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08:00–08:07

ILLUMINATE 301: A randomized phase 3 study of tilsotolimod in combination with ipilimumab compared with ipilimumab alone in patients with advanced melanoma following progression on or after anti-PD-1 therapy

By Butler MO, Robert C, Negrier S, In GK, Walker J, Krajsova I, Atkinson V, Hansson J, Kapiteijn EH, Loquai C, Shaw H, Cheng T, Mansard S, Grob JJ, Guidoboni M, Mehta M, Ascierto PA, Diab A.

Princess Margaret Cancer Center, Toronto, CA; Institut Gustave-Roussy and Paris-Sud University, Villejuif Paris-Sud, FR; Centre Léon Bérard, Lyon, FR; Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, US; Cross Cancer Institute, Edmonton, CA; Charles University, Prague, CZ; Gallipoli Medical Research Foundation and University of Queensland, Brisbane, Australia; Karolinska Institutet, Stockholm, SE; Leiden University Medical Center, Leiden, NL; University Hospital of Mainz, Mainz, DE; University College London, London, UK; Tom Baker Cancer Centre, Calgary, AB; Dermatology Department, CHU de Clermont Ferrand, Clermont Ferrand, FR; Aix-Marseille University, Marseille, FR; Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola (FC), IT; Idera Pharmaceuticals, Inc., Exton, US; Istituto Nazionale dei Tumori IRCCS Fondazione, Naples, IT; University of Texas MD Anderson Cancer Center, Houston, US.

Background
Tilsotolimod (IMO-2125) is a Toll-like receptor (TLR) 9 agonist with potent immunostimulating activity. In an ongoing Phase 1/2 clinical study in patients with advanced melanoma who progressed on or after anti-PD-1 therapy (NCT02644967), intratumoral (IT) tilsotolimod with ipilimumab was well-tolerated, demonstrating durable responses (including complete response >21 months), dendritic cell activation, type I interferon response, CD8+ T-cell proliferation in responders, and an abscopal effect.1–2

Methods
ILLUMINATE 301 (NCT03445533) is a randomized phase 3 global, multi-center, open-label study of IT tilsotolimod (8 mg) in combination with ipilimumab (3 mg/kg) versus ipilimumab monotherapy in patients with advanced melanoma and progression on or after anti-PD-1 therapy. Eligible patients are ≥18 years with histologically confirmed unresectable Stage III or Stage IV melanoma, ≥1 measurable lesion accessible for injection (superficial or visceral, the latter with image guidance), ECOG PS ≤1, and adequate organ function. Exclusion criteria include prior TLR agonists, prior ipilimumab (except adjuvant ≥12 weeks before progression), and CNS disease other than stable brain metastases. Patients are randomized 1:1 and stratified by duration of prior anti-PD-1 (≥12 weeks vs <12 weeks), stage (M1c vs other), and BRAF status/prior targeted therapy (TT) (BRAF wildtype vs BRAF mutation+ with TT vs BRAF mutation+ without TT). Primary endpoints are overall response rate (RECIST v1.1) by independent central review and overall survival. Secondary endpoints include durable response rate, time to response, progression-free survival, patientreportedoutcomes, and safety. Patients are enrolling at sites in the United States, European Union, Australia, and Canada.

Management of Basosquamous Carcinoma and The Use of Full Thickness Skin Graft for Reconstruction of Temple Defect

2
08:10–08:17

By Isa Al-Alwani, *Ahmed alasfoor*
Fadi Al Tawash, *Salmaniya Medical Complex, Bahrain*

Backgound
Basosquamous Carcinoma (BSC) is a rare aggressive epithelial neoplasm with features of both basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), with a propensity toward local recurrence and a tendency for lymph node and distant metastases. Common sites are the head and neck. It has significant predominance in Caucasian males. In contrast, SCC is uncommon in middle-eastern individuals. The aim of the present study was to report the case of a 70-year-old Middle Eastern female with BSC in the temporal region and its effective surgical management from Plastic and Reconstructive Surgery point of view.

Case presentation
A 70-year-old Bahraini female, without any significant past medical history, presented with a well circumscribed 4.5 cm x 4 cm x 0.8 cm, ulcerated nodular mass of the left temple which had not healed for five years. Excisional biopsy with 1 cm margins and deep to the temporalis muscle was done. It was followed by an immediate full thickness skin graft(FTSG) which was applied on the defect. Histopathology report showed that all peripheral and deep margins are free of tumor with a final diagnosis of aggressive BCC of Basosquamous subtype pT3 . No radiotherapy followed and she was followed up to 6 months with no signs of recurrence. The patient had good recovery with satisfactory wound healing. Discussion: To our knowledge, radical excision of BSC of the temple and closure of extensive temple defect using FTSG has rarely been described. The following example serves to illustrate the principle and feasibility of this reconstructive approach to prevent the high rate of recurrence and metastasis.

3
08:20–08:27

1-year (yr) recurrence-free survival (RFS) from a randomized, open-label phase 2 study of neoadjuvant (neo) talimogene laherparepvec (T-VEC) plus surgery (surgx) vs surgx for resectable stage IIIB-IVM1a melanoma (MEL).

