save your skin FOUNDATION

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Save Your Skin Foundation: ASCO Annual Meeting 2018 Report

The 2018 American Society of Clinical Oncology Annual Meeting took place from June 1-5, 2018 in Chicago, Illinois. This event brings together over thirty thousand oncologists, pharmaceutical representatives, and patient advocates from across the world and cross 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 we attended regarding innovative treatments in the melanoma sphere. Below are detailed recollections of these panels, in chronological order. Each talk (excepting the abstracts) also contains a "highlights" section, which briefly summarize the key topics in each presentation. Additional Save Your Skin coverage of the ASCO Annual Meeting 2018 can be found in a blog detailing our social media reporting during the week, and some abstract updates from the "Best of ASCO 2018: Montréal" event on June 19, 2018. Additionally, we would also recommend video resources recently posted by Oncology Education, including Dr. Jeffrey Weber (NYU) discussing Checkmate 238, Dr. Max Madu (Netherlands Cancer Institute) on the 8th AJCC melanoma staging system, and a roundtable discussion of ASCO highlights with Dr. Marcus Butler (Princess Margaret Cancer Centre), Dr. John Walker (Alberta Cancer Centre), and Dr. Jason Luke (University of Chicago). These videos are available on the Oncology Education website, though you will need to log in to view them.

The informational resources cited in this report are a combination of the personal notes of myself, Taylor Tomko, and my colleague, Amy Jones, both current employees of Save Your Skin Foundation; transcripts and slides from the ASCO meeting library; and, where marked, the pages for current abstracts on the ASCO website. All images are courtesy of the author of the respective talk. Any queries may be directed to taylorkathleen@saveyourskinca.

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Saturday, June 2nd: 1:15-2:30: "Practice-Changing Developments in Stage III Melanoma: Surgery, Adjuvant Targeted Therapy, and Immunotherapy"

This panel, including speakers Alexander Christopher Jonathan Van Akkooi, MD, PhD (Speaker, Netherlands Cancer Institute), Ragini Reiney Kudchadkar, MD (Chair, Winship Cancer Institute), and Olivier Michielin, MD, PhD (Speaker, University Hospital Lausanne) and chaired by Ragini Reiney Kudchadkar, discussed new developments in treatment for stage III melanoma, including surgery, adjuvant (additional) targeted therapy, and immunotherapies.

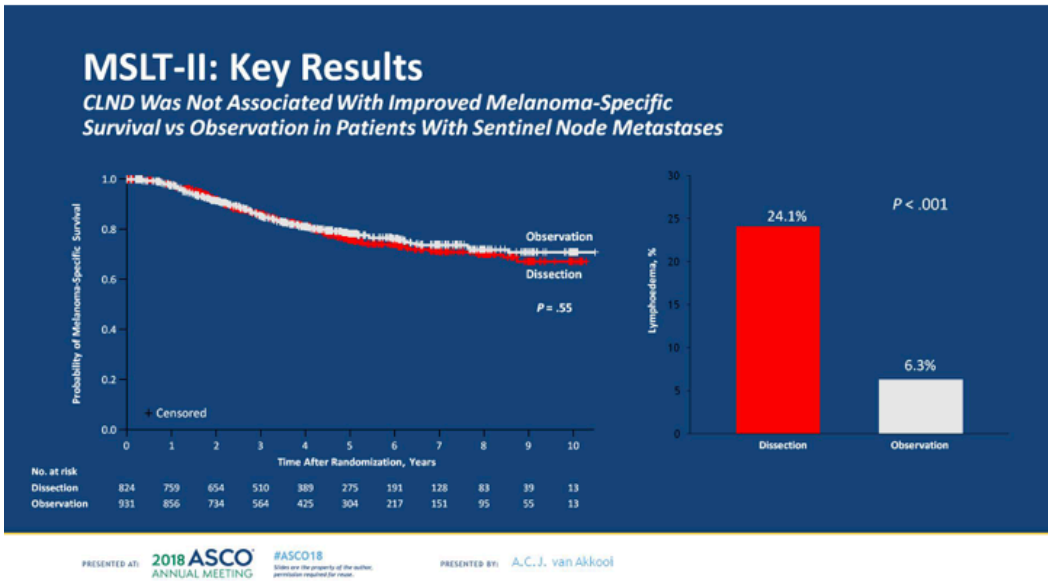
Jonathan van Akkooi: "Extent of Surgery for Stage III Melanoma: How Much is Appropriate?"

Highlights:

- MSLT-I trial: a 60/40 randomization of wide local excision plus sentinel node.
- DeCOG-SLT trial (University Hospital Tuebingen, congoing) saw no benefit to metastasis-free or overall survival with a sentinel node, and the MSLT-II trial (John Wayne Cancer Institute, ongoing) saw an increase in the rate of lymphedema in the patient group with an early completion lymph node dissection, and overall no therapeutic benefit for completion lymph node dissection.
- Citing a study in Amsterdam wherein participants had surgery and then either adjuvant or neoadjuvant therapy, and saw an 80% response rate and progression-free survival rate, van Akkooi is optimistic about the future of adjuvant therapy and believes that sentinel node procedure is the best diagnostic test for patients who may need adjuvant therapy.

Talk description:

In this talk, van Akkooi discussed test results for the MSLT-I trial for the sentinel node, and the DeCOG-SLT and MSLT-II results for lymph node dissection. He concluded by briefly discussing adjuvant and neoadjuvant therapies, and their repercussions for the future of surgery. The MSLT-I trial is predicated on the hypothesis that a metastasis will move from the primary tumour through the regional lymph node vessels to the local regional lymph node, then move to the second echelon lymph nodes, then move to the site of metastasis. Therefore, if metastasis can be interrupted at the local lymph-node level it would prevent further spreading. The MSLT-I trial



Presented By Alexander Van Akkooi at 2018 ASCO Annual Meeting

therefore examines whether a sentinel node has a survival benefit. The study was a 60/40 randomization of wide local excision plus sentinel node.

Figure 1: "MSLT-II: Key Results"

The results of the study (a p-value of 0.18) suggested that the sentinel node itself does not contribute to the therapy, however the early completion lymph node detection might. There have been two studies examining this possibility: the DeCOG-SLT trial in Germany, and the second MSLT trial (MSLT-II) (fig. 1, above) to reassess the benefits. DeCOG-SLT, a small study which only had German participants, saw no benefit to metastasis-free or overall survival with a sentinel node. The MSTL-II, an international trial, had 800 patients in the completion lymph node dissection group, and 900 in the nodal observation group. The endpoint was melanoma-specific survival. The study saw an increase in the rate of lymphedema in the patient group with an early completion lymph node dissection, and overall no therapeutic benefit for completion lymph node dissection. Van Akkooi suggested discontinuing the practice. However, there is an argument that completion lymph node dissection may be necessary for certain patients to allow them to enter adjuvant therapy.

Van Akkooi then discussed a study in Amsterdam, wherein 20 patients were randomized to have either upfront surgery with adjuvant or neoadjuvant therapy, two courses of the ipilimumab and nivolumab, surgery, then two more courses of adjuvant. The neoadjuvant group saw a response rate of 80%, as was the relapse-free survival rate. This is a great improvement to

the relapse-free survival rate of surgery alone, which is 50%. Different neoadjuvants are currently being tested for toxicity reduction. In conclusion, van Akkooi highlights that sentinel node procedure is still the best diagnostic test for patients who have high risk and will need adjuvant therapy.

Ragini Reiney Kudchadkar: "Adjuvant Targeted Therapy: First Choice?"

Highlights:

- Randomized phase III data suggests that BRAK/MEK inhibitors have improved overall and relapse-free survival in patients with resected stage III melanoma.
- A 2018 study by Long et al. has seen BRAF/MEK achieve overall five-year survival of 28%, a five-year survival of 45% for patients with a normal LDH, and 51% for patients with a normal LDH and low-tumour burden.
- Some patients can have significant and long-term responses to BRAF/MEK inhibition, and that patients normal LDH and low-volume disease might benefit the most from this kind of treatment.

Talk description:

This talk discussed the use of adjuvant targeted therapy as a first choice for BRAF-mutated, stage III resected melanoma. Kudchadkar began her presentation by establishing that she was arguing a side in a debate about the merits of adjuvant therapy as a first-line treatment, and therefore the information she is presenting is biased in that direction. Kudchadkar drew attention to some randomized phase III data that has shown that BRAF/MEK inhibitors have improved both overall and relapse-free survival in patients with resected stage III melanoma, and that both stage III and stage IV data have demonstrated that permanent toxicities rarely occur from this treatment. However, there are still theories that you have to be on-drug for BRAF/MEK to suppress cancer growth, which Kudchadkar is attempting to dispel. Kudchadkar cites a recently published phase II dabrafen**i**b and trametinib study (Long GV et al. 2017), which saw BRAF/MEK achieve an overall five-year survival of 28%, which a five-year survival of 45% for patients with a normal LDH, and 51% with a normal LDH and a low-tumor burden (Long et al. 2018). Similar results were seen in the COMBI-d and COMBI-b studies (500 patients treated with dabrafenib and trametinib), wherein the three-year overall survival was 44%, with normal LDH patients having a higher survival of 55% at three years. Based on these results, Kudchadkar suggested that some patients can have long-term responses to BRAF/MEK inhibition, and that normal LDH and low-volume disease are indicators of who might benefit the most from BRAF/MEK inhibition. As patients with resected stage III melanoma generally have normal LDHs, it makes sense to use BRAF/MEK in the adjuvant setting. However, there are risks to using this form of treatment, such as increased rates of secondary skin cancer including melanoma, and risk

of grade 3 and 4 toxicity, though these toxicity rates are reversible. Kudchadkar concluded by suggesting that as these drugs have been shown to achieve maximum benefit with patients with less disease, they should be used before progression, when they are maximally effective.

Olivier Michielin: "Adjuvant Immunotherapy: First Choice!"

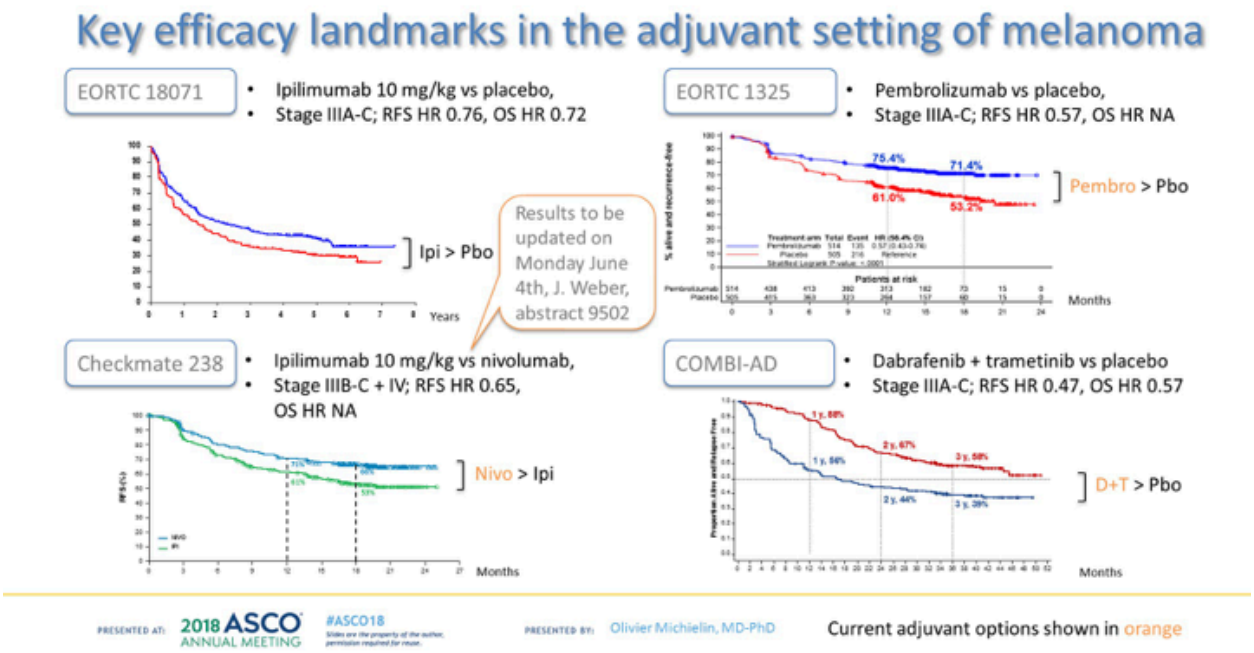
Highlights:

- The EORTC18071 (Bristol-Myers Squibb, Completed 2017) and EORTC1325 (European Organisation for the Research and Treatment of Cancer, completed 2017) respectively demonstrated that ipilimumab and pembrolizumab have greater responses than placebo.
- CheckMate 238 trial (Bristol-Myers Squibb, ongoing) early data is suggesting that nivolumab is superior to ipilimumab.
- While there are currently three active immunotherapy and one active targeted therapy trials, all of which are having optimistic results, no head-to-head comparison has been performed between immunotherapy and targeted therapy; Michielin believes that such a comparison will be essential in making treatment decisions moving forward.
- The future of adjuvant treatment may include personalization, wherein predictive biomarkers could be used to identify which patients require PD1, targeted therapies, or any additional therapies.

