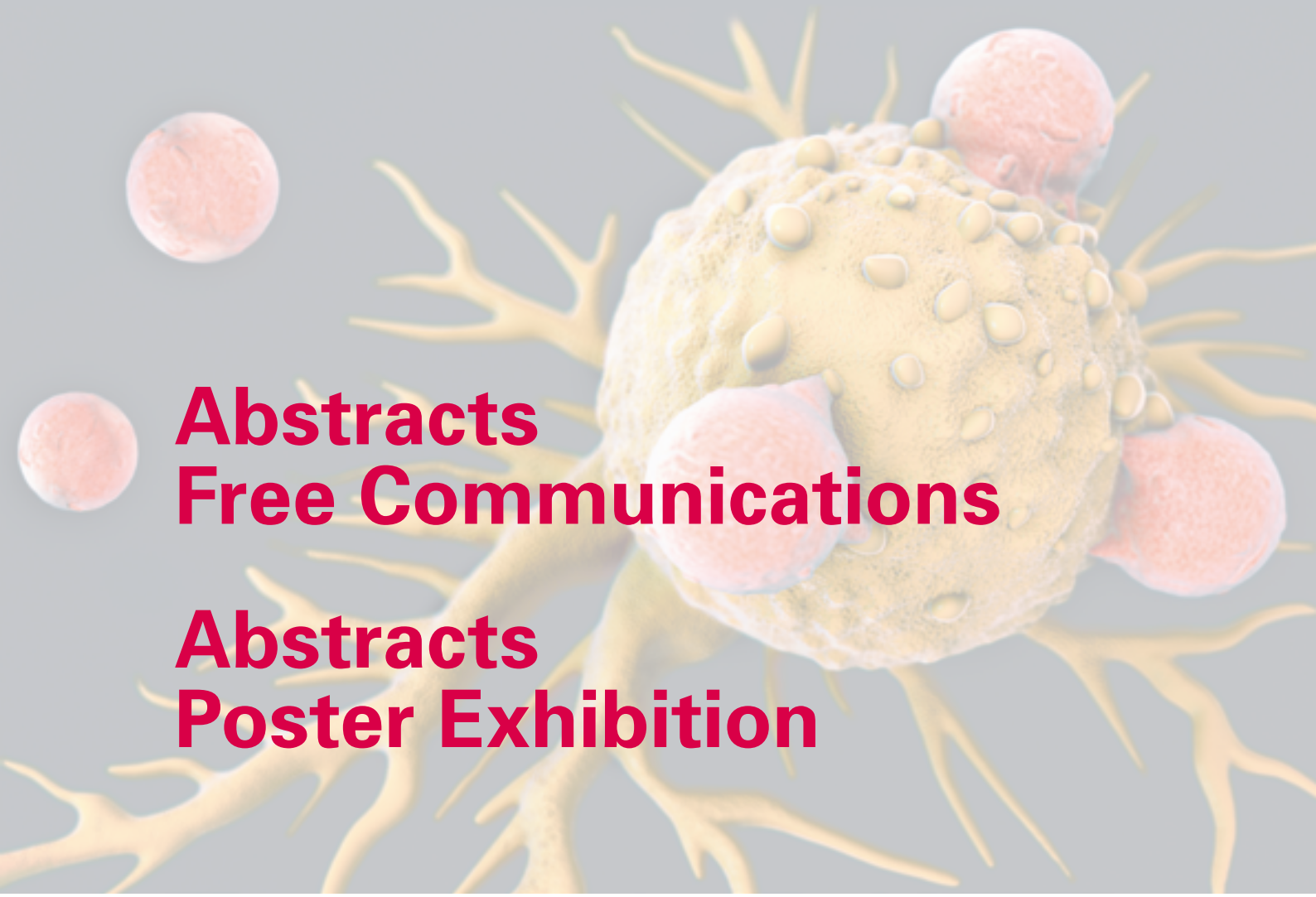
7th European Post-Chicago Melanoma/Skin Cancer Meeting

Results and Interpretations of ASCO Presentations 2017: Interdisciplinary Global Conference on News in Melanoma/Skin Cancer



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June 29th–30th, 2017
Munich, Germany
Leonardo Royal Hotel

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Friday, June 30th, 2017

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1
16:00–16:07

Long-term follow-up (LTFU) of overall survival (OS) data from the phase 3 OPTiM study of talimogene laherparepvec (T-VEC) for metastatic melanoma

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Background: T-VEC is a herpes simplex virus type-1-derived oncolytic immunotherapy designed to selectively replicate in tumors, produce GM-CSF, and enhance systemic antitumor immune responses through release of tumor-derived antigens. The phase 3 OPTiM study of T-VEC in patients (pts) with Stage IIIB-IVM1c melanoma showed limited toxicity and an objective response rate of 26.4% overall (Andtbacka et al., JCO 2015) and 40.5% in Stage IIIBC-IVM1a disease (Harrington et al. OncoTargets and Therapy 2016). At the end of OPTiM, eligible pts could enroll into a registry study for follow-up. Here we report additional survival data from the registry study.

Methods: Pts from OPTiM (conducted between May 2009 and July 2011) were eligible for the registry study if they received ≥1 dose of T-VEC and permanently discontinued participation in the phase 3 trial. Survival was assessed every 3 months until consent withdrawal, death, or end of study (OPTiM or registry). The final OS analysis snapshot in OPTiM was on Aug 8, 2014. This analysis includes LTFU data available for T-VEC-treated pts as of Oct 26, 2016. Pts not recorded as dead were censored based on the date they were last known to be alive.

Results: In OPTiM, 295 pts were randomised to receive T-VEC in the ITT population. Median age was 63 years, 71% had ECOG 0, and 28% had ECOG 1. Of the 295 pts, 7% had Stage IIIB disease, 22% had Stage IIIC disease, 25% had Stage IVM1a disease, and 44% had IVM1b/c disease. Additional LTFU data (via the registry) was available for 234 (79.4%) pts in the ITT population and 125 (76.8%) pts with Stage IIIB-IVM1a disease. Median potential follow up time for all pts (N=295) for the LTFU analysis was 50.1 months. At this time, median OS was 23.3 months (95% CI: 19.5, 29.6) in the ITT population and 46.8 months (95% CI: 31.2, not evaluable) in Stage IIIB-IVM1a melanoma (see Table). The 5-year survival rate estimate was 32.5% (95% CI: 26.8, 38.3) in the ITT population and 46.1% (95% CI: 37.3, 54.5) in Stage IIIB-IVM1a melanoma (see Table). Similar to other immunotherapy studies in melanoma, there is an inflexion point that occurs around 3 years, with survival maintained with longer follow-up.