By Reinhard Dummer, David E Gyorki, John Hyngstrom, Adam Berger, Robert Conry, Lev Demidov, Anjali Sharma, Sheryl A Treichel, Mark Faries, Merrick I Ross

University Hospital of Zurich, Zurich, Switzerland; Olivia Newton-John Cancer Centre, Austin Health, Melbourne, Australia; University of Utah Huntsman Cancer Institute, Salt Lake City, UT; Thomas Jefferson University Hospitals, Philadelphia, PA; University of Alabama School of Medicine, Birmingham, AL; N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; Amgen Inc., Thousand Oaks, CA; John Wayne Cancer Institute, Santa Monica, CA; University of Texas MD Anderson Cancer Center, Houston, TX

Background

We previously reported that neo T-VEC + surgx resulted in a pathologic CR rate of 21% and an OR rate of 14.7% in a randomized trial of neo T-VEC + surgx vs upfront surgx in pts with resectable stage IIIB/C/IVM1a MEL (Andtbacka et al, ASCO 2018; NCT02211131). Here, we present results from an interim 1-yr analysis of RFS.

Methods

Patients (pts) with resectable stage IIIB/C/IVM1a MEL, ≥1 injectable cutaneous, subcutaneous, or nodal lesions ≥ 10 mm, and no systemic tx 3 mos prior were randomized 1:1 to 6 doses/12 wks of T-VEC followed by surgx during wks 13-18 (Arm 1) vs upfront surgx during wks 1–6 (Arm 2). T-VEC was given at standard dosing until surgx, no injectable tumors, or intolerance. This analysis conducted on the ITT set estimated a between-group difference in 1-yr RFS per protocol. An RFS event was defined as the first of local, regional or distant recurrence or death due to any cause after surgx. Pts without a R0 surgical outcome or withdrew prior to surgx were considered an event at randomization for RFS. In a sensitivity analysis, RFS was calculated from randomization to the date of the first post-surgx event regardless of surgical outcome.

Results

150 pts were randomized (76 Arm 1, 74 Arm 2). Median (range) follow-up time was 20.6 (0.1, 38.5) mos in Arm 1 and 20.0 (0.1, 35.3) mos in Arm 2. 75% in Arm 1 and 93% in Arm 2 had surgx as planned. R0, R1, and R2 rates, respectively, for Arm 1 were 42.1%, 31.6%, and 1.3% and for Arm 2 were 37.8%, 51.4%, and 4.1%. At 1 yr, 33.5% of pts in Arm 1 and 21.9% of pts in Arm 2 remained recurrence free (HR 0.73, P=0.048). From the sensitivity analysis, 55.8% of pts in Arm 1 and 39.3 % in Arm 2 remain recurrence free at 1 yr (HR 0.63, P=0.024). OS rates at 1 yr were 95.9% in Arm 1 and 85.8% in Arm 2 (HR 0.47, P=0.076). Pts receiving subsequent adjuvant tx was 8 (11%) in Arm 1 and 20 (29%) in Arm 2- most common was immunotherapy 6 (8.2%) and 8 (11.6%), respectively.

Conclusions

In the largest randomized neo trial to date in resectable stage IIIB-IVM1a MEL, the following outcomes were improved with neo T-VEC monotherapy vs surgx: R0 surgical resections, 1-yr RFS, and OS. Primary analysis of RFS at 2 yrs is expected.

Impressive remission under therapy with the PD-1-antibody cemiplimab in locally metastatic squamous cell carcinoma of the capillitium

4
08:30–08:37

By K. Kosova, A.Bohne, A. Hauschild, K.C. Kaehler
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Background
Squamous cell carcinoma of the skin (CSCC) shows a high UV-related tumor mutation burden and metastasizes in about 5% of all cases. Tumors with high mutation burden show better remission rates under immune checkpoint inhibitors like anti-PD-1 antibodies. The anti-PD-1 antibody cemiplimab has a response rate of approximately 50% and was approved by the FDA for a treatment of metastatic and locally advanced CSCC in September 2018. EMA approval is expected in 2019.

Case report
An 86-year-old patient with a previously resected right temporal CSCC primary tumor (tumor thickness: 3.3 mm) was admitted in June 2016 to the ENT clinic with a cervical lymph node metastasis. The patient underwent a neck dissection of the region II-V on the right side with a partial resection of the sternocleidomastoid muscle and branches of cervical plexus. The patient was evaluated at our clinic in October 2016. He had a local recurrence of CSCC in the ipsi- and contralateral cervical and supraclavicular lymph nodes as well as in his right axillary lymph nodes. Furthermore, the staging revealed a lung metastasis and multiple mediastinal metastases. Due to the extensive findings we needed to give the patient a systemic therapy. Fortunately, the Regeneron study for a metastatic CSCC with anti-PD-1 antibody cemiplimab (REGN2810) was recruiting at the moment and the patient was included in the study. The therapy was initiated with a dosage of 3 mg/kg body weight of cemiplimab every 2 weeks.
The patient's metastatic growth stopped after the second infusion. The first reevaluation after 8 weeks showed an impressive decrease in size of all metastases. After 6 months of the therapy all metastases were in a complete remission.
Except for a mild fatigue syndrome, the patient had no significant side effects related to the treatment. Despite the patient's high age and severity of his disease, the treatment with cemiplimab significantly improved his quality of life.

