



**2019 SMR
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LATE
BREAKING
ABSTRACTS**

Late Breaking Abstracts

TITLE: A role for Osteopontin in bone tropism in a novel murine model of melanoma bone metastasis

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Body: Metastasis is responsible for most deaths in melanoma patients. Five-year relative survival for patients with distant metastatic melanoma is only 22% compared with 98% in patients with only localized tumors. Approximately 40% of patients with metastatic melanoma develop bone metastasis and it is associated with pain and pathologic fractures. Yet, tools to study mechanisms of bone metastasis are lacking. We developed two novel murine bone metastasis models using novel C57BL/6N murine metastatic melanoma cell lines. Bone-tropic lines were generated through serial intracardiac injections of cells harvested from bone lesions. These lines reproducibly metastasize to bone with limited metastasis to other organs. These bone-tropic melanoma cells have persistent in vitro morphologic differences compared to those derived from other organs, suggesting alterations associated with colonization in different tissue microenvironments. Cytokine arrays from in vitro culture of bone-tropic cells revealed differential expression of multiple signaling molecules involved in immune response, ECM structure, and bone metabolism. Interestingly, Osteopontin (OPN), a secreted protein that is known to play a role in bone remodeling and osteoclast activation, is highly upregulated in our brain-tropic cell lines. Additionally, OPN has been implicated in both tumor growth and metastasis and can act on tumor cellular functions and on the microenvironment. Autocrine roles for OPN include regulation of apoptosis, proliferation, and cytoskeletal structure. We are using our novel bone-tropic melanoma cell lines to investigate the role of OPN directly on the melanoma cells, and on the microenvironment and bone metabolism. In summary, our novel models of melanoma bone metastasis are promising tools for identifying potential therapeutic targets and understanding key drivers of melanoma bone metastasis such as OPN.

TITLE: GSK-3 β blockade with 9-ING-41 in melanoma: The 1801 Phase 1/2 study

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Body: Background: GSK-3 β is a serine/threonine kinase that regulates tumor progression, oncogenesis, cell cycle and epithelial-mesenchymal transition. Overexpression of GSK-3 β is associated with advanced stage, aggressive growth and chemotherapy resistance. GSK-3 β inhibition reduced proliferation and induced apoptosis of melanoma cell lines (Kubic Mol Can Res 2012). These data provided the rationale for inclusion of patients with melanoma in a Phase 1/2 study evaluating the small molecule, first-in-class GSK-3 β inhibitor 9-ING-41. Methods: Part 1 of the 1801 study evaluate safety, and delineate the recommended Phase 2 study dose for 9-ING-41 monotherapy in patients with refractory malignancies. Patients receive twice-weekly intravenous infusions of 9-ING-41 until toxicity or progression. Response is defined by RANO criteria for brain metastases and RECIST 1.1 for other masses in evaluable lesions. The study is open in 25 sites globally and will accrue about 300 patients. Results: To date, 3 patients with melanoma were accrued among a total of 70 patients. Five dose levels (1, 2, 3.3, 5, 7 mg/kg) have been completed without 9-ING-41 attributable SAE. A complete radiologic including brain metastases response was observed at 12-week assessment and confirmed on scans at 18 and 24 weeks from initiation of 9-ING-41 (5 mg/kg) monotherapy in one patient with BRAF V600K mutated metastatic melanoma refractory to nivolumab/ipilimumab sequenced with dabrafenib/trametinib. Another patient had stable disease on 6-week scan and a third patient completed one month of therapy. Grade 1 transient color perception changes attributed to 9-ING-41 was observed in 38% (17/45) of patients. Conclusion: A complete response lasting 12 weeks to date was observed in a patient with refractory metastatic melanoma on 9-ING-41. The compound is well tolerated with stable predictable PK. Accrual of patients with advanced melanoma is ongoing.

