ASCO Annual Meeting Report 2021

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Introduction

The 2021 American Society of Clinical Oncology Annual Meeting took place from June 4-8, 2021. Given the COVID-19 pandemic, the convention was conducted entirely online. 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, categorized by topic. All information offered in this report is the intellectual property of the presenter and their team, as cited by the report.

Every year, melanoma and uveal melanoma become more widely covered by clinical trials. While the continued innovation of treatment for these cancers is exciting, it means that we were unable to include every presentation and abstract related to melanoma, uveal melanoma, and non-melanoma skin cancers. Therefore, abstracts and presentations that provide updates on safety profiles of past studies and abstracts that do not produce promising clinical results have been excluded. We have also excluded abstracts which, at the time of the meeting, did not have confirmed data.

The informational resources cited in this report are a combination of the transcripts and slides from the ASCO meeting library. All images are courtesy of the author of the respective talk. Any queries may be directed to natalie@saveyourskin.ca.

If you are interested in more information from the ASCO 2021 annual meeting, Save Your Skin is pleased to offer a Post-ASCO 2021 Update with Dr Omid Hamid video concentrated on melanoma, non-melanoma skin cancers, and ocular melanoma. Oncology Education is also offering a ASCO Highlights in Advanced Cutaneous Squamous Cell Carcinoma video with Drs Shaqil Kassam and Michael Migden. This video requires a free login to view.

Presented Melanoma Abstracts

Crossover and rechallenge with pembrolizumab in recurrent patients from the EORTC 1325-MG/Keynote-054 phase 3 trial, pembrolizumab versus placebo after complete resection of high-risk stage III melanoma

Alexander Eggermont et al.

Abstract#: 9500

Clinical trial number: NCT02362594

In this talk, Alexander Eggermont (FASCO, PhD, MD, Princess Máxima Center) presented the EORTC 1325-MG/Keynote-054 phase III trial, which tested pembrolizumab (pembro) versus placebo in patients who have had a complete resection of high-risk stage III melanoma. The EORTC 1325-MG/Keynote-054 is a double-blind study that evaluated pembrolizumab against placebo in stage III cutaneous melanoma patients who have had complete resection of their lymph nodes. Randomized patients received 200mg of either pembro or placebo intravenously every three weeks for a total of eighteen doses. Patients were eligible to progress to part two of the study if they had recurrence without brain metastasis and ECOG PS 0-2. Patients in part two of the study received 200 mg of pembro every three weeks for a maximum of two years.

The pembro group found improved relapse-free survival and distant metastasis-free survival rates. The rate of immune-related adverse events from grade 1-5 was 37%, with grades 3-5 representing 7% of this population. At the cut-off point (October 16, 2020), 58%

(297) completed the one-year pembro adjuvant treatment, with 20 entering the rechallenge section of the trial and 47 having a recurrence. From the placebo group, 59% (298) patients had a recurrence and of these 155 patients participated in phase II. Of the 175 patients who started pembro in phase II, 160 patients discontinued due to progression of disease (88), completion of therapy (24), investigator decision (21), toxicity (20), or other reasons (7). 15 patients were still receiving treatment at the time of Eggermont's presentation.

Ultimately, this study of pembro versus placebo in patients who have had complete resections of high-risk stage III melanoma demonstrated that after crossover to phase II, patients saw a 39% objective response rate and an overall 3-year progression-free survival rate of 32% (with lower efficacy after rechallenge).

	Crossover (N=155)	Rechallenge (N=20)
Stage at baseline of Part 2, n		
III-resected	50	7
III/IV various	105	13
IV unresected	83	9
III-C unresected	10	
IV resected	12	4
PFS events in Part 2, n	103	12
Median PFS (95% CI), mts	8.5 (5.7-15.2)	4.1 (2.6-NE)
3-yr PFS rate (95% CI), %	32 (25-40)	NE

Eggermont et al., 2021

Final analysis of overall survival (OS) and relapse-free-survival (RFS) in the intergroup S1404 phase III randomized trial comparing either high-dose interferon (HDI) or ipilimumab to pembrolizumab in patients with high-risk resected melanoma

Kenneth F. Grossmann et al.

Abstract #: 9501

Clinical trial number: NCT02506153

In this session, Kenneth Grossman (MD, PhD, Huntsman Cancer Institute, University of Utah) presented abstract #9501. This study assessed whether adjuvant pembrolizumab (pembro) dosed over one year could improve regression-free survival and overall survival relative to either a high dose of ipilimumab (ipi10) or a high dose IFN (interferon), which at the time of the study were the two FDA-approved options for adjuvant treatment of high risk resected melanoma.

In order to be eligible for this study, patients had to be at least 18 years of age with resected melanoma stages IIA, B, C, or IV. At the time of entry into the trial, patients had to have adequate surgery or complete staging to confirm that they are clear of melanoma (including complete node dissection). Patients with central nervous system metastases were excluded from this trial, as were those who had received prior therapy with a PD-1 blockade, interferon, or ipi.

In this trial, two arms were assigned based on intended control arm, PD-L1 status, and stratification by stage. Patients were randomized 1:1 to either the control arm or the experimental arm. In the control arm, patients received either 20 MU of interferon alfa-2b through intravenous for weeks 1-4 followed by 10 MU from weeks five onwards or 10mg of ipi10 q3w

intravenously for four doses, followed by q12w for up to three years. Those on the experimental arm received 200mg of pembro through intravenous q3w for 52 weeks. The primary comparisons of this study were 1) regression-free survival across all patients, 2) overall survival across all patients, and 3) overall survival in patients with PD-L1+ baseline biopsies.

The final analysis was performed at the 3.5-year point from the final patient randomization. The pembro group demonstrated a statistically significant improvement in regression-free survival relative to the control group, while there was no statistically significant improvement in overall survival in neither the randomized patient population nor the patients with PD-L1 positive baseline biopsies. The three treatments saw the following grade 3/4/5 adverse events: high dose IFN 69/9/0%; ipi10 43/5/0.5%; and pembro 17/2/0.3%.

In conclusion, pembro improves regression-free survival compared to high dose IFN or ipi10 in the adjuvant treatment of patients with high-risk resected melanoma, though there was no improvement to overall survival. Further, pembro is a more tolerable treatment regimen relative to high dose IFN or ipi10.

Neoadjuvant and adjuvant nivolumab (nivo) with anti-LAG3 antibody relatlimab (rela) for patients (pts) with resectable clinical stage III melanoma.

Rodabe Navroze Amaria et al.

Abstract #: 9502

Clinical trial number: NCT02519322

Rodabe Navroze Amaria (MD, University of Texas MD Anderson Cancer Centre) presented abstract #9502, which tested neoadjuvant therapy with the combination of adjuvant nivolumab (nivo) + relatlimab (rela). The goal was to safely achieve high rates of pathologic complete response, event-free survival, radiographic response, and overall survival while providing insights into patient response and resistance to this combination of treatments.

This single-arm study was open to patients with clinical stage III or oligometastatic stave IV melanoma with RECIST 1.1 surgically-resectable disease. At two separate sites, patients were 480mg of nivo and 160mg of rela on weeks 1 and 5, both given intravenously. Radiographic response was tested after completion of neoadjuvant therapy and surgery (if applicable) took place at week nine. After surgery, patients received up to ten additional doses of rela and nivo and follow-up scans were conducted every three months. Tissue and blood samples were collected at day 15, day 28, and at surgery.

30 patients (median age 60, 19M/11F) were enrolled in the trial. These patients were at clinical stages IIIB (18 patients), IIIC (8), IIID (2), and IV (2). 29 patients underwent

surgery at week nine, while one patient developed distant metastasis while on the trial. The results of this trial saw a major pathologic response rate of 66%, with a further 7% of patients achieving a partial response. 27% of patients had a pathological non-response to the treatment. The RECIST overall response rate was 57%. The one-year event-free survival rate was 90%, regression-free survival was 93%, and overall survival was 95%. The patients who saw major pathologic response (66%) also saw a one-year regression-free survival rate of 100%, while patients who did not achieve major pathologic response achieved an 80% rate of regression-free survival. While there were no grade 3-4 adverse events during neoadjuvant therapy, 26% of patients had a grade 3-4 adverse event begin during the adjuvant treatment.

Overall, this regime of neoadjuvant and adjuvant treatment with nivolumab + relatlimab achieved high major pathologic response and pathological complete response with a favourable toxicity profile.

The Evolving Role of Systemic Therapy in Stage III Melanoma

Alexander M. Menzies

In this talk, Alexander M. Menzies (MBBS, FRACP, PhD, Melanoma Institute Australia) discussed the changing landscape of systemic therapy for stage III melanoma based on the abstracts presented by Drs Eggermont (NCT02362594), Grossmann (NCT02506153), and

Amaria (NCT02519322).[1] Menzies began by expressing his optimism for the role of adjuvant therapy in treating stage III melanoma, preventing recurrences, and increasing overall survival. Menzies pointed to an older trial with ipilimumab versus placebo alongside a more modern trial of nivolumab versus ipilimumab, which demonstrated that PD-1 immunotherapy has a survival benefit, though it is still not clear whether treatment should be given in the adjuvant setting or upon recurrence. Menzies suggests that a current barrier to answering this question is that, in the crossover setting, patients who are unlikely to recur, those that will recur despite treatment, and the few that will derive benefit are all treated the same way. To determine the most efficacious way to use these drugs, more data is needed on the results of adjuvant PD-1 and how the built-in crossover design impacts overall survival.

Menzies then cited the S1404 study, presented earlier by Grossmann, which randomized stage III and stage IV melanoma patients to either pembrolizumab (pembro) or standard care; 70% of the patients received ipilimumab and 30% interferon. While this study had overall survival as its endpoint, Menzies noted that the 3.5-year results cutoff is quite early to ascertain overall survival and there were also only 199 survival events. The results of this trial demonstrated that recurrence after treatment has the potential to impact overall survival, yet this knowledge is limited by the large number of patients who did not have post-recurrence treatment.

Menzies went on to discuss Eggermont's EORTC trial, which was a pembro versus placebo adjuvant trial. This trial had a built-in crossover for patients who recurred while on the placebo, meaning that they are guaranteed access to the pembro if necessary, on the assumption

[1] More details about these abstracts can be found on pages 5, 7, and 9 of this report, respectively.

that patients who recurred on the placebo would be healthy enough to undergo the pembro. In actuality, only around half of the 300 events of recurrence crossed over to the pembro. 65% of the patients who crossed over had a locoregional recurrence and 52% with distant recurrence. The fact that 48% of those with recurrences did not cross over to the pembro is a gap in data, as is the lack of knowledge of what kind of other treatments these patients may have had. In the crossover group, progression-free survival and recurrence rates were poor, with the first recurrence usually occurring in the first 12 months and only about 33% of patients were progression- or recurrence-free at the three-year cutoff. These results suggest that disease recurrence is being detected at an earlier stage, but patients are unfortunately doing more poorly in their recurrence treatment. This leads Menzies to wonder whether patients who recur at stage III are biologically different than stage IV patients who recur, and therefore should have different therapies. Overall, Menzies notes that this study tested whether treatment after recurrence can have the safe efficacy as the first round of treatment and Menzies concludes that there need to be more rechallenge options, or alternative treatment options, for patients who recur.

The knowledge gaps presented in these abstracts also demonstrate that further research needs to be done to weigh the toxicity and cost of adjuvant immunotherapy versus the benefit of recurrence prevention, especially given the lack of data surrounding overall survival and response and resistance. At this point, survival rates remain poor with adjuvant therapy especially in patients with macrometastases.

Menzies professes optimism for neoadjuvant therapy, a great option for other cancers that will soon be entering clinical trials for melanoma. Stage III patients will have six to eight weeks of drug therapy before surgery and these trials offer the opportunity to assess

pathological response and recurrence-free and overall survival.

Nivolumab (nivo) and relatlimab (rela) are good options given early data which shows that combination immunotherapy with PD-1 and CTLA-4 is superior to monotherapy for survival and pathological response (though toxicity is much higher).