Summary
The anti-PD-1 antibody cemiplimab presents a highly efficient therapy option for metastatic CSCC with a short response time as showed in this particular case. Cemiplimab should be approved by EMA in June 2019. An adjuvant study for the CSCC (REGN1788) will initiate shortly.

5
08:40–08:47

Redirected T cell mediated lysis in patients with metastatic uveal melanoma with gp100-directed TCR tebentafusp: Overall survival findings

By Takami Sato, Paul D. Nathan, Leonel Hernandez-Aya, Joe J. Sacco, Marlana Orloff, Frank Engler, Nicola Little, Rachael Easton, Rich D. Carvajal
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Clinical Development, Immunocore, Oxford, United Kingdom Therapeutics/Melanoma Service, Columbia University Medical Center, New York, NY, United States

Background
Whilst significant advances have been made in the treatment of cutaneous melanoma, there remains an acute need for effective treatments in metastatic uveal melanoma (mUM). Tebentafusp is a first-in-class bispecific biologic, capable of engaging and redirecting CD3+ T cells against melanocyte-associated antigen gp100, resulting in lysis of gp100+ target cells. In this Phase 1/2 study safety, preliminary efficacy and recommended Phase 2 (Ph2) dose of tebentafusp in mUM were investigated.

Methods
In Phase 1 (Ph1), n=19 human leukocyte antigen (HLA)-A*02:01+ patients (pts) with mUM received tebentafusp weekly in escalating doses: Cycle 1, Day 1 (C1D1) 20 µg, C1D8 30 µg and 54, 64, 68 or 73 µg at C1D15 and beyond. All pts had ECOG PS ≤1 and liver metastases; 16/19 were previously treated for mUM: 12/19 received liver-directed therapy and 14/19 systemic therapy. Ph2 is ongoing: n=130 HLA-A*02:01+ pts with mUM will receive tebentafusp (same schedule as Ph1 but 68 µg from C1D15).

Results
In Ph1, median treatment duration was 13, 4-week cycles. All pts experienced related adverse events (AEs), including pruritus (90%), pyrexia and fatigue (84%), and hypotension (74%). Most frequent grade 3/4 AEs included aspartate aminotransferase elevation, fatigue, hypotension and erythema (all 16%), with no treatment discontinuations or deaths. Partial responses were confirmed for 3/17 pts (18%, median duration 31 [17–64] weeks), and 9/17 (53%) had stable disease. One-year overall survival (OS) rate was 74% (95% CI: 48–88); median OS was not reached (median follow-up 19.1 months). A pharmacokinetic/pharmacodynamic (PK/PD) model showed a relationship between tebentafusp dosing, exposure and repeated transient decreases in peripheral lymphocyte count (PLC). In addition, decreased PLC paralleled increased T cell infiltration observed in tumor biopsies. Pooled analysis (n=32) of Ph1 and early Ph2 pts demonstrated an association of OS with more severe skin toxicities, potent IL-6 responses, hypotension and lymphocyte trafficking.

Conclusions
The intra-patient escalation dosing regimen of tebentafusp was tolerable and demonstrated encouraging OS compared to historical data. An association of OS with rash severity was observed. PK/PD modeling showed a relationship between lymphocyte trafficking and exposure to tebentafusp. The Ph2 expansion of this study and a separate Ph2 pivotal study (IMCgp100-202) in previously untreated HLA-A*02:01+ pts with mUM are ongoing.

Patient-reported quality of life (QoL) of advanced melanoma patients in a Phase 3 study of nivolumab (NIVO) with or without ipilimumab (IPI) versus IPI: CheckMate 067 4-year data

6
08:50–08:57

By D. Schadendorf, J. Larkin, J. D. Wolchok, V. Chiarion-Sileni, F. Taylor, R. Lawrance, A. Moreno-Koehler, J. Lord-Bessen, J. I. Rizzo, A. Moshyk, S. Kotapati, F. S. Hodi
Universitaetsklinikum Essen & German Cancer Consortium, Essen, Germany; Royal Marsden NHS Foundation Trust, London, UK; Memorial Sloan Kettering Cancer Center, New York, NY, USA; Weill Cornell Medical College, New York, NY, USA; Veneto Oncology Research Institute, Padua, Italy; Adelphi Values, Boston, MA, USA; Adelphi Values, Bollington, Cheshire, UK; Bristol-Myers Squibb, Princeton, NJ, USA; Dana-Farber Cancer Institute, Boston, MA, USA

Background
Early CheckMate 067 data showed maintenance of QoL in patients with advanced melanoma treated with NIVO with or without IPI based on 1-year data; however, the long-term QoL of these patients has not been evaluated previously. The patient-reported outcomes (PRO) analyses presented here for CheckMate 067 is the first time QoL results have been evaluated in this melanoma population over a 4-year period.