TITLE: CD8+ T cell densities and immune-mediated patient survival are independent of tumour mutation burden or structural aberration mutations in distinct forms of melanoma

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Body: Purpose: Tumor mutation burden (TMB) has been proposed as a key determinant of immune-mediated survival in cancers. The evidence presented thus far however, is often contradictory, and almost exclusively based on RNA sequencing data for the quantification of immune cell phenotypes. Few studies have investigated TMB across acral, mucosal and cutaneous melanoma subtypes which are known to have vastly different TMB. It is also unknown whether types of genomic alterations, such as chromosomal structural mutations, contribute to the immune response in melanoma tumor subtypes, particularly in acral and mucosal melanomas. Experimental Design: We stained 151 cutaneous and 35 acral and mucosal melanoma patient samples using quantitative IHC and correlated immune infiltrate phenotypes with TMB and other genomic profiles. Results: TMB and chromosomal structural mutations did not correlate with the densities of CD8+ lymphocytes, CD103+ tumor resident CD8+ T cells, and CD45RO+ immune cells in cutaneous or acral/mucosal melanoma tumors respectively, including in analyses restricted to specimen type and site of disease. Similar results were found in an independent cohort of 56 cutaneous and 11 acral/mucosal melanoma samples. Multivariate analysis of 43 stage III treatment-naïve melanoma patients with cutaneous melanoma and up to twelve years follow-up found that the density of immune cells, particularly tumor resident CD8+ T cells, was significantly associated with patient melanoma-specific survival and independent of TMB. Conclusions: TMB and chromosomal structural aberrations are not strong determinants of anti-tumor immunity or immune-mediated patient survival in treatment-naïve melanoma.

TITLE: Retrospective analysis of patients with sentinel lymph node(SLN) positive melanoma(MEL) who received adjuvant anti-PD-1 therapy without completion lymph node dissection(CLND)

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Body: Until recently, most patients(pts) with SLN+ MEL underwent CLND, as also mandated in published trials of adjuvant anti-PD-1 therapy to date. Following MSLT-II, most pts no longer undergo a CLND. Our aim was to explore real-world outcomes of adjuvant anti-PD-1 therapy in these pts. A multi-center retrospective analysis of SLN+ MEL pts treated with adjuvant nivolumab or pembrolizumab without immediate CLND was performed in 17 cancer centers in USA, Europe and Australia. 254 pts received adjuvant nivolumab(n=240) or pembrolizumab(n=14) within 3 months of surgery. Median age was 58 (21-93). 73% of patients had 1+ SLN; 52% had ulcerated primary. There were 46, 61, 143 and 4 pts respectively with stage 3A/3B/3C/3D MEL. 38% had BRAF-V600 mutant MEL(of 152 with known status). With median follow-up of 10 months, relapse-free survival(RFS) rate at 12 months was 79%(95% CI, 72-85); 18-month RFS rate was 71%(62-80). There was no difference in RFS in pts with 1+SLN vs ≥ 2 + SLN. There was a difference in 12-month RFS between an ulcerated (69%) vs non-ulcerated primary(87%; p=0.0066). 5 pts died from recurrence and 12-month overall survival rate was 99% (98-100). Of the 43(17%) relapses so far, 19(44%) occurred first in the regional nodal basin (5 with concurrent in-transit mets), while 16 relapsed with distant mets. Post-relapse, 12 pts underwent CLND; 7 received radiation (5 to nodal basin, 2 to brain). 32 received systemic therapy, including 10 who remained on anti-PD1 monotherapy, 5 MAPK-targeted therapy, and 13 either ipilimumab or combination ipi plus nivo, 4 other drugs. This is the largest real-world analysis to date of adjuvant immunotherapy in SLN+ melanoma without CLND, and despite the frequency of nodal relapses, adjuvant anti-PD-1 therapy may be as effective in SLN+ pts who forego immediate CLND.

TITLE: A multi-institutional, prospective, randomized, double-blind, placebo-controlled phase IIb trial of the tumor lysate, particle-loaded, dendritic cell (TLPLDC) vaccine to prevent recurrence in high-risk melanoma patients

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Body: A novel vaccine strategy may prevent recurrences in patients (pts) with high risk melanoma. The TLPLDC vaccine uses yeast cell wall particles (YCWP) to load autologous tumor lysate into autologous DC. Here, we present the primary analysis of a randomized trial of the TLPLDC vaccine to prevent recurrence in pts with resected stage III/IV melanoma.