Talk description:

Michielin's talk centered on the benefits of adjuvant immunotherapy as a first choice, and to investigate whether immunotherapy can have the same results in the adjuvant setting as in the metastatic setting. To describe the landscape of current immunotherapy trials, Michielin points to EORTC18071 and EORTC1325, which respectively demonstrated that ipilimumab and pembrolizumab are better than placebo. Michielin also mentioned the ECOG 1609 trial, which compares EP10, EP3, and high dose interferon, which will have reported results in the near future, and CheckMate 915, which is testing ipilimumab and nivolumab in stages 3 and 4, and does not require complete lymph node dissection for entry. In summary, the EORTC treatments are showing superiority of ipilimumab and pembrolizumab to placebo, and CheckMate 238 showing nivolumab as superior to ipilimumab.

Michielin referenced figure 2 (below), wherein the drugs highlighted in orange are the drugs reasonable for treatment in the adjuvant setting, noting that while treatment options are



Presented By Olivier Michielin at 2018 ASCO Annual Meeting

Figure 2: "Key Efficacy Landmarks in the Adjuvant Setting of Melanoma"

great, decisions are becoming more complex, especially as key pieces of data are still missing. These include most hazard ratios for survival in immunotherapy trials. Additionally, many of the patients participating in these trials were undergoing complete lymph node dissection, so it is not reflective of the current melanoma population and statistics related to these treatments will shift. Michielin pointed out that in the EORTC1325 and CheckMate trials, the hazard ratios are consistent across the different stages, and some have lower hazard ratios. Regarding toxicity, Michielin cites the data from a CheckMate trial testing both nivolumab and pembrolizumab, which demonstrates a higher rate of grade 3 and 4 toxicity and a higher rate of adverse effects leading to treatment discontinuation. There are also some long-term immune-related adverse effects associated with immunotherapy, which will be maintained once the immune system has been engaged until you do the proper treatment; the patient's detection and management abilities are essential in treating these effects.

Discussing how these results can guide treatment decisions, Michielin points out that there are three prospective immunotherapy randomized trials, and one targeted therapy trial, all

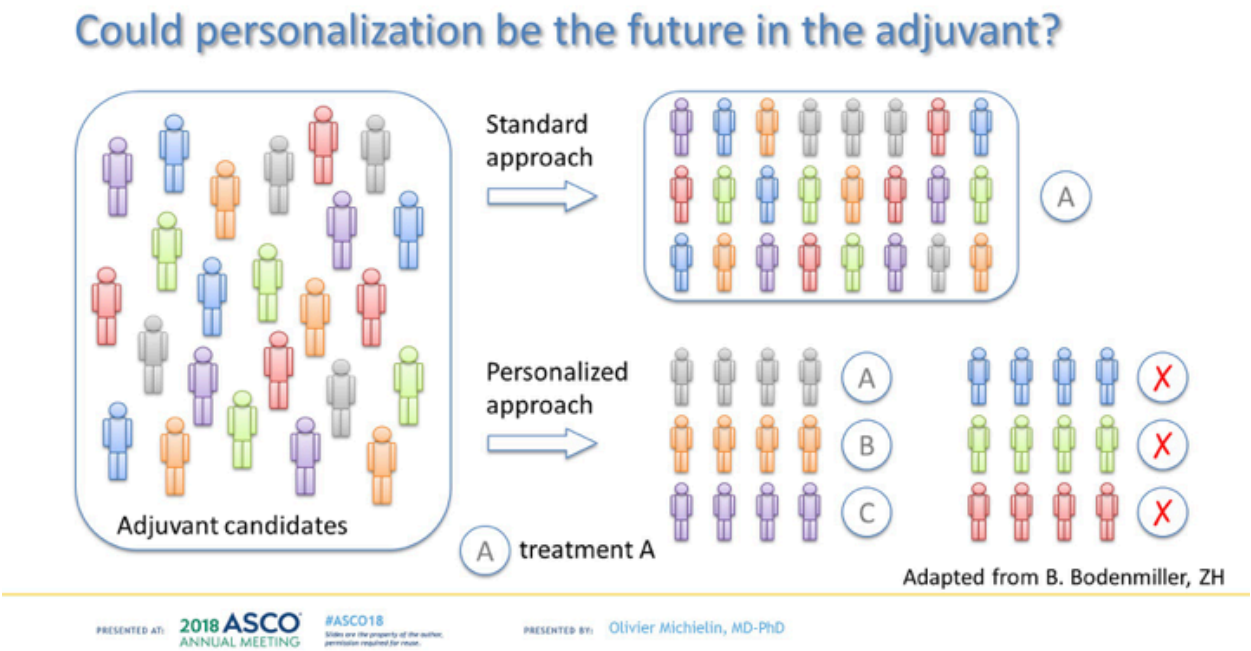


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Figure 3: "Could Personalization be the Future in the Adjuvant?"

of which have positive primary endpoint relapse-free survival. However, no head-to-head comparison has ever been performed between these immunotherapies and this targeted therapy, which Michielin said will be essential for making treatment decisions moving forward. Looking to the future, Michielin suggested that he hopes the future of adjuvant treatment will include personalization, or being able to assess which patients will benefit most from which kinds of treatment, or no treatment at all (fig. 3, above). After establishing whether a patient has been cured by surgery, predictive biomarkers could be used to identify which patients require PD1, targeted therapies, or any additional therapies. Looking at data from the OpACIN trial, Michielin suggested that future results regarding a patient's ability to mount new clones against a tumour after a relapse may also be helpful in creating personalized treatment plans. Michielin concluded by recapping that patients with a stage 3a of more than one millimeter, b, and c require adjuvant therapy if they are candidates. He suggests a PD1 blockade for BRAF wild-type patients, and PD1 blockade or targeted therapies for BRAF-mutated patients. However, a patient's ability to manage side effects is always important in treatment selection. Ideally, in the future, biomarkers may be used to make the best possible treatment choices for patients.

Saturday, June 2nd: 3:00-4:15PM: "Emerging Personalized Strategies in Systemic Therapy for the Treatment of Melanoma"

The next panel "Emerging Personalized Strategies in Systemic Therapy for the Treatment of Melanoma" included talks by Paolo Antonio Ascierto, MD (National Tumour Institute Fondazione G. Pascale), Keith Flaherty, MD (Massachusetts General Hospital), and Stephanie L. Goff, MD (National Cancer Institute at the National Institutes of Health). The panel was chaired by Paolo Antonio Ascierto.

Paolo Antonio Ascierto: "Novel Combinations of Therapy in Melanoma"

Highlights:

- Data for T-VEC immunotherapy combination trials is looking optimistic, with data incoming for a phase III trial which compares the combination of T-VEC and pembrolizmub with pembrolizumab alone (Long et al. 2015).
- Promising data is also emerging about the combination of checkpoint inhibitors with other checkpoint inhibitors, including the combination of IDO inhibitions and epacadostat pembrolizumab from phase I/II (MC Anderson, ongoing), and incoming data from the ECHO-204 trial, the combination of epacadostat with nivolumab (Incyte Corporation, ongoing).
- A phase I/II trial presented at ASCO and ESMO last year that combined nivolumab and relatimab in patients who had been previously treated with anti-PD1 and PD-L1 will be repeated in the near future in phase II/III in patients with untreated melanoma.
- Ascierto's team developed a study that checks CD73 enzymatic activity in adenosine when patients are treated with anti-PD1, they found that patients with a higher CD73 threshold had lower overall survival and progression-free survival outcomes than those with lower CD73 in the blood.

Talk description:

Ascierto opened this talk with the suggestion that while remarkable advances in melanoma have been made in the last ten years, there is still a lack of data regarding long-term

benefits of some of these treatments. It can be confidently said that at least 50% of melanoma patients get long-term benefit from newer treatments, which, while great progress, means that there are still improvements to be made in how melanoma is treated. Ascietro began his discussion of trials with T-VEC immunotherapy combination trials; notable data has been seen in the combination of T-VEC with pembrolizumab (fig. 4, below), and data is incoming for a phase III trial which compared the T-VAC and pembrolizumab combination with pembrolizumab alone (Long et al. 2015). Ascierto expressed enthusiasm about the potential for treatment combinations, including of checkpoint inhibitors with other checkpoint inhibitors. This includes several studies, including

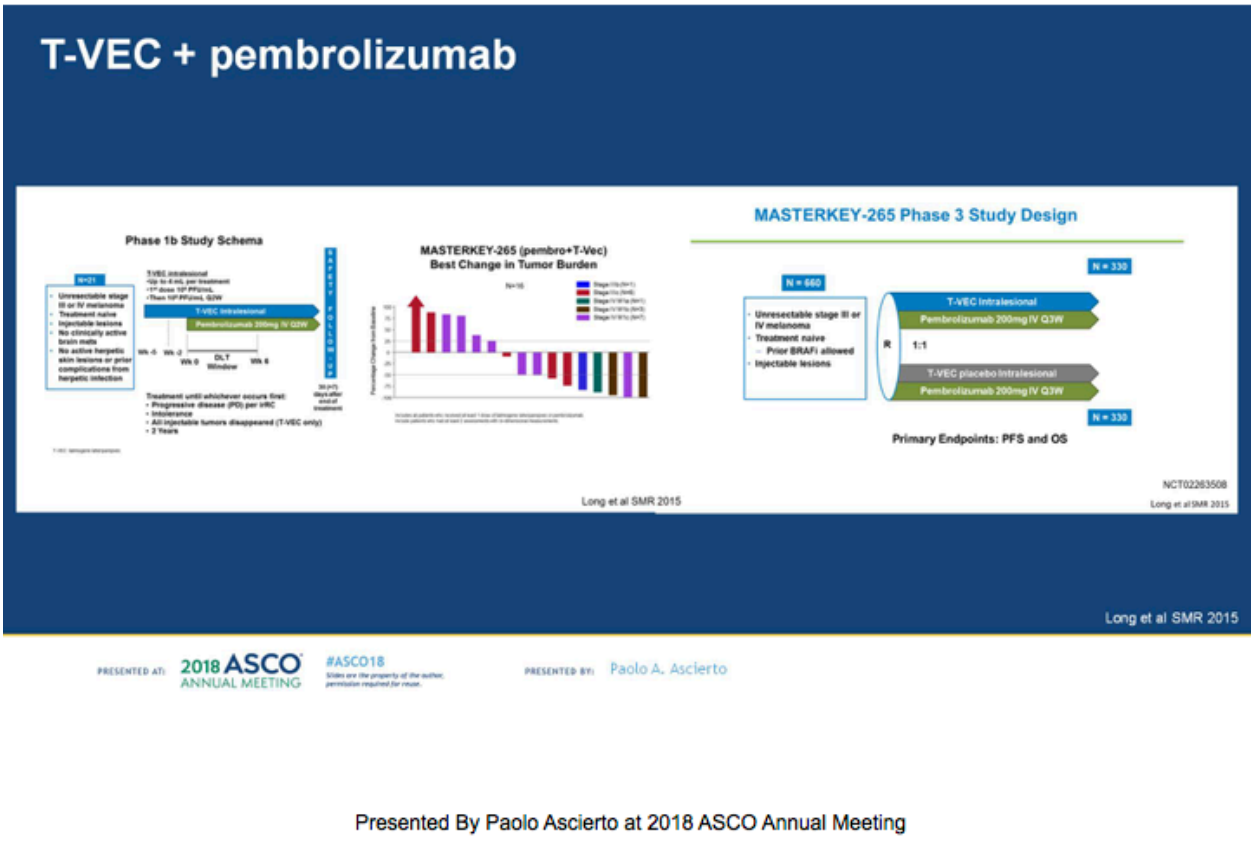

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Figure 3: “T-VEC + Pembrolizumab”

recent and promising data about the combination of IDO inhibitions and epacadostat pembrolizumab from phase I/II (MD Anderson, ongoing), and incoming data from the ECHO-204 trial, the combination of epacadostat with nivolumab, the results of which have so far been consistent with trials of epacadostat and pembrolizumab (Incyte Corportation, ongoing).