Menzies then discussed Amaria's abstract, which tested the combination of nivo and rela. In this trial, 30 patients showed a high RECIST response rate, and overall there were high pathological complete response rates, major pathological response rates, and durable survival in the patients that responded to treatment. Menzies noted that by comparing PD1 monotherapy, the combination of PD1 + CTLA4, and the combination of PD1 + LAG 3, it becomes clear that the efficacy of the combination therapies are similar. While the toxicity rates also appear to be close, Menzies notes that the combinations offer risks for different types of toxicity, with the nivolumab + relatlimab combination (PD1 + LAG 3) creating toxicity-related side effects that are easier to manage. Therefore, Menzies views the nivolumab + relatlimab combination as the most promising, though more data is needed on the biological profiles of the trial participants to see if this skews percentages of toxicity, pathological response, recurrence-free survival, and overall survival.

In conclusion, Menzies believes that adjuvant therapy will continue to be developed as a promising care option in the coming years, though more research is needed to determine whether it is a first-line therapy or a later option. He believes that neoadjuvant therapy in particular is a solid option for clinical care and a robust model for future drug development.

Relatlimab (RELA) plus nivolumab (NIVO) versus NIVO in first-line advanced melanoma: Primary phase III results from RELATIVITY-047 (CA224-047)

Evan J. Lipson et al.

Abstract#: 9503

Clinical trial number: NCT03470922

Evan J. Lipson (MD, Sidney Kimmel Comprehensive Cancer Center) presented abstract #9503, a double-blind, randomized, phase II+III study that tested the combination of relalimab (rela) + nivolumab (nivo) as a novel checkpoint inhibitor and fixed-dose combination for the treatment of first-line advanced melanoma. The primary endpoint for this study was progression-free survival per RECIST v1.1. Secondary endpoints were objective response rates and overall survival.

This study accepted patients with untreated advanced melanoma, who were randomized 1:1 to receive either rela (160mg) + nivo (480mg) as a fixed-dose combination every four weeks, or nivo monotherapy (480mg) for four weeks, depending on LAG-3 expression, BRAF mutation status, programmed death ligand 1 expression, and AJCC (v8) stage. All treatments were administered intravenously. 714 patients were randomized to either the rela+nivo combination (355 patients) or the nivo monotherapy (359 patients), with patient characteristics being well balanced between the treatment groups. The median follow-up was 13.2 months. The patients in the rela + nivo group saw a longer median progression-free survival than the nivo monotherapy group, with 10.1 months for the combination and 4.6 months

for the monotherapy group. Progression-free survival rates at 12 months were 47.7% for the rela+nivo group and 36% for the nivo monotherapy group. Yet, the frequency of grade 3-4 treatment-related adverse events was higher in the combination group (18.9%) than in the nivo monotherapy group (9.7%); these adverse effects led to treatment discontinuation in 14.6% in the combination group and 6.7% in the nivo monotherapy group. There were three treatment-related deaths in the combination group and 2 in the monotherapy group.

In conclusion, the combination of rela + nivo as a first-line treatment for advanced melanoma offers a statistically significant progression-free survival benefit compared to nivo monotherapy. The combination had a manageable safety profile and was well tolerated.

Lenvatinib (len) plus pembrolizumab (pembro) for patients (pts) with advanced melanoma and confirmed progression on a PD-1 or PD-L1 inhibitor: Updated findings of LEAP-004

Ana Maria Arance et al.

Abstract #: 9504

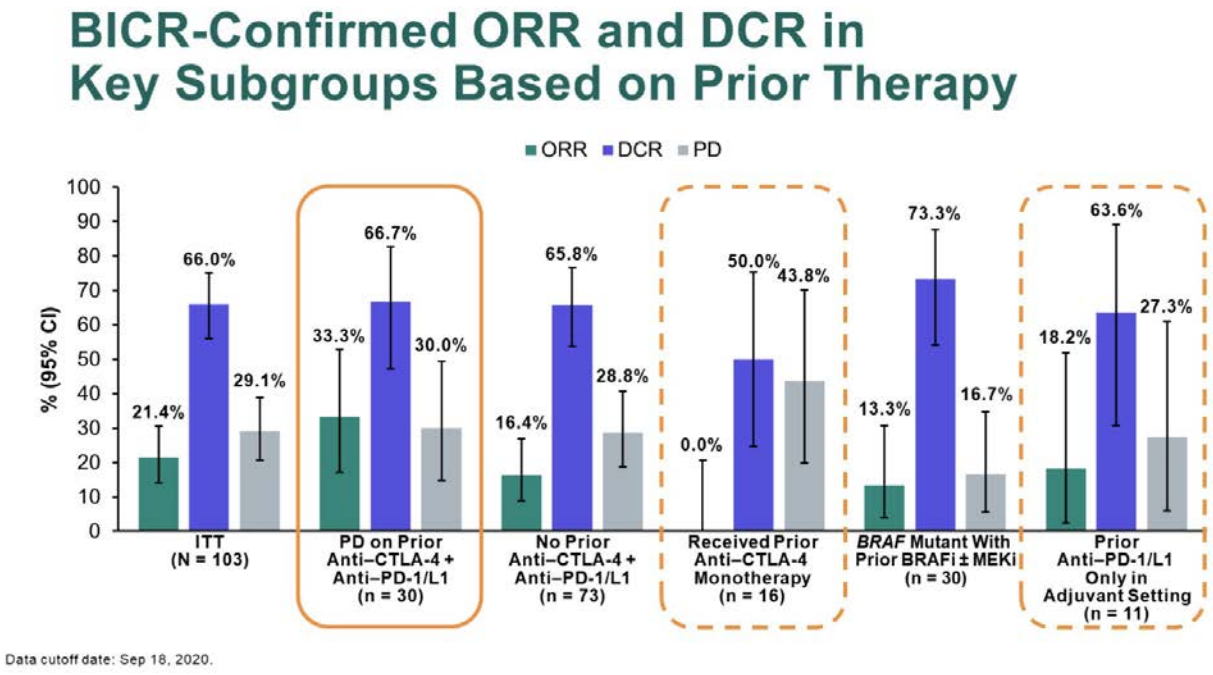
Clinical trial number: NCT03776136

In LEAP-004, Ana Maria Arance (MD, PhD, Hospital Clinic Barcelona) and her colleagues pursued the combination of lenvatinib (len) + pembrolizumab (pembro) for unresectable stage III-IV melanoma and confirmed PD on a PD-(L)1 inhibitor. This was a single-arm, open-label, phase 2 study that aimed to test the manageable safety and efficacy of the len +

pembro combination. The primary endpoint of this study was objective response rate per RECIST v1.1 with secondary endpoints of progression-free survival and duration of response per RECIST v1.1, overall survival and safety. The data being presented at ASCO is updated information from the LEAP-004 study with additional objective response rate subgroup analyses.

Patients received len (20mg) daily + pembro (200mg) every three weeks until unacceptable toxicity or PD, provided they were within 12 weeks of the last dose of a PD-(L)1 inhibitor. 103 patients were enrolled in the study; 68% of these patients had stage M1c/M1d disease, 55.3% had greater lactate dehydrogenase than the upper limits of normal, 94.2% received therapy for advanced disease, 58.3% received more than 2 prior treatments, and 32% received BRAF ± MEK. The objective response rate to the len + pembro combination was 21.4% and 31% in patients with PD on prior anti-PD-1 and anti-CTLA-4 with a 6.3-month median duration of response. This study collected data surrounding the objective response rate and disease control rates based on previous treatment types; these results are detailed in the slide included below.

Overall, LEAP-004 demonstrated that the combination of lenvatinib + pembrolizumab shows clinically meaningful and durable responses in patients with advanced melanoma who have had confirmed progression on a prior PD-(L)1 inhibitor. This includes patients with PD on anti-PD-1 + anti-CTLA-4 therapy, regardless of primary or secondary resistance to prior anti-PD-L(1) therapy. As this population currently has limited treatment options, this combination is a promising start to filling the gap.



Arance et al., 2021.

Slide taken from presentation

Lifileucel (LN-144), a cryopreserved autologous tumor infiltrating lymphocyte (TIL) therapy in patients with advanced melanoma: Evaluation of impact of prior anti-PD-1 therapy

James Larkin et al.

Abstract #: 9505

Clinical trial number: NCT02360579

James Larkin (MD, PhD Brown Cancer Center, University of Louisville) presented abstract #9505, which tested Lifileucel (LN-144) in patients with advanced melanoma who have had prior anti-PD-1 therapy. Lifileucel is an adoptive cell therapy that uses tumour-infiltrating lymphocytes which a study by Amod Sarnaik et al. in 2020 demonstrated efficacy in advanced melanoma patients who had progressed after an anti-PD-1 treatment. In this presentation, Larkin presented follow-up data at the 28-month mark for the second cohort (66 patients) while focusing on the impact of previous anti-PD-1 treatment for those treated with lifileucel.

The original study, C-144-01 (Sarnaik et al.), was an open-label, phase 2, multicentre study measuring the safety and efficacy of lifileucel in advanced melanoma who had previously received either anti-PD-1 treatment or BRAF, if applicable. After local tumour resection, patients were given therapy of nonmyeloablative lymphodepletion by using two days of cyclophosphamide, five days of fludarabine, and a singular infusion of lifileuecel. This regimen was followed by up to IL-2.

The results of Larkin et al.'s study demonstrated that in responders, the median prior lines of anti-PD-1 were 1.5 months and the median cumulative duration was 4.4 months. A meaningful increase in the duration of response to tumour-infiltrating lymphocytes was demonstrated, alongside primary anti-PD-1 resistance. No new safety risks were identified during Larkin et al.'s follow-up study. The follow-up study reached the further conclusions that the addition of lifileuecel to anti-PD-1 treatment resulted in a 36.4% overall response rate. The duration of response was associated with resistance to prior anti-PD-1 therapy and shorter prior duration of anti-PD-1 therapy. Overall, the study demonstrated that lifileuecel has the potential to offer a

better clinical outcome when used upon detection of progression after anti-PD-1 treatment, instead of the repeated use of anti-PD-1.

Novel Therapeutic Strategies as the Next Step for Advanced Melanoma

Jason Luke (MD, FACP, UPMC Hillman Cancer Center, Pittsburgh) discussed the previous three abstracts that were presented by Lipson (NCT03470922), Arance (NCT03776136), and Larkin (NCT02360579), or the combinations of lenvatinib + pembrolizumab, lenvatinib + lifileucel, and relatlimab + nivolimab.[2]

Luke prefaced his discussion of Lipson et al.'s research on the lenva + pembro combination by noting that combination therapy generally has an overall response rate of 24%, duration of response of 7.6 months, and progression-free survival of 6.5 months. Moving on to discuss Lipson's study, Luke notes that advanced melanoma patients did not previously have many options for first-line therapy and that in the treatment population 1/2 had elevated lactate dehydrogenase and 1/3 had four or more lines of prior therapy. While the response rate was 21.4%, Luke notes that the duration of response (8.3 months at second data collection) is less than one would hope for a checkpoint blockade treatment and that VEGFR2 TKI drugs are very hard on the patient, often resulting in grade 3-5 adverse events. Given the less-than-ideal duration of response and adverse events, Luke questions which particular group of patients would best benefit from this combination. While Lipson's study did not contain data regarding particular groups of patients, other studies of the use of lenvatinib for melanoma have demonstrated that progression-free survival can be associated

[2] For more information on these abstracts, see pages 14, 15, and 17 of this report, respectively

with low baseline serum angiopoietin-2 and prior research of VEGF blockade use across cancers has shown that early induction of hypertension is associated with improved outcomes. Currently, the combination of lenva + pembro is being used in the post-PD1/CTLA-4 setting and has results similar to other combination regimens. Therefore, it is important to consider that this regimen is relatively much harder on patients. Further data comparing this regimen to other combinations will help elucidate whether this combination is going to be the best approach for patients in this setting.