Methods
In CheckMate 067, 945 patients were randomized 1:1:1 to receive NIVO (3mg/kg Q2W) + placebo (PBO), NIVO+IPI (1mg/kg+3mg/kg Q3W × 4) followed by NIVO (3mg/kg Q2W), or IPI (3mg/kg Q3W × 4) + PBO. PRO data were collected using the EORTC QLQ-C30 (5 functional domains, 9 symptoms, global health status) and EQ-5D-3L (utility index, VAS) at baseline, weeks 1 and 5 of each 6-week tx cycle, and off-tx follow-up (FU) visits. Mean changes in PRO scores from baseline (randomization) were evaluated descriptively for the PRO analysis population, with conclusions drawn from time points with ≥30 patients completing assessments per tx arm. Least square mean changes from baseline were assessed using a longitudinal mixed model analysis adjusting for repeated measures, including all on-tx data for patients.

Results
Completion rates at baseline ranged from 89-92% across tx arms. Of 813 patients included in the PRO analysis population (278 NIVO, 274 NIVO+IPI, 261 IPI), >200 receiving tx remained for the first year, >100 receiving tx remained after 2 years, and >50 receiving tx remained after 3 years. QoL, including assessment of functioning and symptom burden, was maintained for the duration of tx and in FU, with no sustained clinically meaningful deterioration in any tx arm. Global health status (EORTC QLQ-C30) and general QoL (EQ-5D-3L VAS) were also maintained during prolonged tx. Overall, results from the mixed model analysis support the long-term maintenance of QoL over the course of tx.

Conclusions
Patient-reported QoL and symptoms in patients with advanced melanoma were maintained from baseline during extended tx with NIVO with or without IPI.

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1 Mucositis of the upper intestinal tract – a rare adverse event in combined immune checkpoint inhibition therapy in a patient with metastasized malignant melanoma

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Background
Therapy with combined immune checkpoint inhibition in patients with metastatic melanoma can cause immune related adverse events. One of the most common one is colitis, therefore every clinician administering this therapy is well aware of the symptoms. But so far only four cases of upper gastrointestinal tract autoimmune adverse events have been described – therefore this side effect is easily missed.

Case Report
In December 2017 a 62 year old patient presented herself with weight loss of 8 kilograms, inappetence, nausea, but denied diarrhea after having received three doses of ipilimumab and nivolumab for metastasized malignant melanoma. C-reactive protein levels were slightly elevated (18.1 mg/l; normal range < 5.0 mg/l) with normal white blood cell count. Abdominal ultrasound was performed and revealed thickening of the wall of the pyloric orifice. Gastroscopy showed extensive erythema with desquamation of the esophagus, gastric wall and bulbus duodeni, hence mucositis of the upper gastrointestinal tract was diagnosed and confirmed by punch biopsy. Calprotectin levels in the patients feces were 2731.0 mg/kg (normal range: ≤ 50 mg/kg).
The patient received prednisone (2 mg/kg/day) intravenously along with a proton pump inhibitor therapy. Only after a few administrations of therapy the patient's symptoms improved and prednisone dosage was reduced gradually by 25% every third day. Since toxicity declined the patient was able to continue combined immune therapy. Although no change regarding the inflammatory process was observed in the subsequent gastroscopy the patient's symptoms were regressive and calprotectin levels were lower (798.0 mg/kg; normal range: ≤ 50 mg/kg). Follow-up gastroscopy was performed after terminating the proton pump inhibitor therapy only showing minor inflammatory lesions of the gastric antrum. Until today the patient still needs intermittent proton pump therapy but has received 15 administrations of nivolumab monotherapy as maintenance therapy. Persisting inflammatory lesions of the oral mucosa are well controlled with topical administration of prednisone oral paste and lidocaine hydrochloride oral gel. The specific tumor marker S100 is within the normal range again (0.06 µg/l; normal range: <0.11 µg/l). Until today the patient shows a partial remission.

Conclusion
Rare immune related adverse events such as mucositis of the upper gastrointestinal tract should be kept in mind when treating patients with combined immune therapy and do not necessarily dictate a change in treatment regimen.

Inhibition of RSK family members can effectively target malignant melanoma cells with MAPK pathway hyperactivation

2

By Corinna Kosnopfel, Tobias Sinnberg, Heike Niessner, Anja Schmitt, Elena Makino, Sandra Dunn, Claus Garbe, Birgit Schittek
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The MAPK signalling pathway is frequently hyperactivated in malignant melanoma and plays a central role in tumour cell proliferation and survival. Accordingly, its inhibition has proved to be an efficient treatment option in melanomas harbouring BRAF mutations. However, there is still a considerable need for effective targeted therapies for other melanoma subgroups with constitutive MAPK activation, such as RAS and NF-1 mutated tumours, as well as for therapeutic options targeting MAPK pathway inhibitor resistant BRAF mutated melanomas, which commonly exhibit a striking reactivation of this pathway. The p90 ribosomal S6 kinases (RSKs) are central effectors of MAPK signalling regulating cell cycle progression and survival.
Indeed, we can show an increased RSK activity going along with a MAPK pathway hyperactivation in BRAF mutated melanoma cells. Interestingly, RSK inhibition can effectively target those cells, particularly in the case of MAPK pathway inhibitor resistance. In line with an enhanced activity of the MAPK pathway based on activating RAS mutations or loss-of-function of the tumour suppressor NF-1, the anti-tumoural activity of RSK inhibitors appears to extend to melanoma cells of these genetic subgroups.