The data from these trials will ideally be able to shed some light on the role of IDO inhibition in melanoma treatment (fig. 5, below).

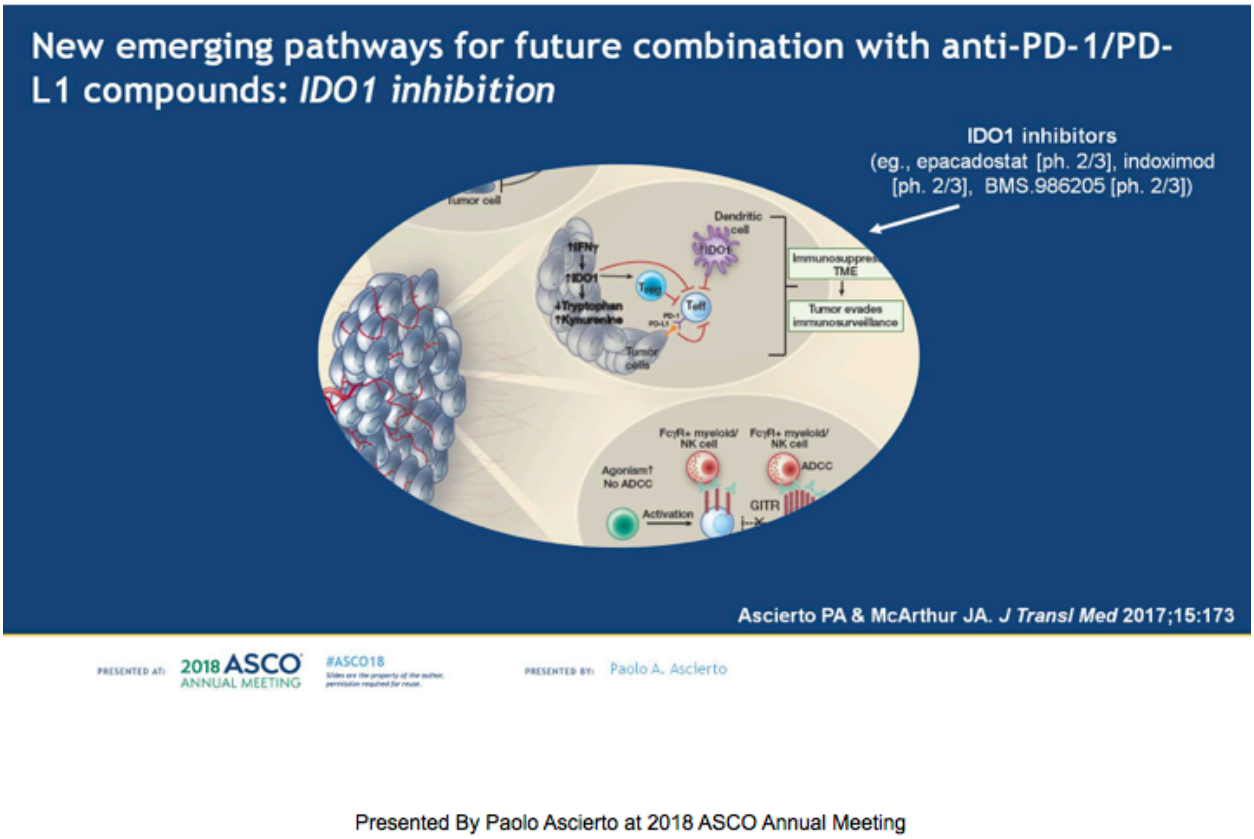

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Figure 5: "New Emerging Pathways for Future Combination with Anti-PD-1/PD-LI Compounds: IDO1 Inhibition"

Ascierto then discussed another pathway, the response evaluation criteria in solid tumours from checkpoint inhibitors, such as data revealed at ASCO and ESMO last year regarding a phase I/II trial that combined nivolumab and relatimab in patients who had been previously treated with anti-PD1 and PD-L1. Ascierto revealed that in the near future, this trial will be repeated in phase II/III in patients with melanoma that has been untreated. Ascierto also noted that relatlimab is not the only LAT3, and more compounds are currently under development in combination with anti-PD1. Overall, the combinations tested in these trials have been deemed safe, and Ascierto is looking forward to the possibility of new combinations in the future.

Ascierto then moved onto his own work, discussing a trial he coordinated last year to test whether adenosine would affect outcomes in patients treated with a checkpoint inhibitor. In checking CD73 enzymatic activity in adenosine when patients are treated with anti-PD1, they found that patients with a higher CD73 threshold had lower overall survival and progression-free

survival outcomes than those with lower CD73 in the blood. While there is no efficacy data, recent trials combining anti-PD1 and anti-CD73 have also been having positive safety results. Overall, Ascierto is optimistic about the future of combinations in trial treatments, and that these new possibilities will continue to increase long term benefit for patients.

Keith Flaherty: "Novel Targets for Therapy in Melanoma"

Highlights:

- Research conducted by Flaherty's team suggests that patients who received BRAF-MEK therapy were much less likely to respond or have disease control if they were in the low MITF/high AXL state at baseline versus tumours that were high-MITF/AXL low.

- A follow-up study in collaboration with Levi Garraway's lab at Harvard found that most tumours are high-MITF/AXL low, which is good as most patients will respond to BRAF or BRAF-MEK; however, there is a sub-population of cells in the high-MITF/low AXL end of the spectrum that are predicted to be resistant to the available therapies. Additionally, tumours that are low-MITF/high AXL are predicted non-responders to the BRAF-inhibitor-based therapy, immunotherapy, and targeted therapy.

- A phase I/II trial is being conducted at Sloan Kettering in which phenformin (a complex 1 inhibitor in the mitochondrial respiratory chain) has been added to the BRAF-MEK combo to see if it can overcome phenotypes of resistance to these therapies.

Talk description:

The next talk largely addressed the internal workings of the tumour cell and next-generation therapeutic strategies, including tumour cell autonomous signalling perspectives. Flaherty discussed the role of the CDK4/6 (cyclin-dependent kinase 4) in the pathogenesis of melanoma, believing that there is adequate clinical data to support research in this field. Flaherty began by reviewing the groups of tumours currently present in the melanoma landscape: BRAF mutant, BRAF wild, NRAS-mutated, and NF1 inactivating mutant subset. The standard targeted therapy for these groups is BRAF-MEK, which tends to have durable, if shallow responses. The research Flaherty presented here was based on the evidence of an asymptotic limit to BRAF inhibitor treatment, and the phenotype of resistance against BRAF which arose in some patients, as demonstrated in figure 6 (below). These include coordinated upregulation in multi-receptor targets and kinases, inactivation of P10, markers of activation in the PI3-kinase pathway; there have been previous attempts at activating the PI3-kinase pathway, however the therapeutic index of these combos has remained limiting. Therefore, Flaherty does not foresee the possibility of overcoming receptor targets and kinase components within the PI3-kinase pathway.

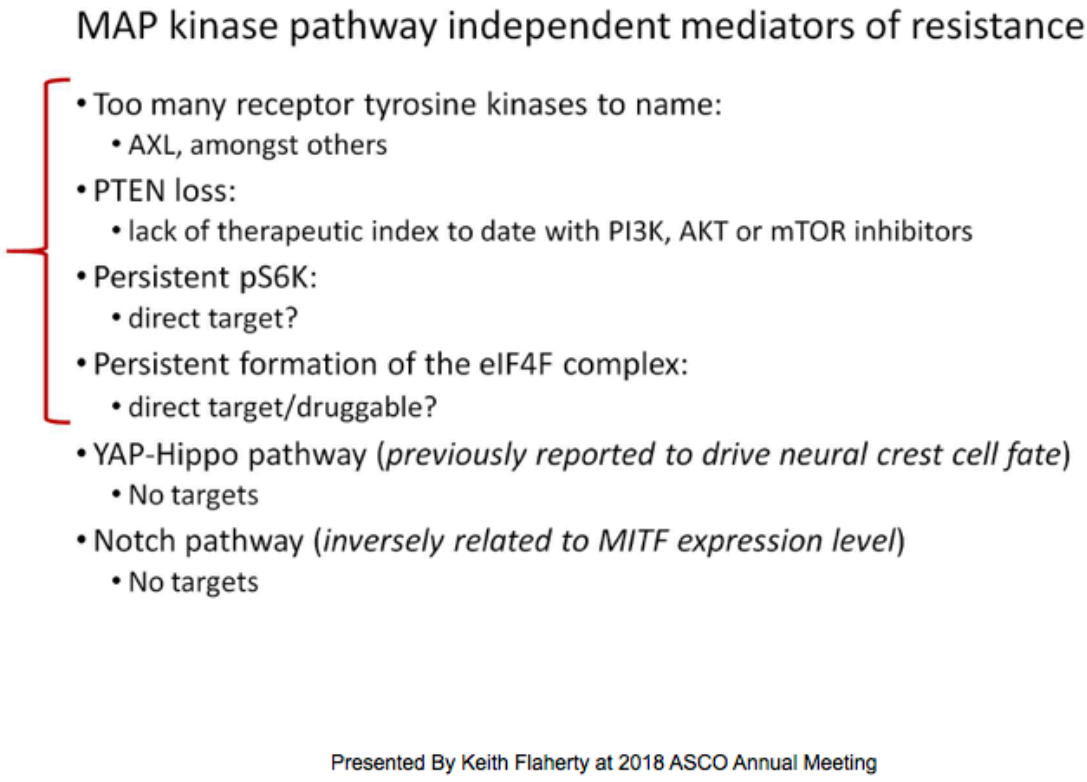

Figure 6: "MAP Kinase Pathway Independent Mediators of Resistance"

A few years ago, Flaherty's group began to to try phenotype resistance to optimize MAP kinase pathway therapy in the BRAF mutant context, to try and understand other ways to characterize this refractory cell population and how to conceive of new therapeutic strategies. They found that MITF sorted sensitivity and resistance most powerfully, therefore those with absent or low expression MITF had the resistant cell population. In a sample analysis, they found that patients who received BRAF-MEK therapy were much less likely to respond or have disease control if they were in the low MITF/high AXL state at baseline versus tumours that were high-MITF/AXL low. Flaherty's team then partnered with Levi Garraway's lab (Harvard) to produce a single-tumour analysis across a cohort of patients using single-cell RNA sequencing to understand the heterogeneity of this phenotype. It can be seen that most tumours are high-MITF/AXL low, which is good as most patients will respond to BRAF or BRAF-MEK; the study also includes patients who have never received any melanoma therapy who are at the other end of the spectrum, with low-MITF/high-AXL tumours. Unfortunately, there is a sub-population of cells in

the high-MITF/low AXL end of the spectrum that are predicted to be resistant to the available therapies. Additionally, the tumors that were low-MITF/high AXL both predicted non-responders to the BRAF-inhibitor-based therapy and were immunologically cold tumors, meaning they were predicted non-responders to both immunotherapy and targeted therapy. After these discoveries, Flaherty considers to how to damage this cell population. Possibilities include the beta-catenin pathway, and BCL2A1. However, beta-catenin is currently an undruggable pathway, and there are no BCL2A1 antagonists in clinical development at this time.