Luke moved on to discuss Arance et al.'s abstract, clinical trial number NCT03776136. This study collected data on the combination of lenvatinib + lifileucel. Luke noted that the use of tumour-infiltrating lymphocytes, such as this combination, are considered to have much potential as a treatment for melanoma. Luke restated that in this trial the patient's tumour is harvested, the tumour-infiltrating lymphocytes (TIL) is made in three to four weeks, patients receive lymphodepleting chemotherapy, and finally, patients are given their TIL infusion and up to six doses of interleukin-2 (IL-2). Luke notes that the use of IL-2 and lymphodepletion excludes patients with brain metastases with edema, elderly patients, concurrent cardiopulmonary disease, and poor treatment performance status. However, patients who were able to receive this treatment saw a good duration of response, particularly for patients who did well on previous anti-PD1. This study also demonstrated that having a total cell dose above ten did not impact response and the site of tumour resection did not seem to have an effect on the ability to generate the TIL. However, duration of response was affected by cumulative time on anti-PD1 and baseline lactate dehydrogenase. However, Luke notes that there is more research to be done in terms of ideal patient selection for this study. Overall, this treatment regime offers a

mechanically different option from other systemic therapies in the post-PD1/CTLA-4 setting with a similar response rate to the aforementioned combination of pembro + ipi for the post-PD1 setting. Trying to determine how research such as Arance et al.'s would fit into the landscape of cancer treatments, Luke suggested that a solid approach might be front line anti-PD1 plus LAG-3. If patients progressed on this line, a TIL harvest would be a good potential second option, along with PD1 and low dose CTLA-4. Currently, FDA approval of this regimen is pending, with a registration goal of 2022.

Finally, Luke moved on to Larkin et al.'s combination trial of relatlimab + nivolumab (NCT02360579). Rela is an anti-LAG-3 antibody, which can cause effector T cells to become dysfunctional and potentially unable to perform their effector function, which Luke notes is often associated with increased expression of PD-L1 molecules. The correlation between LAG-3 expression in immune-relevant molecules is an area that is continually being investigated.
In terms of Larkin et al.'s trial, Luke had a few preliminary notes, including that the fixed dose of both rela and nivo limits further investigation of whether an increased dose of relatlimab might have more benefit and the fact that, unfortunately, only progression-free survival data for this trial was available at the time of ASCO 2021. Yet, a statistically significant improvement was reported for progression-free survival in this combination at 10.1 months, relative to nivolumab as a monotherapy which had a progression-free survival of 4.6 months. Furthermore, rela + nivo is active across all PD-L1 levels, and LAG-3 expression does not alter progression-free survival. While this does not further knowledge regarding biomarker stratification, it does suggest that the combination is superior to nivo as a monotherapy across all settings. In terms of toxicity, the combination has only mildly increased levels relative to nivo as a monotherapy and is

significantly less toxic than the combination of nivo + ipi. Overall, the combination of rela + nivo has manageable toxicity and offers a clinically meaningful improvement in progression-free survival. However, given the current lack of overall response and overall survival data, Luke mentioned that he would not use this regimen to treat those with high LDH brain, liver, and bone metastases or those progressing on adjuvant anti-PD1.

Highlights of Developmental Therapeutics - Immunotherapy

In this talk, Jonathan Goldman (MD, University of California Los Angeles) presented some highlights of the Developmental Therapeutics Immunotherapy session at ASCO 2021. He divided this session into three sections: novel CAR T-cell therapies, targeting virally mediated cancers, and novel immunotherapies added to PD-1 antibodies.

Goldman reminds us that CAR T-cell therapies use an engineered T-cell receptor, which is transfected into a patient's own T-cells, which are then expanded outside of the patient's body and re-infused after the patient has undergone a short course of lymphodepleting chemotherapy. Anti-CD19 CAR-T therapies have created new options with promising response rates for the treatment of chronic lymphocytic leukemia, B-cell acute lymphocytic leukemia, and refractory diffuse large B-cell lymphoma. Accordingly, several bispecific CAR T-cell constructs that recognize two antigens, as one of the mechanisms of resistance against CAR T-cell therapies is tumour downregulation of the targeted antigen. One trial Goldman cites is a

program developed by Liang et al.,[3] which arranges the anti-CD19, anti-CD20, CD28, and 4-1BB components arranged sequentially and conducts the gene transfer and expansion process in six days.[4] This trial treated 34 subjects for refractory or relapsed B-cell non-Hodgkin lymphoma, with the largest group of patients (diffuse large B-cell lymphoma) having an objective response rate of 91.7% and a complete response rate of 83.3%. In a separate study, Liang et al. tested anti-CD20 CAR-T for patients who had progressed on an anti-CD19 CAR. 100% of these patients responded to the anti-CD20 CAR-T and 70% saw a complete response. However, four of these patients ultimately relapsed, which Goldman believes could suggest that multi-antigen targeting can delay tumour resistance.

Goldman then moved to therapies for virally medicated oncogenesis, oncogenesis being the process by which healthy cells become cancerous cells. Goldman notes that the incorporation of oncogenic genes into host cells and initiation of genomic instability, a part of the oncogenesis process, could make tumours vulnerable to immunotherapy. As an example, Goldman cited a report by Strauss et al. (clinical trial number: NCT04287868) which was a triple combination for HPV positive cancers. The combination of bintrafusp alfa (a PD-L1-blocking antibody fused with a TGF-beta trap) + PDS0101 + M9241 (an IL-2 fused with an antibody targeted to histones on free DNA fragments) was designed to target the tumour microenvironment with T-cells. Of the 79 patients in this trial, checkpoint inhibitor naïve patients had a response rate of 30%, while checkpoint inhibitor refractory patients had a response rate of 10%. There were 18 HVP 16-positive patients, 10 of these had an objective response.

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[3] The clinical trial numbers for this program are NCT04317885, NCT04655677, NCT04696432, NCT04693676.

[4] The clinical trial numbers for this program are NCT04317885, NCT04655677, NCT04696432, NCT04693676.

Lastly, Goldman moved onto immunotherapy combinations. Goldman notes that since there are so many immunotherapy trials in progress that it is important to remain critical, vigilant, and to demand confirmatory studies. One study Goldman cited was Tolcher et al.'s research with the MDM2 inhibitor APG-115, which Goldman explains inhibits p53 activity and has therefore been studied for use in tumours with MDM2 amplification and wild-type TP53 and as an agent for tumour immunobiology (clinical trial number: NCT03611868). 102 subjects were enrolled in Tolcher's et al.'s study, with 32 of these patients having checkpoint inhibitor refractory melanoma, with a combination of uveal and mucosal melanoma. While these melanoma types are usually unresponsive to immunotherapy, this regime saw a 24% response rate in the melanoma patients. Goldman also referenced a report by Boni et al. (clinical trial number: NCT02799095), who studied nemvaleukin, an engineered IL-2 pathway agent which is designed to activate CD8-positive effector T-cells.[5] Part B of this study included 18 patients with melanoma. Two patients, both with mucosal melanoma, achieved a partial response. However, there were constitutional toxicities, and grade 3 or greater treatment-related adverse effects caused by cytopenias.

Current Data on KIT Mutations in Melanoma

Scott Eric Woodman (MD, PhD, MD Anderson Cancer Center) presented on KIT mutations in melanoma, which has a type-3 receptor tyrosine kinase. When the KIT receptor binds to the stem cell, receptor dimerization occurs, causing auto-inhibition of the tyrosine kinase

domain. There are several steps in the activation of the KIT receptor tyrosine kinase, meaning that mutations occur at specific places in the KIT molecule.

However, unlike KIT mutations in other settings, melanoma KIT mutations often have amplifications in the KIT gene and copy number gains. KIT mutations are generally mutually exclusive from recurrent NRAS driver mutations and BRAF B600 mutations. Acral mucosal melanoma has the highest occurrence of KIT mutations, at approximately 15%, whereas melanoma related to chronic sun damage sees lower rates of KIT mutation.

The first results of treatment for KIT mutated melanoma with imatinib saw an overall response rate of 16-29%, with more durable clinical response being seen at higher rates (Carvajal et al., 2011). Later, Woodman et al. analyzed the response of patients with the KIT mutation to anti-CTLA4, which saw a nearly 50% disease control rate and 20% overall response rate. Woodman et al. have also tested anti-PD1 for KIT-mutant melanoma, which saw a 55% disease control rate and 35% overall response rate, demonstrating a response to checkpoint inhibitors. Currently, the first-line therapy for melanoma with KIT mutation is anti-PD1 monotherapy or the combination of nivolumab + ipilimumab.

Given the growth of immune checkpoint therapies, and the success of imatinib in KIT mutated melanoma, Woodman believes that more agents targeting this mutation are down the pipeline, such as ripretinib DDC 2618 and avapritinib, both kinase inhibitors. Trials are currently running for KIT mutated melanoma, which include binimetinib + imatinib and imatinib + ipilimumab.

NRAS and Other Emerging Targetable Mutations in Melanoma

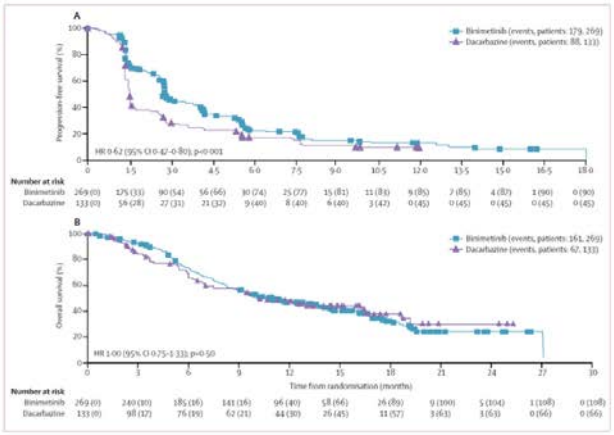
In this session, Matteo Carlino (MBBS, FRACP, PhD, Westmead Hospital and Melanoma Institute Australia) discussed targetable mutations in metastatic melanoma, which is of special interest since the emergence of checkpoint inhibitors that target PD1 and CTLA-4 and BRAF MEK inhibition, which have changed the treatment landscape for metastatic melanoma. However, BRAF wild-type patients have fewer treatment options, so Carlino focused on targeted therapy for this population. As an example of the size and difficulty of the BRAF wild-type population, Carlino cited the CheckMate 067 study, wherein the BRAF wild-type subgroup was 2/3 of the included patients. In five years, 50% of this group died, demonstrating that this patient population usually requires more treatment than a singular anti-PD1 agent as either a monotherapy or in combination with ipilimumab.

Other mutations can be potential targets for treatment, such as NRAS and NF1 mutations, CDKN2A and CDK4 mutations, GNAQ mutations, and non-basic BRAF mutations. These mutations were not covered in the initial clinical trials for BRAF inhibitors. Currently, data regarding the NRAS mutation is conflicting, with some reports suggesting that there is an increased possibility of response to checkpoint inhibitors and others seeing poorer survival. Carlino cites the NEMO study (Dumrer et al., 2017, below), a randomized phase III trial that compared binimetnib to dacarbazine (chemotherapy). There was an overall response rate of 15% to binimetnib, which was higher than dacarbazine, however, there was no notable difference in overall survival.

11

NRAS mutations- MEK inhibition (NEMO)

- Nemo: RCT comparing Binimetinib to DTIC
  - 21% prior immunotherapy, 5% prior anti-PD1
- Binimetinib ORR-15% (DTIC-9%)
- Suggestion of greater activity in those treated with prior immunotherapy



Presented By: Matteo Carlino

Dumrer et al., Lancet Onc 2017

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2021 ASCO ANNUAL MEETING

Dumrer et al. 2017, quoted by Carlino et al., 2021

Slide taken from presentation

In terms of non-V600 BRAF mutations, Carlino cites a multi-centre retrospective analysis that studied patients with this mutation and their response to MEK and/or BRAF inhibitors (Menzer et al., 2019). Out of the 103 patients included in the study, zero responses were seen to single-agent BRAF inhibitors. However, there was a 40% response rate towards single-agent MEK inhibition and similar results to combination BRAF and MEK inhibitors.

A larger question for Carlino is whether it is possible to leverage these rare, targetable mutations within a clinically relevant time frame. Despite the increasing number of studies being done with checkpoint inhibitors for patients with mutations, several mutations still show only

marginal activity from these treatments. Therefore, Carlino suggests that prospective trials are needed for individualized targeted therapy for patients that are refractory to checkpoint inhibitors.

Hot Off the Press in Melanoma Management: Celebrations and Cautions

In this session, Katy Tsai (MD, University of California San Francisco) went over the recent developments in treating patients with advanced melanoma and highlighted promising forthcoming data from ASCO 2021. Tsai suggests that, while the past fifteen years dramatically changed the landscape of melanoma treatments, more recent years have been spent refining these approaches.

For example, the success of the CheckMate-067 trial cemented the use of the combination ipilimumab (ipi) + nivolumab (nivo) as a first-line treatment for advanced melanoma. However, the high toxicity profile of this regimen leaves room for continued testing to improve safety and reduce dosage. Tsai pointed to a study from 2020 (Postow et al.) which demonstrated that patients can still derive clinical benefit from just two doses of the combination with a 48% best objective response rate at week 12. Final analysis of this study is still pending. Further, CheckMate-511 also tested lower dosages of ipi + nivo, which produced fewer adverse effects. That said, forthcoming data is required to shed light on whether this regime is still effective.