Conclusion
Overall, these data indicate a potential general usefulness of the p90 ribosomal S6 kinase family members as prospective targets in malignant melanoma with hyperactivated MAPK signalling pathway.

3 Queen Alexandra Hospital Melanoma Service Development Joint Working Project 2017–2018

By H. Wilkes, S. Ellis, A. Suovuori, CC. Yeoh, A. Virgo, B. Howson, S. Philp, A. Greenhalgh
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Background
Queen Alexandra Hospital, Portsmouth Hospitals NHS Trust (PHT) is a Cancer Centre covering a population of 2.5 Million. A Joint working project (JWP) was set up between Novartis and PHT Oncology to develop a new advanced Melanoma service. Previously, patients with locally advanced or metastatic melanoma travelled to University Hospital Southampton. A Clinical Nurse Specialist (CNS) was identified to support outpatient clinics, lead dedicated telephone clinics, provide tailored support and facilitate pathway coordination. The melanoma service also aimed to reduce patient travel time and distance, reduce time from decision to treatment, assess patient satisfaction, generate melanoma treatment algorithms and surveillance guidelines.

Method
A JWP Agreement for the pooling of resources, milestones and timelines between Novartis and the Trust was completed. Novartis funded a melanoma band 7 CNS for 12 months. The NHS team provided clinical oversight, CNS training and generated a service protocol, treatment algorithms, surveillance guidelines, patient satisfaction assessment and business case. Baseline patient experience data, travel time and distance, and time until treatment was collected prior to the JWP and at 12 months following commencement.

Results
Over the 12 month period the Melanoma service at PHT saw a CNS-supporting Consultant clinics and CNS led telephone clinic. The CNS undertakes clinical reviews and tailored support for patients. A business case secured permanent CNS-funding, service protocol, melanoma treatment algorithms and surveillance guidelines were created. Average reduction in miles travelled by patients was 36 to 15 (42%). Average reduction in minutes travelled from 60 to 33 (55%). MDT discussion to treatment was reduced from 17.5 days in 2017 to 8.8 days in 2018. Patient satisfaction results (n=14): 92% felt time waiting in clinic about right; 86% understood all/some of the explanations given;100% agreed their views were taken into consideration. All patients knew who to contact if they had concerns after leaving hospital.

Conclusions
PHT now has a fully comprehensive advanced Melanoma service providing systemic treatment and follow-up for patients. The patient satisfaction survey results show excellent feedback for the CNS led activities and service as a whole. The business case was successful and the role is now a permanent position, which maintains patient safety, quality of care and patient satisfaction.

Real-world patient (pt) profiles and clinical outcomes among pts with BRAF-positive advanced melanoma treated with first-line (1L) anti-PD1 monotherapies (anti-PD1 mono) or BRAF/MEK inhibitor combination (BRAF/MEKi) therapy in the United States (US) community oncology setting.

By C. L. Cowey, E. Taymor, M. Boyd, K. M. Aguilar, C. Krepler
Texas Oncology/US Oncology; Merck & Co., Inc.; McKesson Life Sciences

Background
While clinical trials have demonstrated favorable safety and efficacy profiles for anti-PD1 mono (pembrolizumab and nivolumab) and BRAF/MEKi, optimal 1L advanced melanoma treatment remains uncertain. This study assessed pt characteristics and clinical outcomes among BRAFpositive advanced melanoma pts initiating anti-PD1 mono or BRAF/MEKi therapy in the US.

Methods
This was a retrospective cohort study of adult BRAF-positive advanced melanoma pts who initiated 1L anti-PD1 mono or BRAF/MEKi therapy within the US Oncology Network (USON) between 1/1/14–12/31/16. Study data were sourced from USON's electronic health records and pts were followed through 1/1/17. The Kaplan-Meier (KM) method was used to descriptively evaluate overall survival (OS) and progression-free survival (PFS) from initiation of 1L therapy. Multivariable Cox regression models were constructed to evaluate independent risk factors for OS and PFS.

Results
Among the 186 pts included, 52 received anti-PD1 mono and 134 BRAF/MEKi. The median age of the study population was 61 years (range 26,90+), with 93.0% Caucasian and 63.4% male. Based on KM estimates, median OS was 24.3 mo (95% confidence interval [CI] 19.6, not reached [NR]) among anti-PD1 mono pts and 13.9 mo (95% CI 11.5,31.2) among BRAF/MEKi pts (log-rank P=0.0320). Median PFS was 6.1 mo (95% CI 4.2,15.8) among anti-PD1 mono pts and 6.5 mo (95% CI 5.3,7.7) among BRAF/MEKi pts (log-rank P=0.0354). Based on the multivariable Cox regression analysis, age at 1L treatment initiation (hazard ratio [HR] 1.037 with each year increase [95% CI 1.018,1.056]; P<0.0001) and presence of brain metastases (HR 1.911 [95% CI 1.231,2.968]; P=0.0039) were associated with increased risk of death, while receipt of anti-PD1 mono was associated with lower risk of death (HR 0.554 vs. BRAF/MEKi [95%CI 0.328,0.937]; P=0.0275). Prior surgical resection was associated with lower risk of progression or death (HR 0.662 [95% CI 0.465,0.944]; P=0.0226).
During the first 6 mo of follow-up, 1L treatment was not significantly associated with PFS; among pts who had not progressed or died within 6 mo, receipt of anti-PD1 mono was associated with lower risk of progression or death (HR 0.223 vs. BRAF/MEKi [95% CI 0.094,0.532]; P=0.0007).