Flaherty then turned to a focal point in his presentation, a common phenotype among low-MITF/high AXL cells with increased oxidative phosphorylation and increased mitochondrial biogenesis, which also sometimes occurs in tumors that haven't received therapy. A few years ago, research began to emerge that the TCA gene set was the most altered after exposure to a BRAF inhibitor among BRAF-mutant cell lines, therefore demonstrating that mitochondrial respiration was altered under exposure of therapy. With electron microscopy, it could be seen that increased mitochondrial biogenesis was striking in treated versus control cells, suggesting that the program was instigated by BRAF-mutated therapy. However, a fraction of patients are resistant to BRAF therapy. So it is worthwhile to consider how it may be possible to attack this potential vulnerability. Flaherty mentions phenformin, a complex 1 inhibitor in the mitochondrial respiratory chain, which was able to overcome phenotypes of resistance. Phenformin is a generally well-tolerated therapy that was originally marketed as an anti-diabetic drug (and is no longer available for these purposes). There is currently a phase I/II trial being conducted at Sloan Kettering in which phenformin has been added to the BRAF-MEK combo to see if it can overcome resistance in this setting as well. There is potential that the addition of phenformin to attack resistance to BRAF-MEK could work for other kinds of tumors, including NF1-mutant melanomas and NRAS-mutant melanomas.

Flaherty concluded by briefly citing a study by Meenhard Herlyn's team (the Wistar Institute) which analysed a mitochondrial-specific hsp90 inhibitor called gamitribib, which has been explored pre-clinically and is on track towards clinical development, as an example of future work being done in this field. He then reiterated that there is a resistance cell state against BRAF treatment, a key feature of which is altered mitochondrial biology and increased oxidative phosphorylation, which, Flaherty suggests, is an area ripe for future exploration.

Stephanie L. Goff: "Is There a Role for Adoptive Cell Therapy in the Treatment of Melanoma"

Highlights:

- Adoptive cell transfer, or TIL (tumour-infiltrating lymphoctye) therapy, is a process wherein a patient's tumour is resected, new cultures are grown in the tumour fragments, and then these tumour cell lines are tested in the same patient; Goff's team has achieved 46 complete responses in a total of 194 patients, with an overall response rate of 55% and a complete response rate of 24%.

- TIL therapy is still possible in patients that have undergone immunotherapy and checkpoint blockades.

- The survival curve of the 194 patients that have been treated with adoptive cell therapy is about 40% at 36 months, which is the most mature survival data available from current combinations of checkpoint inhibitors.

- Cell therapies such as TIL and CAR are becoming more easily deliverable in hospitals in an inpatient setting.

Talk description:

In the next talk, Stephanie L. Goff discussed adoptive cell therapy for melanoma. Adoptive cell transfer is the use of TIL, or tumour-infiltrating lymphocytes. TIL therapy begins with the resection of a tumour, so if there are immune cells with the capacity to attack a tumour cell, they can do a metastatic deposit (fig. 7, below). The tumour is then minced into tiny fragments and grown in a lab process using high-dose Il2 and other cytokines. The lab grows

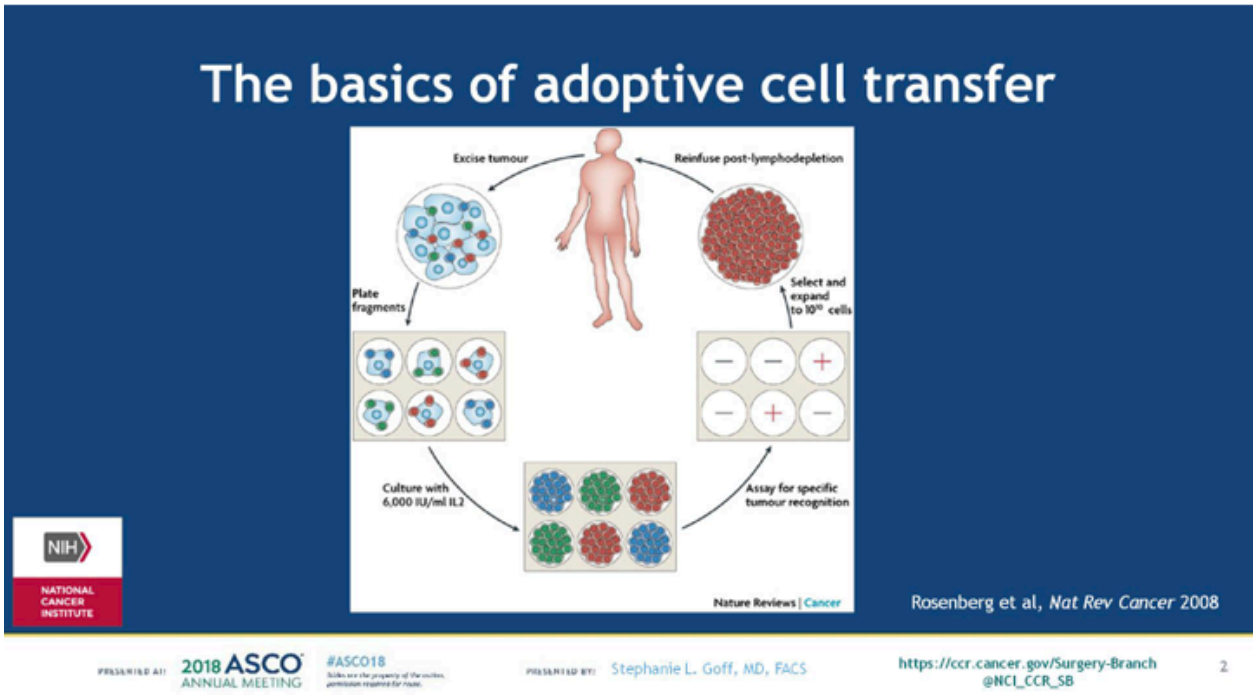

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Figure 7: “The Basics of Adoptive Cell Transfer”

different cultures from each of these 24 fragments, then test these tumour cell lines with the same patient. The process uses high-dose Il2 and OKT3 simulation, cells are generated on the order of 10 to the 10th, which are returned to the patient after a week of chemotherapy and then supported with some high-dose Il2.

Goff then presented two case studies demonstrating past patients of TIL, one of which demonstrated that 12 days after the patient’s infusion with TIL, there was a reduction of the size of his subcutaneous lesions. Five years later, the patient was living his life normally, which no evidence of disease, after not having received another treatment for his metastatic melanoma. The next case study (fig. 8, below) tells of a patient with multiple liver lesions, many of which disappeared one month after his transfer of cells. Seven years later, the tumours were still absent, and the man is living without any further therapy.

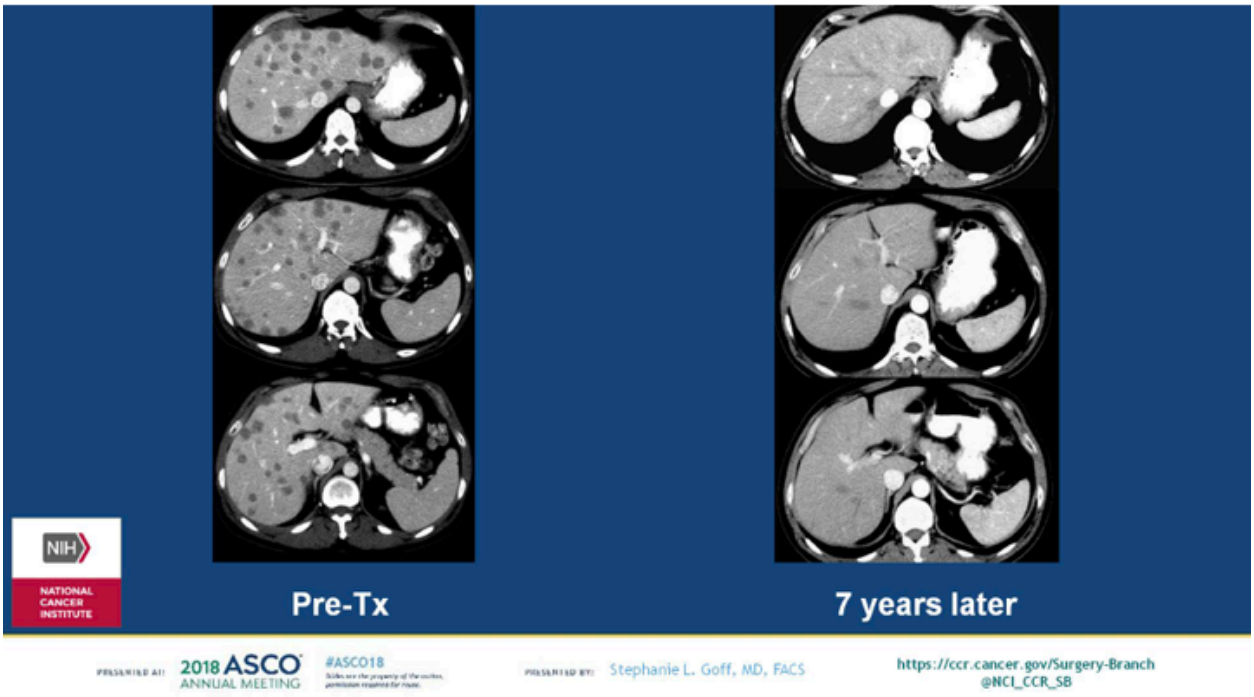

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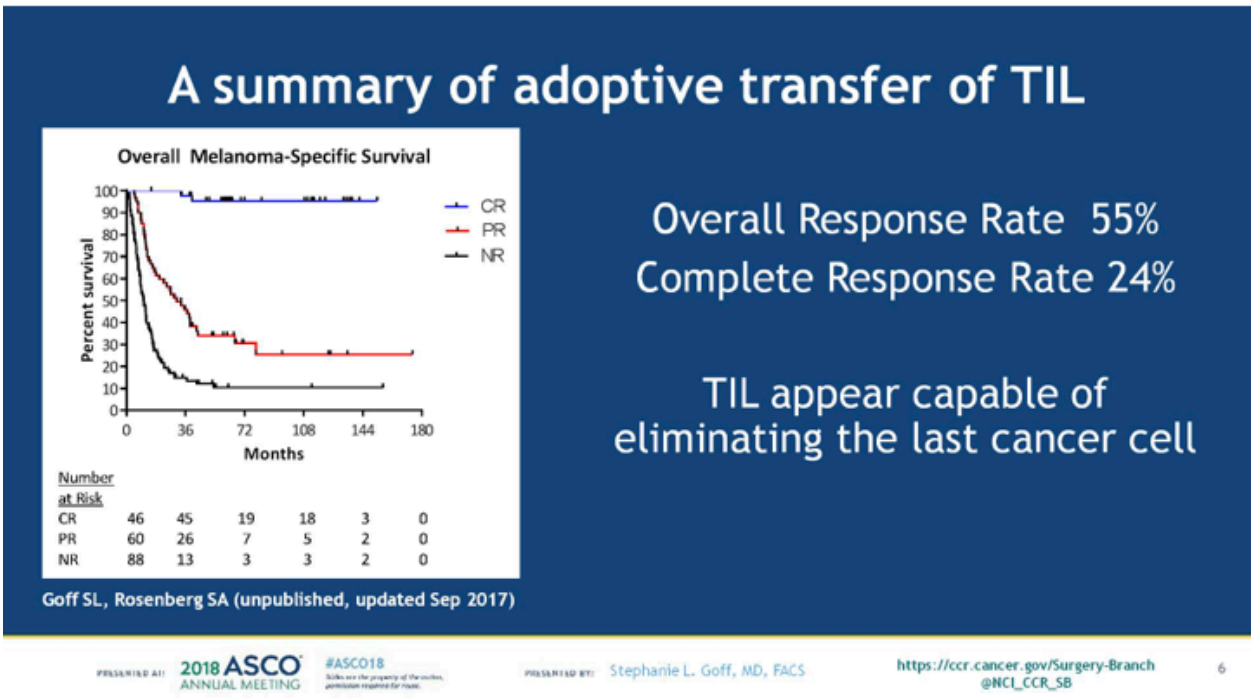
Figure 8: Depicts Progress of TIL treatment on liver lesions.