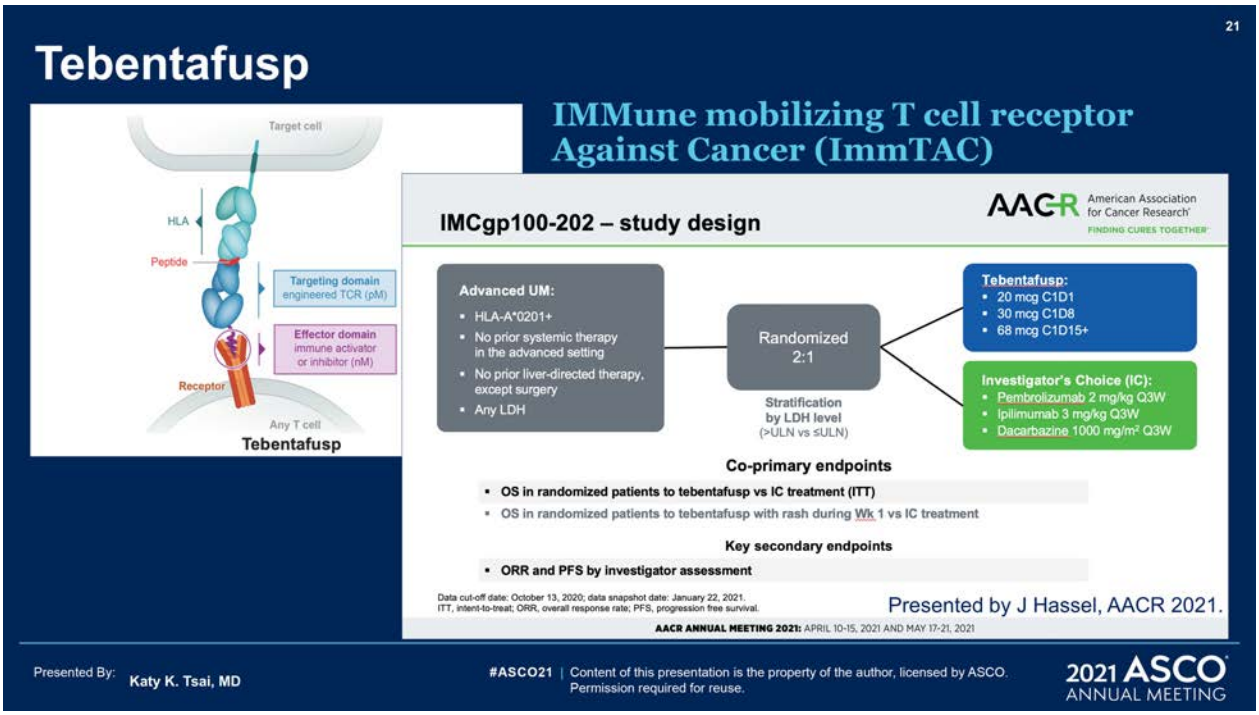
Tsai then moved into combinations of immunotherapy with targeted therapy, which aim to combine the high response rate of targeted therapy with the durability of immunotherapy. One

recent trial to this end was the phase III IMspire150 study (McArthur et al., 2020), which compared the combination of atezolizumab (combination therapy) + vemerafenib (BRAF inhibitor) + cobimetinib (MEK inhibitor) against placebo + vemurafenib + cobimetinib for advanced BRAF600 melanoma. The progression-free survival of the triple combination was 15.1 months while the placebo combination saw 10.6 months. Across both groups, objective response rates were similar, however, toxicity was slightly higher for the triple combination. Survival analysis has not been formally conducted, but preliminary results favour the triple combination. Further, the KEYNOTE-022 study (pembro + dabra + trame versus dabra + trame) saw the double combination meet 26.3 months of overall survival, but the median was not reached by the triple combination. These studies suggest that triple combinations are unlikely to become a routine treatment for advanced BRAF V600 melanoma.

Tsai suggests that these gaps could be filled in by other immunotherapy-centric regimes, such as LAG-3. In combination with anti-PD-1, anti-LAG-3 might boost response and overcome immune resistance. Another trial, CheckMate-915, analyzed the regression-free survival of ipi + nivo at a lower dosage rate in stage IIIb-d to IV melanoma. This combination did not improve regression-free survival over nivo as a monotherapy.

Tsai then moved on to an exciting development in the field of uveal melanoma, which does not currently have a standard therapy in the post-metastasis stage. Currently, the standard of care for uveal melanoma is ipi + nivo, which does not have an especially high efficacy rate. However, a recent phase III trial with tebentafusp (T-cell receptor) (Hassel et al., 2021; below). While progression-free survival and objective response from tebentafusp are not substantially

different from the investigator's choice alternative, there is a notable difference in overall survival, as shown below. Tsai suggests that this difference may illustrate an initial progression and later stabilization in patients, demonstrating a slowing of tumour growth. While this treatment requires HLA 0201, limiting the eligibility pool, Tsai is still optimistic about the possibility of a new therapy in a field with limited options.



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Hassel et al., 2021, quoted in Tsai 2021

Slide taken from presentation

The Evolving Management of Melanoma CNS Metastases

Here, Priscilla Kaliopi Brastianos (MD, Massachusetts General) discussed three posters presented at ASCO 2021 that were concerned with the management of central nervous system melanoma metastasis, an area of unmet clinical need despite 50% of advanced melanoma patients developing central nervous system metastases. Brastianos first went over a poster entitled "intrathecal and intravenous nivolumab for metastatic melanoma patients with leptomeni ngeal disease," wherein the three-month overall survival was 65% and 12-month overall survival was 35% (NCT03025256). There were no grade 4 nervous system adverse events. This research demonstrates, per Brastianos, that immune checkpoint blockade can have activity in leptomeningeal carcinoma ptosis and is well-tolerated.

The next poster was "Phase II Study of TRIplet combination Nivolumab (N) with Dabrafenib (D) and Trametinib (T) (TRIDeNT) in patients (pts) with PD-1 naïve or refractory BRAF-mutated metastatic melanoma (MM) with or without active brain metastases," which included PD1 refractory and naive patients with and without brain metastases (Burton et al., 2021).[6] There were 3 complete responses and a 92% response rate. Five of the eight patients with viable intracranial lesions also achieved a response. Progression-free survival was not dramatically different across patients with and without brain metastases. However, every patient on the study did experience a grade 3 or 4 treatment-related adverse effect, and 22% of patients ultimately discontinued all agents due to toxicity.

[6] More information about this abstract can be found on page 36 of this report.

Melanoma Abstracts

Atezolizumab in combination with bevacizumab in patients with unresectable locally advanced or metastatic mucosal melanoma: Interim analysis of an open-label phase II trial

Lu Si et al.

Abstract #: 9511

Clinical trial number: NCT04091217

This abstract reported the interim analysis results of ML41186, a multicentre, open-label, single-arm phase II study that aimed to determine the safety and efficacy of the combination atezolizumab + bevacizumab in advanced mucosal melanoma patients. The 35 enrolled patients had unresectable locally advanced or metastatic mucosal melanoma, were aged 18 to 75 years, had at least one lesion per RECIST 1.1, with adequate hematologic and organ function, and an EGOC PS 0 or 1.

Atezolizumab + bevacizumab were administered at a fixed dose, 1200mg of atezolizumab and 7.5mg/kg of bevacizumab in a 21-day cycle. Dosage ended upon loss of clinical benefit or unacceptable toxicity. The primary endpoint of this study was objective response rate, with secondary endpoints of duration of objective response, progression-free survival, safety, and disease control rate. In the stage I analysis, the best confirmed objective response rate was 36,4%, progression-free survival rate 5.32 months, and disease control rate 59.1%. The median confirmed duration of response was not reached. 80% of patients experienced one or more adverse events, with 14.3% experiencing at least one grade 3-4 adverse events.

Overall, the combination of atezolizumab + bevacizumab demonstrated promising clinical benefit, while being tolerable for patients with advanced mucosal melanoma. This study will be moving into stage II.

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 et al.

Abstract #: 9510

Clinical trial number: NCT01584648

This abstract describes Syeda et al.'s examination of the connection between serial changes in circulating tumour DNA (ctDNA) and survival after patients had undergone MEK and/or BRAF inhibitor therapy. This study measured BRAF V600E/k ctDNA at baseline and week four plasma samples from a population of patients who had been treated with dabrafenib as a monotherapy or the combination of dabrafenib + trametinib (phase III COMBI-d trial (clinical trial number: NCT01584648)) for metastatic or unresectable melanoma. Overall survival and progression-free survival were measured in all patients and categorized by baseline lactate dehydrogenase level.

Of the 345 patients enrolled, baseline ctDNA was found in 320 (92.7%) and was not associated with survival. After four weeks of therapy, nearly all patients with

detectable ctDNA saw a decrease. In 80/201 patients who transitioned from positive to negative ctDNA over these four weeks, progression-free survival and overall survival were prolonged relative to the 121 patients (60%) whose ctDNA remained positive.

This project demonstrated that for patients with high lactate dehydrogenase levels, ctDNA monitoring on-treatment may help identify patients likely to benefit from either dabrafenib or dabrafenib + trametinib.

	All Pts n = 224	High LDH n = 81	Low LDH n = 143
Pos/neg at wk 4, n	128/96	64/17	64/79
Median PFS, pos/neg, mo	7.4/13.0	5.5/10.3	9.3/13.9
HR (95% CI)	1.68 (1.24-2.27)	1.99 (1.08-3.64)	1.29 (0.88-1.90)
	P = .0009	*P* = .027	*P* = .19
Median OS, pos/neg, mo	15.3/27.9	10.8/21.1	36.3/28.6
HR (95% CI)	1.64 (1.20-2.25)	2.38 (1.24-4.54)	1.05 (0.70-1.58)
	P = .0021	*P* = .0089	*P* = .8

Syeda et al., 2021

Phase II study of ceralasertib (AZD6738), in combination with durvalumab in patients with metastatic melanoma who have failed prior anti-PD-1 therapy

Minsuk Kwon et al.

Abstract #: 9514

Clinical trial number: NCT03780608

Kwon et al. researched the safety and efficacy of ceralasertib, an oral inhibitor of the protein kinase Ataxia Telangiectasia and Rad3 related, in combination with durvalumab. This

phase II trial was designed for patients who had failed on anti-PD-1 therapy.

The primary endpoint, overall response rate, was 30%. The disease control rate was 63.3%, median overall survival was 14.2 months, and median progression-free survival was 7.1 months. These results demonstrate that ceralasertib + durvalumab offers anti-tumour activity, particularly in patients who have failed anti-PD-1 treatment.

Phase II Study of TRIplet combination Nivolumab (N) with Dabrafenib (D) and Trametinib (T) (TRIDeNT) in patients (pts) with PD-1 naïve or refractory BRAF-mutated metastatic melanoma (MM) with or without active brain metastases

Elizabeth Burton et al.

Abstract #: 9520

Clinical trial number: NCT02910700

This study tested nivolumab + dabrafenib + trametinib as a treatment for PD1 naïve or refractory patients with BRAF mutations or with brain metastases. It was a phase II single-arm study. The objective response rate for the evaluable PD1 refractory patients was 88%, with the remaining evaluable patients having a response rate of 92%. 57% of patients with brain metastases achieved an intracranial response. The median progression-free survival for all patients was 8.5 months. However, treatment-related grade 3-4 adverse events were experienced by 78% of patients.

These results demonstrate that the combination of nivolumab + dabrafenib + trametinib shows promising results for patients with brain metastases and immunotherapy refractory disease,

with no significant difference in outcome between these populations. The toxicity is consistent with other triple combinations.

Pembrolizumab and all-trans retinoic acid combination treatment of advanced melanoma

Martin McCarter et al.

