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Melanoma Abstracts ASCO 2015

102 Clinical Science Symposium

Sun, 9:45 AM-11:15 AM

OVERALL SURVIVAL IN COMBI-D, A RANDOMIZED, DOUBLE-BLINDED, PHASE III STUDY COMPARING THE COMBINATION OF DABRAFENIB (D) AND TRAMETINIB (T) WITH DABRAFENIB AND PLACEBO (P) AS FIRST-LINE THERAPY IN PATIENTS (PTS) WITH UNRESECTABLE OR METASTATIC BRAF V600E/K MUTATION-POSITIVE CUTANEOUS MELANOMA

FIRST AUTHOR: GEORGINA V. LONG

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Background: This phase III study (NCT01584648) of dabrafenib (D) + trametinib (T) compared with D + placebo (P) demonstrated superior progression-free survival (PFS) for D+T compared with D+P (HR: 0.75; 95% CI: 0.57-0.99; p = 0.035) in patients (pts) with BRAF V600E/K mutant, metastatic melanoma at the primary analysis (N Engl J Med. 2014;371:1877-88). The interim overall survival (OS) favored D+T (40 deaths on D+T vs. 55 on D+P), but did not cross the pre-planned stopping boundary for efficacy. Median time on study at the primary analysis was nine months (0-16 months). Rates of adverse events (AE) were similar for both arms. More pts had AEs leading to dose modifications with D+T vs. D+P, and fewer hyperproliferative skin AEs were reported with D+T. The study was continued after the primary analysis to evaluate OS without crossover from D+P to D+T. **Methods:** Patients were randomized 1:1 to receive D (150 mg twice daily) + T (2 mg once daily) or D+P as first-line therapy. Eligible pts were age 18 or older, ECOG performance status ≤ 1, and had histologically confirmed unresectable stage IIIC or IV, BRAF V600E/K mutant cutaneous melanoma. The primary endpoint was investigator-assessed progression-free survival (PFS); secondary endpoints were OS, objective response rate (ORR), duration of response (DoR), and safety. The final statistical OS comparison was to be initiated when 220 events were reported. **Results:** From May 2012 to January 2013, 423 pts were randomized (211 to D+T, 212 to D+P). The 220th death was reported on January 12, 2015; analysis is expected to be completed in March 2015. Estimated median time on study at data cutoff is 20 months (0-31 months). **Conclusions:** The statistical analysis will evaluate the superiority of D+T vs. D+P for OS. A two-year OS landmark analysis, updated PFS, ORR, DoR, and safety will be presented.

Clinical trial information: **NCT01584648**

103 Clinical Science Symposium

Sun, 9:45 AM-11:15 AM

UPDATED EFFICACY OF THE MEK INHIBITOR TRAMETINIB (T), BRAF INHIBITOR DABRAFENIB (D), AND ANTI-EGFR ANTIBODY PANITUMUMAB (P) IN PATIENTS (PTS) WITH *BRAF* V600E-MUTATED (BRAFM) METASTATIC COLORECTAL CANCER (MCRC)

First Author: Chloe Evelyn Atreya

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Background: *BRAF* V600E mutations (BRAFm) occur in 5-10% of metastatic colorectal cancer (mCRC) and confer a poor prognosis. Unlike BRAFm melanoma, BRAF and MEK inhibitors have minimal activity in BRAFm mCRC. Preclinical data suggest that combined inhibition of the EGFR and MAPK pathways is required to maximally inhibit growth of BRAFm mCRC. This study evaluates the activity of the combination of panitumumab (P) with dabrafenib (D) and/or trametinib (T) in BRAFm mCRC. **Methods:** Eligible patients (pts) with BRAFm mCRC received doublet, D+P or T+P, or triplet, D+T+P. **Results:** Doublet D+P: 20 pts received the full doublet dose (D 150 mg twice daily [BID] + P 6 mg/kg every two weeks [Q2W]). Triplet D+T+P: 35 pts received D+T+P including 24 pts that received full triplet dose (D 150 mg BID + T 2 mg once daily [QD] + P 6 mg/kg Q2W). No dose-limiting toxicities were observed. As of October 20, 2014, the most common adverse events were dermatitis acneform (Grade [G] 1/2 55%) and fatigue (G1/2 45%) for D+P, and diarrhea (G1/2 60%; G3 9%) and dermatitis acneform (G1/2 47%; G3 9%) for triplet. The confirmed response rate for D+P was 10% and for D+T+P was 26% (Table 1). Treatment with either regimen reduced levels of pERK in on-treatment biopsies relative to pre-dose biopsies (median reduction D+P 23%; D+T+P 54%). Pts are currently being enrolled to T+P. Updated results including progression-free survival and duration of response will be presented. **Conclusions:** Encouraging clinical activity with acceptable tolerability is seen with the triplet D+T+P in BRAFm mCRC.