Conclusions: Intralesional T-VEC treatment continues to demonstrate durable, long-term survival in a proportion of patients with stage IIIB-IVM1c melanoma. A limitation of this analysis is that additional LTFU data were not available for all pts originally enrolled in OPTiM.

	T-VEC-treated patients OPTiM ITT population (N=295)	T-VEC-treated patients OPTiM Stage IIIB-IVM1a subpopulation (N=163)
Subject status		
Deaths – n (%)	192 (65.1)	82 (50.3)
Censored [a] – n (%)	103 (34.9)	81 (49.7)
Overall survival – months[b]		
Median (95% CI)	23.3 (19.5, 29.6)	46.8 (31.2, NE)
Kaplan-Meier estimate of survival – % (95% CI)		
At Month 12	73.7 (68.3, 78.4)	87.0 (80.8, 91.3)
At Month 24	49.8 (44.0, 55.4)	64.8 (56.9, 71.6)
At Month 36	38.9 (33.3, 44.4)	54.9 (46.9, 62.2)
At Month 48	34.9 (29.4, 40.4)	49.6 (41.5, 57.2)
At Month 60	32.5 (26.8, 38.3)	46.1 (37.3, 54.5)
At Month 72	32.5 (26.8, 38.3)	46.1 (37.3, 54.5)

[a] Subjects that have not been recorded as dead are included as censored.
[b] Overall survival is calculated as the number of months from randomization date to death date or last known to be alive date.
Follow-up time is calculated for ITT T-VEC subjects in OPTiM only and for those OPTiM T-VEC subjects who continued into the 139 registry study.

N = Number of subjects in the analysis set.
CI = Confidence Interval. One month = 365.25/12 days.
NE = not estimable

2
16:09–16:16

Molecular gene profiling predicts outcome for surgical resection of metastatic melanoma

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Background: The approach to the treatment of advanced stage melanoma has been revolutionized by the development of immune checkpoint and signal pathway inhibitors. Surgical resection has been reserved for patients with limited sites and numbers of metastases. In the last few years the role of surgical resection has been further questioned as there is little new data to help select those patients that would benefit from resection. We undertook this investigation to evaluate molecular gene array profiling and signature development from the tumors as an approach to select patients who may benefit from surgery.

Methods: We prospectively collected tissue specimens from consented surgical patients with either primary or metastatic melanoma. Extracted RNA was used to generate cDNA for the microarrays. Clinicopathologic features and differential gene expression profiling from the arrays was correlated with melanoma-specific survival.

Results: Seventy-five patients underwent surgical resection: 40 with primary tumors and 35 with distant metastases. Most patients (60%) were men with a median age of 57 years. Primary tumors were most commonly on the extremities while the metastases (both close and distant from the primary) were most commonly subcutaneous (29%), small bowel (14%), or lung (14%). From over 17,000 genes evaluated in the microarray we first identified a cohort of 11 genes that had significantly (false discovery rate, FDR < 0.05) different expression in the metastatic vs the primary melanoma and were significantly ($p < 0.05$) related to survival. When we did the forward stepwise analysis we selected five genes (TENC1, PNMAL1, ATP12A, HSPA13 and S100A7A) that individually and as a group were predictive of outcome after surgical resection of distant metastases (estimated 5-year survival of 87+/- 8% vs 20+/–10%, $p < 0.001$). Patient age, gender, primary thickness or site of the metastasis were not predictive of survival.

Conclusions: We identified a molecular gene signature from metastatic melanoma that predicts survival following surgical resection. This gene profiling of the metastases may be an important first step in understanding which patients are best served by resection.

Combination of talimogene laherparepvec and ipilimumab versus ipilimumab alone in unresected stage IIIB-IV melanoma: primary results from a randomized (1:1), open-label phase 2 study.

3
16:18–16:25

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Background: Talimogene laherparepvec, a herpes simplex virus 1-based oncolytic virus, is designed to selectively replicate in tumors and produce GM-CSF, thereby stimulating antitumor immune responses. Ipilimumab, a monoclonal antibody directed against human CTLA-4, blocks inhibition of activated T-cells. We report the first randomized study to evaluate the combination of an oncolytic virus and a checkpoint inhibitor.

Methods: Eligible patients had unresected stage IIIB-IV melanoma and measurable/injectable tumor(s), with no evidence of immunosuppression. Prior treatment was permitted, but not a requirement for study entry. The primary endpoint was objective response rate (ORR) assessed by immune-related response criteria. Key secondary endpoints included duration of response, disease control rate (DCR), PFS, OS and safety. Talimogene laherparepvec was administered according to approved dosing guidelines until disease progression (PD), intolerance, or the absence of injectable tumors. Ipilimumab was administered at 3 mg/kg IV q3w for 4 cycles starting from w6 in the combination group and from w1 in the ipilimumab alone group. Primary analysis was performed 6 months after enrollment of the last patient.

Results: Of the 198 patients randomized, 98 were to talimogene laherparepvec + ipilimumab (T+I) and 100 were to ipilimumab alone (I). Baseline characteristics were similar between treatment arms. Overall, 54% of patients had stage IIIB-IVM1a and 46% had stage IVM1b/c disease. After a median follow-up time of 68 weeks (T+I) and 58 weeks (I), ORR was 38.8% vs 18.0%, respectively (P = 0.002, odds ratio (OR) 2.9). To date, 89% of patients in the T+I arm and 83% in the I arm remain in response. Reductions in total visceral tumor areas by at least 50% from baseline were 35.5% (T+I) and 13.6% (I). OS data are immature. The safety population consisted of 95 patients per arm. For T+I vs I, the most common adverse events (AEs) were fatigue (59% vs 42%), chills (53% vs 3%), and diarrhea (42% vs 35%). Treatment-related grade ≥3 AEs were observed in 28% and 18% of patients treated with T+I or I, respectively. Three deaths (all unrelated) in the T+I group were attributed to PD (n=2) and myocardial infarction (n=1).

Conclusions: The study met the primary endpoint. ORR was significantly higher with T+I combination treatment vs I alone. Responses were not limited to injected lesions. The combination of T+I was tolerable with no unexpected AEs observed.