Disease-free melanoma pts were randomized 2:1 to the TLPLDC vaccine vs. unloaded YCWP and autologous DC at 0, 1, 2, 6, 12, 18 mos. The protocol was amended to allow concurrent checkpoint inhibitor therapy once approved for the adjuvant setting. The primary endpoint was 24-mo disease-free survival (DFS). The pre-specified per treatment (PT) analysis included only pts completing the primary vaccine/placebo series (PVS) at 6 mos. The primary analysis occurred 24 mos after the last pt enrolled.

144 pts were randomized (103 vaccine, 41 control). There were no clinicopathologic or treatment differences between groups. Therapy was well-tolerated with 31.7% of control pts and 35.9% of TLPLDC pts experiencing a related adverse event (>90% grade 1 or 2). There was no significant difference between the TLPLDC and placebo arms for 24 mo DFS in the ITT analysis (38.5% vs 27%, p=0.974). In the PT analysis, 24 mo DFS was significantly improved in the TLPLDC group compared to placebo (62.9% vs 34.8%; HR 0.52, 95% CI 0.27-0.98, p=0.041). The 24 mo OS for TLPLDC vs placebo was 86.4% vs 75.1%, p=0.15.

This randomized phase IIb trial of the TLPLDC vaccine to prevent recurrence in stage III/IV resected melanoma pts shows the vaccine is safe and improves DFS in pts who complete the PVS. The TLPLDC vaccine warrants further study in a phase III trial.

TITLE: Updated survival in patients (pts) with BRAF-mutant melanoma administered pembrolizumab (pembro), dabrafenib (D), and trametinib (T)

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Body: In the phase 2 KEYNOTE-022 study, pts with treatment-naïve BRAF^{V600E/K}-mutant advanced melanoma received pembro (2 mg/kg Q3W) (n=60) or placebo (PBO) plus D (150 mg BID) and T (2 mg QD) (n=60). With a median follow-up of 9.6 mo, pembro/D/T numerically increased PFS, but had a higher rate of grade (G) 3-5 TRAEs vs PBO/D/T. Baseline characteristics were similar across arms, except M1c: 82% in pembro, 63% in PBO. In updated analyses (Jun 26, 2019) with a median follow-up of 28.0 mo (range, 2.7-42.9), median PFS (primary end point) by investigator review per RECIST v1.1 was 16.9 mo (95% CI, 11.3-27.9) in the pembro and 10.7 mo (95% CI, 7.2-16.8) in the PBO arms (HR, 0.53; 95% CI, 0.34-0.83). PFS rates at 24 mo were 41.0% vs 16.3%. Median OS was not reached (95% CI, 23.9-NR) in the pembro and was 26.3 mo (95% CI 18.2-NR) in the PBO arms (HR, 0.64; 95% CI, 0.38-1.06). OS rates at 24 mo were 63.0% vs 51.7%. ORR per RECIST v1.1 was 63.3% and 71.7%; median DOR was 25.1 mo (range, 1.2+ to 36.6+) and 12.1 mo (range, 1.4+ to 36.4+) in the pembro and PBO arms, respectively (HR, 0.32; 95% CI, 0.17-0.59). DOR rates at 24 mo were 54.9% and 15.9%, respectively. Any-grade and G3-5 TRAEs occurred in 57 pts (95.0%) and 35 pts (58.3%) in the pembro and 56 pts (93.3%) and 15 pts (25.0%) in the PBO arms. One pt died of pembro-related pneumonitis. The most common (≥5% of pts) G3-5 TRAEs were pyrexia (10.0% [n=6] vs 3.3% [n=2]), increased AST (6.7% [n=4] vs 3.3% [n=2]), and increased γ-glutamyl transferase (6.7% [n=4] vs 5.0% [n=3]). Immune-mediated AEs occurred in 31 pts (51.7%) in the pembro vs 9 pts (15.0%) in the PBO arms. With longer follow-up, pembro/D/T vs PBO/D/T continued to show improved PFS and median DOR, and 24-mo OS and DOR rates were numerically higher. However, these improvements were accompanied by a higher incidence of G3-5 TRAEs.