Abstract #: 9536

Clinical Trial Number: NCT03200847

This study tested whether inducing the differentiation of myeloid-derived suppressor cells (MDSCs) using all-trans retinoic acid (ATRA) can reduce the frequency of MDSCs, which are suppressors of antitumour activity. McCarter et al. assessed the efficacy and safety of combining ATRA + pembrolizumab for advanced melanoma patients. The phase I/II single-arm study enrolled 24 stage IV melanoma patients who have not been previously treated with anti-PD-1 therapy. Patients received 200mg Q3W pembrolizumab + 150mg/m2 ATRA orally for the three days surrounding the four infusions of pembrolizumab. The primary endpoints of this study were reduction of circulating MDSCs and safety, with secondary endpoints of disease control rate, overall response rate, and progression-free survival.

This combination was well-tolerated, with most treatment-related adverse events being limited to grades 1 and 2. The disease control rate was 83%, overall response rate was 60%, and the six-month progression-free survival rate was 62%. Two patients were diagnosed with uveal

melanoma during the study; the aforementioned statistics without these patients included were 86%, 72%, and 68% respectively. Therefore, the combination of pembrolizumab + ATRA is well tolerated and the efficacy results demonstrate that the inclusion of ATRA to reduce MDSCs may enhance the success of pembrolizumab.

Adjuvant nivolumab in high-risk stage IIb/IIc melanoma patients: Results from investigator initiated clinical trial

Melissa Wilson et al.

Abstract #: 9583

Clinical trial number: NCT03405155

This study assessed whether adjuvant nivolumab (PD1 inhibitor) could improve recurrence-free survival rates of patients with stage IIB and IIC melanoma, who have been shown to have five-year recurrence rates of up to 46%. This multi-centre, single-arm phase II trial evaluated recurrence-free survival of patients at 24 months after they had received nivolumab at 480mg intravenously every four weeks in 12 cycles. Recurrence-free survival (RFS) was the primary endpoint of this study and overall survival was the secondary endpoint.

Of the 22 patients who remain in follow-up for this study, two patients demonstrated melanoma recurrence. Therefore, the RFS percentage at two years was 87.8%, whereas the historical RFS at two years for this population is 70%. No nivolumab-related adverse events were recorded, with 98% of adverse events being grades 1-2. Therefore, this regimen is not only

tolerable but also shows a climb toward improved RFS in patients with stage IIB and IIC melanoma. However, this study has not yet hit the two-year follow-up benchmark for RFS, so more time is needed to reveal what effects nivolumab can have on disease relapse, overall survival, and metastasis-free survival.

A phase 1b clinical trial of anti-PD-1 ab (Toripalimab) plus intralesional injection of OrienX010 in stage IV melanoma with liver metastases

Jun Guo et al.

Abstract #: 9559

Clinical trial number: NCT04206358

This trial tested whether intratumoural oncolytic virus injection combined with systemic anti-PD-1 therapy might increase CD8+ T cell infiltration and therefore improve the efficacy of anti-PD-1 in melanoma patients with liver metastases. The primary endpoint of this study was toxicity, with secondary endpoints including overall response rate, disease control rate, and progression-free survival. Patients received intravenous toripalimab Q2W + intratumoral injection of OrienX010 Q2W. Liver biopsies were performed at baseline and first tumour evaluation.

All of the adverse events seen by patients in this study were grades 1-2, demonstrating that this combination is tolerable. The overall response rate was 13.3%, disease control rate 46.7%, and progression-free survival has reached 72 weeks for one patient currently, though overall the median progression-free survival was not reached. Therefore, alongside good

tolerance, the combination of toripalimab + OrienX010 has demonstrated solid pathological responses for melanoma patients with liver metastases.

Safety and efficacy of HX008: A humanized immunoglobulin G4 monoclonal antibody in patients with locally advanced or metastatic melanoma—A single-arm, multicenter, phase II study

Bin Lian et al.

Abstract #: 9554

Clinical trial number: NCT04749485

This phase II clinical trial tested HX008, a recombinant humanized anti-PD-1 monoclonal antibody, which is known to block the binding of PD-1 with the ligands PD-L1 and PD-L2. This study included patients who have previously failed conventional treatment for metastatic or locally advanced melanoma and had measurable lesions according to RECIST criteria. Patients received HX008 3mg/kg every three weeks until disease progression, intolerable toxicity, or treatment discontinuations for other reasons. The primary endpoint of this study was overall response rate, with secondary endpoints of overall survival, progression-free survival, disease control rate, and toxicity.

The overall response rate demonstrated in this cohort was 15.09% for PD-L1 positive patients and 12% for PD-L1 negative patients. In terms of subtypes, the overall response rate for acral primary was 14.52%; 36.36% for cutaneous melanoma; 8.7% for mucosal primary; and 25% for unknown primary. The disease control rate was 44.54% and the progression-free survival

rate at one year was 25.8%. The one-year duration of response rate was 80.64%. Grades 3-4 treatment-related adverse events occurred in 31.9% of trial patients. Therefore, HX008 is safe and shows efficacy in metastatic or locally advanced melanoma patients as a second-line treatment or above.

Results from the phase Ib of the SENSITIZE trial combining domatinostat with pembrolizumab in advanced melanoma patients refractory to prior checkpoint inhibitor therapy

Jessica C. Hassel et al.

Abstract #: 9545

Clinical trial number: NCT03278665

This trial assessed whether histone deacetylase (HDAC) inhibition can negate tumour escape mechanisms and increase susceptibility to immunotherapy treatments. Patients with advanced metastatic or unresectable melanoma who had not previously responded to prior checkpoint inhibitor therapy were given domatinostat at five different dosage levels in combination with pembrolizumab (2mg/kg) q3w. Tolerability and safety were evaluated and tumour assessments were performed every 12 weeks.

The results from this study that were presented at ASCO 2021 were preliminary results from the phase Ib section of the ongoing trial. At this time, 20% of patients had experienced adverse events greater than grade 3, however, these were consistent with historical reactions to domatinostat and pembrolizumab. While four patients discontinued treatment due to grade

three adverse events, clinical activity was observed with one complete response, two partial responses, and nine stable diseases, which together ultimately resulted in a disease control rate of 30%. Three out of seven participants achieved disease control at dosage level three (200mg BID D1-14 of domatinostat q3w), which the study authors suggest indicates a trend of dose-dependent clinical activity. Overall, therefore, domatinostat + pembrolizumab was safe and reasonably well-tolerated, and therefore the observed clinical activity in this study warrants further investigation.

Triplet therapy with pembrolizumab (PEM), encorafenib (ENC) and binimetinib (BIN) in advanced, BRAF V600 mutant melanoma: Final results from the dose-finding phase I part of the IMMU-Target trial

Lisa Zimmer et al.

Abstract #: 9532

Clinical trial number: NCT02902042

This phase I/II (safety/randomized) trial evaluated the combination of checkpoint inhibitor therapy and MAPK pathway inhibitors, which both affect the tumour immune microenvironment in a way that has produced positive results in patients with BRAF-mutated melanoma. This study, IMMU-Target, tested the triple combination of pembrolizumab + encorafenib + binimetinib at two dosage levels for patients with advanced BRAF V600 mutated melanoma. The primary endpoints of phase I of this study were tolerability and safety.

50% of patients enrolled in this study experienced a grade three or higher treatment-related adverse event. The overall response rate to this regimen was 64% and progression-free survival at 12 months was 37.5% for DL 0 patients and 60% for patients at DL-1. Therefore, this

triple combination was demonstrated to be safe at both dosage levels while leading to clinically significant disease control. As the efficacy of pembrolizumab + encorafenib + binimetinib is currently being evaluated in the STARBOARD trial (NCT04567991), the second phase of this study was not initiated.

Safety and efficacy of lifileucel (LN-144), an autologous, tumor infiltrating lymphocyte cell therapy in combination with pembrolizumab for immune checkpoint inhibitor naïve patients with advanced melanoma

Sajeve S. Thomas et al.

Abstract #: 9537

Clinical trial number: NCT03645928

This trial tested the combination of the tumour-infiltrating lymphoctye therapy (TIL) LN-144 + pembrolizumab in immune checkpoint inhibitor-naïve patients with advanced melanoma. The LN-144 is created at good manufacturing practices facilities over 22 days, after which a nonmyeloablative lymphodepletion (NMA-LD) with cyclophosphamide and fludarabine is administered to participants before an LN-144 infusion, with pembrolizumab being administered between tumour harvest and the nonmyeloablative lymphodepletion.

The objective response rate to this regimen was 86% and the longest duration of response at the time of reporting was 16.8 months. Treatment-related adverse events are consistent with the known profiles of NMA-LD, IL-2, and pembrolizumab. These results demonstrate that the

combination of lifileucel + pembrolizumab is safe and effective for patients with immune checkpoint inhibitor-naïve advanced melanoma.

The use of cryoablation to overcome resistance to PD-1 blockade in unresectable melanoma

Meghan Mooradian et al.

Abstract #: 9538

Clinical trial number: NCT032900677

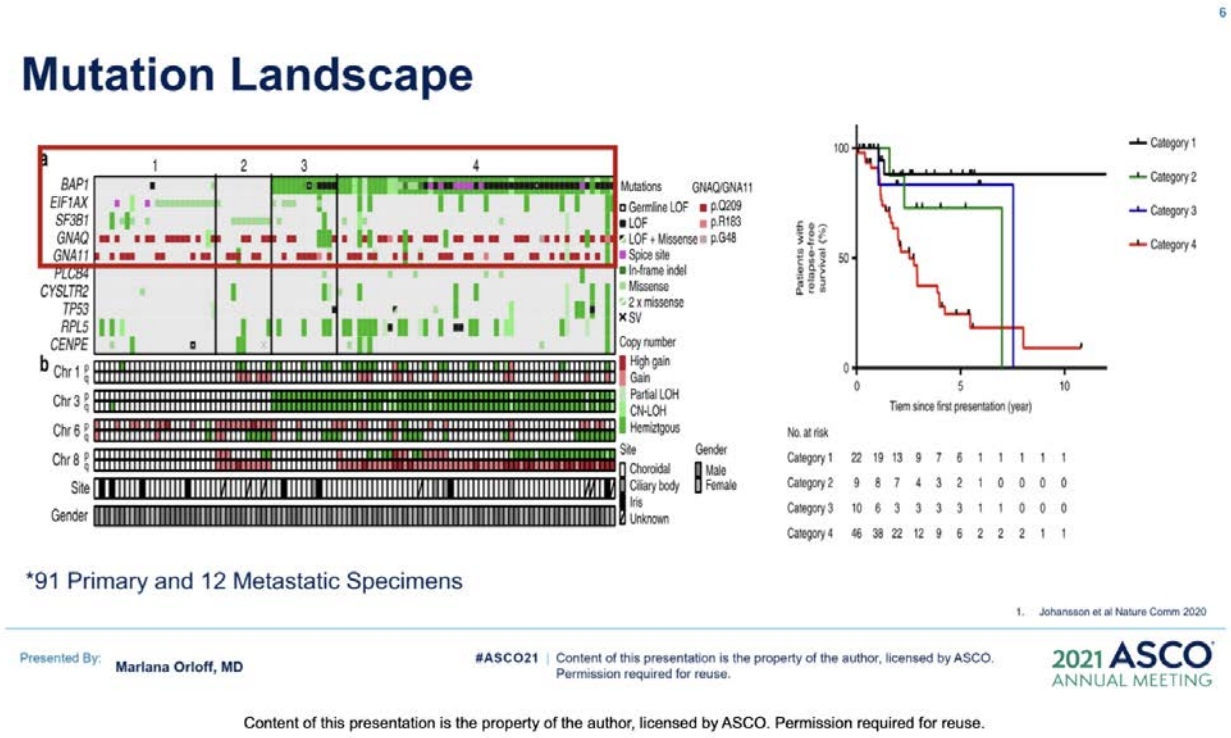
This study tested whether percutaneous image-guided cryoblation (cryo) is able to augment anti-tumour responses in melanoma patients who are progressing on immune checkpoint inhibitors. These patients received cyro for an enlarging lesion and immune checkpoint inhibitor continuation for a minimum of two additional cycles. The primary endpoints of this study were feasibility and safety, while secondary endpoints were disease control rate (partial response, complete response, and stable disease) and overall response rate.

All patients enrolled in this study had previously received PD-1/PD-L1 therapy and 67% also experienced primary resistance to immune checkpoint inhibitors. There were no grade 4-5 adverse events in the cohort. Data from evaluable patients found that the objective response rate was 18% and the disease control rate was 47%. Overall, these results show that the use of cryoablation following progression on immune checkpoint inhibitors is feasible and tolerable for patients with unresectable melanoma. Currently, correlative studies are underway to identify biomarkers of response to this strategy.