	T+I N=98	I N=100
ORR [a] – n (%) (95% CI)	38 (38.8) (29.1, 49.2)	18 (18.0) (11.0, 26.9)
OR (95% CI)	2.9 (1.5, 5.5), P = 0.002 [b]	
CR – n (%) PR – n (%)	13 (13.3) 25 (25.5)	7 (7.0) 11 (11.0)
DCR – n (%) (95% CI)	57 (58.2) (47.8, 68.1)	42 (42.0) (32.2, 52.3)
PFS, events/N (%) Median (95% CI) – m	52/98 (53.1) 8.2 (4.2, 21.5)	51/100 (51) 6.4 (3.2, 16.5)

[a] CR/PR required confirmation ≥ 4 w apart
[b] Chi-square test with continuity correction
CI, confidence interval; CR, complete response; DCR, disease control rate; I, ipilimumab; m, months; OR, odds ratio; ORR, objective response rate; PFS, progression-free survival; PR, partial response; T, talimogene.

4

16:27–16:34

Age effect on advanced melanoma treatment options

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Background: The incidence of melanoma increases with age, which is an independent poor prognostic factor. The aim of this study is to examine whether different age groups have different treatment scenarios which may impact on their outcomes.

Methods: 150 patients (pts) with advanced melanoma (unresectable/metastatic) were retrospectively identified between 2015 and 2016. 75 pts per year were selected by chronological order into 3 age groups: young (<40), middle age (40–69) and elderly (≥70 years). This was determined by the age at diagnosis of advanced melanoma. Data analysed on treatment history and survival outcome. The Cumulative Illness Rating Scale (CIRS) was applied as a comprehensive review of comorbidities with a total score of 0 to 56.

Results: A total of 27 young pts, 63 middle age pts and 60 elderly pts were identified. Similarly across groups, 53% presented with M1c disease and 28% with a high LDH. The elderly group had a significantly worse performance status (PS) at baseline with 24% being PS 2–3 vs. 12% in the non-elderly groups ($p=0.046$). The median CIRS total score for the elderly group was 14 vs. 6 in the non-elderly groups. The incidence of BRAF mutations between the younger, middle age and elderly groups was respectively 83%, 52% and 30% ($p<0.01$). An initial decision to treat was less frequent in the elderly group (83% vs. 97%, $p<0.01$). The period between the diagnosis of advanced disease and the start of systemic treatment was a median of 16 days longer in the elderly group. Similarly across groups, 85% of pts received immunotherapy and 90% of BRAF mutants were treated with targeted-agents. 10% of elderly pts received ≥3 treatment lines vs. 28% across the other groups ($p<0.01$). Non-elderly pts had a higher enrolment rate in clinical trials (33% vs. 20%, $p=0.04$). Median overall survival was only reached in the elderly group with 17 months. The 2 years survival rate between the younger, middle age and elderly groups was respectively 62%, 51% and 38% ($p=0.047$).

Conclusions: Despite the revolution in the treatment landscape of advanced melanoma, the treatment options and outcomes of elderly patients still fall behind. This analysis suggests that the stage and burden of disease at presentation are similar across age groups. However elderly patients have a smaller incidence of BRAF mutation, worse baseline PS and higher comorbidity burden, which are the main factors limiting access to treatments and their outcomes.

Single-dose therapy with Pembrolizumab in a patient with metastatic Merkel cell carcinoma

5
16:36–16:43

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Merkel cell carcinoma (MCC) is a rare, but highly aggressive neuroendocrine skin cancer with limited treatment options for advanced stages of the disease. Metastatic MCC responds to chemotherapy, but responses are transient. Recently, agents blocking the PD-1/PD-L1 pathway have demonstrated objective, durable tumor regressions in stage IV MCC patients, leading to its approval for the treatment of metastatic MCC by the FDA.
This study reports a 79-year-old woman who presented with multiple firm, red-colored tumors on her left leg in February 2016. Pathological and immunohistochemical analysis of excision biopsy specimen revealed a MCC. A PET-CT scan showed multiple lymphnodal metastases. Because of her poor general conditionit was decided to treat her with Pembrolizumab 2mg/kg combined with local radiotherapy. Ten days after the first cycle with Pembrolizumab the patient developed a sudden bilateral visual loss. A MRT scan revealed an optic neuritis that required treatment with a high dosage of steroids. This severe adverse event forced us to permanently discontinue Pembrolizumab. 5 months after single-dose therapy with Pembrolizumab both cutaneous and lymphnodal metastases disappeared completely, and the patient recovered fully from the optic neuritis. The patient remained relapse-free for almost one year. In February 2017 a new lymph node metastasis in her left groin was detected. Local radiation was again initiated.
Our case supports recent trials showing the effectiveness of PD-1 blockade in patients with metastatic MCC. Here a single dose of Pembrolizumab induced a long lasting response. As PD-1/PD-L1 checkpoint inhibitors are well tolerable, severe side effects can occur anytime during immunotherapy. However, they are usually manageable and reversible when early recognized and treated.

6
16:45–16:52

Interim efficacy, safety and biomarker results of a Phase 2 study evaluating the relationship between talimogene laherparepvec and intratumoral CD8+ T-cell density in patients with unresectable stage IIIB-IVM1c melanoma

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Background: Talimogene laherparepvec was efficacious (overall response rate [ORR] of 26.4% at a median follow-up of 44.4 months) and well tolerated for the treatment of patients with unresectable stage IIIB-IVM1c melanoma in the phase 3 OPTiM study. This Phase 2, open-label, single-arm study examined the relationship between tumor CD8+ T-cell density and objective response with talimogene laherparepvec. Systemic effects of treatment were assessed through measurement of CD8 T-cell density in non-injected tumors biopsied 5 weeks after the start of treatment.

Methods: Eligible patients, enrolled from 36 sites, had unresectable stage IIIB-IVM1c melanoma and received talimogene laherparepvec until achieving complete response, disappearance of injectable tumors, unacceptable toxicity, or disease progression. The primary endpoint was correlation between baseline CD8+ cell density and objective response to talimogene laherparepvec treatment. Secondary endpoints included ORR per modified WHO criteria.

Results: This interim analysis includes the first 47 (out of 112) enrolled patients treated with talimogene laherparepvec with CD8+ density recorded at baseline and who had the opportunity to be in study for ≥6 months (treatment or follow-up). Median follow-up was 28.7 weeks (range 2.7–72.9 weeks). Key patient disposition information, baseline characteristics, and efficacy results are shown in the Table. In total, 74% (35/47) of patients had stage IIIB-IVM1a melanoma. ORR was 25.5% in all patients, 34.4% in patients with stage IIIB-IVM1a disease and 0% in stage IVM1b/c melanoma. Safety outcomes were consistent with those previously reported in the OPTiM study. Data will be presented on the correlation between response and both baseline tumor CD8+ density, and change from baseline in tumor CD8+ density. Changes in CD8+ density up to week 6 will also be examined in non-injected lesions.