TITLE: Safety Data from a Single-Center Phase I/Ib Study of Concurrent Intravenous (IV) and Intrathecal (IT) Nivolumab (N) for Metastatic Melanoma (MM) Patients (pts) with Leptomeningeal Disease (LMD)

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Body: MM pts with LMD have a dismal prognosis (median survival 6 wks) and no approved therapies. IT administration of interleukin-2 has demonstrated durable disease control and survival in ~13% of pts, but with significant toxicity. Given the favorable clinical activity and safety of anti-PD-1 antibodies, we are conducting a First-In-Human clinical trial evaluating the safety of concurrent IV and IT Nivo in MM pts with LMD (NCT03025256). Eligible pts have MM, ECOG PS <2, and evidence of LMD by MRI and/or CSF cytology. ITN is administered via Ommaya reservoir on C1D1 and pts are observed for 24 hrs with multiple blood and CSF collections. Starting with C2, pts receive ITN on D1 and IV Nivo (IVN) 240mg on D2 q14 days. Dose escalation was performed using Bayesian mTPI to define the MTD, and 3 ITN levels of 5, 10, and 20mg were tested. Primary objectives are to determine safety and feasibility of ITN and the recommended dosage of ITN and IVN.

9 pts have been treated to date: 2 at 5mg, 3 at 10mg, and 4 at 20mg ITN. All pts had MRI evidence of LMD, including 4 pts with positive CSF cytology. 7 pts received prior systemic therapies: Checkpoint inhibitor (n=6), BRAFi/MEKi (n=5), other (n=3). 8 pts had prior radiotherapy. No AEs ≥ gr3 were attributed to ITN or IVN and no AEs were observed with the IT administration. Four pts continue on treatment and the median treatment duration is 7.9 (2.1-61.4) wks.

The combination of ITN and IVN is safe and can be feasibly administered in this population, with no additive toxicity. The intrathecal dose of N was established at 20mg q 14 days. An expansion phase is ongoing to further characterize the safety profile and preliminary efficacy of ITN in pts with MM and LMD. Studies are ongoing to characterize clinical activity, PK and immune effects.

TITLE: Lifileucel (a cryopreserved autologous tumor infiltrating lymphocyte therapy) produces durable responses at one-year median study follow-up in patients with advanced metastatic melanoma previously progressed/ refractory to multiple prior therapies including anti-PD-1

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Body: Treatment options are limited for patients with advanced melanoma who have progressed on checkpoint inhibitors & targeted therapies such as BRAF/MEK inhibitors. Adoptive cell therapy using tumor-infiltrating lymphocytes (TIL) has shown durable responses in heavily pretreated melanoma patients.

C-144-01 is a global Phase 2 open-label, multicenter study of efficacy & safety of lifileucel in patients with unresectable metastatic melanoma. We report on Cohort 2 (N=66) patients. Tumors were resected at local institutions, processed in central GMP facilities for TIL production, manufactured, cryopreserved & shipped back to sites in a 22-day process. Therapy consisted of one week of lymphodepletion, a single lifileucel infusion, & ≥6 f IL-2 doses.

Baseline characteristics: 3.3 mean prior therapies (anti-PD1 100%; anti-CTLA-4 80%; BRAF/MEK inhibitor 23%), high tumor burden (106 mm mean target lesion sum of diameters), 44% liver/brain lesions, median LDH 244 U/L. ORR by investigator was 36.4% (2 CR, 22 PR) & Disease Control Rate was 80.3%. At median study follow up of 12.0 months, the median Duration of Response (mDOR) has still not been reached (95% CI [6.4, NR]). 63% of responders continue in response. In some patients, response improves over time. The AE profile was consistent with previous data sets. ORR of 40.5% (17/42) was demonstrated in patients who were primary refractory to checkpoint inhibitors (Best Overall Response of PD to the earliest anti-PD1/L1 treatment).

Lifileucel treatment results in 36.4% ORR & mDOR not reached at one-year median study follow up in heavily pretreated metastatic melanoma patients with high baseline disease burden who received prior anti-PD1 & BRAF/MEK inhibitors if BRAF mutated.