Uveal (Ocular) Melanoma

Mutation Landscape and Emerging Therapies in Uveal Melanoma

In this talk, Marlana Orloff (MD, Sidney Kimmel Cancer Center) gave an overview of emerging therapies in uveal melanoma. Uveal melanoma, or ocular melanoma, has an incidence rate of 2,500 diagnoses per year in the United States. There are three major subtypes: ciliary body, choroidal, and iris. There is recent evidence to suggest that iris uveal melanoma is linked to UV exposure. While there is a strong response rate to primary therapy, approximately 50% of patients recur with metastatic disease. There is currently no FDA approved systemic therapy for metastatic uveal melanoma and the survival of metastatic disease is limited. Uveal melanoma has different mutations than mucosal or cutaneous melanoma, in that there are mutations in GNAQ, GNA11, BAP1, SF3B1, and EIF1X. The majority of existing data has looked at mutations in the primary uveal tumour and risks of development for metastatic disease there are very few studies strictly on metastatic specimens of uveal melanoma. Often, regardless of sample origin, the mutation profile is similar. Oncologists generally see very few high-frequency mutations and a low overall mutational burden. Orloff cites data from a study (below) consisting of 91 primary and 12 metastatic specimens, grouped into categories from 1-4 based on relapse-free survival (with one having the highest survival rate, four the lowest). The category three and four cases had the highest rates of BAP1 mutation, with SF3B1 being concentrated in categories 1-3, EIF1X in category 1, and distribution of GNAQ and GNA11 throughout all categories.



Orloff et al., 2021

Slide taken from presentation

Orloff then moved into discussing these mutations as biomarkers. The GNAQ and GNA11 mutations are the most common uveal melanoma mutation, occurring in upwards of 80% of cases. Mutations are through to impact downstream signalling of the MAP kinase pathway, which leads to cancer initiation and cancer cell growth. These mutations can be present in choroidal nevi before they develop into melanoma, meaning that they are often detected early. Orloff notes that there is currently little data on the prognostic impact of different mutations, so there is limited knowledge about any of them being more aggressive than others.

To illustrate the probability of primary metastasis and time of survival after metastasis (in months), Orloff cites a study by Terai et al. (2019), which looked at 72 metastatic specimens and

categorized them by mutations GNAQ209P, GNAQ209L, and GNA11209L. The results of this study demonstrated that were was little difference in the occurrence of metastasis and survival time after metastasis between the GNAQ209L and GNA11209L, however, the GNA209P seemed to have metastasis occur slightly later than the other mutations, and also may have better survival from the metastatic setting (Terai et al., 2019).

Next, Orloff spent time discussing the BRCA Associated Protein (BAP1) biomarker, which exists on chromosome 3p.21.1. BAP1 is considered to be a later mutation, and loss of BAP1 is predicted to cause melanoma cells to develop a more stem-like quality. At this time, most prognostic data surrounding BAP2 informs metastatic risk after primary diagnosis, but not post-metastasis survival. The lack of difference for survival suggests that while BAP1 is an important tumour for enabling metastasis it may not impact the aggressiveness of the disease after metastasis occurs.

Orloff then covered SF3B1, a mutation that is seen in around 20% of uveal melanoma cases. This mutation may promote the production of neoantigens which are recognized by the immune system, meaning that this mutation may have better survival. For data, Orloff cited Grimes et al.'s research (2021), which analyzed the clinical characteristics of uveal melanoma with the SF3B1 mutation in response to immune checkpoint inhibitors. This study included 58 participants with 49 of these having metastatic uveal melanoma. The survival rates found by this study for SF3B1-mutated melanoma demonstrated a one-year overall survival (OS) rate of 94% and a median OS rate of 3.94 years, suggesting the overall better survival for those with the SF3B1 mutation.

These mutations also provide for more specific therapeutic targets. The most promising data for the GNAQ and GNA11 mutations has been PKC inhibition as both a monotherapy and in combination with MEK inhibitors. One PKC inhibitor, darovasertib (IDE196), has demonstrated some results in metastatic uveal melanoma. In an analysis with 81 patients (many of them pretreated), 61% of patients experienced a target lesion reduction with IDE196, with 20% of these results being a 30% target lesion reduction (IDEAYA Biosciences). There was a one-year overall survival rate of 57%. IDE196 has also been tested in combination with the MEK inhibitor binimetinib, wherein 79% of evaluable patients (n: 14) saw tumour reduction. IDE196 has been further combined with crizotinib, a MET inhibitor, in an ongoing clinical trial.

Two mutations with clinical trials ongoing, but little current data, are the BAP1 and SF3B1 mutations. In terms of the BAP1 mutation, the target is often not the mutation itself but instead ways to change it epigenetically. There are several trials ongoing concerning BAP1, including BET inhibitor studies. The SF3B1 mutation shows improved survival in the metastatic setting and there are a number of PRMT5 trials ongoing to test this hypothesis.

Orloff concludes by noting that, despite the assumption that uveal melanoma is a genetically simple tumour, these mutations offer insight into survival patterns and metastatic potential. Orloff notes, too, that these mutations may even have different impacts in the adjuvant versus the metastatic setting. While the importance of mutations for primary tumours has been well-studied, Orloff argues that more comprehensive profiling is needed for metastatic samples.

Percutaneous hepatic perfusion (PHP) with melphalan for patients with ocular melanoma liver metastases: Preliminary results of FOCUS (PHP-OCM-301/301A) phase III trial

Jonathan Zager et al.

Abstract #: 9501

Clinical trial number: NCT02678572

This abstract reported on the FOCUS trial, a randomized phase III trial that compared percutaneous hepatic perfusion (PHP) with best alternative care, which was either dacarbazine, pembrolizumab, ipililumab, or transarterial chemoembolization. However, this trial was later amended to eliminate the best alternative care arm. Eligible patients had hepatic-dominant ocular melanoma. All patients will be followed until death and patients were discontinued from the study if they developed progressive disease. The primary endpoint was objective response rate.

The 144 enrolled patients were randomized 1:1 to receive PHP or best alternative care; in the amended trial, all received PHP. Patients receiving PHP could receive up to 6 doses every 6-8 weeks. Patients were imaged every 12 weeks. 102 (91 received treatment) patients were assigned to the PHP arm, while 42 (32 received treatment) were assigned to best alternative care. The objective response rate was 32.9% for the PHP arm and 13.8% for best alternative care. Median progression-free survival was 9.03 months for PHP patients and 3.06 months for best alternative care patients. 40.4% of the 94 patients who were examined for safety after PHP treatment experienced a serious treatment-related adverse event. The majority of these were hematological.

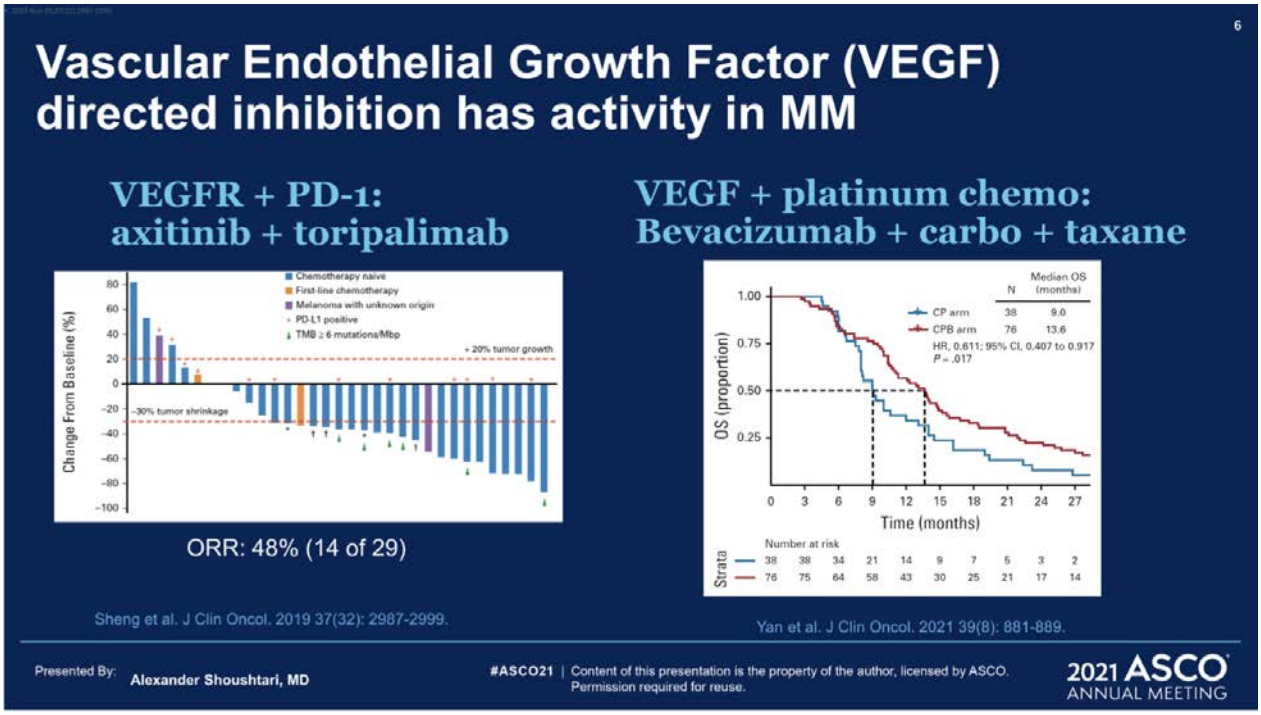
Overall, this preliminary data suggests that PHP demonstrates a superior objective response rate and prolonged progression-free survival relative to best alternative care in patients with hepatic metastases from uveal melanoma.

Mucosal Melanoma

Combination Approaches in Advanced Mucosal Melanoma

In this talk, Alex Shoushtari (MD, Memorial Sloan Kettering Cancer Center) discussed the treatment of advanced mucosal melanoma with combination therapies. As Shoushtari notes, mucosal melanomas are genomically distinct, meaning that there is a higher rate of structural genomic alterations, such as deletions and amplifications, relative to cutaneous melanoma. Mucosal melanoma also has fewer MAP kinase drivers, BRAF V600 mutations, and mutations relative to cutaneous melanoma. Furthermore, mucosal melanomas have a higher rate of distant metastasis, increasing the need for metastatic recurrence and death. Therefore, mucosal melanoma is an area of high unmet need.

While not to the same extent as cutaneous melanomas, mucosal melanomas are reactive to immune checkpoint inhibitors. Shoushtari cites two Chinese studies as examples, Sheng et al. and Yan et al.. Sheng et al. (2019) saw a 48% response rate with the combination of VEGF receptor blockade and PD1 blockade + axtinib + toripalimab in the frontline setting. Yan et al. (2021) demonstrated that combining the VEGF inhibitor bevacizumab with carboplatin + paclitaxel as a frontline treatment improved progression-free survival. These successes beg the question of whether PD1 and VEGF therapy for mucosal melanoma is a reproducible and sustainable option.



Sheng et al., 2019 and Yan et al., 2021, quoted by Shoushtari 2021

Slide taken from presentation

Shoushtari then moved to abstract #9511 (Si et al., 2021), a phase II study of atezolizumab (PD-L1 inhibitor) + bevacizumab (VEGF inhibitor) in patients with locally advanced, unresectable, or metastatic mucosal melanoma.[7] There was an objective response rate of 36% (partial responses), though Shoushtari notes that there was also a relatively low number of metastatic disease sites in this cohort. The safety profile was also reasonably strong for PD1 therapy. The results of this study demonstrate that VEGF is promising as a treatment for mucosal melanoma.

[7] For more information on this abstract, see page 32 of this report.

In abstract #9512, which Shoushtari discussed next, Cui et al. (2021) ran a phase II study of axitinib (VEGF receptor inhibitor) and toripalimab (PD1 inhibitor) as a neoadjuvant therapy for mucosal melanoma.[8] In the 14 participants they were able to collect data from, there was a 30% pathologic response rate after the median follow-up of one year. There is also promising activity in this study regarding regression-free survival, though it is too preliminary for data collection. CD3 and PD-L1 status were not associated with responses, however, response was positively impacted by CD3 and CD8 infiltration by lymphocytes. Overall, this study demonstrates that there is a subset of mucosal melanomas which have a pathologic response to neoadjuvant treatment.