Goff notes that this treatment has also worked in the brain, which is generally thought to be a site of immune privilege due to the brain-blood barrier.

As demonstrated in figure 9 (below), Goff’s team has achieved 46 complete responses in a total of 194 patients, with an overall response rate of 55% and a complete response rate of

24%. Two of these complete responders have recurred, one at 19 and one at 27 months. Patients that have had a prolonged partial response have sometimes had prolonged survival with the addition of surgery or additional immunotherapy.



Presented By Stephanie Goff at 2018 ASCO Annual Meeting

Figure 9: "A Summary of Adoptive Transfer of TIL"

While TIL has had positive data, this has become less exciting as immunotherapies such as ipilimumab, nivolumab, and pembrolizumab, and combinations of those drugs gained approval for use among the oncology community, as it is easier to send a patient to an infusion centre than it is to have an inpatient for a three-week process. The question then became whether TIL is dead, or whether it's something worth continuing to explore-- which depends largely on whether effective TIL can be found in patients who have progressed through these immunotherapies. Retrospectively, Goff's team realized that they had done some early phase I work with what became ipilimumab, and had harvested a tumour from a gentleman who had progressed through that therapy. They resected a tumour from the contralateral side in his cervical lymph node chain, grew TIL from that, and saw complete removal of his fungating scalp lesion. Eight years later, he is alive with no further treatment.

Goff's team next examined whether they could still identify TIL and induce responses after checkpoint blockade inhibition, so they conducted a randomized trial where they treated

101 patients with TIL and had 26 complete responses. The subgroup of the trial that had received checkpoint blockade inhibition (the vast majority had received anti-CTLA-4 therapy) was very similar to the trial as a whole, so they believed the checkpoint blockade would not affect their ability to use TIL.

Goff's team then wanted to examine their cohort as a whole, so they took nine patients from this aforementioned trial and looked at two other trials they currently have in progress, with 40 patients overall. This includes a single-arm evaluation of TIL, and a randomized evaluation where adoptive cell transfer of TIL is used with and without pembrolizumab given two days prior to the cells. Of these 40 patients, most had been through ipilimumab and an anti-PD1 inhibitor, a couple had managed to get into anti-PD1 as first-line therapy, and around a quarter had gone through ipilimumab and nivolumab combination therapy. Ultimately, they found that in the median of cultures grown from the TIL cells of patients who had progressed through anti-PD1 therapy, there were fewer CD3s and CD8s. This is an initial evaluation, and the group has not examined whether there are other phenotypic markers that are different in these two groups. Goff encourages us to think about whether there is a role for adoptive cell therapy in the treatment of melanoma in three different ways: as a research strategy, as salvage therapy, and as initial therapy. As a research strategy, TIL may be helpful in investigating whether there are response mechanisms at the tumour and t-cell interaction that are independent of checkpoint blockade, whether combining TIL with checkpoint blockade will have good responses, and whether TIL cultures can be manipulated to a 'pre-PD1 phenotype' to see if that has great efficacy. As salvage therapy, TIL can be used to induce responses in patients that have previously undergone anti-PD1, ipilimumab, and the combination. Goff suggests that TIL could be explored as an initial therapy because, as Goff points out, the survival curve of the 194 patients that have been treated with adoptive cell therapy is about 40% at 36 months, which is the most mature survival data available from current combinations of checkpoint inhibitors. Goff concluded by noting that it may be worth watching the data for immunotherapy to see if the result remain as positive as they have for TIL, as an infusion is easier than the TIL process. Additionally, cell therapies such as TIL and CAR are becoming more easily deliverable in hospitals in an inpatient setting, and with a reminder that adoptive transfer can mediate regression in patients who have or have not undergone anti-PD1 therapies.

Sunday, June 3rd: 9:45-11:00AM: "A New Era in the Management of Melanoma Brain Metastases"

The next panel, "A New Era in the Management of Melanoma Brain Metastases" included talks by Grant A. McArthur, MBBS, PhD, FRACP (Peter MacCallum Cancer Centre, University of Melbourne), Caroline Robert, MD, PhD (Gustave Roussy Institute), Hussein Abdul-Hassan Tawbi, MD, PhD (The University of Texas MD Anderson Cancer Center), all regarding melanoma brain metastasis. The panel was chaired by Hussein Abdul-Hassan Tawbi.

Grant A. McArthur: "Biology of Melanoma Brain Metastases: Incidence, Prognosis, Surveillance, and More"

Highlights:

- Studies by MD Anderson Cancer Center suggest traditional therapies, including surgery, radiation, and chemotherapy have had minimal impact on the survival of patients with brain metastases.

- McArthur believes that certain processes required for establishment and survival of brain metastases can have weak points, wherein intervention may be possible.

- As progressive brain metastases can result in neurologic disability in a patient, it is imperative to detect brain metastasis as early as possible. The NCCN has recommended imaging every 3-12 months for stage 2B-4 patients with no evidence of metastases, based on conditional probability, and periodic brain MRIs for patients with 3C melanoma or higher. In order to work with the limited resources available, McArthur performs surveillance MRI scans for patients at stages 3C, 3D, or 4.

Talk description:

The first talk in this session focussed on the incidence, prognosis, biology, and potential therapies for brain metastases in melanoma. McArthur began the talk by asserting his belief that current therapeutic advances in melanoma treatment will have an impact on the total mortality from melanoma; however, there is still the challenge of brain metastases, which is a site currently being researched for new therapeutic possibilities. Melanoma is the third most common primary tissue of origin for brain metastases, however McArthur claims the proportion of patients that have developed brain metastases during their metastatic cancer experience puts melanoma at number one, a statistic based on both clinical detection and post-mortem evidence, which suggests that 40-50% of patients will develop brain metastases during their time with metastatic melanoma. Regarding prognosis, McArthur suggests that traditional therapies, including surgery, radiation, and chemotherapy have had minimal impact on the survival of patients with brain metastases, citing MD Anderson publications (2011, Mike Davies).

Hence, discovery of new, more effective therapies for brain metastases is imperative. The brain is unusual in that it has unique and specialized cells (astrocytes) relative to the rest of the body, and the 'blood barrier,' which selects which molecules can diffuse into the brain and excludes others. The barrier does so through both tight junctions in the cerebral vascular endothelium and the basement membrane that contributes to the tissue of the barrier and which molecules can travel through the cerebral vasculature. Therefore, for tumours to metastasize in the brain, they need to enter the circulation of this specialized environment, which only a fraction of cells are capable of doing. McArthur believes that understanding the process of brain metastasis as a cycle may be helpful in identifying weak points for therapeutic intervention.

McArthur continues by pointing out that there are molecules expressed from melanoma cells which allow adherence of melanoma cells to the cerebral endothelium, such as melanoma cells with a high expression of CCR4. Therefore, CCR4 may be a potential target for therapies to reduce the possibility of brain metastases. Additionally, melanoma molecules secrete serine proteases that can disrupt the blood barrier's junctions, and metallo-matrix proteinases and heparanases that can disrupt the basement membrane and facilitate the movement of melanoma cells into the brain, which also offer opportunities for therapies to disrupt cerebral metastasis. McArthur here suggests checkpoint inhibitors as a possible therapy option for brain metastases, suggesting that the process of metastasis can also move T-cells from the cerebral vasculature into the brain, and that melanoma has the highest concentration of SD3, SD8, and PD-1 positive T-cells in the brain of all solid tumour brain metastasis.

McArthur then moves into potential ways for therapies to intervene in brain metastasis through the resources metastases need to grow once they reach the brain, such as the activation of the activated tyrosine kenases pathway and BRAF mutated pathways, which are more likely to develop metastases. Additionally, melanoma cells secrete growth factors such as fibroblasts and vas endothelial, and brain astrocytes can secrete neurogenic growth factors, assisting the proliferation of melanoma in the brain. While McArthur does not believe targeting growth factors for brain metastasis could be a monotherapy, it may be useful in combination.

McArthur concluded his talk by discussing surveillance for melanoma brain metastasis. As progressive brain metastases can result in neurologic disability in a patient, it is imperative to detect brain metastasis as early as possible. The NCCN has recommended imaging every 3-12 months for stage 2B-4 patients with no evidence of metastasis, based on conditional probability, and periodic brain MRIs for patients with 3C melanoma or higher. However, the issue with this use of resources based on conditional probability, as research from McArthur's institution has suggested, is that the odds of an individual patient developing cerebral metastasis is relatively low; the study McArthur references found that out of 43 stage 3C patients, five developed cerebral metastases. However, to maintain the chance of early detection for brain metastasis, McArthur performs surveillance MRI scans for patients at stages 3C, 3D, or 4. McArthur urges for more investment in clinical trials for patients with brain metastases, so the prognosis for those with this disease can continue to improve.

Caroline Robert: "Different Combinations of Systemic Therapy for Melanoma Brain Metastases"

Highlights:

- Often, including in the dabrafenib BREAK-MB phase II trial which Robert cites, response in the brain is lower than it is outside of the brain. This is also true of the combination of dabrafenib and anti-BRAF, though the responses were stronger than to dabrafenib as a monotherapy.

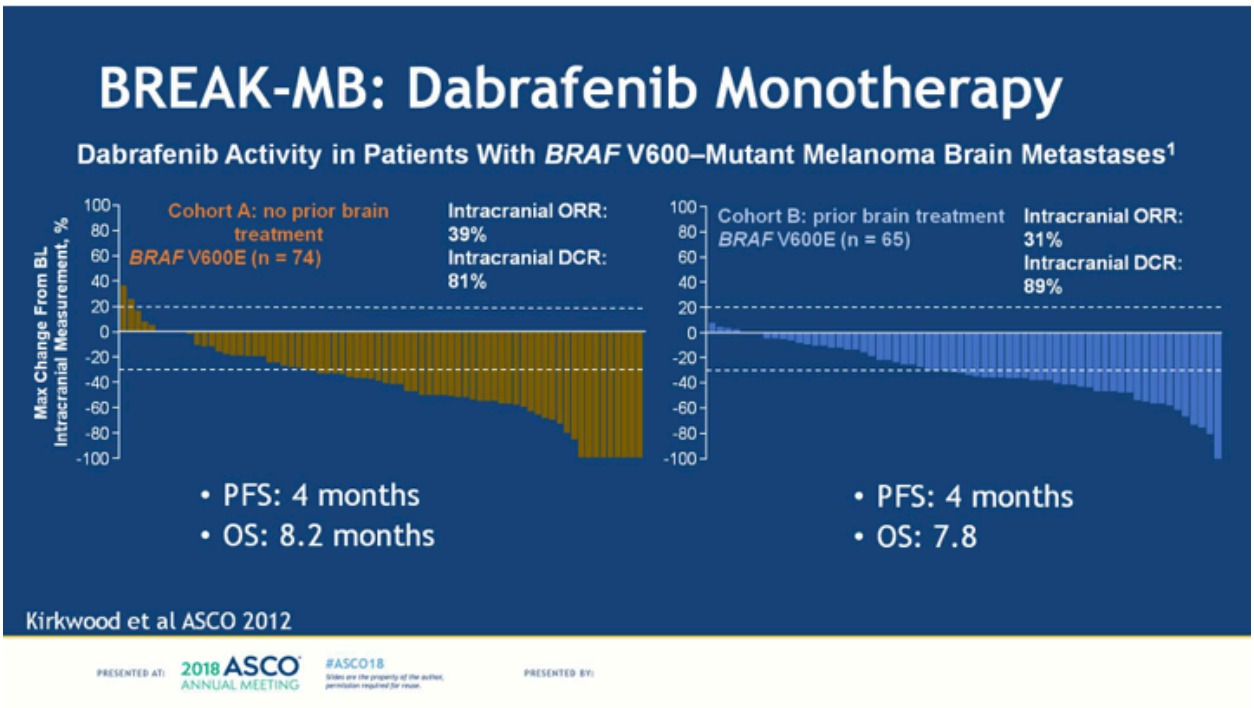
- A study led by Laurent Mortier testing a combination of high-dose ipilimumab, and stereotactic surgery between the first and second doses of ipilimumab, found that the

combination of ipilimumab and stereotactic surgery increased survival from the 6 months seen in radiotherapy alone to 13.2 months.