TITLE: Prognostic Significance of CD200 Protein Expression and its Correlation with COX-2 in Cutaneous Melanoma

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Body: CD200 is an immunosuppressive glycoprotein known to have anti-tumour properties. Cyclooxygenase-2 (COX-2), plays a role in the carcinogenesis in solid organ tumors. We evaluated CD200 and COX-2 protein expression and their correlation in melanoma tissues and determined their effects on clinicopathological characteristics and biological responses in melanoma. Diagnostic tissue from 118 cases of melanoma was evaluated by immunohistochemistry for CD200 and COX-2 expression. Clinicopathological features and survivals were analysed according to CD200 and COX-2 expression. BRAF^{V600E} A375 melanoma cell lines were used to evaluate the effect of COX-2 inhibition by celecoxib on CD200 expression in vitro. CD200 expression was positively correlated with COX-2 expression in melanoma tissue. CD200 and COX-2 expression was significantly associated with negative prognostic factors: deeper Breslow thickness, vertical growth phase, lymph node involvement, and advanced stage of melanoma. CD200 and COX-2 were also found to be independent prognostic indicators of a poorer overall survival. The inhibition of COX-2 activity by celecoxib downregulated CD200 expression in BRAF^{V600E} melanoma cell lines. In conclusion, expression of CD200 represents an independent unfavorable prognostic factor in melanoma. CD200 expression is correlated with COX-2 and could be downregulated by COX-2 inhibition.

TITLE: Characteristics of Long-Term Survivors and Subgroup Analyses With Combination Nivolumab Plus Ipilimumab (NIVO+IPI) for Advanced Melanoma (CheckMate 067)

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Body: 5-y CheckMate 067 results showed sustained and significantly improved outcomes with NIVO+IPI and NIVO vs IPI alone (5-y overall survival [OS], 52%, 44%, and 26%, respectively; 5-y progression-free survival [PFS] rates, 36%, 29%, and 8%). Here, we report analyses of clinically important patient (pt) subgroups.

In this multicenter, double-blind, phase 3 trial, pts with previously untreated, unresectable stage III or stage IV melanoma received NIVO 1 mg/kg + IPI 3 mg/kg for 4 doses Q3W followed by NIVO 3 mg/kg Q2W (n=314), NIVO 3 mg/kg Q2W + placebo (n=316), or IPI 3 mg/kg Q3W for 4 doses + placebo (n=315) until progression/unacceptable toxicity. OS and PFS were co-primary endpoints.

At 60 mo minimum follow-up, the objective response rate was highest for NIVO+IPI at 58%/complete response (CR) 22% (NIVO, 45% [CR 19%]; IPI, 19% [CR 6%]). In pts with CR, 5-y PFS was 80%, 79%, and 76% for NIVO+IPI, NIVO, and IPI, respectively, and 5-y OS was 90%, 93%, and 83%. For partial response, these were 45%, 41%, and 15% (PFS), respectively, and 65%, 63%, and 56% (OS). For stable disease, these were 3%, 10%, and 0% (PFS), respectively, and 24%, 40%, and 33% (OS). In pts with BRAF-mutant tumors, 5-y rates were 38%, 22%, and 11% (PFS), respectively, and 60%, 46%, and 30% (OS). In pts with BRAF-wild-type tumors, these were 35%, 32%, and 7% (PFS), respectively, and 48%, 43%, and 25% (OS). In pts with baseline lactate dehydrogenase (LDH) levels $\leq 2x$ the upper limit of normal (ULN), 5-y OS rates were 55%, 48%, and 29%, respectively; in pts with LDH levels $> 2x$ ULN, these were 28%, 14%, and 7%. Clinical features and other analyses of long-term survivors will be presented.

First-line NIVO+IPI and NIVO alone continued to demonstrate durable, sustained survival benefit across clinically relevant subgroups of pts with advanced melanoma at 5 y.