Conclusions
These results suggest that receipt of 1L anti-PD1 mono is associated with favorable OS compared to BRAF/MEKi. Future research should explore factors that contribute to progression or death before and after 6 mo.

5 Combination of PD1 inhibitor and targeted therapy in advanced BRAF-V600E mutant melanoma: a report of five cases

By N. Frischhut, K. Neubauer, F. André, J. Umlauft, D. Dewasurendra, M. Schmuth and V.A. Nguyen
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Background
The aim of this compassionate pilot study was to evaluate the safety, tolerability and efficacy of a combined therapy of PD-1 blockade and targeted-therapy (triple therapy) in patients with advanced BRAF-mutant melanoma. In five patients we escalated therapy due to rapid progression or poor response to initial therapy.

Results
Five patients received triple therapy for 2.5–12 months. Three patients responded to triple therapy: one showed a partial response and two a complete response. The two patients with complete responses remained stable without further therapy for at least 8 months. One patient developed a grade 3 pneumonitis, requiring immunosuppressive therapy with corticosteroids and discontinuation of triple therapy, and subsequently succumbed to cerebral hemorrhage. Two patients died due to progressive disease.

Conclusion
Our preliminary results from compassionate use of triple therapy suggests efficacy. In all of our patients side effects emerged, but were manageable. Currently, the most effective first-line treatment regimens and the optimal sequencing of targeted therapy and immunotherapy are being addressed in ongoing prospective studies.
Keywords: advanced melanoma, BRAF mutation, targeted therapy, checkpoint immunotherapy triple combination

Sustainable responses in metastatic melanoma patients with/without brain metastases after immunotherapy induced CR

6

By Florentia Dimitriou, Egle Ramelyte, Clara Allayous, Camille L. Gérard, Katharina C. Kähler, Frédéric Toussaint, Sarah Schäfer, Reinhard Dummer, Joanna Mangana
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Department of Dermatology, University Hospital Schleswig-Holstein, Kiel, Germany;
Department of Dermatology, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Germany;
Department of Dermatology and National Center for Tumor Diseases, University Hospital Heidelberg, Germany

Background
Immunotherapy (IT) has demonstrated an improved overall survival (OS) in advanced melanoma with 15% complete responses (CR) in treatment-naïve patients (pts) with brain metastases (met) in the anti-PD1/anti-CTLA4 combination. To date, data on brain-met pts who discontinue treatment (EoT) after achieving a CR are lacking.

Methods
Disease characteristics and clinical outcome were retrospectively collected from 6 centers on advanced melanoma pts treated with anti-PD1 or anti-PD1/anti-CTLA4. Pts were followed for at least 10 weeks (10.8–242). Off-treatment survival (OTS) was defined as time between last IT dose to disease progression or death.

Results
Out of 890 pts, 62 achieved a CR; 40 pts stopped treatment due to CR, while 22 due to an adverse event (AE) (n=19) or investigator decision (n=3) with subsequent CR. 14 were treated with anti-PD1/anti-CTLA4 and 48 with anti-PD1. 24 had a BRAF mutation, of which 10 had previously received targeted therapy (TT). The median time to first CR was 31 weeks (6–138), median duration of response and OTS was 91.1 and 60.7 (10.6–242) weeks respectively. OTS was numerically longer for those pts with EoT after AE (85 weeks, 13-242) versus those with EoT due to CR (60 weeks, 11–130). Median OS was not reached. 6/62 (3%) progressed after EoT; 4 locoregionally while 2 were subsequently treated with IT. All pts were alive at last follow-up. 19 pts had brain mets. 8 were BRAF mutated. 10 were treatment naïve, 6 received previously anti-CTLA4, 1 chemotherapy and only 2 TT. Data on reasons for EoT and responses in brain mets are seen in Table 1.

Conclusions
Early data suggest that OTS is numerically longer in patients with EoT due to AE with subsequent CR. EoT due to sustained CR is a feasible option also in brain mets. EoT due to AE with subsequent CR was a more frequent event in the combination treatment.

7 Survival data of 10 patients treated with anti-PD1 immunotherapy for metastatic ocular melanoma. Single institute retrospective study.

By G. Pánczél, T. Balatoni, E. Imrédi, G. Liszkay
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Background
Uveal melanoma is the most common intraocular tumour in adults, and it represents 3–5 % of all melanomas. Its most common site for metastasis is the liver. The pathological background of uveal melanomas and the course of the disease are different than those of cutaneous melanomas. The outcomes of innovative therapies in uveal melanoma are ambiguous. Regarding survival, the best outcomes with anti-PD1 immunotherapy was 2.6–4.5 months median PFS in previous studies. The outcomes of the selective chemotherapy are in line with the results of the innovative therapies. In our study of 50 ocular melanoma patients treated with intra-arterial chemotherapy, the median PFS was 7 months.