Conclusions: Acknowledging the shorter follow-up time of this interim analysis, the efficacy and safety results presented here are consistent with those from OPTiM and provide the first evaluation of the tumor microenvironment as a potential predictive biomarker. This is also the first dedicated study to provide insights into systemic immune system engagement by this novel therapy through examination of non-injected tumors.

Table. Summary of patient disposition, key baseline characteristics and efficacy findings.
Values are n (%) unless stated

	Talimogene laherparepvec (N = 47)
Patient disposition	
Continuing treatment	20 (42.6)
Discontinued treatment	27 (57.4)
Disease progression	15 (31.9)
Death	6 (12.8)
Requirement for alternative therapy	2 (4.3)
Withdrawal of consent	2 (4.3)
Other	2 (4.3)
Baseline characteristics	
Male	23 (48.9)
Median age, years	68
ECOG PS = 0	38 (80.9)
Stage of melanoma	
Stage IIIB	7 (14.9)
Stage IIIC	8 (17.0)
Stage IVM1a	20 (42.6)
Stage IVM1b	7 (14.9)
Stage IVM1c	5 (10.6)
BRAF status	
Mutation	11 (23.4)
Wild-type	35 (74.5)
Missing/unknown	1 (2.1)
Received prior anti-cancer therapy	23 (48.9)
Efficacy	
Response assessment	
Complete response (CR)	3 (6.4)
Partial response (PR)	9 (19.1)
Stable disease (SD)	4 (8.5)
Progressive disease	26 (55.3)
Missing	5 (10.6)
Overall response rate (CR/PR)	12 (25.5)
Disease control rate (CR/PR/SD)	16 (34.0)

7
16:54–17:01

Sentinel lymph node biopsy with double contrast in skin melanoma patients in NCRC of Serbia

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Background: Technetium-99^{m} (Tc-99^{m}) colloidal rhenium sulphide (Nanocolloid) is metastable nuclear isomer which is used in great number of medical diagnostic procedures and represents the most used radioisotope in human medicine. In our institution it is mostly used for mapping sentinel lymph nodes (SLN) in melanoma and breast cancer, individually, or combined with methylene blue dye (MBD). However, due to fund limitations, it is not always possible to apply Tc-99m in all patients – in some we use only vital dye.
Our aim is to present the single institution experience on SLN biopsy in skin melanoma using double contrast technique for mapping SLNs.

Materials & Method: During year 2016, at National Cancer Research Center of Serbia (Surgical Oncology Clinic), 57 patients with pathological confirmation of skin melanoma were surgically treated by SLN biopsy after mapping with Tc-99^{m}and MBD combined. Written consent and multidisciplinary team decision was obtained for all patients. One hour before operation, surgeon injected 0.2–0.5ml of Tc-99m into dermis of scar region, with supervision of nuclear medicine specialist, using protection equipment and containers. MBD was injected the same way 10 minutes prior to skin incision in operating room. Once being detected visually and by hand held GAMMA probe, "hot" and "blue colored" SLN is removed and sent to frozen section analysis. Depending on the pathological finding, we performed further dissections.

Results: There were 21 female and 36 male patients. Medium age was 54.5 years. In melanomas excised from upper trunk or upper extremities (36 patients), arm pit was explored surgically. SLNs were negative in 24 patients, 11 had metastases and one patient was diagnosed with micro-metastases in SLNs. Average radioactivity readings were 2600 units. After positive frozen section finding, we performed arm pit dissection.
In melanomas excised from lower extremities (20 patients), groin was explored surgically. Average radioactivity readings were 600 units. SLNs were negative in 14 patients, while 6 patients had metastases on frozen section, so we performed groin dissection. One patient with skin melanoma on head had negative SLN of the jugular region.

Conclusions: SLN biopsy is of great significance in skin melanoma patients since it provides adequate lymph node staging and timely dissections in patients with proven metastases. Combined treatment with Tc-99m and MBD, in so called "double contrast" technique, results with extraordinary high level of sensitivity and achieves oncological goal.

Long-term outcomes in patients (Pts) with advanced melanoma treated with Pembrolizumab (Pembro): 4-year overall survival (OS) results from KEYNOTE-001

8
17:03–17:10

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Crown Princess Mary Cancer Centre, Westmead Hospital, Melanoma Institute Australia, and Macquarie University, NSW, Sydney, Australia
Merck & Co., Inc., Kenilworth, NJ, USA; Merck & Co., Inc., Kenilworth, NJ, USA; Merck & Co., Inc., Kenilworth, NJ, USA
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Background: The anti–PD-1 antibody pembro is currently approved in more than 60 countries for 1 or more advanced malignancies, including unresectable or metastatic melanoma. Among pts with advanced melanoma treated with pembro in the phase 1b multicohort KEYNOTE-001 study (ClinicalTrials.gov, NCT01295827), median OS was 24.4 mo with an estimated 3-yr survival rate of 40% after a median follow-up of 32 mo. Here, we present 4-yr OS data for these pts.

Methods: Pts with ipilimumab (ipi)-naive and ipi-treated advanced melanoma received pembro 2 or 10 mg/kg every 3 weeks (Q3W) or 10 mg/kg Q2W until disease progression, intolerable toxicity, or investigator decision to withdraw the patient. After pembro discontinuation, pts were contacted every 3 mo to assess survival. OS was estimated using the Kaplan-Meier method.

Results: 655 ipi-naive (n=313) and ipi-treated (n=342) pts were enrolled and received pembro 2 mg/kg Q3W (n=162), 10 mg/kg Q3W (n=313), or 10 mg/kg Q2W (n=180). As of the September 1, 2016, data cutoff date, median follow-up was 43.3 mo (range, 36.0–57.1), and 388 (59.2%) pts had died, compared with 358 (54.7%) at the 3-yr analysis. Median time on pembro was 5.6 mo (range, 0.03–55.2); 238 (36.3%) pts received pembro for >12 mo; at the time of data cutoff, 104 (15.9%) pts were either still on treatment (n=47) or had discontinued treatment for complete response (n=57). In the overall population, median OS was 23.8 mo (95% CI, 20.2–30.4); the estimated 4-yr OS rate was 37.3%. Median OS was 29.1 mo (95% CI, 22.8–39.0) and 20.2 mo (95% CI, 17.8–27.1) in pts with ipi-naive and ipi-treated melanoma, respectively. Estimated 4-yr OS rates were 41.7% for pts with ipi-naive and 32.7% for pts with ipi-treated melanoma. The tail of the Kaplan-Meier OS curves suggests a long-term benefit for a fraction of pts treated with pembro. There was no increase in the rate of grade 3-4 treatment-related AEs in the overall population as of the data cutoff compared with the 3-yr analysis (17% for both). Additional data, including analysis of pts in complete response, will be available for presentation.