TITLE: High dimensional digital pathology to investigate melanoma progression and evolution of the tumor microenvironment

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Body: Recent advances in highly-multiplexed imaging, data science and multi-omics integration can provide a deeper understanding of melanoma initiation and progression by histology-driven analysis of archival diagnostic skin biopsies. The center for precancer atlases of cutaneous and hematologic origin (PATCH) identifies and analyzes skin biopsies containing melanocytic atypia alongside normal skin and primary melanoma or precursors lesions. The core technology, cyclic immunofluorescence (CyCIF) microscopy is a highly-multiplexed (30+ biomarkers) imaging technology that is compatible with 5 µm FFPE tissue sections from clinical workflows and uses conventional fluorescence microscopes, commercially available antibody (300+ biomarkers validated) conjugates (Lin, et. al. 2018). Optical imaging permits rapid scanning of whole slides at sub-cellular resolution. Image processing (illumination, stitching, registration, feature extraction) of the multiplexed image data sets is performed with open-source software that is publicly available, with the aim of sharing annotated image data as outreach (www.cycif.org) and data depositories as part of the Human Tumor Atlas Network (HTAN). Single-cell immunophenotyping of cells in FFPE tissue include stromal, immune lineage and checkpoint markers to provide a cell census in regions of interest identified in H&E stained sections. This data is integrated with spatial RNA sequencing as a discovery tool to identify novel markers of progression and stratification. Here we describe immunophenotyping of melanocytic atypia, primary melanomas and precursor lesions to investigate tissue architecture, develop tissue level biomarkers and characterize mechanisms of immune surveillance and evasion in order to build a Precancer Atlas (PCA) for melanoma

TITLE: Implications of intratumor heterogeneity in immunotherapy

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Body: While the clinical management of melanoma using immune checkpoint blockade (ICB), such as anti-CTLA-4 and anti-PD-1/PD-L1, are well established, low response rates and disease recurrence continues to be an urgent clinical issue. In order to address these gaps, we must better understand the resistant mechanism to ICB. Through the comparative analysis of mouse melanoma models, we have recently characterized a “melanocytic plasticity signature” (MPS) that predicts melanoma response to ICB. Interestingly, we have found that residual disease following response to ICB exhibited high MPS score, implying the high-plasticity subpopulation in melanoma was responsible for resistance. We were able to validate this finding within a dataset of on-treatment melanoma from patients receiving ICB therapy. To prove the existence of such subpopulation, we isolated single-cell clones from one of our melanoma models. We found that these clones exhibited diverse MPS scores, and that tumors derived from high-MPS clones were resistant to anti-CTLA-4. Moreover, within these clones, we found the MPS scores significantly correlated with expression of neural crest lineage markers, NGFR and AXL, which maintain the high potency of precursor cells during development. These results indicated that a high-plasticity subpopulation in melanoma is responsible for resistance and/or recurrence following ICB treatment. Targeting NGFR and AXL may promote efficacy of ICB therapy for melanoma, which may result in significant clinical-implications.

TITLE: 5-Year Survival Update of Cobimetinib Plus Vemurafenib in BRAF^{V600} Mutation-Positive Advanced Melanoma: Final Analysis of the coBRIM Study

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Body: The pivotal randomized placebo-controlled double-blind phase 3 coBRIM study showed that cobimetinib plus vemurafenib (C+V) prolonged progression-free survival (PFS) and overall survival (OS) compared to placebo plus vemurafenib (P+V) in patients with BRAF^{V600} mutation-positive advanced melanoma (Larkin J et al. *N Engl J Med* 2014;371:1867-76). We report the final analysis of this study 65 months after the last patient was randomized. The coBRIM study (ClinicalTrials.gov NCT01689519) assigned patients with previously untreated BRAF^{V600} mutation-positive advanced melanoma to C+V (n=247) or P+V (n=248). PFS and OS were the primary and key secondary endpoints, respectively. At database lock, median follow-up duration was 21.2 mo (C+V arm) and 16.6 mo (P+V arm); 157 patients (C+V arm) and 167 patients (P+V arm) died. In the C+V arm, median OS was 22.5 mo (95% CI 20.3-28.8); OS rates at 4 and 5 years were 34% (95% CI 28-40) and 31% (95% CI 25-37). In the P+V arm, median OS was 17.4 mo (95% CI 15.0-19.8); OS rates at 4 and 5 years were 29% (95% CI 23-35) and 26% (95% CI 20-32). Adverse events (AEs) of special interest with C+V and P+V, respectively, included rash (73% vs 68%), photosensitivity (49% vs 38%), retinal detachment/retinopathy (27% vs 5%), cutaneous primary malignancies (13% vs 23%), and reduction in left ventricular ejection fraction (13% vs 5%). AE-related treatment discontinuation rates were 20% (C+V) and 9% (P+V). Results of overall safety analyses were similar to previously reported results; no late treatment safety concerns were observed.