While both of the aforementioned studies need more verification of their results from larger trials, Shoushtari suggests that these results offer good benchmark data for testing new approaches for mucosal melanoma. Shoushtari is optimistic about the future for this population.

A phase 2 clinical trial of neoadjuvant anti-PD-1 ab (toripalimab) plus axitinib in resectable mucosal melanoma

Chuanliang Cui et al.

Abstract #: 9512

Clinical trial number: NCT04180995

[8] For more information on this abstract, see page 52 of this report.

This study was a single-arm phase II trial of toripalimab + axtinib for resectable mucosal melanoma in the neoadjuvant setting. Patients with unknown primary or ocular melanoma, previous use of anti-PD-1 ab, or distant metastatic disease. The primary endpoint was pathologic response rate, with a secondary endpoint of recurrence-free survival. Patients were given neoadjuvant toripalimab (3mg/kg) + axitinib (5mg) for 8 weeks, then surgery, followed by adjuvant toripalimab (3mg/kg) after surgery for up to 52 weeks.

21 patients were enrolled in this study. At the median follow-up time of 59 weeks, 28.6% of participants saw pathologic response. Of the patients who had surgery, 61.5% demonstrated notable tumour-infiltrating lymphocyte (TIL) infiltration. Recurrence-free survival lasted at least 58 weeks. This study demonstrates that neoadjuvant toripalimab + axitinib has shown hopeful results in generating pathologic responses and good tolerance in patients with resectable mucosal melanoma.

Non-Melanoma Skin Cancer

Checkpoint inhibition in immunosuppressed or immunocompromised patients with advanced cutaneous squamous cell carcinoma (CSCC): Data from prospective CemiplimAb-rwlc Survivorship and Epidemiology (C.A.S.E.) study

Guilherme Rabinowits et al.

Abstract #: 9547

Clinical trial number: NCT03836105

This trial tested the efficacy and safety of immune checkpoint inhibitors for patients with advanced cutaneous squamous cell carcinoma (CSCC) who are also immunocompromised or immunosuppressed, a population that is often excluded from clinical studies. The C.A.S.E. study evaluated safety, effectiveness, survivorship, and quality of life for patients with CSCC who were treated with 350mg of cemiplimab intravenously every three weeks. Causes for immunosuppression among this group were varied.

Among the 19 patients who enrolled in the C.A.S.E. study before receiving a third dose of cemiphlimab, the objective response rate was 47% and there were treatment-related adverse events in 23% of patients. These results suggest that the effectiveness, safety, and tolerability of cemiplimab for immunosuppressed or immunocompromised patients with advanced cutaneous squamous cell carcinoma is consistent with data from clinical trials that excluded immunocompromised patients.

A phase Ib clinical trial of neoadjuvant OrienX010, an oncolytic virus, in combination with toripalimab in patients with resectable stage IIIb to stage IVM1a acral melanoma

Xuan Wang et al.

Abstract #: 9570

Clinical trial number: NCT04197882

This clinical trial evaluated the use of OrienX010, a granulocyte-macrophage colony-stimulating factor that expresses the herpes simplex type-1 virus oncolytic virus, in combination with checkpoint inhibitors in acral melanoma. This phase Ib neoadjuvant trial combined OrienX010 + toripalimab (anti-PD-1 monoclonal antibody) for patients with resectable stage IIIB-IVM1a acral melanoma. The primary endpoints of this study were radiographic response rate and pathological response rate, with secondary endpoints of safety and 1- and 2- year recurrence-free survival.

The results of this study demonstrated 33% radiographic responses and 81% pathologic responses in patients with resected metastases. After the median follow-up of 8.9 months, 0% of patients who underwent resection have recurred. Only 10% of patients experienced a grade 3-4 treatment-related adverse event. Therefore, this combination of OrienX010 + toripalimab produced a significant pathologic response rate and was well-tolerated by patients with resectable stage IIIB-IVM1a acral melanoma. Recurrence-free survival evaluation for this trial is ongoing.

Apatinib in combination with camrelizumab, a humanized immunoglobulin G4 monoclonal antibody against programmed cell death-1, in patients with metastatic acral melanoma

Xuan Wang et al.

Abstract #: 9539

Clinical trial number: NCT03955354

This single-centre trial evaluated the efficacy and safety of camrelizumab + apatinib in treatment-naïve advanced acral melanoma patients. Patients received 200mg of camrelizumab intravenously every two weeks alongside 250mg of apatinib orally once per day. The primary endpoint was objective response rate and the secondary endpoints were recurrence-free survival and safety.

Of the 27 patients who could be evaluated as of January 2021, 63% experienced tumour shrinkage, the disease control rate was 77.8%, and the objective response rate was 22.2%. Within the median follow-up of 8.3 months, progression-free survival was 8 months and the one-year durable response rate was 83.3%. 96.7% of patients experienced treatment-related adverse events, with 33.3% of these falling into grades 3-4. None of these adverse events were unexpected, nor did they cause any dose limitation. Given this data, the combination of camrelizumab + apatinib shows promising antitumour activity and progression-free survival rates, while being tolerable, in patients with treatment-naïve metastatic acral melanoma.

Clinical Trials

The Role of the FDA in Making Clinical Trials More Efficient, Accessible, and Equitable

The goal of this session was to open discussion about how the FDA can make clinical trials as efficient, accessible, and equitable as possible for all cancer patients, including perspectives on what we have learned from the COVID-19 pandemic and what we might be able to look forward to as life returns to normal. The speaker was Dr Lola Fashoyin-Aje (MD, MPH) who is a medical oncologist at the US Food and Drug Administration (FDA). She discussed the role of the FDA in promoting equity and access in drug development. These tactics include the identification of demographic subgroups and broadening eligibility requirements. Other goals include increased efficiencies in generating data to inform the safe usage of these treatments while reducing the burden to patients.

The primary interest of the FDA, Fashoyin-Aje states, is to ensure that approved drugs are as safe as possible for the intended population, therefore it is important to have data from clinical trials that reflects this population. To this end, the Oncologists Center of Excellence at the FDA provide the opportunity to participate in clinical trials to historically underrepresented groups. Fashoyin-Aje reminds us that clinical trials are also subject to the societal challenges that contribute to inequity in clinical research, which highlights the importance of conducting and designing clinical trials that are focused on equitable access.

One barrier to clinical trial access that the FDA is attempting to mitigate is eligibility criteria, which Fashoyin-Aje argues is not adequately adaptive to new clinical settings and

continues to be overly restrictive. These restrictions make the study population overly homogeneous, limiting the viability of the response for a larger population. While broadening acceptance criteria improves the generalization of drugs for a larger population, it can also help identify which drugs are not effective for a broader population and can lead to faster accrual. However, broadening trial populations can lead to additional difficulty in interpreting trial data and the need for increased safety monitoring, a burden for trial participants. Therefore, following in the footsteps of ASCO and Friends of Cancer, the FDA has outlined some recommendations to adapt eligibility requirements based on the care setting. Part of this project has included gathering experts across disease indications in order to assess existing eligibility criteria practices, to identify what is imperative to trials that support regulatory action, and when certain criterions are appropriate in different situations. The goal is to streamline and generalize eligibility criterions while making them flexible enough to be adjustable for each trial, including disease-specific barriers.

Fashoyin-Aje went on to describe innovations in trial designs that are aiming to improve efficacy in cancer therapy development. One example is platform trials, which simultaneously study multiple drugs using a single-trial design and protocol and use a common control pool which limits the need for large patient populations across multiple trials. Another option being pursued by the FDA is enrolling cohorts with less intensive criteria alongside a primary cohort who were selected with more restrictive criteria. This allows for data collection for the standard, more homogeneous, population while also being able to study the drug in populations with more comorbidities. A final option that Fashoyin-Aje pointed to is the

broadening of eligibility criteria of a trial as it continues, allowing for data regarding a greater variety of patient populations.

An ongoing issue that Fashoyin-Aje points to, which needs to be addressed in future clinical trial models, is the need to geographically expand trials outside of university cancer centres to be more accessible for patients in rural areas and to alleviate the financial burden of travelling for care. At the very least, certain trial-related activities could be undertaken at a greater variety of sites to increase patient convenience.

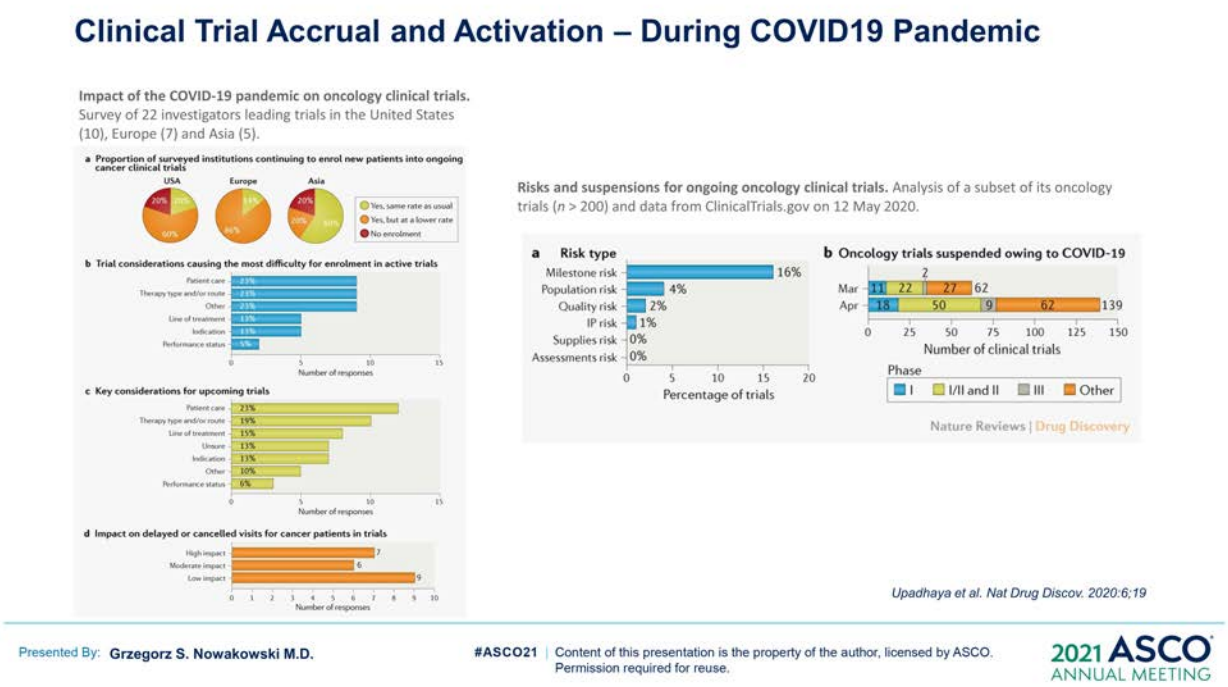
In closing, Fashoyin-Aje highlighted some ongoing issues surrounding care access for underserved populations. The COVID-19 pandemic made it clear that one of these issues is having access to adequate technology for telehealth appointments. This technology issue applies to both individuals and care cancers in underserved areas, which may not have the resources or infrastructure to be involved in clinical trials. Alongside the reconsideration of eligibility criteria, addressing these issues could go a long way in the equitable distribution of care to underserved populations.

Improved Access to Trials: Lessons Learned from COVID-19

In “Improved Access to Trials: Lessons Learned from COVID-19" Grzegorz Nowakowski (MD, Mayo Clinic, Rochester) offered perspective on what lessons have been learned about clinical trial procedures during the COVID-19 pandemic and how these lessons offer the potential for changes in efficiency. Nowakowski began by noting that

COVID-19 caused several disruptions in clinical trial procedures, such as a strain on resources, interruption of the supply chain, workforce strain, the need for personal protective equipment, and how to deliver care while adhering to social distancing guidelines. Nowakowski argues that in times of crisis, we often come to ask ourselves fundamental questions, in this case, whether clinical trials are essential at this time. Given the stress on the medical system during COVID, Nowakowski suggests that there is an argument to have halted clinical trials in order to preserve the currently limited resources. However, there is still the eternal argument that whenever the resources are available, the potential benefits of clinical trials to patients makes them a valuable exercise. Nowakowski returned to this question later in his talk, suggesting that the determinations of what is essential to trials that have been made during the pandemic should be considered in a broader context, to reassess whether the restrictions placed on clinical trials in normal circumstances are actually essential. Nowakowski also notes that there is a long-term cost of not continuing to develop therapies for the period of the pandemic.

