pathway programs. The policy statement conveys a cautionary note that no current mechanism is in place to ensure the integrity, efficient implementation, and outcome assessments for these treatment-management tools. The statement includes nine recommendations intended to engage all stakeholders in facilitating a constructive dialogue for moving forward (Table 1).

| | |
|---|---|
| 1. | Pursue a collaborative, national approach to reduce the unsustainable administrative burdens associated with the unmanaged proliferation of oncology pathways. |
| 2. | Adopt a process for development of oncology pathways that is consistent and transparent to all stakeholders. |
| 3. | Ensure that pathways address the full spectrum of cancer care, from diagnostic evaluation through medical, surgical, and radiation treatments, and include imaging, laboratory testing, survivorship, and end-of-life care. |
| 4. | Update pathways continuously to reflect new scientific knowledge, as well as insights gained from clinical experience and patient outcomes, to promote the best possible evidence-based care. |
| 5. | Recognize patient variability and autonomy and allow for physicians to easily diverge from pathways when evidence and patient needs dictate. |
| 6. | Implement oncology pathways in ways that promote administrative efficiencies for both oncology providers and payers. |
| 7. | Promote education, research, and access to clinical trials in oncology clinical pathways. |
| 8. | Develop robust criteria to support certification of oncology pathway programs; pathway programs should be required to qualify based on these criteria, and payers should accept all oncology pathway programs that achieve certification through such a process. |
| 9. | Support research to understand the impact of pathways on care and outcomes. |

**Table 1. ASCO Recommendations to Improve the Development and Use of Clinical Pathways in Oncology**

The nine individual criteria for high-quality clinical pathways in oncology, released in January 2017, formulate an overarching framework to assess pathway programs in three key areas: development, implementation/use, and analytics (Table 2). Notably, in the process of developing the criteria, the task force thoughtfully elicited and considered all stakeholder perspectives by initiating collaborative dialogue through direct stakeholder meetings and interviews with patient advocates, payers, vendors, and providers.

**Table 2. Criteria for High-Value Pathways**

| Development | Implementation and Use | Analytics |
|---|---|---|
| Expert Driven and Reflects Stakeholder Input | Clear and Achievable Expected Outcomes | Efficient and Public Reporting of Performance Metrics |
| Transparent, Evidence Based, Patient Focused, Clinically Driven, and Up-to-Date | Integrated, Cost Effective Technology and Decision Support | Outcomes-Driven Incentives |
| Comprehensive and Promotes Participation in Clinical Trials | Efficient Processes for Communication and Adjudication | Promotes Research in Value and Impact of Pathways and Care Transformation |

The Oncology Care Model demonstration program—considered an alternative payment model in the QPP—requires utilization of nationally recognized guidelines, including pathways derived from these guidelines, for treatment planning. In addition, ASCO's proposed alternative payment model, the Patient Centered-Oncology Payment (PCOP) model, adjusts payment based on quality of care and resource utilization and can also include pathway adherence performance.

Current ASCO work includes integrating high-quality, high-value pathways into PCOP. Furthermore, pathway programs compliant with selected criteria should be considered for reporting quality measurements and reducing practice/physician administrative work. Pathways that are comprehensive, that integrate components of the care continuum beyond treatment, and that are continuously updated with advancing scientific knowledge and validated real-world evidence should be able to not only meet patient expectations but also protect patients' concerns of undertreatment in the alternative payment model universe.

ASCO policy priorities for 2017–2018 include advancing policies and delivery system reform that support oncology providers in their delivery of high-quality, high-value care. Pathway programs guided by the Task Force's policy statement recommendations and criteria for high-quality clinical pathways in oncology are essential in supporting this goal and, as discussed, help leverage pathways in payment model reform.

## Tumour-Agnostic Drug Approvals: In the distant future or already here?

June 6, 2017 Keith Flaherty, Massachusetts General Hospital's Cancer Center, Dung Le, Sidney Kimmel Cancer Center Johns Hopkins and Steven Lemery, medical officer US Food and Drug Administration's (FDA) Office of Hematology and Oncology Products

On May 23, 2017 the FDA approved pembrolizumab (Keytruda) for the treatment of Micro-Satellite High/mismatched repair deficiency solid tumours (MSI-H/dMMR), agnostic of tumour type. Prior to this approval, FDA had only approved cancer drugs to treat tumours based on their location in the body, rather than solely based on a biomarker.

Recent scientific and technological advances have shown there are numerous genetic mutations that are common in multiple cancer types, raising the possibility of developing drugs targeting those mutations irrespective of their location in the body. As the tools to unravel the molecular biology of cancer have enabled complete characterization of the hundreds of cases of all common cancers and many uncommon ones, it is clear that cancers arise from common somatic genetic building blocks.

Treatments targeting a specific mutation may perform differently against different tumour types. Perhaps most striking is the case of BRAF, where BRAF inhibitor monotherapy has profound efficacy in melanoma that is not yet equaled in colorectal cancer. This precedent established the principle that one should assume heterogeneity, not homogeneity, when investigating novel targeted therapy strategies.

More recently, even immunotherapy has been subject to similar considerations. For the field-changing class of PD-1/PD-L1 antibodies, it has been established that higher mutation burden, infiltration of CD8+ T cells, and expression of PD-L1 on tumour and/or infiltrating immune cells can predict response. But, the predictive accuracy varies across cancer types.

As new immunotherapies are being developed, the question arises as to whether their development would be accelerated by understanding whether new single agents or combinations building on a PD-1/PD-L1 antibody backbone might confer benefit similarly or differently in various cancer types that are profiled at the level of these analyses.

Extensive investigation into the causes of de novo resistance and susceptibility have highlighted the contribution of cells in the tumour microenvironment providing growth factor-mediated survival signals, compensatory signalling as a consequence of dysregulated feedback mechanisms, and concomitant somatic genetic alterations present at baseline that mediate compensatory signalling. It is logical to hypothesize that heterogeneity in one or more of these features would account for variable response to a new therapy being prospectively investigated.

The promise of developing mismatch repair (MMR) deficiency as the first predictive biomarker across multiple tumour types for response to a novel therapeutic is supported by strong biologic rationale, availability of commercially used diagnostics for patient identification, and the urgent, unmet medical needs of patients with refractory cancers. The accumulation of evidence that PD-1 inhibition can provide durable benefit in patients with MMR deficiency, coupled with the explosion of technologies to identify these patients, leaves traditional approval pathways that require substantial evidence of effectiveness for each tumour type inadequate to help those in desperate need of therapy today.

Federal regulations governing drug development do not require disease to be defined based on a single tumour type. Nevertheless, prior to determining whether a drug can be developed based on a molecular pathway, investigators or drug developers should determine whether the approach is scientifically and clinically appropriate. In the BRAF example cited above, tissue-agnostic development may not have been appropriate.

Ultimately, determining whether a sponsor should develop a drug irrespective of histology will depend on several preclinical and clinical factors, including data supporting the scientific rationale and the context of treatment of patients with different tumour types. It may be more appropriate to consider tissue-agnostic development in situations where a drug-target combination appears to demonstrate very high activity (e.g., breakthrough-like) across multiple tumour types where the clinical effect can easily be demonstrated. Other developmental considerations may include differences in natural history across diverse cancers, and how investigators or sponsors will propose to generate data in a sufficient number of patients with various tumour types.

An indication that is truly tissue agnostic would allow for the treatment of both adults and children. Such a tissue-agnostic approach, if appropriate, could therefore benefit children by bringing drugs to treat children with cancer more expeditiously. Sponsors who are assessing the effects of a drug across various tumour sites based on a biomarker should consider how they will address the needs of children who have a tumour that possesses that biomarker.

An analytically and clinically validated device reduces the risk of withholding appropriate therapy from a patient who is mutation/biomarker positive who receives a false negative test result or administering inappropriate therapy in the case of a false positive result.[67] From a practical perspective, for rare mutation-tumour combinations, it may be preferable to develop an IVD test as part of a larger panel of tests (e.g., as part of a next-generation sequencing panel). Sponsors are encouraged to meet with the FDA early to facilitate companion diagnostic development. FDA can provide advice to sponsors to determine whether an investigational device exemption is necessary to use an IVD in the trial and to provide guidance in regards to what data would be necessary to approve a companion IVD if the device is necessary for the safe use of the drug.

Uncertainty may arise in a development program about a drug's effectiveness in all tumour types with a specific fusion, mutation, or biomarker, particularly because some tumour-biomarker

combinations may be exceedingly rare. The rarity of certain tumour-biomarker combinations may also make it impossible to conduct randomized trials, especially in settings where equipoise would not exist based on unprecedented anti-tumour activity observed in single-arm trials.

Depending on the strength of evidence across tumour types, multiple regulatory mechanisms exist to address this residual uncertainty. These range from requiring additional data in the premarket setting to requiring post-marketing data in the setting of accelerated approval. If data are adequately collected, "real-world" evidence also may provide supportive data regarding tumour response or lack thereof across rare tumour types.

Ultimately, the goal of drug development is to bring effective drugs that benefit patients as quickly as possible. Investigating the effects of a drug agnostic of tumour type may be one pathway for drug development; however, every drug presents unique circumstances in regard to the population of patients who might benefit from it. Furthermore, development agnostic of tumour type could actually slow drug development if there are differential effects across tumour types, by diverting resources from enrolling patients in a predominant population or in the tumour type most likely to respond. Therefore, input from all stakeholders is recommended prior to embarking on such an approach.

## Performance of a high-intensity 508-gene circulating-tumor DNA (ctDNA) assay in patients with metastatic breast, lung, and prostate cancer

June 3, 2017 Pedram Razavi, MD, PhD

Circulating tumour DNA (ctDNA ) assays can non-invasively assess tumour burden and biology by identifying tumour-derived somatic alterations. For broad applicability, including early cancer detection, an unprecedented high-intensity approach (ultra-deep sequencing of plasma cell-free DNA (cfDNA) with broad genomic coverage) is needed to address intra-patient and population-level heterogeneity. Initial results with this approach in patients with metastatic breast (BC), non-small cell lung (NSCLC), and castration-resistant prostate cancer (CRPC) were presented.

Of 161 eligible patients, 124 (39 BC, 41 NSCLC, and 44 CRPC) were evaluable for concordance. In tissue, 864 variants were detected across the 3 tumour types, with 627 (73%) also detected in plasma: single nucleotide variants/indels - 75%, fusions - 67%, and copy number alterations - 58%. In 90% of patients, at least 1 of the variants detected in tumour tissue was also detected in plasma: BC - 97%, NSCLC - 85%, CRPC - 84%. Most actionable mutations detected in tissue were also detected in plasma (54/71, 76%; SNVs only: 28/31, 90%). A subset of driver mutations (eg. in ESR1, PIK3CA, *ERBB2*, *EGFR*) were observed in plasma but not tissue. Clonal variants in tissue were more likely to be detected in plasma than sub-clonal variants.

This novel, high-intensity ctDNA assay enabled broad detection of genomic variants in plasma at high rates of concordance with corresponding tumour tissue, providing strong evidence for tumour-derivation of these signals. This study will inform development of a high-intensity sequencing approach for early cancer detection.

**What does this mean?** In the future, doctors may be able to use a blood test to find cancer before it causes signs or symptoms. This could help doctors diagnose cancer earlier.

***Conclusion:*** Findings show that high-intensity circulating tumour DNA sequencing is possible and may provide invaluable information for clinical decision-making, potentially without any need for tumour tissue samples. This study is also an important step in the process of developing blood tests for early detection of cancer.

## Routine molecular screening of advanced refractory cancer patients: An analysis of the first 2490 patients of the ProfilER Study

June 3. 2017 Olivier Tredan, MD, PhD Centre Leon Berard (France)

**ProfiLER** (NCT01774409) is a molecular profiling clinical trial exploring cancer cell genomic alterations in patients with advanced disease to guide treatment.

As of Jan 2017, 2490 patients were consented; 1826 (73.3%) tumours were analyzed, 301 (12%) are ongoing (not done in 363 patients (14.6%) for technical issues). Tumour types were colorectal (10.3%), gyneco (9.5%), breast (8.8%), head & neck (7.1%) carcinomas, sarcomas (7.1%), and brain tumours (6.5%). 940/1826 patients (51.5%) had at least 1 actionable mutation (AM): 579 patients with only one AM, while 358 with 2 or more AM (up to 6). Mutations (including substitutions and small indels), amplifications and homozygous deletions (HD) were observed respectively in 55.3%, 42.1% and 25.5% of tumour samples. The most common AM were on *KRAS* (n = 156; 8.5%), *PIK3CA* (n = 150; 8.2%), *CDKN2A HD (*n = 174; 9.5%*),PTEN* HD (n = 49, 2.7%), CCND1 (n = 97; 5.3%), *FGFR1* (n = 56; 3.1%), *MDM2* (n = 53; 2.9%), *HER2* (n = 42; 2.3%) and *HER1*(n = 41; 2.2%). Molecular Targeted Therapies (MTT )were recommended in 644 patients. Among them, 101 (gyn [28%], GI [18%], breast [12%]) initiated a recommended MTT. Collection of treatment data is ongoing for 202 patients.

In this series of 2490 cancer patients, CGH and NGS identified actionable alterations on 51% of patients, with treatment recommendation in 35%. Most patients treated derived benefit from the recommended MTT, but these represent a minority of the whole population screened.

***Conclusion:*** This study shows that routine genomic testing can identify more patients who may benefit from targeted therapy, although the actual number of people who may receive treatment

is smaller. If a patient can receive a matched targeted therapy, then he or she has a better chance of living longer. Comprehensive genomic profiling can be performed in routine practice to select patients for targeted cancer therapies. The technology is widely available and requires only a small amount of DNA.

Clinical trial information: NCT01774409