This extended 5-year follow-up of the phase 3 coBRIM study confirmed that the C+V combination provided long-term clinical benefit.

TITLE: The effect of UV radiation and BRAF mutation event sequencing on murine melanomagenesis is model-dependent

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Body: Both UV exposure and BRAF mutations are important factors in melanomagenesis. Childhood and/or intermittent sun exposure are epidemiologically associated with increased risk of melanoma development, suggesting that UV may play a role in melanoma development either early or later in life. Approximately half of melanomas and nevi have a BRAF mutation, and BRAF mutation appears to be an early event in lesion formation. The importance of UV and BRAF event sequence in melanomagenesis remains unclear. We designed a study to evaluate the role of UV and BRAF event sequencing in TyrCre tg/+; Cdkn2a fl/+; BRAF ca/+ mice on an HGF-tg (hB) or HGF-wt (hB) background. UV and tamoxifen (T) administration occurred at either 3 or 30 days postnatal generating 4 groups: UV3+T30, T3+UV30, T3, and T30. While UV+BRAF enhanced tumor formation in both backgrounds, event timing was only important for tumor development in the hB model, in which the T3+UV30 group had the highest tumor formation. While all hB and most HB tumors were amelanotic and histologically had sarcomatous or schwannomatous features, a subset of HB tumors were pigmented with variable histologic appearance. Initial tumor onset was faster in the pigmented than non-pigmented HB tumors. Pigmented tumors were also transcriptomically distinct from non-pigmented HB tumors. Exome sequencing showed that UV-type mutations were common in the UV-exposed pigmented tumors but absent or at low frequency in the UV-exposed nonpigmented tumors, regardless of event sequencing. These data suggest that UV can promote melanomagenesis without many UV-type mutations and that pigmented HB tumors may originate from a different cell of origin and from a different location in the skin than non-pigmented tumors. Overall, these data suggest the consequences of UV and BRAF event sequencing are not universal and vary with circumstances and models.

TITLE: Is IL-8 The Right Target For Melanoma Treatment?

In-vitro studies based on Steroids, IL-8, Curcumin and Active Vitamin-D3 treatments of human melanoma cell models

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Body: Clinical studies showed better protection of younger women in melanoma than post-menopausal women and an increased male mortality in melanoma. Our in-vitro study showed female sex hormone progesterone (P) significantly inhibited human melanoma cell growth. Elisarray showed that P action was mediated by a specific suppression of pro-inflammatory cytokine IL-8. Further research showed that addition of IL-8 (1 ng/ml) to melanoma cells stimulated cell growth (117%) and suppression of IL-8 by curcumin (100 μ M) pre-treatment decreased human melanoma cell growth (26%). This observation prompted us to check the effect of male sex hormones androstenedione (AD) and testosterone (T) on melanoma cell growth. AD and T also suppressed cell growth and IL-8 secretion. However, addition of P (10 μ M) along with androgens increased the inhibitory effect on melanoma cell growth and IL-8 secretion. As steroids (P, AD, T) targeted IL-8 for their action, it was decided to check whether vit-D3 also targeted IL-8. Active form of vit-D3 (25 μ M) also suppressed IL-8 secretion and cell growth. But, addition of P-(50 μ M) along with D3 significantly decreased cell growth and IL-8 secretion. In order to check whether IL-8 was the molecule involved in regulating melanoma cell growth, IL-8 rescue experiment after curcumin (25 μ M) pre-treatment was carried out. IL-8 (100 ng/ml) was able to rescue cell growth completely after pre-treatment with curcumin. Literature suggested a key role for IL-8 in melanoma cell growth. Conditional expression of IL-8 in nude mouse by Singh et al., indicated in-vivo role of IL-8 in melanoma growth and metastasis. Conclusion: In-vitro and in-vivo studies indicated a key role for IL-8 in regulating melanoma growth and metastasis. So, IL-8 could be targeted to arrest melanoma growth and metastasis in-vivo.