Clinical trial information: **NCT01750918**

Table 1. Investigator–assessed best response with confirmation (RECIST 1.1)

	D 150 mg BID+ P 6mg/kg Q2W n = 20	D 150 mg BID, T 1.5 mg QD, P 4.8 mg/kg Q2W n = 3	D 150 mg BID, T 2 mg QD, P 4.8 mg/kg Q2W n = 4	D 150 mg BID, T 1.5 mg QD, P 6 mg/kg Q2W n = 4	D 150 mg BID, T 2 mg QD, P 6 mg/kg Q2W n = 24	D+T+P Total n = 35
Complete response, n (%)	1 (5)	0	1 (25)	0	0	1 (3)
Partial response, n (%)	1 (5)	2 (67)	1 (25)	0	5 (21)	8 (23)
Stable disease, n (%)	16 (80)	1 (33)	2 (50)	2 (50)	15 (63)	20 (57)
Progressive disease, n (%)	2 (10)	0	0	2 (50)	3 (13)	5 (14)
Not evaluable, n (%)	0	0	0	0	1 (4)	1 (3)
Response rate (CR + PR), n (%)	2 (10)	2 (67)	2 (50)	0	5 (21)	9 (26)
95% CI, %	1.2-31.7	9.4-99.2	6.8-93.2	0.0-60.2	7.1-42.2	12.5-43.3

9001 Oral Abstract Session

Sat, 1:15 PM-4:15 PM

LONG-TERM FOLLOW UP OF SURVIVAL IN A RANDOMIZED TRIAL OF WIDE OR NARROW EXCISION MARGINS IN HIGH-RISK PRIMARY MELANOMA

First Author: Andrew J Hayes

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Background: Our randomized trial of 1 vs. 3 cm clinical excision margins for high-risk melanoma showed that narrow margins were associated with an increase in loco-regional relapse, but with no significant difference in melanoma-specific survival (MSS). We now report long-term MSS and overall survival from that trial. **Methods:** Patients with primary cutaneous melanoma 2 mm or more in Breslow thickness were randomized to a 1 or 3 cm excision. **Results:** A total of 453 patients were randomized to a 1 cm margin and 447 patients to a 3 cm margin. Median age was 58.7 years (IQR: 47.2-69.2), median tumor thickness and percentage ulceration were similar in both groups (1 cm group: 3.0 mm and 31.8%; 3 cm group: 3.1 mm and 34.5%). At a median follow-up of 8.8 years (IQR: 6.3-11.3), 494 patients have died, with 359 of these deaths from melanoma. There were 194 melanoma deaths in the 1 cm group and 165 in the 3 cm group. Relative rate of melanoma death was estimated to be 24% higher in the 1 cm group than the 3 cm group on univariate analysis (HR: 1.24; 95% CI: 1.00-1.52; p = 0.05). This effect was similar in multivariate analysis, adjusting for known prognostic factors (Table 1). While there was an increase in the number of overall deaths in the 1 cm group compared to the 3 cm group (253 vs. 241), this difference was not statistically significant in univariate analysis (HR: 1.14; 95% CI: 0.96-1.36; p = 0.14). **Conclusions:** With longer follow-up, the previously reported increase in loco-regional relapse associated with narrow excision margins has translated into a significant increase in melanoma specific mortality.

Table 1.

			Overall survival	Melanoma-specific survival
		n (%)	HR (95% CI) p value	HR (95% CI) p value
Margin	3 cm	387 (50.2)	1.00	1.00
	1 cm	384 (49.8)	1.19 (0.99-1.45) 0.07	1.27 (1.02-1.59) 0.036
Sex	Female	419 (54.3)	1.00	1.00
	Male	352 (45.7)	1.38 (1.11-1.71) 0.003	1.38 (1.07-1.17) 0.013
Thickness		771 (100)	1.18 (1.10-1.27) < 0.001	1.23 (1.13-1.3) < 0.001
Ulceration	Absent	475 (61.6)	1.00	
	Present	296 (38.4)	1.68 (1.38-2.04) < 0.001	1.75 (1.39-2.20) < 0.001
Site	Distal limb	244 (31.6)	1.00	1.00
	Proximal limb	173 (22.4)	1.23 (0.93-1.63) 0.03	1.44 (1.03-2.03) 0.003
	Trunk	354 (45.9)	1.41 (1.09-1.81)	1.69 (1.24-2.29)

9003 Oral Abstract Session

Sat, 1:15 PM-4:15 PM

SURVEILLANCE IMAGING WITH FLUORODEOXYGLUCOSE-POSITRON EMISSION TOMOGRAPHY (FDG-PE) IN THE FOLLOW-UP OF MELANOMA PATIENTS AT HIGH RISK OF RELAPSE

First Author: Jeremy Howard Lewin

Peter MacCallum Cancer Centre, East Melbourne, Australia

Background: In the modern era of melanoma treatment, approaches to imaging surveillance following surgery require reconsideration. The aim of this study was to evaluate disease sub-stage specific schedules of positron emission tomography (PET) surveillance for resected stage III melanoma. **Methods:** Between 2009-2013, patients at the Peter MacCallum Cancer Centre with fully resected AJCC stage III melanoma underwent serial whole body PET/CT scans according to schedules based on Bayesian disease sub-stage relapse probabilities. Schedules were stage IIIA: 6, 18 months; IIIB: 6, 12, 18, 24, 36, 48, 60 months; IIIC: 6, 12, 18, 24, 36 months. Descriptive statistics and contingency table analyses were used to evaluate outcomes for each schedule. **Results:** