The 2019 American Society of Clinical Oncology Annual Meeting took place from May 31-June 4, 2019 in Chicago, Illinois. This event brings together over thirty thousand oncologists, pharmaceutical representatives, and patient advocates from across the world and across cancer types for five days of networking, learning, and presenting new research. Every year, Save Your Skin Foundation puts together a report of the panels regarding innovative treatments in the melanoma sphere. Below are detailed recollections of these panels, in chronological order.

Each talk, with the exception of the abstract discussions, also contains a "highlights" section, which briefly summarizes the key topics in each presentation. Please note that some talks have been excepted from this report where noted, and that we only report panels relating to North American news.

Additionally, we would also recommend video resources recently posted by Oncology Education, including Dr. Jeffrey Weber (NYU) discussing Checkmate 238, and Dr. Max Madu (Netherlands Cancer Institute) on the 8th AJCC melanoma staging system. These videos are available on the Oncology Education website, though you will need a free membership to view them.

The informational resources cited in this report are a combination of the personal notes of myself, Taylor Tomko, and transcripts and slides from the ASCO meeting library. All images are courtesy of the author of the respective talk. Any queries, including for the names of specific abstract authors, may be directed to taylorkathleen@saveyourskin.ca.

Panels

Friday, May 31

Point/Counterpoint: Does the Bar for Oncology Drug Approval Affect Quality of Care/ Life?
Chair: Ariadna Tibau Martorell, MD, PhD, Hospital de la Santa Creu i Sant Pau
Friday May 31, 1-2:15PM

1-1:15PM
Clinical Benefit and Quality of Life Associated with Approved Drugs
Ariadna Tibau Martorell, MD, PhD, Hospital de la Santa Creu i Sant Pau

Highlights:

- While surrogate endpoints help to expedite drug approval processes, they may not be adequate substitutes for overall survival or quality of life
- Patient-reported outcomes are considered important supportive data in benefit-risk assessment, however, reliance on PROs can result in missing data in cases of death or disease progression, and be skewed by other factors
- Cancer care organizations have been placing an increasing emphasis on value frameworks to provide a standardized approach to clinically meaningful outcomes, or outcomes that suggest improvement in overall survival alongside the overall toxicity of a drug

Talk description:

In this session, Tibau discussed how the standards for oncology drugs affect the quality of care and quality of life in patients. Tibau began by noting that while historically patient experience has been a secondary concern in cancer treatment development, patient-focused drug development is becoming increasingly emphasized in oncology. Overall, this session aimed to 1) highlight the different approval processes for cancer drugs, and their impact on patient care, 2) to identify concerns with surrogate endpoints and programs that are used to monitor drug efficacy and post-approval safety, and 3) to weigh both sides of the drug approval process debate.

Tibau first described the difference between a direct measure of clinical benefit and a surrogate endpoint, “clinical benefit” being described by the FDA and EMA as demonstration of prolonged survival, improved quality of life, or an established surrogate for these goals. Given the recent proliferation of new treatments, rapid approval processes and a more efficient approach to drug development have led to an increase in single-arm trials and the use of surrogate endpoints to designate approval. However, this increased use of surrogate endpoints are not necessarily adequate substitutes for overall survival or quality of life.

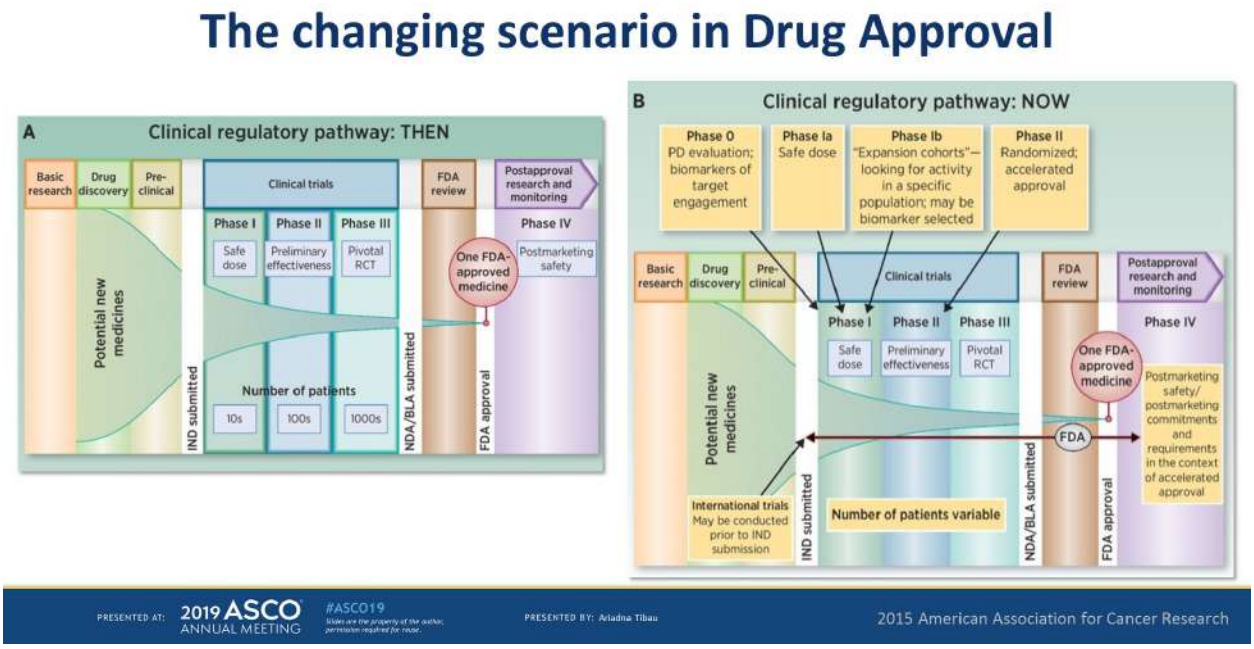


Figure 1: Tibau, "The changing scenario in Drug Approval" (2019)

Tibau moved on to describe the importance of PROs, or patient-reported outcomes, as a measure of clinical benefit and basis for drug approval. The FDA and EMA generally consider PROs important supportive data in benefit-risk assessment, as it is often considered within other clinical endpoints, such as survival, tolerability, and safety. However, reliance on PROs can result in missing data in cases of death or disease progression, and can be skewed by patient knowledge of treatment in open-label and single-arm trials. Additionally, PRO reporting can be altered by the overlap of treatment symptoms and disease symptoms. While PROs are included in drug information and labelling in Europe, this is not the case in the United States.

In an effort to balance the desire for positive PROs with expense, Tibau notes that the phrases "meaningful clinical benefit" and "value in oncology" have emerged as important indicators of cancer care. Meaningful clinical benefit suggests improvement in overall survival alongside the overall toxicity of a drug, while value in oncology describes the intersection between cost and clinical benefit. Therefore, cancer care organizations have been placing an increasing emphasis on value frameworks to provide a standardized approach to clinically meaningful outcomes, such as ASCO's Cancer Research Committee's targets for "clinically meaningful benefit in trials, based on overall survival and progression-free survival thresholds" (Tibau 2019). As a result of these frameworks, there has been a significant improvement in the number of trials reaching the ESMO MCBS threshold for clinical benefit, partially due to increased reporting of improved quality of life and less high-grade toxicity. However, the use of these frameworks still has limitations, such as their dependance on single-arm and randomized controlled trials.

Overall, drug development and approval is consistently considering meaningful clinical benefit to patients as data, defined by improvement in overall survival and toxicity. The oncology community views this as a boon to providing drugs that address patient expectations, to raise the bar for drug approvals, and to provide higher-quality care to patients.

1:15-1:30PM
Expedited Program Use and Patient Experiences in Clinical Trials
Vinay Prasad, MD, MPH, Oregon Health & Science University

Highlights:

- In the United States, there are two forms of treatment approval: accelerated approval, which is a provisional approval, and regular approval, which is a full approval
- A small fraction of cancer drugs on the market that were tested by a surrogate have tangible survival benefit; while approval based on overall survival takes an average of 7.3 years, approval based on surrogates only shortens that process by 11 months, or 12%
- Along the spectrum of patients, some that are willing to live with uncertainty if it allows them faster access to a treatment and others who are more cautious about weighing their options, and would not be willing to take that risk; the social contract of the accelerated approval process is the option for patients at both ends of the spectrum to have their choice

Talk description:

Prasad began his presentation about the patient experience in clinical trials by noting that, from his perspective, patients care about two main aspects of treatment: longer survival, and better quality of life. In addition, Prasad states, they want timely access to drugs, which is why programs such the FDA accelerated approval pathway is relevant for patients. Prasad clarifies here that, in the United States, there are two forms of approval: accelerated approval, which is a provisional approval, and regular approval, which is a full approval. Accelerated approvals, Prasad explains, are generally given based on a surrogate endpoint, which is likely to reach the targeted clinical endpoint.

Prasad then presented data compiled by himself and Chul Kim (Georgetown), which looked at five consecutive years of drug approval in the United States. As Prasad suggests, 1/3 of the approvals are accelerated approvals, 2/3 are regular approvals. 2/3 of these are surrogate approvals, while 1/3 use overall survival and patient-reported outcomes regarding quality of life. If you have accelerated approval, Prasad explains, “that surrogate endpoint typically is response rate or the fraction of patients whose tumours shrink more than an arbitrary threshold,” whereas regular approval sees progression-free survival (Prasad 2019).

Prasad then moves into discussing how to judge a surrogate, which he suggests should be done based on trial-level validity, and how the variability of the surrogate compares to the variability of your desired endpoint. However, Prasad claims that the selection of surrogates thought most 'reasonably likely to predict' an endpoint is often based on the gut feeling of the oncologist. As a result, Prasad points to a study conducted by himself and Kim in *JAMA Internal Medicine* which suggests that a small fraction of cancer drugs on the market that were tested by a surrogate have tangible survival benefit. He also points to a paper in the same journal by Bishal Gyawali, which suggests that the surrogates used for accelerated approval are often changed when the drug is converted to regular approval, meaning that potential issues identified during the accelerated approval process may not be addressed before regular approval (Gyawali quoted in Prasad 2019).

Prasad then returned to the question of timely access, which he believes is an issue of the highest importance for patients. Here, Prasad pointed to a third paper published in *JAMA Internal Medicine* by Emerson Chen, who sought to quantify how much time is actually saved by surrogate endpoints. Chen found that while approval based on overall survival takes an average of 7.3 years, approval based on surrogates only shortens that process by 11 months, or 12% (Chen quoted in Prasad 2019). From Prasad's perspective, this time saving is modest, especially in the face of the resulting uncertainty. While Prasad believes that along the spectrum of patients there are certainly some that are willing to live with that uncertainty if it allows them faster access to a treatment, there are others who are more cautious about weighing their options, and would not be willing to take that risk. Therefore, the social contract of the accelerated approval process is the option for patients at both ends of the spectrum to have their choice. However, Prasad believes that this is a flawed contract, as the patients who are invested in being as informed as possible are often denied sufficient information in terms of follow-up studies regarding overall survival and quality of life.

Overall, Prasad believes that the situation could be improved by greater regulation on surrogates, and a change in the process by which surrogate endpoints for accelerated approvals should be converted to regular approvals. More information on what Prasad believes could help solve these issues is available in the paper he co-authored with Robert Kemp in *BMC Medicine*, titled "Surrogate Endpoints in Oncology, when are they Acceptable for Regulatory and Clinical Decisions, and are they Currently Overused?"

1:30-1:45PM
Clinical Trial Participation from the Patient Perspective
Bishal Gyawali, MD, PhD, Brigham and Women's Hospital

Highlights:

- While only 3-5% of patients in the United States get enrolled in clinical trials, almost 40% of trials don't take place because they fail to reach the accrual target. Simultaneously, 85% percent of patients are willing to consider clinical trials, while 75% are willing to enrol in trials
- The top barriers to patients enrolling in clinical trials are lack of availability, restricted eligibility criteria, physicians not offering trials to patients, and patients not enrolling in trials
- Gyawali suggests that the centre of this conversation is patient education and empowerment, and that patients should be more involved in the designing of clinical trials

Talk description:

Gyawali began by mentioning that, out of all that is said about clinical trials in the medical community, likely the most important criticism is that clinical trials are not representative of real-world patients. However, they are still critical in improving treatment efficacy. So, to solve the former problem, the solution is to be more inclusive of 'real world' patients in clinical trials. Statistics, as Gyawali points out, illustrate this issue: while only 3-5% of patients in the United States get enrolled in clinical trials, almost 40% of trials don't take place because they fail to reach the accrual target. Adversely, Gyawali claims that 85% percent of patients are willing to consider clinical trials, while 75% are willing to enrol in trials. Yet, only approximately 40% of patients recall discussing clinical trials with their medical team, which is the central issue.

Gyawali then cited recent research that discussed key barriers to clinical trial participation. The top barriers listed in said paper were lack of availability, restricted eligibility criteria, physicians not offering trials to patients, and patients not enrolling in trials. He then begins to break down how to solve these issues. If it is assumed that the best predictor of a patient enrolling in a clinical trial is whether that trial is located in a convenient location for them, then a solution to the availability problem would be for a wider selection of community cancer centres to offer trials. In the case that there isn't a trial available at a particular centre, Gyawali suggests that they have resources available to point patients to an appropriate resource for trials. Regarding the restricted eligibility barrier, Gyawali notes that progress has been made by ASCO and the FDA to loosen restrictions, including lowering the minimum age for trial access and including those with chronic illnesses that are controlled, including HIV/AIDS.

However, as Gyawali notes, the centre of this conversation is patient education and empowerment, which should be supplemented by a streamlining of bureaucracy. Additionally, a less often discussed aspect of the clinical trial is the financial burden outside of the treatment

itself. While the treatment is generally free in an industry-sponsored trial, the patient is still responsible for transportation costs and non-drug interventions. While Gyawali believes that policy changes could help to alleviate this problem, patients should be more involved in the designing of clinical trials. As examples, Gyawali notes that acceptable percentages of mortality increases and toxicities in non-inferiority trials are assumed by oncologists, but the patients who are actually undergoing the trials have no say in what is an acceptable percentage for them. Additionally, Gyawali suggests that doctors should be more critical of which trials they enrol their patients in, and only do so if the aims of the trial are to serve the patient agenda; for example, a study that does not report quality of life outcomes does not work to the benefit of patients.

Gyawali ended his talk by suggesting some questions patients should be asking about clinical trials, and therefore the kinds of educational tools they should be given by their medical team. Gyawali suggests that knowledge of the standard of care outside of the trial, what phase the trial is in, what side effects are expected, and the plans for reporting and publishing data. While this information is usually covered in informed consent documents, Gyawali notes that they are often lengthy for patients, especially given the medical jargon they are written in. Therefore, medical professionals need to be doing their best to empower patients to take an active role in their treatments, and to ensure that the ultimate goal of clinical trials is to serve the patient.

Note: the 1:45-2:00PM panel, “Oncology Drug Approval in Europe” by Bradford Richard Hirsch, MD, MBA, (SignalPath), has been excluded from this report.

Saturday, June 1

“The Stage IV Melanoma Consult in 2019: What Biomarkers and Treatments Are Appropriate in the Frontline Setting?”
Chairs: Anna C. Pavlick, MD, MBA, Laura and Isaac Perlmutter Cancer Center, NYU Langone Medical Center
Saturday, June 1, 8-9:15AM

8:00-8:15AM
PD-L1 Testing: Is It Needed to Decide an Immunotherapy Treatment Plan?
Leslie Anne Fecher, MD, University of Michigan

Highlights:

- PDL-1 is currently the most frequently used predictive biomarker in immunotherapy treatment, identifying individuals who may be more likely than others to have an adverse effect from exposure to a medical product

- PDL-1 is not an adequate singular biomarker to determine treatment decisions
- Fecher argues that the decision-making process for first-line treatments should be based on a more holistic analysis

Talk description:

Fecher began her talk, which addressed the necessity of PDL-1 testing when creating an immunotherapy treatment plan for melanoma, by noting that the significant changes in treating melanoma over the past decade have meant that there is a surplus of options when deciding on a treatment plan.

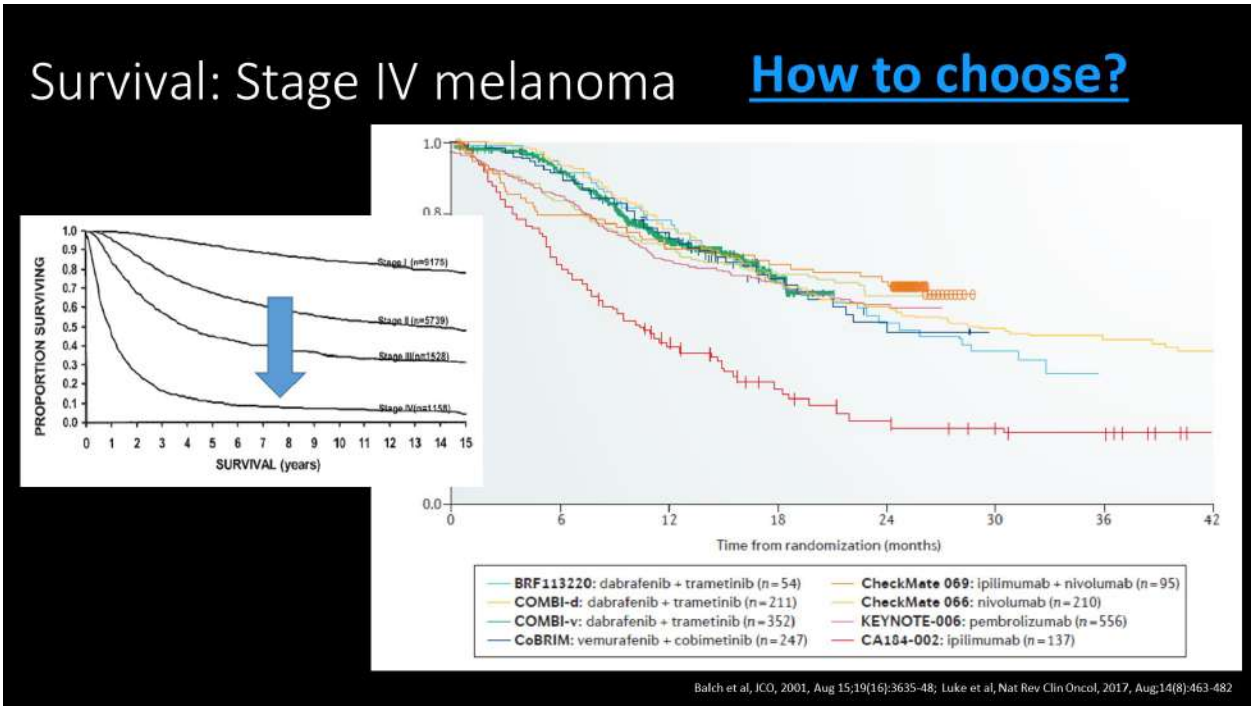


Figure 2: Fecher, “Survival: Stage IV melanoma” (2019)

As Fecher explains, “PD1 is a negative regulator of the immune system and T cell activation, affecting the negative regulatory effects. It's expressed on activated B and T lymphocytes, NK cells, and macrophages, where PDL-1 is widely expressed in a variety of cells, including hematopoietic, non-hematopoietic, tumour cells, and tumour-infiltrating cells” (Fecher 2019). PDL-1 is currently the most frequently used predictive biomarker in immunotherapy treatment, which is meant to identify individuals who, due to a biomarker, may be more likely than others to have an adverse effect from exposure to an environmental agent or medical product.

However, determining the results of PDL-1 involves several variables, including the PLD-1's ability to express membranous and cytoplasmic staining on both tumour cells and infiltrating immune cells. Therefore, it may affect both scoring and the measurements of membranous staining. There is also the possibility of genetic alterations and adaptive immune response in the tumour and T-cell interface, so tissue sample and quality, as well as size, can impact PDL-1 results. Additionally, Fecher notes that older samples may not be timely representations of the immune system at the time of treatment decision-making, and that certain sites of metastases (lymph node, subcutaneous, brain, and bone) can have higher PDL-1 expression levels.

Given conflicting data in PDL-1's use as a biomarker for advanced melanoma, Fecher suggests that a single biomarker is not adequate evidence for treatment decision-making. Ideally, there should be a greater understanding of not only immunotherapy response and duration of benefit, but also the microenvironment of the tumour, and the host immune system, before decisions are made.

Fecher then turned to KEYNOTE-001, in which three blinded pathologists provided a MEL score based on four membraneous PDL-1 tumour cells and interpolated mononuclear cells. Response rates increased with a higher MEL score, which indicated PDL-1 positivity, indicating a correlation between PDL-1 positivity and progression free and overall survival. However, as Fecher points out, the 24-month overall survival rate for PDL-1 negative patients was still relatively high, suggesting that PDL-1 alone does not predict results.

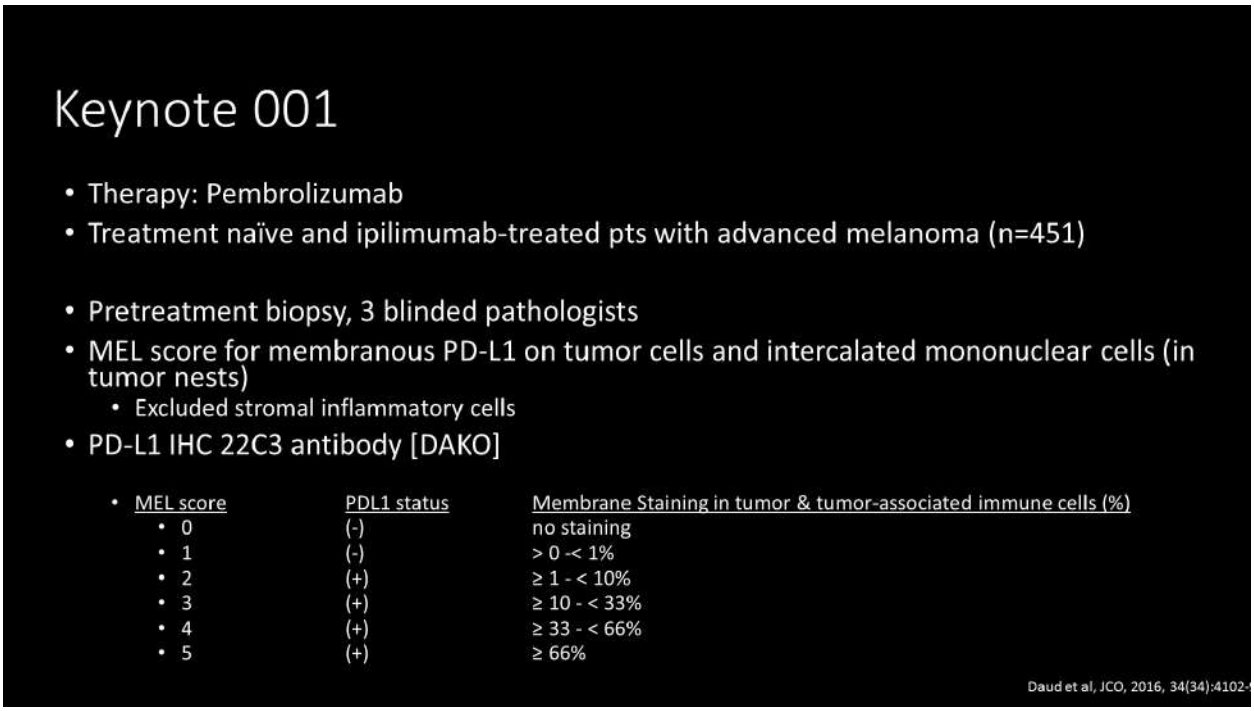


Figure 3: Fecher, "Keynote 001" (2019)

Fecher then pointed to a randomized phase 2 study which compared patients with negative or positive PDL-1 status taking either ipilimumab at three milligrams per kilogram and

1 milligram per kilogram of nivolumab, versus just 3 milligrams per kg of ipilimumab. For the patients taking the combination treatment, there was no statistically significant difference in response rate (two year progression-free survival and two-year overall survival) whether they were positive or negative. The authors ultimately concluded that PDL-1 alone is a poor biomarker to predict overall survival. Thankfully, as Fecher points out, there are other biomarkers that can be used, such as physiologic age and comorbid status. Fecher argues that the decision-making process for first-line treatments should be based on a more holistic analysis, rather than a single biomarker.

8:15-8:30AM
Debate: Immunotherapy Targeted Therapy Versus Immunotherapy Sequencing—Immunotherapy Targeted Therapy Should be Frontline
Paolo Antonio Ascierto, MD, Instituto Nazionale dei Tumori IRCCS Fondazione

Highlights:

- Combining BRAF-MEK inhibition with immunotherapy, would create a more favourable tumour microenvironment for treatment
- As seen in a trial that combined BRAF + trametinib, pembrolizumab + BRAF, and trametinib monotherapy, triple combination demonstrated a higher shrinkage of tumours, and a more complete response relative to targeted therapy or monotherapy
- However, the toxicity resulting from this kind of combination is quite high, so it may only be appropriate for high-risk patients

Talk description:

Ascierto started by discussing the benefits of combining BRAF-MEK inhibition with immunotherapy, which would create a more favourable tumour microenvironment for treatment. The goal, Ascierto suggests, is to increase the results of the combination of immunotherapy and targeted therapy to match those of BRAF/MEK; otherwise, as the debate asks, is there really the need for the combination instead of just sequencing?

There is currently lots of data regarding this question, including a randomized phase II trial from ESMO 2018, which used a triple combination of BRAF + trametinib, pembrolizumab + BRAF, and trametinib monotherapy. 60 patients were enrolled per arm, and the endpoint was median progression-free survival. The results saw six months more benefit with the triple combination with targeted therapy and anti-PD-1, though during the first 6 months the efficacy curves were very similar, then began to separate after 6 months when the PD-1 began to take effect. The triple combination demonstrated a higher shrinkage of tumours, and a more complete response relative to targeted therapy or monotherapy. However, toxicity is a risk that comes with

the triple combination therapies; more than 60% of patients in the trial had grade-3 or -4 adverse effects, and two died due to toxicity-related causes. Additionally, between 40-60% of patients discontinued the trial, likely due to the liver toxicity and pneumonitis. Despite these risks, Ascierto claims that this combination can be good for patients that are at higher risk, those with brain metastases, or high tumour burden. As this treatment line still has promise, so there are ongoing randomized phrase III trials that will give us more information about the treatment.

8:30-8:45AM
Debate: Immunotherapy Targeted Therapy Versus Immunotherapy Sequencing—Immunotherapy Sequencing Should be Frontline
Ryan J. Sullivan, MD, Massachusetts General Hospital

Highlights:

- BRAF-MEK inhibitor combinations, the nivolumab + pembrolizumab combination, anti-PD-1 antibodies, the ipilimumab + nivolumab combination, or intralesional therapy
- Patients who will do well with a PD-1 inhibitor should receive it, even if it is after treatment with BRAF-targeted therapy, which can be effective in some patients
- In the future, it would be ideal if there was a biomarker to identify which patients would benefit from BRAF-MEK inhibitor therapy, and then a clinical trial could be developed for patients who progress after single anti-PD-1 or BRAF-MEK treatments

Talk description:

Sullivan introduced his talk by considering what options are available for patients with BRAF-mutant melanoma: generally, these would be in BRAF-MEK inhibitor combinations, the nivolumab + pembrolizumab combination, anti-PD-1 antibodies, the ipilimumab + nivolumab combination, or intralesional therapy. Sullivan notes that this is not a mutually exclusive choice, and it is likely that all patients who progress while on first-line therapy will also undergo second-line therapy. Therefore, those who progress on immunotherapy will receive BRAF-targeted therapy, and vice versa.

However, as the debate asks, which of these approaches should be considered first? While technically the FDA hasn't approved immunotherapy BRAF-targeted therapy, so immunotherapy sequencing wins by default, Sullivan believes there is potential for great advances with immunotherapy and targeted therapy as well. So in the future, there may be the choice between these options. At this point, however, durable benefit has been seen with BRAF-targeted therapy, single-agent anti-PD-1 antibody therapy, and combined anti-PD-1 and anti-CTLA4 therapies.

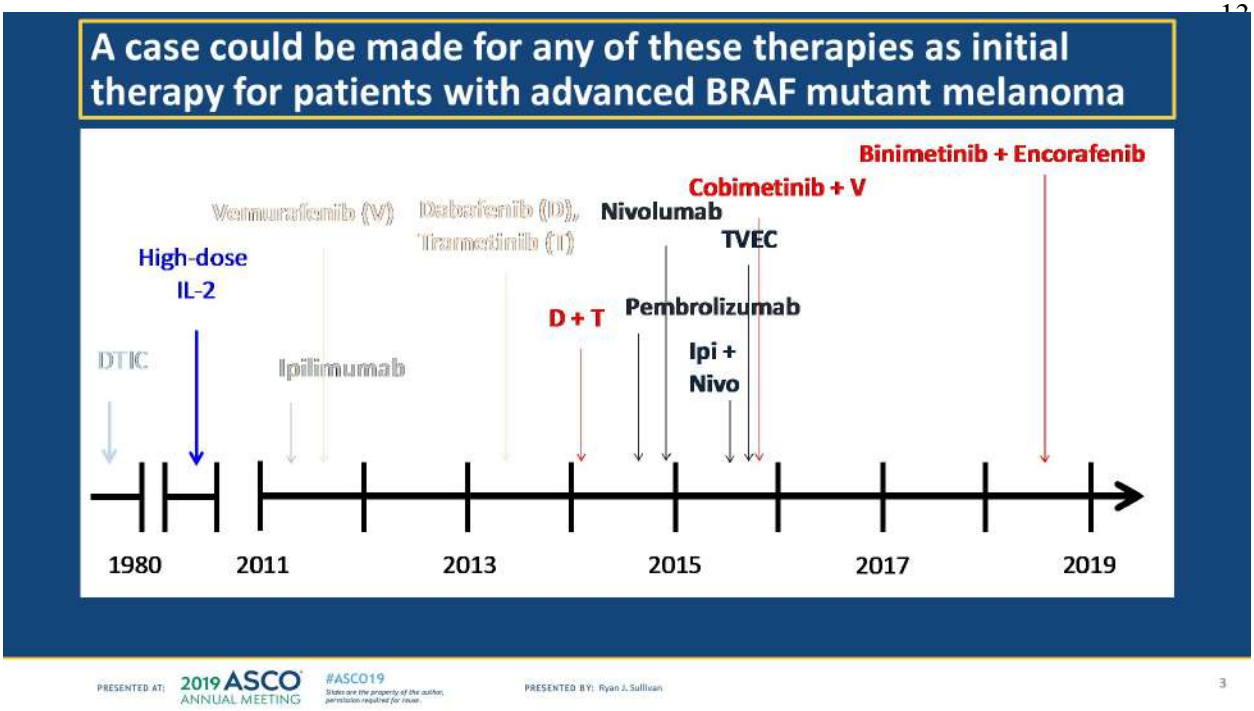


Figure 4: Sullivan, "A case could be made for any of these therapies as initial therapy for patients with advanced BRAF mutant melanoma" (2019)

To demonstrate, Sullivan called on the results of COMBI-d and COMBI-v, two randomized phrase three trials of dabrafenib + trametinib, and CheckMate 067 (nivolumab + ipilimumab versus ipilimumab). The results show that a minority of the patients in these studies are remaining progression-free for up to five years, suggesting that there is the possibility to evolve these treatments to secure meaningful PFS for a larger population of patients. Sullivan hopes that in the future patients will be able to receive the singular treatment that is most effective for them, and have two-year progression-free survival in the 40-70% range.

In addition, Sullivan notes that BRAF-targeted therapy usually leads to changes in the immune system microenvironment that predicts responsiveness to anti-PD-1 or pD-L1 therapy, which can include increased antigen expression, decreased immunosuppressive cytokine production, and increased CD8-positive T-cell infiltration, T-cell clonality, and PD-L1 expression. There is also currently no data about ideal sequencing of BRAF-targeted therapy and anti-PD-1-based therapy, in combination or as a single agent; however, the CECOMBIT trial (randomized encorafenib and binimetinib, hence BRAF-MEK) and the DREAMseq/ECOG-ACRIN 6134 study (randomized ipilimumab or nivolumab verses dabrafenib or trametinib), the former being at accrual and the latter being 2/3 of the way there, should hopefully shed more light on the relationship between BRAF-targeted and anti-PD-1 therapies.

Given this lack of current data, Sullivan looked backwards to a study which involved 114 patients from Dana-Farber, Mass General, and Vanderbilt, with three potential arms: patients who received a PD-1 inhibitor and did not require BRAF-targeted therapy; patients who received BRAF inhibitor therapy first, and then at progression received a PD-1 inhibitor; and then patients who started with a PD-1 inhibitor, progressed, and then were given BRAF-targeted therapy. This slide is included below. Generally, the patients who began with more progression received the BRAF-targeted therapy first. The results suggested that there was no difference in the outcome of

patients who started with the BRAF therapy, versus the PD-1 inhibitor; however, the patients who began with the anti-PD-1, then moved onto the BRAF-targeted therapy did less well than the patients who did the opposite, while patients who not did not require the BRAF-targeted therapy after the anti-PD-1 did well in terms of overall survival.

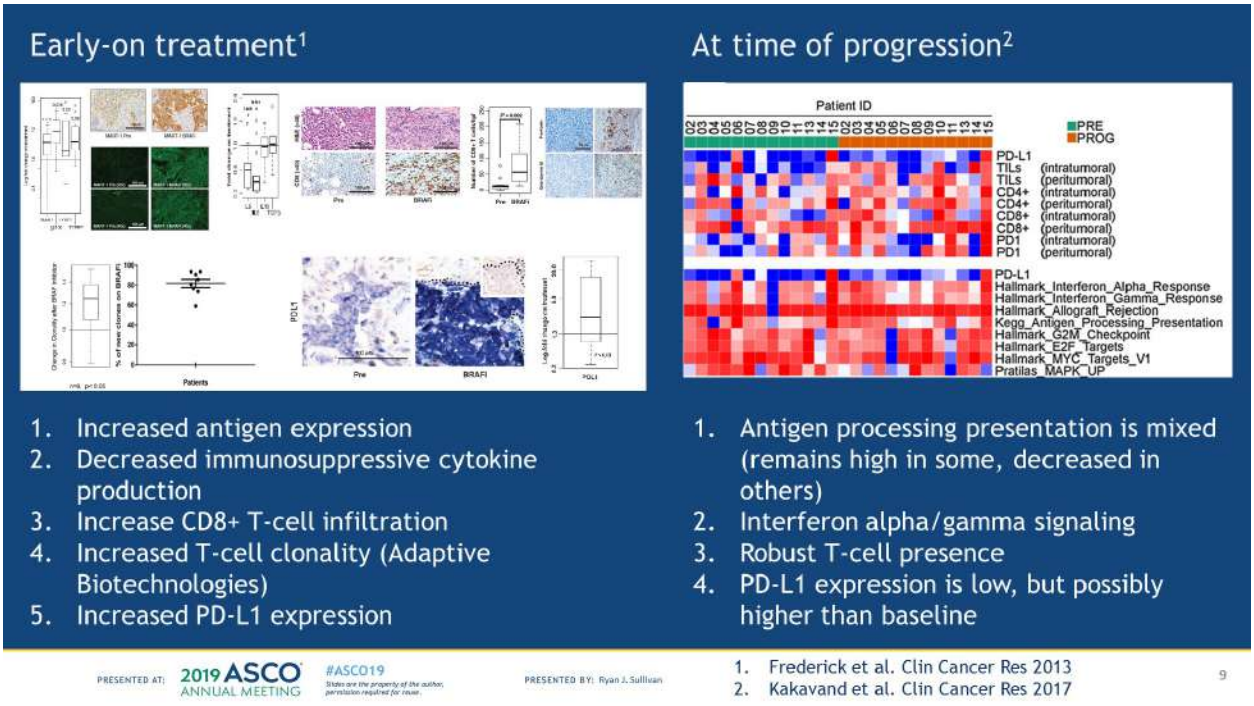


Figure 5: Sullivan, 2019

The conclusion, therefore, is that patients who will do well with a PD-1 inhibitor should receive it, even if it is after treatment with BRAF-targeted therapy, which can be effective in some patients. Additionally, given the poor results of patients who required BRAF-targeted after anti-PD-1 therapy, these therapies may have shared resistance, or that BRAF-targeted therapy may be less effective after immunotherapy. Sullivan believes that though it may be too early to commit to first-line combined therapy and targeted therapy, but thinks it is possible with the right testing. Ideally, he would like to be able to determine whether patients are going to benefit from a single-agent PD-1 inhibitor, so he can use that therapy as a first option. It would be ideal if there was a biomarker to identify which patients would benefit from BRAF-MEK inhibitor therapy, and then a clinical trial could be developed for patients who progress after single anti-PD-1 or BRAF-MEK treatments.

8:45-9:00AM
Is There One Answer to Correct Frontline Therapy?
Anna C. Pavlick, MD, MBA, Laura and Isaac Perlmutter Cancer Center, NYU Langone Medical Center

Highlights:

- While the number of treatment options has increased, there still needs to be some protocol on first-line treatments, and what to do as a second-line when those treatments progress
- There currently isn't one ideal biomarker for tumour responsiveness in melanoma

Talk description:

To conclude the "The Stage IV Melanoma Consult in 2019: What Biomarkers and Treatments Are Appropriate in the Frontline Setting?" panel, Pavlick reiterated some highlights of the previous panels. Overall, Pavlick suggests, the presentations have highlighted that there is no singular correct answer for first-line therapy for BRAF-mutated metastatic melanoma patients. However, as the number of options and combinations have increased, so have durable responses; yet there still needs to be some protocol on first-line treatments, and what to do as a second-line when those treatments progress. But, as each patient is different, this is a complicated question.

Given the presentations in this panel and the other research at ASCO, Pavlick reiterates that PD-L1 has not proven to be the same perfect tumour biomarker for melanoma that it is for other indications. Additionally, there is hope that the gut microbiome could give insights about melanoma tumour immunotherapy responsiveness and toxicity risks. However, at this point, there isn't one ideal biomarker for tumour responsiveness in melanoma.

In terms of combinations, there are currently no combination immunotherapy and targeted therapy courses that have been approved by the FDA. Phase III data for studies in this area is currently being completed, so there should be more certainty within the next two years. However, when available, Pavlick believes that combination immuno- and targeted therapies should be considered for patients who have not responded positively to other treatments.

Regarding sequential therapies, it must be considered that if BRAF-targeted therapies are given first-line, it may change the microenvironment for immuno- and targeted therapies given afterward, and toxicity may be a risk. However, ideally patients that do well with immunotherapy will not require a second-line therapy.

Overall, Pavlick believes the session narrows down to the question of biomarkers. As treatment decisions are largely based on patient-by-patient mutational status, effective biomarkers will be ideal for helping to decide effective treatments for melanoma patients. However, finding this particular biomarker is a work-in-progress, as is the combination of IO with targeted therapies, and correct sequencing for these therapies.

Next-Generation Therapeutics and Biomarkers in Melanoma
Jessica Cecile Hassel, MD, Department of Dermatology and National Center for Tumor Diseases, University Hospital Heidelberg, Heidelberg, Germany; Suzanne Louise Topalian, MD, The Sidney Kimmel Comprehensive Cancer Center and Bloomberg-Kimmel Institute for Cancer Immunotherapy at Johns Hopkins
Sat, Jun 01, 3:00 PM - 4:30 PM

3:00 PM - 3:12 PM
Abstract #9509: Phase 1 study of MK-4166, an anti-human glucocorticoid-induced tumor necrosis factor receptor (GITR) antibody, as monotherapy or with pembrolizumab (pembro) in patients (pts) with advanced solid tumors.
Kyriakos P. Papadopoulos, MD, South Texas Accelerated Research Therapeutics

Highlights:

- The results suggest that MK-4166 as a monotherapy and combined with pembrolizumab seems to be tolerable, and is especially efficacious in immune checkpoint inhibitor naive patients

Talk description:

This talk was based off of abstract #9509, the results of which suggested that MK-4166 as a singular therapy or as a combination with pembrolizumab was well tolerated, with results in patients naive to immune checkpoint inhibitors. This trial was a phase I study of MK-4166 anti-human glucocorticoid-induced tumour necrosis factor receptor (GITR) antibody, as either a monotherapy (113 patients) or with pembrolizumab (65 patients) in patients with advanced solid tumours. GITR enhances T-cell proliferation and survival and effector function, both of which work against tumours. The primary endpoints of this study were safety and tolerability, and the trial allowed all patient types including immune checkpoint inhibitor naive and pre-treated advanced melanoma patients. 13 of the patients enrolled in the trial completed the study medication. Of these 13, 9 patients had objective responses, including four patients with complete response and five with partial responses; all of these patients were immune checkpoint inhibitor naive. Overall, MK-4166 as a monotherapy and combined with pembrolizumab seems to be tolerable, and is especially efficacious in immune checkpoint inhibitor naive patients.

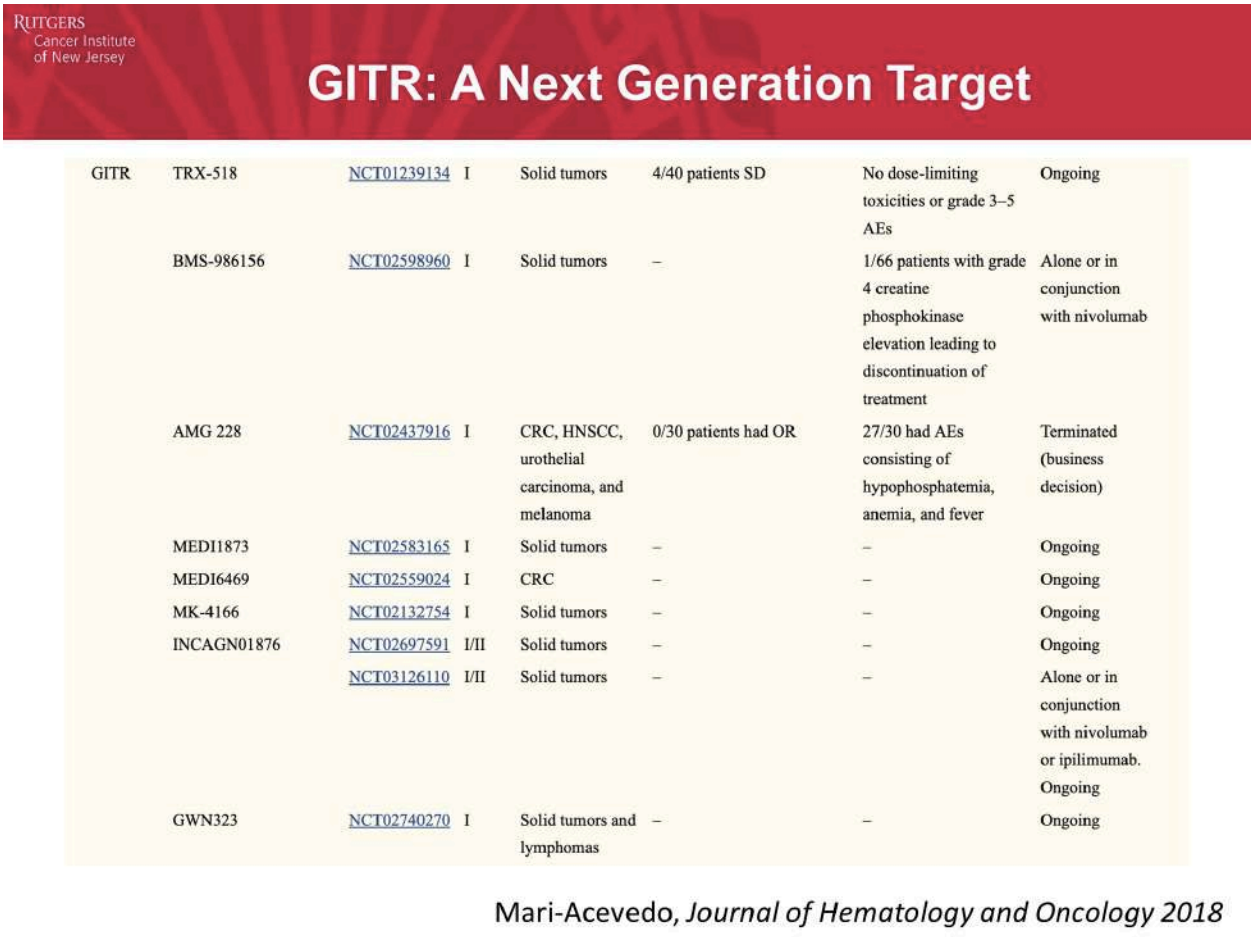
3:12 PM - 3:24 PM
GITR as an Emerging Novel Checkpoint in Immunotherapy
Janice M. Mehnert, MD, Rutgers Cancer Institute of New Jersey

Highlights:

- MK4166 demonstrates a tolerable side effect profile alone, but the results in the checkpoint inhibitor naive patient melanoma cohort requires additional validation

Talk description:

Mehnert discussed the possibility of GITR, an antagonistic antibody, as a new checkpoint for immunotherapy treatment plans. Antagonistic antibodies have been pre-clinically demonstrated to modulate and potentiate anti-tumour CD8 positive T-cell functions. To illustrate the results associated with GITR antibodies, Mehnert showed the results of all of the GITR antibodies currently in development.



GITR	TRX-518	NCT01239134	I	Solid tumors	4/40 patients SD	No dose-limiting toxicities or grade 3–5 AEs	Ongoing
	BMS-986156	NCT02598960	I	Solid tumors	–	1/66 patients with grade 4 creatine phosphokinase elevation leading to discontinuation of treatment	Alone or in conjunction with nivolumab
	AMG 228	NCT02437916	I	CRC, HNSCC, urothelial carcinoma, and melanoma	0/30 patients had OR	27/30 had AEs consisting of hypophosphatemia, anemia, and fever	Terminated (business decision)
	MEDI1873	NCT02583165	I	Solid tumors	–	–	Ongoing
	MEDI6469	NCT02559024	I	CRC	–	–	Ongoing
	MK-4166	NCT02132754	I	Solid tumors	–	–	Ongoing
	INCAGN01876	NCT02697591	I/II	Solid tumors	–	–	Ongoing
		NCT03126110	I/II	Solid tumors	–	–	Alone or in conjunction with nivolumab or ipilimumab. Ongoing
	GWN323	NCT02740270	I	Solid tumors and lymphomas	–	–	Ongoing

Figure 6: Mari-Acevedo (2018), cited in Mehnert (2019)

Mehnert began by discussing the TRX518 antibody (Leap Therapeutics), which is being tested in a Phase I study with 48 patients with MK4166 monotherapy and 20 melanoma patients with added pembrolizumab. While monotherapy hasn't been seen as an especially effective approach for immune checkpoint naive melanoma patients, Mehnert believes that it could be worth using PD-1 blockades to reinvigorate T-cells and potentiate the preclinical data regarding anti-GITR antibodies. However, regarding dosage, Mehnert thinks it is important to consider whether receptor assays could be changing in availability or appearance, or whether the cells may be disappearing. While determining the ideal dose is still in process, the current toxicity rates seem reasonable, though response rates are low. In the case of the melanoma cohort, patients that have been treated with immune checkpoints have had no responses, while there is a 69% response rate in the checkpoint inhibitor naive patients.

Ultimately, the results suggest that there is a gene expression profile that has been shown to enrich response in KEYNOTE-6 patients treated with pembrolizumab monotherapy, but there isn't the same pattern in patients with combination therapy. There is still room for improvement in developing tumour biomarkers, but Mehnert believes it is still worth seeing what measurements of composite tumour mutation burden PD-L1 gene expression profiling may reveal. So while MK4166 demonstrates a tolerable side effect profile alone, and in combination with immune checkpoint therapy, the results in the checkpoint inhibitor naive patient melanoma cohort requires additional validation.

3:24 PM - 3:36 PM
Abstract #9510
Circulating tumor DNA (ctDNA) kinetics to predict survival in patients (pts) with unresectable or metastatic melanoma treated with dabrafenib (D) or D + trametinib (T).
Mahrukh M Syeda, MS, NYU Langone Medical Center

Highlights:

- In patients with high lactate dehydrogenase, cell free circulating tumour DNA monitoring may help determine which patients would benefit from dabrafenib or the dabrafenib + tramenib combination

- In the baseline setting, pre-treatment ctDNA has indicated poor prognosis in a variety of treatments in patients treated with BRAF inhibitors, chemotherapy, and immune checkpoint blockade

- While BRAF V600 mutant ctDNA was detectable in 93% of patients with unmistakable or metastatic melanoma, this study suggests that elevated pre-treatment levels of ctDNA are associated with shorter survival outcomes, while negative ctDNA at week 4 is significantly associated with extended progression-free survival and overall survival

Talk description:

This talk was based off of abstract #9510, which examined the connection between serial ctDNA changes and survival after BRAf/MEK inhibitor therapy. The results found that in patients with high lactate dehydrogenase, cell free circulating tumour DNA monitoring may help determine which patients would benefit from dabrafenib or the dabrafenib + tramenib combination.

As Syeda explained in her talk, advanced metastatic melanoma lacks blood-based markers. However, Syeda suggests that cell free circulating tumour DNA (ctDNA) can be a promising biomarker for many cancer indications. CtDNA constitutes a subset of cell free circulating DNA that is present at low levels due to normal cell turnover in a healthy donor. In cancer patients, the higher cell turnover means that ctDNA can be identified by tumour mutations, such as BRAF. In melanoma, there have been studies that looked at ctDNA as a biomarker. In the baseline setting, pre-treatment ctDNA has indicated poor prognosis in a variety of treatments in patients treated with BRAF inhibitors, chemotherapy, and immune checkpoint blockade. In two small case studies, a connection has been observed between ctDNA levels and the outcomes after targeted therapy or immune checkpoint blockade. In both groups, one of which underwent only immune checkpoint blockade, while the other had trametinib and BRAF inhibitor after immune checkpoint blockade, the patients with no detectable ctDNA prior to treatment had longer progression-free survival curves than those who had ctDNA before treatment.

For the study Syeda was presenting, they analyzed ctDNA kinetics in the COMBI-d randomized phase III trial, to determine whether high levels of ctDNA before treatment were predictive of lesser survival, while week four on-treatment ctDNA levels would suggest survival outcomes. The COMBiI-d trial had 423 patients with unresectable or metastatic melanoma, who were all V600E positive and had received no prior systemic therapy. They were randomized 1:1 to the combination to BRAF inhibitor and trametinib, or trametinib + placebo. For this project, the arms were combined for analysis. They found that elevated ctDNA at baseline was associated with survival, but not as a categorical variable. However, as a continuous variable, the baseline levels were associated with overall survival and progression-free survival. Higher ctDNA detected at baseline was associated with worse clinical outcome. At week four of treatment, undetectable ctDNA was connected to greater progression-free survival and overall survival. Patients with positive ctDNA at baseline, who at week four had negative ctDNA, had median progression-free survival of 13 months, verses those patients who maintained ctDNA positivity had a progression-free survival of 7 months. In patients with elevated lactate dehydrogenase, those with negative ctDNA at four weeks had a longer progression-free survival and overall survival curves than those who remained ctDNA positive. Ultimately, while BRAF V600 mutant ctDNA was detectable in 93% of patients with unmistakable or metastatic melanoma, this study suggests that elevated pre-treatment levels of ctDNA are associated with shorter survival outcomes, while negative ctDNA at week 4 is significantly associated with extended progression-free survival and overall survival.

3:36 PM - 3:48 PM
Toward the Future of Noninvasive Monitoring of Response to Targeted Therapy
Genevieve Marie Boland, MD, PhD, The University of Texas MD Anderson Cancer Center

Highlights:

Talk description:

The aspect of blood-based biomarkers that Boland most wanted to highlight was the importance of tracking them over time. Boland demonstrated this by citing a study which assessed circulating tumour DNA in the COMBI-d trial. All of the patients chosen were on targeted therapy, and all had BRAF-mutant ctDNA. As seen in the slide below, BRAF mutant ctDNA was detected in about 40% of the pairs. The curve is consistent with other published date on ctDNA and CTC BRAF levels, as it reflects a drop in the vast majority of patients.

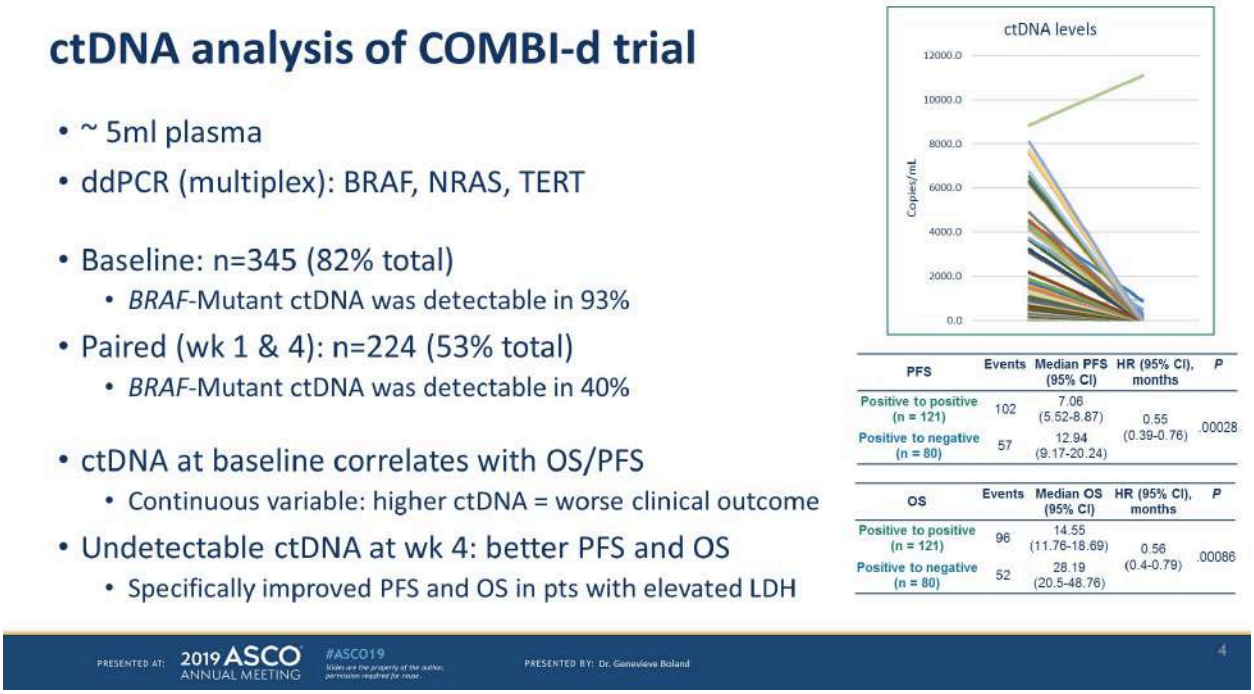


Figure 7: Boland, "ctDNA analysis of COMBI-d trial" (2019)

According to Boland, there is a variety of interesting information that can be found when circulation is looked at as a biomarker. This makes sense, as circulation includes a pool of free-cell DNA which is shed from a variety of cells, including tumour DNA, which is a small portion of circulation. There is also the ability to genotype or sequence from blood, probe for genetic mutations, and get methylation data (the chromosomal patterns in DNA), or to assess the tumour as it is in circulation through circulating tumour cells. Additionally, circulating biomarkers can be used to class low-risk populations from those that have a higher risk of recurrence.

Studies are currently being undertaken in other types of tumours to assist in making clinical decisions, such as whether or not to change a patient's therapy. While more research and standardization of practice needs to be undertaken, Boland feels that it is worth trying to refine this technique for the future. Some current considerations for blood biomarker testing that Boland notes are the importance of recognizing tumour burden, the quantity of input, and the clinical context of the patient at the time. While the sensitivity of circulating DNA tests is lower, as it is a new practice, the breadth of analysis and data you can get from this kind of testing is great. Therefore, Boland believes that biomarker correlative analysis should be done in all large clinical trials.

Sunday, June 02

Management of Rare Melanomas and Non-melanoma Skin Cancers
Michael Robert Migden, MA, The University of Texas MD Anderson Cancer Center
Sun, June 02, 8:00 AM - 9:15 AM

8:00 AM - 8:15 AM
Recent Advances in Cutaneous Squamous Cell Carcinoma
Michael Robert Migden, MA, The University of Texas MD Anderson Cancer Center

Highlights:

- Cutaneous Squamous Cell Carcinoma is the second most common skin cancer, behind Basal Cell Carcinoma, though the frequency of CSCC is increasing
- In September 2018, cemiplimab was approved for patients in the United States with locally-advanced and metastatic CSCC who were not candidates for curative surgery or radiation
- Other trials related to CSCC will be opening soon, or are in progress, including one that will combine oncolytic modified herpes virus in a checkpoint blockade, and a pembrolizumab study called KEYNOTE-629 that does not have data yet

Talk description:

To begin the panel on rare melanomas and non-melanoma skin cancers, Migden presented recent advances that have taken place in the field of cutaneous squamous cell carcinoma (CSCC). Cutaneous squamous cell carcinoma is the second most common skin cancer, behind basal cell carcinoma, though it appears that the frequency of CSCC is increasing. The majority of CSCC cases are treated with surgery, and the risk factors are common for skin cancers: fair skin, advanced age, immunosuppression, and ultraviolet radiation exposure.

While prior systemic treatments for this disease had shorter progression-free survival and overall survival, this changed in September 2018, when cemiplimab was approved for patients with locally-advanced and metastatic CSCC who were not candidates for curative surgery or radiation. Immunotherapy treatments are well suited to CSCC, which has a higher tumour-mutational burden of any cancer in the Cancer Genome Atlas, and immunosuppression is a recognized risk factor for CSCC. Thus, in a phase I study of cemiplimab in patients with multiple solid-tumour types, a durable response was achieved. These results led to the development of a phase II trial, which was the largest prospective systemic therapy trial for advanced CSCC. Migden also showed images of patients on the trial who had their tumours either shrink or disappear. Overall, cemiplimab showed strong anti-tumour activity, with durable responses, and a good safety profile in patients with metastatic and locally-advanced disease.

Migden concluded by giving a brief overview of other trials related to CSCC that will be opening soon, or are in progress, including one that will combine oncolytic modified herpes virus in a checkpoint blockade, and a pembrolizumab study called KEYNOTE-629 that does not have data yet.

"How to Appropriately Use Hedgehog in Advanced Basal Cell Carcinoma?" with Aleksandar Sekulic (Mayo Clinic, Scottsdale) has been excluded from this report.

8:30 AM - 8:45 AM
Biomarkers and Treatment Updates for Merkel Cell Carcinoma
Shailender Bhatia, MA, University of Washington and Fred Hutchinson Cancer Research Centre

Highlights:

- Are also currently trials of adjuvant therapy for merkel cell carcinoma (MCC) in the United States and abroad, and there is an existing cancer detection blood test called AMERK, which has been good for surveilling high-risk MCC patients

- While there has been no head-to-head study of chemotherapy versus immunotherapy for MCC patients, Bhatia claims that the historical data suggests only 6% of patients are progression-free one year after immunotherapy, while almost 50% of patients on immunotherapy reach that goal

- The NCCN has officially recognized immunotherapies as a treatment for MCC, and efforts are now being made to prevent recurrences

Talk descriptions:

Bhatia's talk was an update on developments regarding merkel cell carcinoma (MCC), an aggressive form of skin cancer. Chemotherapy is still often being used as a front-line therapy for MCC, which Bhatia believes should be foregone in favour of immune checkpoint inhibitors, which have a high and durable response rate. There are also currently trials of adjuvant therapy for MCC in the United States and abroad, and there is an existing cancer detection blood test called AMERK, which has been good for surveilling high-risk MCC patients.

In the past year, there have been some excellent trial results regarding MCC. PD-1 and PD-L1 blockade in MCC have been successful, with the PD-1 being used in addition to pembrolizumab, which had an initial response rate of 56% in 24 patients. Additionally, in a smaller study, nivolumab had a response rate above 60%. So, while there has been no head-to-head study of chemotherapy versus immunotherapy, Bhatia claims that the historical data suggests only 6% of patients are progression-free one year after immunotherapy, while almost 50% of patients on immunotherapy reach that goal.

As the NCCN has officially recognized immunotherapies as a treatment for MCC, efforts are now being made to prevent recurrences. Currently, the ADAM trial is using adjuvant avelumab versus placebo, and 100 patients will be enrolled. This is the first phase III trial to be conducted for MCC, and is targeting high-risk MCC patients. There is also a larger trial happening in Germany, which is using observation versus one year of nivolumab. Additionally, there is hope for a future predictive biomarker for immunotherapy responses in the metastatic setting.

While there have been great advances in MCC over the past year, there is still work to do. Bhatia points out three unmet populations: patients who don't respond to PD-1 blockade, those who progress after the initial response, and those with contraindications to immune-checkpoint inhibitors. However, Bhatia is optimistic about the future, especially as there is work being done to uncover mechanisms of resistance.

8:45 AM - 9:00 AM
What Is Available for the Treatment of Uveal/Mucosal Melanoma?
Marlana M. Orloff, MD, Sidney Kimmel Medical College at Thomas Jefferson University

Highlights:

- It is important to recognize the differences in incidents, causes, and treatments between uveal and mucosal melanoma, as confusion between them has impacted outcomes
- Uveal melanoma has a greater resistance to immunotherapy than other skin cancers; thus, there are ongoing trials regarding liver-directed treatments for metastatic uveal melanoma
- Current treatment options for mucosal melanoma include adjuvant chemotherapy, checkpoint inhibitor treatment, and KIT and BRAF-targeted therapy

Talk description:

Orloff's presentation gave an overview of what treatments are available for both uveal and mucosa melanoma. While these melanomas are often lumped into a category, Orloff claims that it is important to recognize the differences in incidents, causes, and treatments of these diseases. Confusion between these two cancers, Orloff notes, has impacted outcomes.

Orloff began by discussing uveal melanoma. Uveal melanoma is the most common primary intraocular malignant tumour for adults, with a five-year survival rate of approximately 70-80%. However, around 50% will develop metastatic disease from uveal melanoma, with the liver being the most common location for metastasis. Currently, there is no FDA-approved therapy specifically for uveal melanoma in both the adjuvant or metastatic setting, and no standardized care across the United States or abroad. Checkpoint inhibitor and targeted therapy results have been disappointing overall. However, recently the NCCN have prioritized clinical trial, systemic therapies, and liver-directed therapies as options for patients.

The first treatment for uveal melanoma Orloff discussed that localized transarterial therapy for hepatic metastasis in the liver. This approach allows a higher dosage to be delivered to the liver while minimizing systemic toxicity. Data from ASCO 2016 suggests that liver-directed therapy saw better results than kinase inhibitor, antigenic agents, chemotherapy, and liver-directed therapy for patients with metastasized uveal melanoma. There are a variety of ongoing trials regarding liver-directed treatments for uveal melanoma, as this slide from Orloff's presentation demonstrates.

Figure 8: Orloff, "Types of 'Liver Directed' Treatments" (2019)

Orloff then moved onto immunotherapies for metastatic uveal melanoma. While studies were running that looked at ipilimumab in cutaneous melanoma, parallel studies tested ipilimumab for uveal melanoma and saw inferior responses. Further investigation demonstrates that uveal melanoma has a greater resistance to immunotherapy than other skin cancers, in addition to a lack of PDL-1 expression and a lack of tumour mutational burden.

Currently, there is a drug in development for uveal melanoma that seeks to make the immune system better target the tumour. Tebentafusp (IMCgp100), a T-cell receptor, acts as an immunological magnet for melanoma cells. In a study of 19 patients, this treatment demonstrated a one-year overall survival of 74%, which is a very positive statistic. In terms of targeted therapy, the drug LXS196 was recently tested on patients with uveal melanoma, and a number of patients saw a durable response beyond ten months.

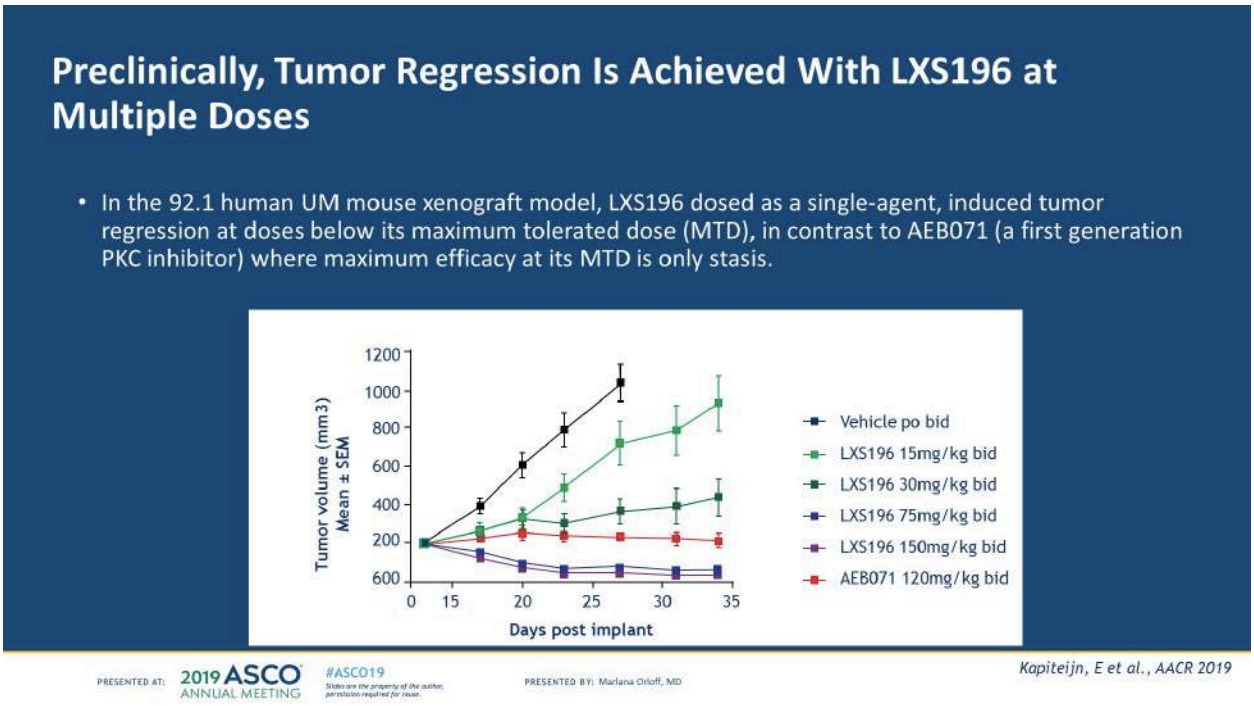


Figure 9: Orloff, "Preclinically, Tumor Regression Is Achieved With LXS196 at Multiple Doses"

Orloff then shifted to talk about musocal melanoma, which sometimes sees shorter reported survivals than metastatic uveal melanoma. Due to varied anatomic locations and presentation types, there can be difficulty with staging mucosal melanoma, and due to occult disease sites uveal melanoma is often diagnosed after metastasis. There are currently no FDA-approved treatments for mucosal melanoma, and the NCCN guidelines for sinonasal mucosal that is in the head or neck actually refers to cutaneous melanoma, and not the mucosal subtypes. In terms of trials for mucosal melanoma, adjuvant chemotherapy has shown some promise for recurrence-free survival, and checkpoint inhibitor treatment, along with KIT and BRAF-targeted therapy, are options. Orloff concluded by noting there were several uveal melanoma-related abstracts at ASCO this year, so she is optimistic about the field moving forward.

Abstract Discussions

Advances in Immune Checkpoint Inhibition
David B. Page, MD, Earle A. Chiles Research Institute at the Robert W. Franz Cancer Center
Discussing Abstract(s):
#2512: "Safety and tolerability of increasing doses of CB-839, a first-in-class, orally administered small molecule inhibitor of glutaminase, in solid tumors"
#2513: "CX-072, a PD-L1 Probody therapeutic, as monotherapy in patients with advanced solid tumors: Preliminary results of PROCLAIM-CX-072"
#2514: "A phase I study of ALX148, a CD47 blocker, in combination with established anticancer antibodies in patients with advanced malignancy"

In his talk, Page discussed abstracts #2512, #2513, and #2514. Abstract #2512 tested ipilimumab versus placebo after complete resection of stage III melanoma, with a 6.9 year follow-up. The results suggested that ipilimumab demonstrated a sustained improvement in metastasis-free survival and overall survival in patients with high-risk stage III melanoma. Abstract #2513 was a trial of CX-072, a PD-L1 probody therapeutic monotherapy in patients with advanced solid tumours, which was seen to demonstrate anticancer activity in this population of patients. Abstract #2514 was a phase I study of ALX148 (a CD47 blocker) + anticancer antibodies in advanced malignancy. The results suggest that ALX148 demonstrates excellent tolerability and favourable characteristics, and that responses were observed in patients with prior CPI and HER2-targeted therapies.

Given these studies, Page suggested that there are three objectives to discuss in this context: reviewing the progress in melanoma and immune checkpoint inhibition, and two different approaches to improve upon success in the next ten years. While melanoma survival curves are at their highest, the next step is to look for recurrence-free curves. The first abstract, #2512, addressed this question. It also questions how to resolve the high toxicity of the ipilimumab + nivolumab combination, which is also considered by abstracts #2513 and #2514. There is the additional question of how to diversify beyond T-cells, which is questioned in abstract #2514. Page concludes by claiming that these abstracts in conversation demonstrate how far we've come, with a productive past and an optimistic future.

The Evolving Role of Biomarkers in Immune Checkpoint Inhibition
Kurt A. Schalper, MD, PhD, Yale School of Medicine
Discussing Abstract(s):
#2515: "Distinct immunogenomic properties of melanomas with stable disease as best response to immune checkpoint blockade (ICB)"
#2516: "Analysis of early mortality in randomized clinical trials evaluating anti-PD-1/PD-L1 antibodies: A systematic analysis by the United States Food and Drug Administration (FDA)"
#2517: "Prognostic and predictive value of an immune-related adverse event among stage III melanoma patients included in the EORTC 1325/KEYNOTE-054 pembrolizumab versus placebo trial"

Schalper's talk centred around abstracts #2515, #2516, and #2517. Abstract #2515 analyzed the immunogenomic properties for melanoma patients had the best response to immune checkpoint treatments, and found that pre-treatment melanomas from patients with stable disease contain more anti-genetic mutations and demonstrate an increase in immune signalling, which may suggest a set of patients with pre-existing dysfunctional immune response. Abstract #2516, a study undertaken by the FDA, ran an analysis of early mortality in randomized clinical trials that evaluated anti-PD-1/PD-L1 antibodies; their results require further analysis. Abstract #2517 studied the prognostic value of an immune-related adverse event among stage III melanoma patients included in the EORTC 1325/KEYNOTE-054 pembrolizumab versus placebo trial, and found that the occurrence of an adverse event was associated with a longer recurrence free survival in those treated with pembrolizumab, but not with a placebo.

Schalper themed his discussion of these abstracts around the interrogation of sensitivity markers and the resistance to immune checkpoint blockers in solid tumours. Abstract #2515, entitled "Distinct Immune Genomic Properties of Melanomas, with Stable Disease as Best Response to Immune Checkpoint Blockade," asks about the molecular context of tumours that are halfway between responders. The significance of these studies is that melanomas with stable disease have a distinct immune composition characterized by prominent T cell activation, but also prominent regulation and antigenic potential. A key biological observation here is the potential for a clinical biomarker to detect patients that are more likely to present stable disease. Abstract #2516 or "Analysis of Early Mortality in Randomized Clinical Trials Evaluating anti-PD-1, PD-L1 Antibodies" has a goal of identifying whether early mortality during immune-oncology agents is due to natural disease progression, or is mediated by some adverse effect of immune-oncology. The authors determined that in fact a specific clinical subgroup defined by negative PD-L1 or ECOG status and high LDH-only melanoma were associated with the discussed high mortality. Abstract #2517, or "Prognostic and Predictive Value of an Immune-related Adverse Event Among Stage III Melanoma Patients, Including an EoTC 1325 Keynote-054 Pembrolizumab versus Placebo Trial," aimed to demonstrate the relationship between the presence of immune-related adverse events and sensitivity to pembrolizumab. This study is significant because it demonstrates that a better outcome occurs in patients treated with pembrolizumab, however it is not necessarily applicable to patients at different stages, which highlights the need for context in clinical applications of this and other trials. This study also supports a possible biological link between anti-tumour response and toxicity.

Long-term Clinical Outcomes in Advanced Melanoma
Douglas Buckner Johnson, MD, Vanderbilt University Medical Center
Discussing Abstract(s):
#9512: "Update on Overall Survival in COLUMBUS: A randomized phase III trial of encorafenib (ENCO) plus binimetinib (BINI) versus vemurafenib (VEM) or ENCO in patients with BRAF V600–mutant melanoma"
#9513: "Responders to anti-PD1 therapy: Long-term outcomes and responses to retreatment in melanoma (mel)"
#9514: "Standard-dose pembrolizumab (pembro) plus alternate-dose ipilimumab (ipi) in advanced melanoma: Initial analysis of KEYNOTE-029 cohort 1C"

Johnson discussed abstracts #9512, #9513, and #9514. Abstract #9512 gave updates on the progression-free and overall survival results for COMBO 450, which continues to represent new benchmarks for BRAF/MEK inhibitor combinations for the treatment of mutated melanoma; abstract #9513 presented the largest dataset of melanoma patients treated with a second dose of anti-PD-1, which had low response rates; and abstract #9514, which presented the results of KEYNOTE-029 cohort 1C, which tested two different dosages of the pembrolizumab + ipilimumab combination and showed strong antitumour activity in initial analysis.

Considering these three abstracts, Johnson's talk discussed long-term outcomes for metastatic melanoma. From 2010-2012, there were more glimmers of hope for long-term melanoma survival with the appearance of BRAF inhibitors and immunotherapies. However, Johnson claims that the modern era of melanoma treatment is exemplified by the breadth and hope of the abstracts he discussed. These studies show that long-term survival is now fairly common, and occurs in 40-50% of patients. This increasing population of survivors brings up new questions about life after treatment, such as how long treatment responses last, and how chronic toxicities affect survivors.

Peripheral Blood and Tumour Microenvironment Considerations for Immunotherapy
Jason J. Luke, MD, FACP, University of Pittsburgh Medical Center
Discussing Abstract(s):
#9515: "Tumor microenvironment (TME), longitudinal biomarker changes, and clinical outcome in patients (pts) with advanced BRAF V600–mutant melanoma treated with first-line spartalizumab (S) + dabrafenib (D) + trametinib (T)"
#9516: "Impact of body composition on outcomes from anti-programmed death-1 (PD-1) treatment"
#9517: "Circulating PD-L1-exosomes to monitor tumor response in melanoma patients"

Luke's talk centred around abstracts #9515, #9516, #9517. Abstract #9515 was an analysis of the tumour microenvironment, longitudinal biomarker changes, and clinical outcome in patients with BRAF V600–mutant melanoma treated with first-line spartalizumab + dabrafenib + trametinib. The results suggested that this combination had an early impact on tumour cells and microenvironment, and might promote anti-tumour activity. Abstract #9516 studied the impact of body composition on outcomes from anti-programmed death-1 (PD-1) treatment, which found that a high skeletal muscle gauge is associated with improved survival in treated patients. Abstract #9517 tested the use of circulating PD-L1 exosomes to monitor tumour response in melanoma patients, and found that circulating exosomes may be a more promising biomarker to predict tumour response than PD-L1 expression in tumour tissue.

Luke linked these abstracts in his talk by discussing peripheral blood and tumour microenvironment as considerations for immunotherapy. For Luke, all three abstracts can be connected to the question of responder versus non-responder phenotypes. He notes that other important data includes host fitness, so age, sex, metabolism, and BMI, and environmental differences such as microbial flora. While tumour-based biomarkers are currently the strongest discriminators of outcome, they don't seem to be useful enough for clinical application. Luke imagines that the future will be focused on treatments that are multidimensional in nature, and that analyzing patient wellbeing on multiple levels is essential.

Phase 3 international trial of adjuvant whole brain radiotherapy (WBRT) or observation (Obs) following local treatment of 1-3 melanoma brain metastases (MBMs).
Gerald Fogarty, BSc, MD, MBBS, PhD, Melanoma Institute Australia, The University of Sydney, Mater Hospital, Genesis Care, Australia and New Zealand Melanoma Trials Group, University of Notre Dame, University of Technology
Discussing abstract: #9500

Fogarty's talk was based off of abstract #9500, which was a phase III trial of adjuvant adjuvant whole brain radiotherapy versus observation following local treatment of 1-3 melanoma brain metastases. 107 patients were put on the observation course, and 100 were given whole brain radiation. The results suggest that whole brain radiation therapy does not improve outcomes for melanoma brain metastases.

In his talk, Fogarty notes that in the case of a single brain metastases, surgery and stereostatic treatment can be highly effective. However, local treatment puts patients at risk of developing further brain metastases, so an effective therapy to target the brain while preventing intracranial progression is needed. Past whole brain radio therapy trials have demonstrated positive intracranial control, however there is no overall survival benefit and neurocognitive decline. However, this trial only had 5% of patients with metastatic melanoma, so Fogarty's team looked specifically at metastatic melanoma. Eligible patients for Fogarty's team's study had between 1-3 melanoma brain metastases, and the primary endpoint of the study was distant intracranial control at twelve months; secondary endpoints were intracranial failure rate, time to deterioration, quality of life, and neuro-cognitive function. Failure was defined as a new lesion more than 1 cm away from the initial site. Ten percent of the trial patients were on adjacent chemotherapy, 5% on targeted therapy, and 5% on checkpoint inhibitor therapy. In the observation arm, intracranial therapy appeared at a 62.6% rate, while it appeared at 50% for the patients undergoing whole brain radiation. The overall survival at 12 months was 54% for the observation group, and 58.4% for the whole brain radiation group. As there is no significant benefit to whole brain radiation therapy in terms of intracranial control, survival benefit, or improvement in performance status, but a high risk of neurological damage, the authors do not recommend whole brain radiation therapy for patients in this setting.

Efficacy and safety of the combination of nivolumab (NIVO) plus ipilimumab (IPI) in patients with symptomatic melanoma brain metastases (CheckMate 204).
Hussein Abdul-Hassan Tawbi, MD, PhD, The University of Texas MD Anderson Cancer Center
Discussing abstract: #9501

Tawbi's talk was based off of abstract #9501, which studied the results of the ipilimumab + nivolumab combination for melanoma brain metastases versus nivolumab monotherapy. The results suggest that patients with asymptomatic melanoma brain metastases show a high rate of durable intracranial responses, further supporting ipilimumab + nivolumab as a first-line treatment for this population.

Tawbi began his talk by noting that brain metastases are a major cause of mortality in melanoma, and that more than 50% of metastatic melanoma patients will have a brain metastases over the course of their disease. Currently, strategies for the treatment of brain metastases are limited to radiation or surgery, though immunotherapy has been demonstrated to have a response rate of 16-20% with clinical benefit, depending on the drug. Participants in Tawbi's study were allowed to have undergone prior radiation, as long as it was limited to less than three sites. Patients were treated for 24 months, or until progression or toxicity made this treatment untenable, with a primary endpoint of complete response, partial response, or stable disease over six months. The initial results reported clinically meaningful intracranial efficacy for 57% of trial participants, and at the 14-month point 29% of patients saw a complete intracranial response rate, 26% partial response, for a combined response rate of 58%. These conclusions suggest durable responses for patients with melanoma brain metastases, and Tawbi suggests that people consider incorporating the ipilimumab + nivlumab combination into their treatment plans.

A New Era for the Treatment of Brain Metastases in Melanoma
Harriet M. Kluger, MD, Yale School of Medicine and Smilow Cancer Center, Yale New Haven Hospital
Discussing Abstract(s):
#9500
#9501

Kluger's talk was an overview of abstracts #9500 and #9501, which were discussed in greater depth by Fogarty and Tawbi respectively. Abstract #9500 tested the efficacy of whole brain radiation therapy versus observation for melanoma brain metastases, which did not produce a notable difference in results in terms of intracranial control, survival benefit, or improvement in performance status. The second study, abstract #9501, tested the ipilimumab + nivolumab combination for melanoma brain metastases versus nivolumab monotherapy, and found that patients with asymptomatic melanoma brain metastases show a high rate of durable intracranial responses to the ipilimumab + nivolumab combination.

Considering these two studies together, Kluger suggests that it is worth thinking about how local therapy has evolved in melanoma brain metastases within contemporary systemic therapy, what the frontline systemic therapy for melanoma brain metastases should be, and whether brain metastases should be treated differently than extra cerebral metastases or should be treated like other organs. In terms of the first issue, Kluger believes that localized therapies should be more thoroughly tested for melanoma brain metastases, as they have been seen to be very effective, but not without risks. In terms of frontline systemic therapy, Kluger believes that as ipilimumab + nivolumab shows better response rates than nivolumab monotherapy, the combination should be the standard frontline choice.