TITLE: Dabrafenib Plus Trametinib in Chinese Patients with Advanced BRAF V600–Mutant Cutaneous Melanoma: an Open-Label, Phase IIa Study Update (NCT02083354)

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Body: Background

Approximately 40%-50% of melanomas carry BRAF mutations, and more than 97% of BRAF mutations are at the V600 position. Here the efficacy and safety of dabrafenib (BRAF inhibitor) plus trametinib (MEK inhibitor) combination therapy was studied in Chinese patients with unresectable or metastatic BRAF V600–mutant acral lentiginous or cutaneous melanoma, who currently lack effective treatment options.

Methods

This is an analysis of single-arm, open-label, multicenter, phase IIa study in 55 Chinese pretreated patients aged ≥ 18 years with stage III and IV BRAF V600–mutant cutaneous melanoma. Patients were assigned to receive dabrafenib 150 mg twice daily and trametinib 2 mg once daily. The primary outcome was the overall response rate (ORR) by investigator assessment using RECIST v1.1. The secondary outcomes included progress-free survival (PFS), duration of response, overall survival (OS) (NCT02083354).

Results

The ORR was 65.9% and the disease control rate was 97.7%. The mean PFS was 10.3 month (95% CI, 8.1-12.5). Almost all the patients had tumor shrink. The complete response was observed in 1 patient. 28 patients had partial responses, and 14 patients had stable diseases. The median OS was 14 month (95%CI, 12.7-17.5). The most common treatment-related AE was pyrexia .

Conclusions

This phase IIa study demonstrates clinically meaningful efficacy of dabrafenib plus trametinib in Chinese patients with advanced BRAF V600–mutant cutaneous melanoma.

TITLE: Efficacy and safety of anti-PD-1 antibody combined with ipilimumab in patients with metastatic melanoma in China: a real-world study

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Body: Background: There is limited data on the efficacy and safety of combining PD-1 inhibitor and CTLA-4 inhibitor in Chinese melanoma patients.

Method: Patients with metastatic melanoma treated with nivolumab or pembrolizumab in combination with ipilimumab followed by anti-PD-1 monotherapy were retrospectively analyzed. Efficacy was evaluated by RECIST 1.1. Safety was assessed by the CTCAE.

Results: A total of 39 patients were included. There were 19 cutaneous melanoma, 6 acral melanoma, 5 mucosal melanoma, 4 uveal melanoma and 5 melanoma originated from the brain. BRAF V600 mutations were detected in 38.5% of patients. 12 (30.8%) patients had brain metastases, 11 (28.2%) with liver metastases, 10 (25.6%) had elevated LDH. Twenty-four (61.5%) patients had prior systemic therapy, 15 (38.5%) with anti-PD-1 therapy.

The objective response rate (ORR) was 12.8% and disease control rate (DCR) was 43.6%. For patients treated with prior anti-PD-1 therapy, the ORR and DCR were 13.3% and 26.7%, respectively. Intracranial responses were observed in 2 patients. The mPFS was 4.4 months (95% CI, 2.4–6.4 months), and the mOS was 15 months. PFS was longer in immunotherapy naïve patients compared to those had prior anti-PD-1 therapy (6.1 months vs 2.9 months, P=0.04). Liver/brain metastasis did not relate to efficacy.

Treatment-related adverse events (TRAEs) of any grade were observed in 89.5% of patients, with 12.8% having grade 3–4 adverse events. Treatment discontinuation due to adverse events occurred in 25.6% of patients.

Conclusion: In this study, the responses rate to the combined immunotherapy were lower than reported. Patients treated with prior immunotherapy or those with liver or brain metastasis can benefit from combined immunotherapy. The toxicity profile is similar to that reported in clinical trials.