Conclusions: The long-term OS benefit of pembro for pts with ipi-naive and ipi-treated advanced melanoma was maintained over a median follow-up of 43.3 mo. Along with the manageable safety profile observed with long-term follow-up, these data support the use of pembro in pts with advanced melanoma.

Abstracts
Poster Exhibition

1 Double melanoma within quadruple metachronous malignancy in a single patient with multiple sclerosis

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Introduction: Multiple primary malignancies are two or more malignancies in an individual without any relationship between the tumors. Multiple malignancies in a single patient are rare but have increased in frequency in recent years. Multiple primary cancers occurs in 3 to 5% of malignant tumors and they are frequent in the head and neck, triple tumors occur in only 0.5%, but quadruple tumors in 0.1 to 0.3%.

Patient and method: We present a female patient with a multiple sclerosis and quadruple cancers from different embryological origin. The patient had two melanomas, 1.24 and 0.85 mm thick (Clark II, Breslow II), medullary thyroid carcinoma (stage III-T3, N1a, M0), multicentric micropapillary carcinomas and breast cancer (T1a, N0, M0). The patient was treated according to current guidelines for each diseases.

Result: Patient is on regular follow-up without signs of recurrence. Last FDG-PET scan performed was negative, CA 15-3 level was within normal limits and calcitonin level was 81 ng/l and CEA 5 ng/l. Brain MRI indicated multiple foci of demyelination, without active lesions, and in comparison with the previous MRI findingsthere were no signs of the disease progression. Also, neurological examination did not show any signs of disease progression. There were no signs of disease recurrence during the 7 years.

Conslusion: Further genomic studies and closer clinical attention are needed to clarify the relation between secondary malignancies, applied treatments and endogenous and exogenous carcinogens in the process of carcinogenesis in quadruple malignancies.

Long term (60 months) survival with vemurafenib monotherapy in a metastatic melanoma patient. Case report.

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Background: Until 2011 metastatic melanoma had no accepted effective therapy and the prognosis of the metastatic melanoma patients was poor, the five-year survival rates were estimated to be less than 5 per cent. Vemurafenib achieved improved overall survival over chemotherapy and have been approved by the FDA in August of 2011 and EMA in February of 2012 for the treatment of BRAF-mutated metastatic melanoma, demonstrating a median progression-free survival of 6.9 months, and a median overall survival of 13.6 months.

Case presentation: A 31-year-old male with good performance status (ECOG-0) was found to have a pigmented lesion on the chest. Excision revealed a superficial spreading malignant melanoma with a Breslow thickness of 0,73 mm. 14 years later, in 2010, a recidiv tumor was found locally, the patient underwent a local excision, postoperativ radiotherapy and we started interferon immunotherapy. In 2011 PET-CT scan showed metastatic disease with lyphadenopathy in 3 mediastinal lymphnodes, with the largest target node measureing 28 mm. We started with Dacarbasine chemotherapy but due to pancytopenia we had to discontinue the treatment. In 2012 the mutation testing revealed presence of BRAF V600E mutation, so in April we randomised the patient with normal lactate dehydrogenase (LDH) level to the MO25515 clinical trial and he was started vemurafenib monotherapy at the recommended dose (960 mg twice daily). The CT scan 3 months later showed significant treatment response with reduction in size of mediastinal lymphnodes and than for every 3 months after responding metastatic disease was shown. Only Gr1 toxicities were reported (photosensitivity, follicular hyperkeratosis, episcleritis, arthralgia). The CT scan 5 years after starting treatment showed a complete radiological response.

Conclusions: With our case, we report a long-tem, 60 months progression-free survival with vemurafenib monotherapy. An extended follow-up of BRIM 3 trial results had shown a median PFS of 6.9 months and median OS of 13.6 months in patients with BRAF V600E mutation.
This report also shows that long-term survival is reachable with vemurafenib monotherapy in a selected population of patients. Further biomarker investigations are needed for the selection of these BRAF mutated metastatic melanoma patients.

3 Dabrafenib therapy in 30 patients with melanoma metastatic to the brain: a single-centre controlled retrospective study in Hungary.

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Background: Dabrafenib is a potent BRAF inhibitor, which showed intracranial tumor activity. The purpose of our retrospective analysis was to evaluate the efficacy of dabrafenib for patients with melanoma brain metastasis (BM).

Methods: We studied 30 BRAF mutant melanoma patients with BM, who received dabrafenib after local control of the brain between 2014 and 2017. Eastern Cooperative Oncology Group Performance Status (ECOG) was 0-2. The control arm consisted of 204 melanoma patients from our institutional melanoma database with BM and ECOG 0-2 treated with local therapies and/or chemotherapy, between 2003 and 2015.

Results: We found the intracranial disease control rate (DCR) was 83% including 4 (13%) complete remissions (CR), 9 (30%) partial remissions (PR) and 12 (40%) stable diseases (SD) while there were 5 (17%) progressive diseases (PD). With a median follow-up of 14 months, median progression-free survival (PFS) and overall survival (OS) were 5.5 months, and 8.8 months, respectively. If calculated from BM onset, the OS turned to be 11.8 months on the dabrafenib arm, while it was only 6.0 months on the control arm (HR=0.45, p=0.0014). Higher risk of progression was observed with increasing ECOG (HR =4.06, p=0.00027) and if more than 2 extracranial organs were involved (HR=3.4, p=0.0077). Elevated lactate dehydrogenase (LDH) was non-significantly associated with worse clinical outcome.

Conclusions: Remarkable intracranial activity of dabrafenib in real practice was confirmed by our analysis.

Impressive response of a symptomatic metastasized melanoma patient with vemurafenib and cobimetinib combinational treatment

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Background: In BRAF-positive metastatic melanoma patients treatment with BRAF/MEK inhibitor combinations is currently the treatment of choice. Especially metastatic melanoma patients with symptomatic metastases benefit from a treatment with a BRAF/MEK inhibitor due to the quick treatment response.