Method
We processed the data of 10 metastatic ocular melanoma patients treated with anti-PD1 immunotherapy at the National Institute of Oncology between 2015 and 2018. Response rate, progression-free survival and overall survival were retrospectively determined. The analysis was performed using the Microsoft Office Excel program. Disease response was measured by iRECIST.

Results
5 female (50 %) and 5 male (50 %) patients were enrolled. The average age of the patients was 64y (49–79y) at the time of dissemination, and had a good performance status (ECOG 0–1). 6 patients had localised liver metastasis, and 4 patients had extrahepatic dissemination. 2 patients received anti-PD1 therapy in first-line, 6 patients in second line, and 2 patients received subsequent lines of therapy. 8 patients received pembrolizumab, 2 patients nivolumab immunotherapy. One of the nivolumab treated patients had prior ipilimumab therapy. 6 patients (60 %) received intra-arterial hepatic chemotherapy previously. At the time of analysis 6 patients (60 %) were alive. Of the patients, there was 1 partial remission, 4 stable disease and 5 progressive disease. No complete remission was observed. The median PFS was 5 months (2-15 months), and the median OS was 9 months (3–32 months). Toxicities were as expected.

Conclusion
Although this cohort of patients was small, the PFS and OS rates are in line with the data found in the literature. The PFS rate does not reach the result of the intra-arterial chemotherapy in our previous study (5 months vs. 7 months), nor the PFS rate of cutaneous melanoma (CheckMate 067: 6.9 months). Further development of immunology and molecular pathology may result in better therapeutic outcomes of uveal melanoma.

Raising MAPK pathway inhibition to a new level using ERK inhibitor combinations

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Abstract
The clinical availability of small molecule inhibitors specifically targeting BRAF mutated at V600 and its downstream target MEK marked a significant breakthrough in the therapy of BRAF mutant melanoma. Despite a vast anti-tumour activity and improved patient survival, rapidly emerging resistance to these inhibitors, however, greatly limits their clinical benefit. A large number of different resistance mechanisms have already been described, yet common to many of them is a reactivation of the MAPK signalling pathway. The extracellular signal-regulated kinases 1 and 2 (ERK1/2) represent the ultimate kinases and consequently the central effectors of the MAPK signalling cascade. Based on that, the aim of this study was to asses a potential benefit of the ERK1/2-specific small molecule inhibitor Ravoxertinib (GDC-0994) in the treatment of BRAF mutant melanoma cells.

To this end, melanoma cell lines with an acquired resistance to BRAF inhibitors or to the combination of BRAF and MEK inhibitors as well as the respective parental cells were tested. Intriguingly, long-term treatment with the ERK inhibitor could considerably reduce melanoma cell growth, which seemed to be independent of the sensitivity to BRAF or MEK inhibitors. Moreover, cell cycle analyses and cell viability assays revealed a distinct benefit of adding ERK1/2 inhibitor to BRAF and/or MEK inhibitors to effectively target the melanoma cells with BRAF mutation. These data suggest that combinatorial treatment regimens including ERK1/2 inhibitors might be an attractive therapeutic strategy in BRAF mutated melanoma cells.

9 Rapid and impressive remission under therapy with the PD-1-antibody pembrolizumab in locally metastatic squamous cell carcinoma of the capillitium

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Background
Squamous cell carcinoma of the skin (CSCC) shows a high UV-related tumor mutation burden and metastasizes in about 5% of all cases. Tumors with high mutation burden show better remission rates under immune checkpoint inhibitors like anti-PD-1 antibodies. The anti-PD-1 antibody cemiplimab has a response rate of approximately 50% and was approved by the FDA for a treatment of metastatic and locally advanced CSCC in September 2018. EMA approval is expected in 2019.

Case report
An 88-year-old patient with a previously resected right parietal CSCC primary tumor (tumor thickness: 7.5 mm) was admitted to our clinic in June 2018 with a local recurrence and multiple subcutaneous metastases at the capillitium. A parotidectomy with a neck dissection of the regio II on the left side due to a parotid metastasis as well as an operative removal of a occipital localized skin metastasis were performed in 2017. Due to the extensive local findings and consequent inoperability, we decided to start a treatment with anti-PD-1-antibody. It is known that this treatment is exteremely effective for patients with this diagnosis. The therapy was initiated with the anti-PD-1 antibody pembrolizumab (dosage 2 mg/kg body weight every 3 weeks) which is approved for a treatment of other tumors in Germany. The treatment started as soon as we received the payment authorization from the patient's insurance company.
The multiple erythematous, partly ulcerated metastases with an initial size of 4x3 cm were decreasing in size after the first infusion and were almost fully regressive after 12 weeks of the therapy. After 6 months of the therapy, all tumors including the accompanying actinic keratoses were in a complete remission.
Except for a mild fatigue syndrome, the patient had no significant side effects. We achieved a significantly improved quality of life even for the patient in such a high age with previously unresectable disease.

Summary
The PD-1 antibody pembrolizumab presents a highly efficient therapy option in the inoperable CSCCs with a short response time as showed in this particular case. The PD-1 antibody pembrolizumab is currently undergoing a pivotal trial (KEYNOTE-629) for the CSCC indication internationally and an adjuvant study (KEYNOTE-630) for the CSCC will initiate shortly.