- There is retrospective data available on the combination with anti-PD-1, including a study from Robert's team which looked at 58 lesions from 25 patients that had been treated with anti-PD-1; the median survival was 15.3 months.

Talk description:

The next talk discussed systemic advances for melanoma brain metastases. Robert began by discussing some past trials for melanoma brain metastases, including a dabrafenib BREAK-MB phase II, which was tested with two cohorts of anti-BRAF targeted agents. Patients in cohort A (89 patients) had received no treatment, while cohort B (83 patients) had previously received treatment for brain metastasis. As evidenced in figure 10 (below), response within the brain was



Presented By Caroline Robert at 2018 ASCO Annual Meeting

Figure 10: "BREAK-MB: Dabrafenib Monotherapy"

weaker than outside the brain, and progression-free survival and overall survival were both low. Seen in the next slide, when the dabrafenib was combined with anti-BRAF the responses were higher than with dabrafenib as a monotherapy, though still inferior to responses outside of the brain.

Robert then turned to the typical steps that are taken in cases of melanoma brain metastases, first recommending combining treatment with stereotactic surgery; however, there is minimal prospective data on this approach. Robert here cites a study led by Laurent Mortier with a combination of high-dose ipilimumab, and stereotactic surgery between the first and second doses of ipilimumab. In comparison to only radiotherapy, the combination of ipilimumab and stereotactic surgery increased survival from 6 to 13.2 months. There is also retrospective data available on the combination with anti-PD-1, including a study from Robert's team which looked at 58 lesions from 25 patients that had been treated with anti-PD-1; the median survival was 15.3 months.

To conclude, Robert shared a case study of a patient who presented with adrenal gland, lung, and multiple brain metastases and was treated with ipilimumab, anti-PD-1 pembrolizumab, and other systemic treatments. Over ten lesions in the brain were treated with stereotactic reduce surgery, with two surgeries in the brain and one in the lung. For the last year, he has been in complete remission and off of therapy, suggesting that these results are possible, even with brain metastases. While the combination of nivolumab and ipilimumab is currently the most promising treatment, there is a push to continue investigating which drugs may be effective against brain metastasis.

Hussein Abdul-Hassan Tawbi: "What to Do First in Case of Melanoma Brain Metastases and Simultaneous Extracerebral Disease"

Highlights:

- While targeted and immunotherapy are currently the first line of treatment for melanoma brain metastases, many trials for these therapies initially excluded brain metastases, so this field has had to catch up.

- Tawbi suggests that targeted therapies only produces results for brain metastases approximately three-quarters of the time, whereas immunotherapies have seen an objective response rate of 55% and a clinical benefit rate of 60%, and a progression-free survival at 9-12 months.

- Data for the combination of stereotactic radiosurgery with immunotherapy is early but optimistic.

- Despite the relatively positive results with more recently melanoma therapies for brain metastases, Tawbi suggests that more research should be done in developing therapies that are suited to the unique microenvironment of the brain.

Talk description:

Tawbi began this talk by stating that brain metastases requires multi-disciplinary management, and should be approached as such. Surgery and stereotactic radiosurgery are both possible solutions, though they are limited by size and the kind of lesions they can treat. Tawbi agrees with Robert that targeted and immunotherapy are currently the first systemic choice for

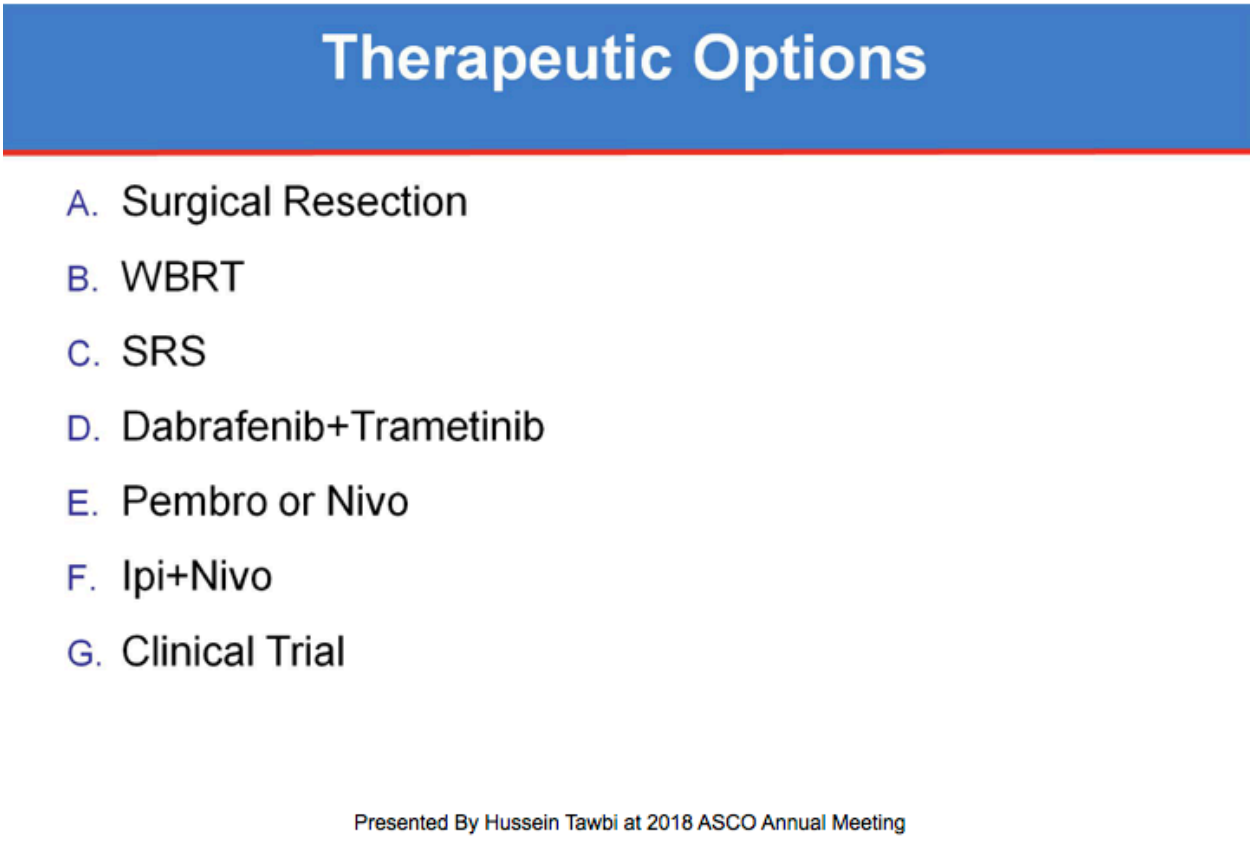


Figure 11: “Therapeutic Options”

melanoma brain metastases (fig. 11, above), and points out that many initial trials for these therapies excluded brain metastases, so the brain metastases field has had to catch up with their own trials. Tawbi suggests that targeted therapy actually professes shortcomings in treatment of brain metastases, with progression in the brain three-quarters of the time, and only in the brain

almost half of the time. The responses to the CheckMate-204 ipilimumab and nivolumab trial, seen below (fig. 12,), are more optimistic, with an objective response rate of 55% and a clinical benefit rate of 60%, and a progression-free survival at 9-12 months. Overall, there is difference in response between targeted and immunotherapy in the case of melanoma brain metastases.

CheckMate-204 Ipi+Nivo in MBM

	Global	Intracranial	Extracranial
Best overall response, n (%)			
Complete response	4 (5)	16 (21)	5 (7)
Partial response	36 (48)	25 (33)	32 (43)
Stable disease	4 (5)	4 (5)	2 (3)
Progressive disease[a]	18 (24)	18 (24)	16 (21)
Not evaluable[b]	13 (17)	12 (16)	20 (27)
Objective response rate, % (95% CI)	53 (41–65)	55 (43–66)	49 (38–61)
Clinical benefit rate[c], % (95% CI)	59 (47–70)	60 (48–71)	52 (40–64)

[a]Confirmed and unconfirmed progressive disease

[b]Includes unconfirmed responses [c]Clinical benefit rate = complete response + partial response + stable disease ≥ 6 months

Tawbi H, et al. *J Clin Oncol*. 2017;35(suppl): Abstract 9507.

Presented By Hussein Tawbi at 2018 ASCO Annual Meeting

Figure 12: "CheckMate-204 Ipi + Nivo in MBM"

Tawbi lists the options in figure 11 (above) as possible therapeutic options for melanoma brain metastases, before discussing how to choose which therapy to start with in the clinical setting. Size, location, and number of lesions are imperative in choosing a treatment option for each patient, as are the steroid requirement, BRAF mutation status, progression speed, and status of extracranial disease. After giving some case studies highlighting various options for treatment, Tawbi discussed the possibility of novel combinations other than ipilimumab + nivolumab, such as current testing of the activity in low dose ipilimumab and pembrolizumab. However, Tawbi suggests that it may be time to turn focus from attempting to adapt existing treatments for extracranial disease for the brain, and instead create treatments that target the specific microenvironment of the brain. Further, Tawbi cites leptomeningeal disease as a completely

unmet need and calls attention to a trial being led by Isabella Glitza at MD Anderson, which will be the first intrathecal nivolumab study in humans for leptomeningeal disease.

Tawbi concluded by returning to the current active therapies for melanoma brain metastases, including stereotactic radiosurgery. Most of the data regarding this treatment in combination with immunotherapy is retrospective or early, however it is optimistic. Overall, he feels that the safety and intracranial efficacy of targeted immunotherapy, potentially supplemented by stereotactic radiosurgery, are clear, and he looks forward to the future of research in melanoma brain metastases.

Monday, June 04: 8:00-11:00AM: "Abstract Session: Melanoma/ Skin Cancers"

This session featured abstracts on current studies in the melanoma and skin cancer field. Presentations included abstracts by Max Fullah Madhu, MD et al. (Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital), Ulrike M. Leiter, MD et al. (Department of Dermatooncology, University of Tübingen), and Jeffrey S. Weber, MD, PhD et al. (New York University Perlmutter Cancer Center). The discussant was April K.S. Salama, MD. Information on these abstracts, as well as others presented at the meeting, can be found on the ASCO website by searching their title or abstract number. As there are no transcriptions available for these sessions, their brevity, and their public availability on the ASCO website, these sessions will be quoted in full in this report, sans disclosures.

"Abstract # 9500: External Validation of the 8th Edition Melanoma Staging System of the American Joint Committee on Cancer (AJCC): Effect of Adding EORTC Sentinel Node (SN) Tumour Burden Criteria on Prognostic Accuracy in Stage III"

Authors: Max Fullah Madu, Viola Franke, Bart Van De Wiel, Willem M.C. Klop, Katarzyna Józwiak, Michel W.J.M. Wouters, Alexander Christopher Jonathan Van Akkooi.

Retrieved from: http://abstracts.asco.org/214/AbstView_214_223383.html

"**Background:**
Now that effective adjuvant therapy has arrived in melanoma, accurate staging and patient selection to optimize a risk/benefit ratio is crucial. The new 8th Edition AJCC staging system for melanoma aims to improve risk stratification. The goal of this study was to externally validate the prognostic and discriminatory ability for survival of the 8th Edition in comparison to the 7th.