Nowakowski turns to a series of reports on the effects of COVID-19 on clinical trial activation and accrual, which generally source their data from a combination of publicly available information and patient and site surveys (Upadhaya et al., 2020; below). These reports demonstrate that, in both the United States and Europe, accrual to clinical trials significantly slowed during the pandemic, with criteria surrounding the feasibility of the trial, patient care needs, and importance of the trials; therefore, the trials that were deemed the most pragmatic had the advantage during this time. Further, trials have been suspended by sponsors given the restrictions on trial delivery during the pandemic.

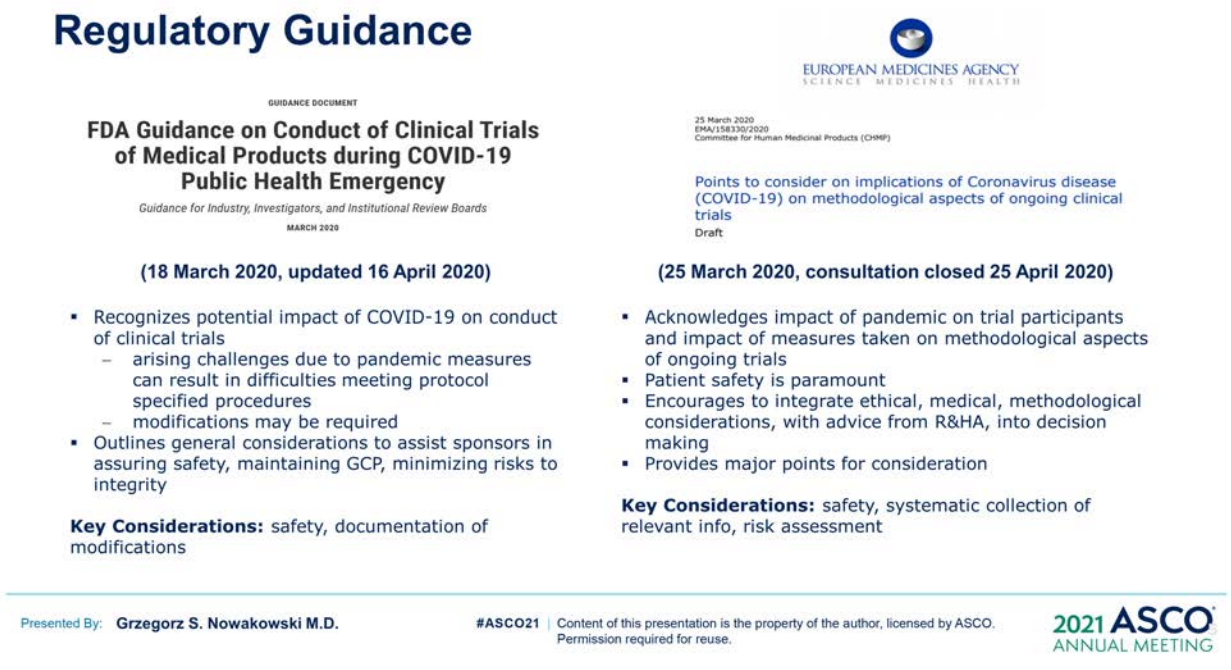


Upadhaya et al., 2020, quoted by Nowakowsko 2021

Slide taken from presentation

Like Fashoyin-Aje, Nowakowski noted the publishing of safety guidelines for delivering care during COVID, such as that released by the FDA. According to these guidelines, many sites switched to telehealth, reviewed their existing systems, and enlisted more local sites for patient monitoring (Food and Drug Administration, 2020 and European Medicines Agency, 2020; below). Of the reports Nowakowski is citing, over 50% of the programs reported prioritization of enrolment in certain clinical trials are based on safety, disease severity, and patient needs. Nowakowski hopes that continuing to focus on these factors will help to negate some of the inessential obstacles that have historically restricted access to trials. Additionally, there is concern that trials may become less popular if some of the more

restrictive aspects of pre-COVID trial recommendations are reintroduced, such as the ability to have certain tests performed locally. Overall, a decentralization of clinical trials, meaning that tests that can be performed locally are being implemented, would make clinical trials feasible for more patients.



Food and Drug Administration, 2020 and European Medicines Agency, 2020, quoted in Nowakowski 2021

Slide taken from presentation

Overall, Nowakowski believes that three overarching lessons have been learned in the clinical trial sphere during the COVID-19 pandemic. The options that Nowakowski outlines are 1) streamlining and standardizing the clinical trial process to reduce the burden on patients, 2) minimizing and standardizing questions to improve consistency between research

sites, and 3) leveraging technology in order to improve efficiency and information exchange. These follow the specific improvements that are sought after in clinical trial assessment: improving equity, accessibility, the efficacy of clinical trials while ensuring scientific integrity and data quality, recruiting and supporting a clinical trial workforce and promoting oversight, and review of clinical trial research and conduct.

Changes in Clinical Trial Operation, Management, and Accessibility in a Post-COVID-19 World

In this talk, Dr Connie Szczepanek (Director, Cancer Research Consortium of West Michigan, National Cancer Institute Community Oncology Research Program) also discussed the changes and disruptions in clinical research caused by the COVID-19 pandemic, and what can be learned from how the medical system has adapted over the past year. One area that has seen changes is the streamlining and standardization of clinical trials in order to reduce administrative burdens. While the negotiation of clinical trial criteria has been an ongoing issue since before the pandemic, the pandemic has added to the urgency of these concerns. Szczepanek notes that at the beginning of the pandemic (March 2020), ASCO conducted an early impact survey regarding clinical trial interruptions due to COVID-19 in both academic and community centres. The most frequently reported changes were the movement to a telehealth model, including remote consent, the shipment of medication to patients' homes, the limitation of ancillary services (surgery, labs, cardiology, radiology), and the need to have lab and clinical assessments closer to home.

In terms of clinical trials, staff were having difficulty maintaining consistency in trial procedures, which resulted in the postponement of studies, declining enrolments, and pauses in

studies. There was also a decrease in efficiency due to the need to physically distance and limit patient contact. In response, multiple government bodies stepped in to provide recommendations on policy and operational strategies for the pandemic and beyond. These pointers aimed to improve equity and accessibility for patients, enhance the efficiency of clinical trials, and protect scientific integrity and data quality.

One of the of the ways in which these recommendations are being acted upon is increased bringing of trials to patients, which means increased remote follow-ups, data collection, labs, and testing, and remote consenting measures. These changes made trials more convenient for the patient, improved access, and improved efficiency. Szczepanek hopes that these changes will be permanent. The implementation of remote consent has been considered with the needs of individual patients (and their comfort levels with technology) in mind.

Unsurprisingly, there have been many rapid changes in the clinical research workforce, which can make it difficult to identify reliable processes. However, some innovations catalysed by the pandemic might stay in operation. Some of these may be new technologies introduced during the pandemic, such as the new methods of collecting data, screening patients, and having follow-up appointments. Even though in-person visits are beginning to resume, Szczepanek anticipates that some of the virtual tools will be kept moving forward, though she notes that this has the potential for doctors to miss subtle or non-verbal cues from patients and might increase fragmentation between teams. Szczepanek also notes that remote work has increased among medical professionals, which, while being more cost-effective, safer, and convenient for staff, may risk a loss of coverage and experiential learning. This is especially true for clinical trials, which are customized based on the patient need, site, and

study. Ideally, between the pre-COVID efforts towards increasing equity and access for patients and the technological innovations necessitated by the pandemic, we will continue to move towards clinical trials that are more efficient and convenient for patients.

Survivorship

Telehealth to Improve Access to Survivorship Care

In this presentation, Terry Mulvey (MD, FASCO, Massachusetts General) discussed the implications of the growing telehealth movement for cancer survivorship. For the purposes of this talk, Mulvey focussed on patients who have completed the initial phase of therapy for either hematologic malignancy or solid tumours, and who are currently stable. While Mulvey suggests that the survivor phase is uniquely suited to telehealth care, ultimately the decision of whether telehealth is suitable for the patient falls to the patient and the healthcare provider.

Telehealth care can consist of both synchronous and asynchronous care. Online patient portals allow the patient to contact care providers asynchronously, to which the care provider can determine whether to reply through synchronous or asynchronous means. Synchronous telehealth most obviously applies to follow-up and check-up appointments, but can also be utilized in the survivorship sphere through support groups, which Mulvey notes includes exercise programs, resiliency programs, and cooking classes that have been developed by Massachusetts General Hospital (MGH).

Asynchronous care can apply to patient-reported outcomes, questionnaires which patients expect to fill out in their own time or web-based resources for patients. These tools can be facilitated through online patient portals. MGH has also developed an asynchronous e-consult program, which allows clinician-to-clinician feedback on non-urgent questions. The feedback from the e-consults would then be communicated to patients through either synchronous or asynchronous means. Mulvey also notes that patient portals have been used to pair patients to

clinical trials during survivorship. However, all information gathered through asynchronous means needs to be paired with a management strategy in terms of both triaging responses and training patients to utilize patient portals to their full potential.

Mulvey returned to the online classes being offered for patients, which at the time of ASCO 2021 were seeing upwards of 100 attendees per session. These classes, which include yoga and exercise, resiliency, support groups, and cooking and nutrition classes, are offered synchronously online and then made available to patients for asynchronous viewing. These classes aim to address the specific issues patients face in the transition to survivorship, such as the body image changes that may have come with antineoplastic therapies, radiation, or surgery, and other psychosocial issues such as interpersonal relationships and going back to work. This being said, more long-term effects of survivorship, such as fear of recurrence or disease progression, require in-person care to be addressed.

Mulvey noted that there may be issues with access for certain demographics of patients, such as the elderly or those without reliable internet access. Therefore, while video call appointments are ideal in the telehealth setting, it is important for care providers to be open to phone appointments as well. She also advises having virtual visits during clinic opening hours while support staff is there, in case the patient needs to be brought in. However, the removal of the restraints surrounding scheduling means that care providers and patients can potentially have more contact than they would in the traditional setting.

Meeting Survivor's Needs

In this session, Niki Patel (MD, City of Hope) discussed survivor care, which she characterized as “the uncharted middle ground” of cancer care. Globally, the rates of cancer survivors are increasing, with over half of all diagnosed patients surviving up to ten years.

Patel began by citing research by Woopen et al. (2021), who investigated the health effects of long-term survivorship. This study included more than 1,000 long-term ovarian cancer survivors and the results demonstrated that these survivors experienced symptoms beyond the standard five years of follow-up. The results also demonstrated that almost 40% of these survivors, who were at the ten-year mark, still regard themselves as cancer patients, not survivors. Overall, it was clear that long-term survivors have both physical and mental continuing adverse effects. However, more investigation is necessary to determine which of these events are actually correlated with ageing and what long-term events will come out of newer therapies. Given the lack of evidence-based interventions in survivorship care, this study inspired further relevant multidisciplinary care and interventions.

Next, Patel cited Di Meglio et al.’s (2013-2021, NCT01993498) predictive tool which identifies breast cancer survivors who are at high risk for severe fatigue based on a cohort study that monitored toxicity for 10,000 breast cancer patients. The next steps for this tool are determining whether there are biomarker or genomic factors to the risk of fatigue and whether this model could be expanded to identify risks for other symptoms. Patel also cited Snyder et al.’s (2017-2021, NCT03035773) report of a high-quality randomized controlled trial that compared three approaches to delivering survivorship care plans. 300 early-stage cancer patients were

randomized to receive their care plans either by mail, with one transition visit, or one transition visit plus a six-month follow-up visit. The results demonstrated that there was no difference across the delivery methods in terms of non-oral medications and recommended procedures and tests. However, a further question Patel notes is whether there is a significant consequence of delivery method on non-English speakers.

Despite this evidence that survivorship plan delivery does not affect most populations, the purpose and content of survivorship plans need to be continuously developed, as Patel does not believe that the oncology community is prepared to deliver high-quality and equitable care to a growing population of survivors. Therefore, programs that help with personalized risk assessment are essential. Greater institutional funding support will be required to continue developing these strategies. Patient-reported outcomes could be utilized to this end, but evidence-based interventions and research also need to be prioritized.