Methods: In January 2017 a 48 year old patient presented himself at our skin cancer center with a bulky, exophytic tumor in the left groin (16.5 x 15.5cm) which had progressed in size since summer 2016. A biopsy showed a melanoma metastasis with unknown primary. A CT scan of the abdominal cavity revealed an infiltration of the adductor muscles, a protrusion to the pelvic region, and encircling of the left femoral vessels with a consecutive thrombosis. Additionally, a suspicion of a metastasis in the neighboring lymph nodes has been made. We performed an additional biopsy for the mutational analysis with the finding of a BRAF V600E mutation. After an interdisciplinary discussion in our tumor board, we initiated a combinational treatment with vemurafenib and cobimetinib on March 1st, 2017. The tumor marker S100 was elevated with a value of 2.51µg/l (normal range: <0.11 µg/l).

Results: During the first follow-up exam after just 2 weeks the tumor showed an impressive reduction in size. The patient tolerates the treatment very well, only a maculopapular exanthema on the chest and arms was observed, but well controlled by topical steroids. The specific tumor marker is within the normal range again (0.07 µg/l). After 4 weeks of treatment the metastases showed an even further regression which is ongoing until today.

Conclusion: Our case report shows a dramatic regression of a metastasized melanoma with a combinational treatment with a BRAF and MEK inhibitor. This treatment is especially favorable in BRAF-mutated patients with a high tumor burden and associated clinical symptoms like pain, compression of relevant structures, and recurrent bleedings. The potential of a rapid response and therefore the possibility of a non-surgical tumor debulking is the goal for patients like ours.

5 Melanoma cells resistant to MAPK inhibitors can be effectively targeted by inhibition of the p90 ribosomal S6 kinase

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Background: The clinical availability of small molecule inhibitors specifically targeting mutated BRAF marked a significant breakthrough in melanoma therapy. Despite a dramatic anti-tumour activity and improved patient survival, rapidly emerging resistance, however, greatly limits the clinical benefit. The majority of the already described resistance mechanisms involve a reactivation of the MAPK signalling pathway. The p90 ribosomal S6 kinase (RSK), a downstream effector of the MAPK signalling cascade, has been reported to enhance survival of melanoma cells in response to chemotherapy. Based on that, the aim of this study was to asses a potential role of the RSK in melanoma cells resistant to the BRAFV600E/K inhibitor vemurafenib or to the combinatorial treatment with an additional MEK inhibitor (trametinib).

Methods: Melanoma cells with acquired resistance to vemurafenib were compared to their sensitive counterparts in terms of expression and phosphorylation of the RSK isoforms as well as their activity. With the help of small molecule inhibitors targeting the MAPK signalling pathway and RSK itself, the dependency of enhanced RSK activation on upstream signalling pathways and its relevance in MAPK inhibitor resistant cells was evaluated in both two- and three-dimensional culture systems. The functional role of active RSK signalling was further addressed by downregulation of the Y-box binding protein 1 (YB-1), an important RSK target.

Results: The phosphorylation as well as the activity of the RSK is significantly enhanced in human melanoma cells with acquired resistance to vemurafenib, which seems to be mainly based on elevated MAPK signalling. Interestingly, inhibition of RSK signalling markedly impairs the viability of BRAF inhibitor resistant melanoma cells and is effective both in two-dimensional and in three-dimensional culture systems, especially in a chronic, long-term application. The effect of RSK inhibition can be partly replicated by downregulation YB-1. Intriguingly, RSK inhibition also retains its efficacy in melanoma cells with combined resistance to vemurafenib and the MEK inhibitor trametinib.

Conclusions: These data suggest that active RSK signalling might be an attractive novel therapeutic target in malignant melanoma with acquired resistance to MAPK pathway inhibitors.

The efficacy of talimogene laherparepvec in combination with pembrolizumab in unresected, stage IIIB-IV melanoma: a phase 1b/3, multicenter trial (MASTERKEY-265) 6

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Background: Talimogene laherparepvec, a herpes simplex virus 1-based oncolytic immunotherapy, is designed to selectively replicate in tumors and produce GM-CSF, which stimulates antitumor immune responses. In a phase 3 trial, treatment of patients with unresectable stage IIIB-IV melanoma with talimogene laherparepvec resulted in improved durable response rates compared with GM-CSF (16% vs 2%; Andtbacka et al, JCO 2015). Pembrolizumab is a monoclonal antibody directed against human programmed death receptor-1 that was approved for the treatment of advanced or unresectable melanoma following demonstration of its superiority over ipilimumab in patients with stage III-IV melanoma who received no more than one prior line of systemic therapy (PFS HR 0.58, OS HR 0.63–0.69; Robert et al, NEJM 2015). The antitumor immune responses stimulated by talimogene laherparepvec or pembrolizumab alone may be enhanced by combining the two therapies. In a phase 1b study, no dose-limiting toxicities were observed among 21 patients treated with talimogene laherparepvec + pembrolizumab (Long et al, ASCO 2016). The phase 3 portion of the double-blind, placebo-controlled study described here, is currently assessing the safety and efficacy of talimogene laherparepvec + pembrolizumab in unresected stage IIIB-IV melanoma (NCT02263508).

Methods: Approximately 660 patients will be randomized in a 1:1 ratio to receive either pembrolizumab + placebo or pembrolizumab + talimogene laherparepvec. The co-primary endpoints are PFS and OS. Key secondary endpoints include safety, response-based endpoints, and patient-reported outcomes. Eligible patients are those with unresectable stage IIIB-IV melanoma naïve to systemic therapy or previously treated with one line of BRAF inhibitor-based treatment, measurable/injectable lesions, and ECOG PS 0–1. Patients with autoimmunity/immunosuppression, active cerebral metastases or active herpetic infection are excluded. Talimogene laherparepvec (106 PFU/mL first dose, 108 PFU/mL subsequent doses; maximum of 4mL total injection volume per visit) and placebo is administered by injection into cutaneous or nodal lesions on day 1 of weeks 0, 3, 5, 7 then q3w from day 1 of week 9. Pembrolizumab (200mg) is administered IV q3w starting on day 1 week 0. Treatment continues for up to 2 years or until confirmed complete response, disease progression, intolerance, or the absence of injectable lesions.

7 Acquired resistance of melanoma cells to MAPK inhibitor treatment correlates with reduced expression of TA-p73 isoform and enhanced susceptibility to cisplatin/carboplatin treatment and radiation

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Background: The long-term efficacy of mutated BRAF and MEK inhibitors in metastatic melanoma therapy is limited due to the evolution of different resistance mechanisms. Therefore, genotoxic therapies including the treatments with cytostatic drugs and radiation are still part of the metastatic melanoma therapy even after the manifestation of MAPK inhibitor (MAPKi) resistance. The functional role of the p53 family member, TA-p73 isoforms in treatment resistance of metastatic melanoma cells is widely unknown.

Methods: Melanoma cell lines which are sensitive or resistant to BRAF inhibitor vemurafenib as well as additionally resistant to MEK inhibitor trametinib were used. They were transfected with specific siRNAs to ectopically downregulate the expression of TA-p73. These cells were further treated with cytostatic drugs, namely cisplatin or carboplatin as well as they were irradiated or treated with an inhibitor of the DNA repair related protein RAD51 to analyse the cellular responses.

Results: We observed a melanoma cell specific predominant endogenous expression of TA-p73α isoform in all analyzed melanoma cell lines among the different p73 isoforms. Furthermore, down-regulation of endogenous TA-p73 expression was sufficient to induce DNA damage accumulation, viability decline and apoptosis of metastatic melanoma cell lines. The endogenous level of the TA-p73 isoform was also relevant for the sensitivity towards genotoxic treatments. In addition, MAPKi resistance-acquired melanoma cells had a reduced basal TAp73 level and were more susceptible towards these DNA damaging treatments including the treatment with cytotoxic drugs (cisplatin/carboplatin) or ionizing radiation, than MAPKi sensitive melanoma cells. We could show that inhibition of specific DNA damage repair can further enhance the susceptibility of the melanoma cells to genotoxic treatments in a TAp73 expression dependent manner.

Conclusions: Our data let assume that the expression of TA-p73α isoform determines the susceptibility of melanoma cells to the treatments with chemotherapeutic drugs or irradiation. We observed an enhanced response of MAPKi resistance-acquired cells to these genotoxic treatments.

Impressive response of intra- and extracranial melanoma metastases with nivolumab re-challenge

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Background: The programmed-cell-death (PD)1-antibody nivolumab was approved for the treatment of metastatic melanoma in 2015. The opportunity of a long term response by a durable tumour control is well known. However, there is limited data available on the efficacy of the PD-1-blockade in the setting of a re-induction scheme and in patients with brain metastases. The following case demonstrates a successful re-induction of nivolumab with a partial remission.

Case Report: A 75-year-old patient was diagnosed in November 2014 with a cutaneous metastasis (BRAF wildtype) of a malignant melanoma on the right helix with an unknown primary. In April 2015 a CT scan showed a solitary pulmonary metastasis, which was surgically removed via wedge resection. Shortly thereafter, in July 2015, there was evidence of four liver metastases, a hilar lymph node metastasis and a singular brain metastasis. A therapy with the PD-1-antibody nivolumab, given bi-weekly, was started in combination with a stereotactic irradiation of the brain metastasis. Initial examinations after three months showed an extracranial partial remission but four new brain metastases. While continuing the nivolumab treatment the patient received concomitant stereotactic irradiation of the new brain metastases and showed a complete remission thereafter. Treatment was continued until March 2016 and paused due to arthralgia, which required high dose systemic steroids. In September 2016 a new solitary metastasis in the ileum was surgically removed. As CT scans in January 2017 showed new peritoneal and pararectal metastases therapy with nivolumab was re-induced. At this point the patient was still receiving 10mg prednisone for arthralgia and was asymptomatic. Examinations in April 2017 confirmed an ongoing complete remission of the brain lesions and a partial remission of the intestinal metastases.

Conclusion: This case demonstrates the possibility of complete intra- and extracranial remissions of metastases with concurrent PD-1-blockade and irradiation, which has been well documented in previous case reports. However, the most striking feature of this particular case remains the possibility of successful re-induction of the PD-1-antibody, paused due to toxicity, with repeated partial remission.

9 Targeted Therapy of Inoperable Orbital Basal Cell Carcinoma accompanied with Lung Metastases of Cutaneous Squamous Cell Carcinoma

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Background: The hedgehog inhibitors (HHI), such as vismodegib and sonidegib, offer an excellent option in the treatment of locally advanced (la) or metastatic (met) basal cell carcinoma (BCC). However, the development cutaneous squamous cell carcinoma (cSCC) in HHI-treated patients with laBCC or metBCC has been reported. On the other hand, studies on mice with squamous lung cancer showed a tumor response to GLI inhibition.

Case report: An 81-year-old patient presented with progressive laBCC of his left orbit and a history of multiple cSCCs. He had undergone multiple surgical excisions including exenteration of his left orbital cavity and partial excision of the nasal septum. Palliative radiotherapy had no stabilizing effect. Upon CT staging slowly progressing bilateral pulmonary nodules had been identified and histopathological examination revealed metastasis of cSCC. Chemotherapy regimen was discussed at first but refused by the patient with respect to his multiple morbidities. Eventually HHI vismodegib (150mg/day p.o.) was started for his laBCC. After 4 months of therapy CT scan not only showed local tumor reduction, but also major regression of the lung metastases. Clinically, the laBCC was regressive and stopped from spontaneous bleeding which went along with a significant increase in the patient´s quality of life. Further follow-up CT assessments confirmed stable disease of the laBCC as well as of the lung lesions up to 21 months on treatment. After 29 months local progression of the laBCC was found and the patient died shortly after.

Conclusion: Although the findings from our case should be interpreted with caution, a possible therapeutic effect of HHI on pulmonary metastasis of cSCC should be further investigated.

Application of Paramedian Forehead Flap for Large Nasal Defects in Skin Cancer Surgery

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Background: Interpolated paramedian forehead flap has been used from ancient times to repair difficult-to-treat large nasal defects. Since it draws blood supply from the supratrochlear artery, it is a robust flap that can be utilized to repair large nasal defects that are functionally and cosmetically challenging.

Objective: Success in the execution of a forehead flap relies on a careful stepwise approach to the defect, the patient, and the surgical technique. Characterization of these steps was analyzed for achievement of consistent post-operative results.

Method: The process of executing a paramedian forehead flap from preoperative assessment, intraoperative procedure and postoperative care is elucidated and discussed.

Results: By combining cartilage graft, the forehead flap can correct the issue of collapsing external nasal valve that is an inevitable complication of large nasal defects. Also, due to the rich and robust blood supply, this flap can be designed to replace a whole subunit of the nose and therefore can result in superior cosmetic outcome eventually.

Conclusion: With careful attention to the reconstruction of all components of a nasal defect, paramedian forehead flap can restore virtually any large nasal defect with excellent functional and cosmetic results.

11 Patient derived organotypic slice cultures for preclinical profiling of human BRAF wildtype melanomas

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Background: Response to targeted therapy is strongly influenced by the cancer genome. However, the present genomic classification of melanoma subtypes does not suffice for a reliable prediction of drug efficacy including the duration of response. It is well accepted that characteristics like epigenetic mechanisms, the microenvironment and the immune status play decisive roles for therapy success. That is especially true for patients with BRAF wildtype melanomas. This population comprises about 50% of the melanoma patients which can be subdivided into NRAS mutated and NF-1 mutated tumors or melanomas with different low frequency mutations. So far, there is no approved targeted therapy for these patients. However, there is evidence that the MAPK and PI3K signaling pathways, as classical driver pathways, are equally important in these tumors compared to BRAF mutated melanomas.
Thus, the prediction of drug response for BRAF wildtype melanoma patients remains a major challenge. Therefore, a solid and fast functional test system that preserves melanoma microenvironment and tumor heterogeneity is of great interest.

Methods: We have established an ex vivo model which allows the investigation of anti-tumoral and pharmacological properties of drug combinations. Melanoma punch biopsies or patient derived xenograft tumors were used to prepare tissue slices, which were treated for four days with clinical relevant drugs like BRAF/MEK (dabrafenib/trametinib) and PI3K (buparlisib) inhibitors before measuring viability. Tissue slices were further used for immunohistochemical evaluation of proliferation and apoptosis induction. The results were correlated to the genetic background of the tumor and the clinical data of the patient.

Results: Our results show that this model preserves tissue 3D architecture, cell viability and pathway activity. Treatment of melanoma slice cultures with BRAF/MEK or PI3K inhibitors reduced tissue viability in a reproducible manner and correlated with clinical efficiency and underlying resistant mechanisms. Effects of the drugs on tumor cell proliferation and apoptosis were successfully determined.

Conclusions: Our new reproducible preclinical model can be used to evaluate the effects of small molecule inhibitors directly and can help to individualize melanoma therapy.

Visual communication as an effective tool for patient education on coping with adverse events

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Background: Targeted immune checkpoint blockade, which leads to melanoma regression and cure, is associated with frequent immune-related adverse events (irAEs), which include gastrointestinal, dermatological, hepatic and endocrine toxicities. Pre-treatment instructions should be a critical part of the information conferred to patients in order to maximize treatment efficacy and minimize complication rate.
IrAEs should be treated as early as possible, but we have often witnessed that patients reported immune-related adverse events when these were already at an advanced stage. The outcome was treatment delay, unnecessary patient discomfort, and decreased success rate.
In order to reduce late reporting of irAEs, and based on a literature review, we prepared a 20-page handout of colorful illustrations, with each page emphasizing a single aspect of treatment, which was used as part of an introductory talk before the initiation of a new therapy course.

Method: In addition to the standard written material provided by the pharmaceutic companies, a short series of pictures and images which includes the following information was added: (1) possible irAEs, with recommendation when to come to the clinic or be treated at home; (2) information on combinations of PD-1 and CTLA-4 blockade; (3) information on other combinations (e.g. radiation with immunotherapy, surgery with immunotherapy). (4) An illustration of the human body where the patient or a family member can easily mark the area of the relevant adverse event. Patients were requested to mark which part is involved in the AE.

Results: Twenty patients received information regarding irAEs based on visual material in addition to the standard information. We have found that the visual reporting method was received much better by the patient than the accepted EQ-5D-3L and QLQ-C30. The feedback from the patients has been highly enthusiastic, and other staff members reported a positive attitude towards the treatment in all cases. All patients arrived in the clinic to report and receive treatment for irAEs according to the instructions. The eager response from the patients has motivated us to share this information with the conference's participants, in order to encourage other centers to use this or a similar visual communications approach.

Conclusion: Visual information is easily understood and gratefully accepted by the patients, and may be helpful to shorten the time from appearance to treatment of irAEs.

13 Real world management and costs in unresectable Metastatic Melanoma (uMM) patients treated at the Antwerp University Hospital (UZA)

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Background: Physicians should be aware of the increasing costs of cancer care, which might become unaffordable even in rich countries.

Methods: To assess the management and associated lifetime costs as from the diagnosis of unresectable recurrent or metastatic disease until death, we performed a retrospective patient chart review to obtain data on resource use related to the management of uMM. A complete registry of all patients diagnosed with melanoma at UZA between 2006 and December 2016 was compiled. Eligible for this retrospective chart review were patients with uMM with sufficient data available and who deceased before Jan 2017. Data on demographics, disease characteristics and management were collected. Direct costs were calculated by multiplying each item of resource use with its unit cost (2017, €) using the Belgian public health care payer's perspective (PHCP) and patient's perspective. Average (bootstrap 95%CI) overall costs per patient were calculated.

Results: 309 patients were both diagnosed and followed up in UZA for melanoma of which 60 fulfilled the eligibility criteria for this chart review. 85% (n=51) of patients were treated by systemic treatment(s) of which 16% (n=8) received up to 4 different treatment lines. 28 (55%) patients received one or more of the "new drugs" (ipilimumab: 22; vemurafenib: 7, pembrolizumab: 6, nivolumab: 1). 61/179 (34%) hospitalizations were for treatment administration. Mean overall cost/patient was € 55,470 (bootstrap 95% CI: 42,062–69,762), of which € 54,481 (95%CI: 41,491–68,750) was reimbursed. The PHCP cost was driven by systemic treatments costs (59% of cost). Mean PHCP cost was € 92,018 (95% CI: 72,314–112,809) for patients of whom treatment included "new drugs", € 26,575 (95% CI: 17,156–37,540) for patients treated with chemotherapy but no "new drugs", and € 9,011 (95% CI: 3,920–14,968) for patients on best supportive care (BSC) only. Median overall survival was 6.4 months (95% CI: 4.6–8.2) for all patients. It was 9.9 months (95% CI: 7.3–12.6) for patients treated with "new drugs", 5.5 months (95% CI: 3.3–7.7) for patients treated with chemotherapy only (difference 4.4 months; 95% CI: 1.0–7.8), and 1 month (95% CI: -0.4–2.3) for patients treated with BSC only.

Conclusions: Management of uMM results in considerable costs for the PHCP, mainly driven by systemic treatment costs. The better outcome with "new drugs" reported in clinical trials was also observed in a real life setting.