Methods:
Analysis of a prospective cohort of patients treated in the Netherlands Cancer Institute for AJCC 7/8th Edition stage III melanoma between 2000 and 2016. Stage III melanoma was defined as regional lymph node metastases, with or without concurrent local recurrence, (micro)satellite or

in-transit metastases. Prognostic factors for melanoma-specific survival (MSS) and distant metastasis-free survival (DMFS) were analyzed. Survival differentiation of the 7th and 8th edition was assessed with log-rank tests and Cox proportional hazards models. Discriminatory ability was compared using the area under the curve (AUC) of the receiver operating statistic (ROC) obtained with Cox models.

Results:
640 patients were included with a median follow-up of 59 months (interquartile range 32-108). Median MSS was 138 months, DMFS 96 months. Age, Breslow thickness, ulceration of the primary tumor and number of positive lymph nodes (N) were significant prognostic parameters for MSS and DMFS. The 8th Edition performed similarly to the 7th in terms of survival discrimination, but failed to differentiate MSS between stage IIIA and IIIB after correction for sex and age. Both in 7th and 8th edition stage IIIA melanoma, patients with an SN metastasis size < 1 had excellent DMFS and MSS.

Conclusions:
The AJCC 8th edition staging system differentiates survival slightly worse than the 7th edition. Survival in both 7th and 8th edition stage IIIA melanoma is heterogeneous and can be sub-classified according to EORTC SN tumor burden, which can aid clinical decision-making concerning adjuvant therapy."

"Abstract #9501: Final Analysis of DECOG-SLT Trial: Survival Outcomes of Complete Lymph Node Dissection in Melanoma Patients with Positive Sentinel Node"

Authors: Ulrike M. Leiter, Rudolf Stadler, Cornelia Mauch, Werner Hohenberger, Norbert Brockmeyer, Carola Berking, Cord Sunderkötter, Martin Kaatz, Kerstin Schatton, Percy Lehmann, Thomas Michael Martin Vogt, Jens Ulrich, Rudolf Herbst, Wolfgang Gehring, Jan-Christoph Simon, Ulrike Keim, Peter Martus, Claus Garbe

Retrieved from: http://abstracts.asco.org/214/AbstView_214_216115.html

Background:
The multicenter DeCOG-SLT trial assessed in a randomized phase 3 trial whether complete lymph node dissection (CLND) resulted in increased survival compared with observation in patients with positive sentinel node biopsy (SLNB). This study now gives an update three years after inclusion of the last patient.

Methods:
Outcomes of 473 patients in the intent-to-treat population (ITT) randomly assigned into the DeCOG trial were evaluated with an additional 3 years follow-up observation after randomization has ended. A total of 233 patients was analyzed in the observation group, 240 in

the CLND group. The primary endpoint was distant metastasis-free survival (DMFS); recurrence-free (RFS) and overall (OS) survival were secondary endpoints.

Results:
Patient enrolment was performed from January 2006 to December 2014 followed by an observation period from January 2015 to December 2017. The median follow-up time was 72 months (95% CI 67.2;76.8) No significant treatment-related difference was seen in the 5-years DMFS: 68% (90%CI: 62.1%;72.5%, 79 events) in the observation arm and 65% (90%CI: 59.3%; 70.5%, 85 events) in the CLND arm (HR1.08 (90%CI 0.83; 1.39), P = 0.65). The 5 years RFS (HR 1.01 (90%CI 0.8; 1.28), P = 0.94) and OS (HR 0.99 (90%CI 0.74; 1.31), P = 0.93), also showed no differences with respect to the treatment arms. The 5-year DMFS differed according to the tumor load in the SLNB, but again not between CLND and observation arm (≤ 1.0 mm: 78.7% vs 72.5%, HR 1.12, P = 0.58 and > 1.0 mm 54.7% vs 51.7%, HR 0.98, P = 0.95) Regional lymph node metastases occurred in 10.8% of the CLND and in 16.3% of the observation arm (P = 0.11) The multivariate proportional hazard regression analysis revealed tumor thickness and tumor load in the SLNB to be independent prognostic factors for RFS, DMFS and OS.

Conclusions:
After a median follow-up time of 72 months there was no survival benefit in melanoma patients with positive SLNB undergoing CLND compared to observation only. Clinical trial information: NCT02434107.

"Abstract 9502: Adjuvant Therapy with Nivolumab (NIVO) versus Ipilimumab (IPI) after Complete Resection of Stage III/IV Melanoma: Updated Results from a Phase III Trial (CheckMate 238)"

Authors: Jeffrey S. Weber, Mario Mandalà, Michele Del Vecchio, Helen Gogas, Ana M. Arance, Charles Lance Cowey, Stéphane Dalle, Michael Schenker, Vanna Chiarion-Sileni, Ivan Marquez Rodas, Jean-Jacques Grob, Marcus Butler, Mark R. Middleton, Michele Maio, Victoria Atkinson, Reinhard Dummer, Veerle de Pril, Anila H. Qureshi, James M. G. Larkin, Paolo Antonio Ascierto

Retrieved from: http://abstracts.asco.org/214/AbstView_214_214567.html

Background:
In the initial report of data from CheckMate 238, at a minimum follow-up of 18 mo, NIVO demonstrated significantly longer recurrence-free survival (RFS) vs IPI in patients (pts) with resected stage III or IV melanoma. Here, we report updated efficacy results from this phase III study with an additional 6 mo of follow-up.

Methods:
Eligible pts included those ≥15 yrs of age who underwent complete resection of stage IIIB/C or IV melanoma. 906 pts were randomized 1:1 (stratified by disease stage and PD-L1 status at a 5%

cutoff) to receive NIVO 3 mg/kg Q2W (N=453) or IPI 10 mg/kg Q3W for 4 doses, then Q12W (from week 24) (N=453) for up to 1 yr, or until disease recurrence or unacceptable toxicity. The primary endpoint was RFS; distant metastasis-free survival (DMFS) in pts with stage III disease was an exploratory endpoint.

Results:
At a minimum follow-up of 24 mo, RFS continued to be significantly longer for NIVO vs IPI (hazard ratio 0.66, P<0.0001), with 171/453 and 221/453 events, respectively. The 24-mo RFS rates were higher for NIVO vs IPI in subgroups defined by disease stage, PD-L1 expression, and BRAF mutation status (Table). DMFS also continued to be significantly longer for NIVO vs IPI, with 24-mo rates of 70.5% and 63.7%, respectively (hazard ratio 0.76, P=0.034). Subsequent therapies were received by 31.1% of pts in the NIVO group and 41.1% in the IPI group. Per protocol, there was no additional safety assessment for the current analysis given that all pts had been off study treatment >100 days at the time of the previous data cutoff.

Conclusions:
With extended follow-up, NIVO demonstrated a sustained efficacy benefit vs IPI in pts with resected stage III/IV melanoma at high risk of recurrence, regardless of disease stage, PD-L1 expression, or BRAF mutation status. Clinical trial information: NCT02388906.

Additional: Ocular Melanoma-Related Abstracts from ASCO 2018

"Abstract 9521: Redirected T Cell Lysis in Patients with Metastatic Uveal Melanoma with gp100-Directed TCR IMCgp100: Overall Survival Findings"

Authors: Takami Sato, Paul D. Nathan, Leonel Hernandez-Aya, Joseph J Sacco, Marlana M. Orloff, Jennifer Visich, Nicola Little, Ann-Marie Hulstine, Christina Marie Coughlin, Richard D. Carvajal

Retrieved from: https://meetinglibrary.asco.org/record/162309/abstract

Background:
IMCgp100 is a bispecific biologic comprised of a soluble T cell receptor recognizing the gp100 antigen fused to a scFV anti-CD3 and redirects T cell lysis of melanoma cells expressing gp100. Safety and preliminary efficacy of IMCgp100 were assessed in a Ph 1/2 study in metastatic UM (mUM).

Methods:
HLA-A*0201+ pts with mUM were treated with QW dosing of IMCgp100 *iv* at Cycle 1, Day 1 (C1D1, 20 mcg) and C1D8 (30 mcg), followed by the escalated dose administered at C1D15 and beyond.

Results:
Pts with mUM (n = 19), elevated LDH (87%), liver metastases (100%), and median of 4 prior therapies (0 – 8) were treated across 4 doses (54 to 73 mcg) in Ph 1; 23 pts were treated in the Ph 2 RP2D (68 mcg) expansion cohort. Related AE included pruritus (90%), pyrexia and fatigue (84%), and hypotension (74%). Gr 3/4 related AE include AST elevation, erythema and hypotension (all, 16%). Ten of the 19 pts in Ph 1 were treated at or above the RP2D. Objective PR by RECIST in Ph 1 were observed in 2 pts and minor responses in 4 pts (6/19 responses); median duration of response was 30.6 wk. One year PFS rate by irRC was 66% (95% CI [39, 83]). One year OS rate in Ph 1 was 74% (95% CI [48, 88]). Median OS in this cohort has not been reached (median follow up of 15.9 mo). The PKPD relationship of exposure was modeled with extent and duration of lymphocyte trafficking. The EC50 for lymphocyte extravasation to the periphery was estimated at 1.4 ng/mL. At high doses, maximal trafficking of 50% was observed compared to baseline. The extent of lymphocyte trafficking is saturable, however the duration was dose dependent. The EC90 represents the dose of 70 mcg, supporting the RP2D. In the full cohort (n = 42), rash of Gr ≥2 within the first 3 weeks of dosing is associated with prolonged OS when compared to pts with mild (G1) or no occurrence of rash (HR 0.122, 95% CI [0.03, 0.45], p = 0.0015).

Conclusions:
IMCgp100 is tolerable with the intra-patient escalation dosing regimen and leads to prolonged OS. A potential association of prolonged OS with rash severity was observed. PKPD modeling demonstrates a relationship between lymphocyte trafficking and exposure to IMCgp100. Pivotal trials in the setting of metastatic UM continue to enroll (NCT03070392, NCT02570308).
Clinical trial information: NCT02570308

"Abstract 9570: Characterization and Spatial Localization of the Tumour Immune Microenvironment in Metastatic Uveal Melanoma"

Authors: Kimberly Mayumi Komatsubara, Robyn Denise Gartrell, Claire-Audrey Bayan, Jaya Sarin Pradhan, Syed Shabee Hasan, Thomas D Hart, Margaret Borgardus, Yan Lu, Douglas Kanter Marks, Jessica Yang, Adriana Lopez, Codruta Chiuzan, Basil Horst, Bret Taback, Larisa J. Geskin, Brian P. Marr, Gary K. Schwartz, Yvonne M. Saenger, Richard D. Carvajal

Retrieved from: https://meetinglibrary.asco.org/record/163458/abstract

Background:
Uveal melanoma (UM) is a rare subset of melanoma that is resistant to immune checkpoint blockade. High density of macrophages (Mϕ) and TILs is associated with poor prognosis in primary UM but little is known about the tumor microenvironment (TME) in metastatic UM (MUM). Here we performed quantitative spatial analysis using multiplex immunohistochemistry (mIHC) to characterize the TME in MUM, compare the TME of MUM to metastatic cutaneous melanoma (MCM), and identify potential mechanisms of MUM resistance to immunotherapy.

Methods:
We identified pts with untreated metastatic melanoma with clinical follow-up and available pre-treatment tissue who consented to an IRB-approved protocol. 5µm slides were stained using Opal mIHC for DAPI, CD3, CD8, CD68, HLA-DR, Ki67, and SOX10. Tumor areas were pre-selected by a dermatopathologist, visualized using Vectra and analyzed for density and spatial localization using inForm software.

Results:
6 MUM and 8 MCM cases were evaluable at the time of this analysis. CD3+ and CD8+ T-cell density is similar between MUM and MCM, however, there is a trend towards a higher density of proliferating cytotoxic T lymphocytes (CTL) (CD8+Ki67+) in MCM ($p = 0.05$). Interestingly, CD68+ Mϕ density is lower in MUM compared to MCM ($p = 0.03$). Both CD68+HLA-DR+ Mϕ (activated) and CD68+HLA-DR- Mϕ (inactivated) density is lower in MUM. Using nearest neighbor spatial analysis, CD8+ CTLs are significantly farther from activated Mϕ (CD68+HLA-DR+) ($p = 0.01$), but not from inactivated Mϕ (CD68+HLA-DR-) in MUM compared to MCM.