Pharmacologically active high-dose Vitamin C blocks Melanoma Cell Energy Metabolism and efficiently inhibits Tumor Growth in vitro and in vivo

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Abstract
In recent years, we and others have discovered that high-dose vitamin C paradoxically acts as a prooxidant and causes the formation of a large amount of hydrogen peroxide in an oxygen pressuredependent manner, especially in extracellular space. This formation of reactive oxygen species (ROS) could not be compensated by tumor cells, especially melanoma cells, but was rather well tolerated by benign cells such as fibroblasts. Therefore, ROS formation by high-dose vitamin C could be an attractive approach to treat therapy-refractory melanomas such as melanoma metastases with primary resistance to immunotherapy or tumors with secondary resistance to targeted therapies such as BRAF plus MEK inhibitor combinations. Vitamin C is mainly transported into the cancer cell by the facilitative glucose transporter GLUT1 in its oxidized form and by the ATP-dependent sodium transporters SVCT1/2 in its reduced form. Therefore, we have speculated whether there are additional intracellular effects of vitamin C that support the cytotoxicity of vitamin C in high concentrations. Besides the rapid formation of hydrogen peroxide, we have measured a rapid degradation of cellular ATP and a rapid decrease of reduced glutathione (GSH) and NADPH. The decrease in ATP levels coincided with the end of glycolysis in vitamin C-treated melanoma cells. Energy metabolism blockade and redox homeostasis disorder were observed in both NRAS- and BRAF-mutated cell lines. Melanoma cell lines that are resistant to BRAF + MEK inhibitors were similarly sensitive to the induction of cell death after treatment with pharmaceutically active amounts of vitamin C. To investigate the effect of high-dose vitamin C on standard melanoma therapies, we treated three different BL6 mouse models, based on subcutaneously injected B16F10, D4M.3A (BRAFV600E) or 1274 (HgfxCdk4R24C) melanoma cells, with intraperitoneal injections of vitamin C (1–2 g/kg body weight). This resulted in short-term ascorbate serum levels in the pharmacologically active range of 1–10 mM and significantly improved the therapeutic effect of the corresponding combined standard melanoma therapy, which was either surgery, immune checkpoint blockade with anti-PD1 or BRAFV600E inhibition.

Therefore, we conclude that intravenous high-dose vitamin C therapy may be beneficial for melanoma patients by interfering with the tumor's energy metabolism and can be safely combined with standard melanoma therapies without interference.

11 Novel targeted treatment strategies for genetic melanoma subgroups

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Background and Objectives
New therapy concepts, such as immunotherapy as well as targeted therapy with BRAF and MEK inhibitors, have significantly improved the overall survival of melanoma patients. However, about 20% of patients do not respond to initial targeted therapy and at the same time, most of the tumors develop resistance through long-term therapy. For particular melanoma subgroups like the NRAS mutated tumors it is known, that they are associated with aggressive disease, but there is no approved targeted therapy for this subset. In clinical trials, the MEK inhibitor (MEKi) binimetinib displayed modest antitumor activity, making combinations a requisite. In a previous study, the BRAF inhibitor (BRAFi) vemurafenib was shown to induce endoplasmic reticulum (ER) stress that together with inhibition of the RAF-MEK-ERK (MAPK) pathway amplified its pro-apoptotic activity in BRAF-mutant melanoma. The present study investigated whether this effect might extent to NRAS-mutant melanoma, in which MAPK activation would be expected. Other clinical studies in breast cancer show that PI3K inhibitors have antitumor activity. This raises the question of whether these inhibitors are also a therapeutic option for melanoma and whether a combination of them with MEK inhibitors could further restrict growth and prevent possible development of resistance in different melanoma subgroups.

Material and Methods
Melanoma cells of different genetic subtypes, as well as tissue slice cultures of patient tumors are treated with BRAF and PI3K inhibitors alone and in combination with MEK inhibitors. In addition to the investigation of cell cytotoxicity and cell cycleremainder, the altered signal transmission is detected. Furthermore, the patient cells are sequenced in order to identify mutations that
promote a positive therapeutic response.

Results
BRAFi increased pERK, but also significantly increased growth inhibition and apoptosis induced by the MEKi in monolayer and patient-derived tissue slice cultures of NRAS-mutant melanoma. BRAFi such as encorafenib induced ER stress via upregulation of the ER stress-related factors ATF4, CHOP and NUPR1 and the pro-apoptotic protein PUMA. MEKi such as binimetinib induced the expression of the pro-apoptotic protein BIM and activation of the mitochondrial pathway of apoptosis. While the pan-PI3K inhibitor BKM120 is cytotoxic in almost all cell lines and patient cells, the PI3Kα-selective inhibitor BYL719 does not have an antitumour effect. However, the combination of the PI3K inhibitors with the MEK inhibitor already shows a significantly stronger cytotoxic effect at lower concentrations compared to monotherapies.

Conclusion
The data presented herein strongly encourage the clinical use of MEKi in combination with ER stress inducing BRAFi as a strategy to treat rapidly progressing NRAS-mutant melanoma; the combination of PI3K inhibitors with MEK inhibitors could be a new therapeutic option for BRAF wild-type melanomas.