Conclusions:
Unlike primary UM, our sample of untreated MUM is not characterized by a high Mϕ density. Fewer Mϕ are present in untreated MUM compared to MCM and activated Mϕ are located farther from CTLs in UM. Density of CTLs is similar in MUM and MCM, although proliferating CTL are more numerous in MCM. These preliminary results suggest that Mϕ may play a less prominent role in innate resistance to immunotherapy in MUM. Gene expression analysis and further classification of Mϕ type is ongoing. Additional cases are ongoing analysis and will be reported.

"Abstract 9566: Treatment of Metastatic Uveal Melanoma (mUM) Directed by a Comprehensive Molecular Tumour Analysis Program"

Authors: Serge Leyvraz, Thomas Kessler, Moritz Schütte, Mario Lamping, Susen Burock, Sebastian Ochsenreither, Vyacheslav Amstislavskiy, Christoph Wierling, Korinna Jöhrens, Frederick Klauschen, Caroline-Anna Peuker, Felix Kiecker, Reinhold Schäfer, Bodo Lange, Hans Lehrach, Antonia Joussen, Damian Tobias Rieke, Konrad Friedrich Klinghammer, Ulrich Keilholz, Marie-Laure Yaspo

Retrieved from: https://meetinglibrary.asco.org/record/163435/abstract

Background:
There is a lack of active treatment against mUM. Such "hard-to-treat" tumour might benefit from treatment decisions driven by a complete genomic and transcriptomic analysis program.

Methods:
From 1.3.2016 to 1.12.2017, mUM were included in the prospective TREAT20Plus study and were subjected to a CMTA including WGS, WES, RNAseq, cell culture and systems biological/ pharmacodynamic modelling. Treatment recommendations were made by a molecular tumour board.

Results:
Twenty six patients (12 F, 14M). Age: 61 (32-80). PS: 0 (0-2). Metastases: 4 (1-10). Abnormal LDH: 19. Pre-treatment: 1 (0-5) and type: iv chemotherapy: 11, checkpoint-inhibitors (-i): 7, intra-hepatic: 13, vaccine: 1. Insufficient material in 3 patients. The mutation burden was low: 32 (15-449). The treatment recommendations (TRec) were based on the different mutations or activation profiles: A) MEK-i. for mutations of *GNAQ*: 11, *GNA11*: 13. B) a MET-i. for MET overexpression: 17. ALK-i. for the oncogenic *ALK*ATI isoform: 3. C) CDK4/6-i. for CDKN2A loss: 1. D) checkpoint-i. for mutation burden > 100: 3. E) For the other alterations no off-label treatment was available: mutation of *BAP1:* 8 or *SF3B1: 10,* overexpression of *MYC*: 14, *BCL2*: 24, *CCND2*: 16, *ERBB3*: 5 , biallelic loss of TNFAIP3: 1. Among novel non-recurring gene-fusions: inactivating gene fusion affecting MITF: 1. In 1 patient repeated biopsies at time of recurrence after MEK-i disclosed biallelic loss of *CDKN2A*. The pharmacodynamic modeling confirmed TREc in 10 and helped with the decision in 8 patients. A treatment was initiated in 15 patients: Trametinib: 6, Cabozantinib: 3, Crizotinib: 6, Palbociclib: 1. A treatment was not initiated for 8 patients: 4 too early, 4 rapid progression. Among the 12 evaluable patients the antitumor response was: minor response: 2, stable disease: 4, progressive disease: 5, too early: 1. Median PFS of the treated patients: 5,5 months.

Conclusions:
Precision medicine in mUM is clinically feasible. It leads to a better understanding of the biology of the tumour and of the potential therapeutic targets. Its clinical efficacy is limited by the non-availability of drugs as single agent or in combination. Clinical trial information: EA4/063/13.

"Abstract 9592: Liver-directed Treatment for Patients with Uveal Melanoma Hepatic Metastasis: A Retrospective Analysis of Overall Survival"

Authors: Rino S Seedor, David J. Eschelman, Carin F. Gonsalves, Robert D. Adamo, Marlana M. Orloff, Anjum Amjad, Erin Sharpe-Mills, Ryan Michael Weight, Allison Gradone, Carol L Shields, Jerry A Shields, Michael J. Mastrangelo, Takami Sato

Retrieved from: https://meetinglibrary.asco.org/record/163666/abstract

Background:
Despite successful treatment of primary uveal melanomas, up to 50% of patients subsequently develop systemic metastasis, with the liver involved in up to 90% of patients. At our institution, recognition of the poor prognosis associated with liver metastasis has led to the use of various liver-directed treatment modalities including transarterial chemoembolization (TACE) with BCNU, drug-eluting beads with doxorubicin (DEBDOX), immunoembolization (IE) with GM-CSF, and radioembolization with Yttrium 90 radioactive microspheres. The purpose of this study is to compare overall survival between uveal melanoma patients with hepatic metastasis before and after the shift of initial treatment from systemic to liver-directed approaches.

Methods:
A retrospective single-institution chart review was performed on consecutive series of uveal melanoma patients with hepatic metastasis who were treated at Thomas Jefferson University between 1971–1993 (Cohort 1, n = 98) and 2000–2017 (Cohort 2, n = 634). The following data was collected from medical records: primary tumor stage and genetic abnormalities, primary eye treatment, date to hepatic and extra-hepatic metastasis, types of liver-directed and systemic treatments utilized, and date of death. Time from development of hepatic metastasis to death (OS-Liver) and time from initial treatment of primary uveal melanoma to death (OS-Eye) in individual cohorts were measured and analyzed.

Results:
81% of cohort 1 patients received systemic chemotherapy as their initial treatment for liver metastasis, while 91% of cohort 2 patients (n = 574) initially received liver-directed treatments including IE (n = 296), BCNU TACE (n = 147), DEBDOX (n = 45), radioembolization (n = 37), and other liver-directed treatments (n = 49). OS-Liver in cohort 1 and cohort 2 was 4.8 months and 16.4 months, respectively ($P < 0.001$). More importantly, OS-Eye in cohort 2 (5.1 years) is much longer than that of cohort 1 (3.3 years) ($P < 0.001$).

Conclusions:
Liver-directed treatments provided significant survival benefit for uveal melanoma patients with hepatic metastasis.

"Abstract 9539: Radioembolization for Treatment of Uveal Melanoma Hepatic Metastasis: Results of a Phase II, Single Institution, Prospective Trial"

Authors: Carin F. Gonsalves, David J. Eschelman, Robert D. Adamo, P. Rani Anne, Marlana M. Orloff, Takami Sato

Retrieved from: https://meetinglibrary.asco.org/record/163597/abstract

Background:
The liver is the first site of metastasis in > 90% of uveal melanoma (UM) patients. Transarterial catheter directed therapies have been used to control growth of liver tumors and prolong overall survival (OS). We report results of the first prospective, phase II trial using radioembolization ([RE] Y-90 resin microspheres) for treatment of UM hepatic metastases.

Methods:
Between November 2011 and January 2017, RE was performed on 24 treatment naïve patients [Group A (13 men; median age 63; range, 29 -77)] and 24 patients who progressed after immunoembolization [Group B (9 men; median age 59, range, 34-77)]. Patients received unilobar or lobar treatments separated by 3-5 weeks. Patients were followed for 1 month for acute toxicity and every 3 months for delayed toxicity (CTCAE v 3.0). MR, CT and PET imaging was obtained every 3 months to evaluate for tumor response (PFS; RECIST) and extrahepatic disease.

Results:
Group A: Unilobar (n = 7) or bilobar (n = 17) RE was performed (median dose, 32.6 mCi; range, 17.7-56.1). One patient was removed from the trial for incomplete lobar treatment. RE response included PR (n = 7), SD (n = 13) and PD (n = 3). Median PFS was 8.1 months (range, 3.3 - 33.7). Median OS was 18.9 months (range, 6.5 -66.9) with 4 surviving patients (range, 14.0-66.9 months). One year survival was 61%. Extrahepatic disease occurred in 17 patients (median, 6.3 months; range, 3.3 – 11.9). Group B: Unilobar (n = 5) or bilobar (n = 19) RE was performed (median dose, 35.0 mCi; range, 19.2 -50.8). RE response included PR (n = 6), SD (n = 8) and PD (n = 10). One patient withdrew from the trial. Median PFS was 4.3 months (range, 2.5 -18.6). Median OS was 19.1 months (range, 4.8-68.4) with 5 surviving patients (range, 18.6 – 68.4 months). One year survival was 70%. Extrahepatic disease occurred in 15 patients (median, 5.5 months; range 0.8-9.9). No procedure-related complications occurred. Grade 3 treatment-related toxicities included transient leukopenia (n = 2), nausea/vomiting (n = 1) and pain (n = 1).

Conclusions:
RE is a safe and effective treatment for UM hepatic metastases and should be considered as a treatment option for patients with and without prior transarterial catheter directed therapies. Clinical trial information: NCT01473004

“Abstract 2589: Phase 1 Study of Pegargiminase Combined with Cisplatin and Pemetrexed in Patients with ASS1-Deficient Uveal Melanoma”

Authors: Pui Ying Chan, Melissa Mary Phillips, Ramsay Khadeir, Stephen Ellis, Jim Thomson, Amanda Johnston, Xiaoxing Feng, Bor-Wen Wu, John S. Bomalaski, Michael Sheaff, Peter Wojciech Szlosarek

Retrieved from: https://meetinglibrary.asco.org/record/158623/abstract

Background:
Argininosuccinate synthetase (ASS1) loss is a biomarker to select for tumors sensitive to arginine deprivation therapy. In a phase 1 dose-escalation study of ASS1-deficient thoracic cancers, we demonstrated tolerability and a high disease control rate using weekly pegargiminase (ADI-PEG 20) combined with first-line pemetrexed (PEM) and cisplatin (CIS) chemotherapy (Beddowes *et al*., JCO 2017; ADIPEMCIS). Here, we report the safety and early activity of ADIPEMCIS in an expansion cohort of patients (pts) with metastatic uveal melanoma (UM).

Methods:
Chemotherapy naïve pts aged 18 years or older with ASS1-deficient, histologically proven metastatic UM were eligible. ADI-PEG 20 (36 mg/m2 i.m.) was administered weekly together with PEM (500mg/m2) and CIS (75 mg/m2) every 3 weeks for a maximum of 18 weeks. Pts with stable disease or better were eligible to continue on ADI-PEG 20 until disease progression. Adverse events (AEs) were graded using CTCAE v4.03. Radiological response was assessed by CT or MRI every 6-8 weeks according to RECIST 1.1, alongside pharmacodynamic and immunogenicity analyses, median progression-free and overall survival (PFS and OS) estimates.

Results:
10 of 14 screened pts with ASS1-ve metastatic UM received ADIPEMCIS with a median of 1 line of prior therapy (i.e. ipilimumab monotherapy; range 0 to 5). Treatment was well tolerated; neutropenic sepsis was the only grade 3 AE (n = 1 pt). The best response was stable disease with a median PFS of 3.0 months (range, 1.3 to 8.1 months) and a median OS of 11.5 months (range, 3.2 to 24.0+ months). Despite the emergence of anti-ADI-PEG 20 antibodies, plasma arginine concentrations remained low by 18 weeks with a reciprocal increase in plasma citrulline. Tumor rebiopsies at progression revealed ASS1 re-expression (n = 2/2 pts).

Conclusions:
ADIPEMCIS is well tolerated and has activity in metastatic UM, for which there is no established therapy. Based on recent preclinical data showing synthetic lethality of combining ADI-PEG 20 with PD-1/PD-L1 inhibition, a phase 1 study of ADI-PEG 20 with immune checkpoint blockade is planned in advanced UM. ClinicalTrials.gov identifier: NCT02029690.
Clinical trial information: NCT02029690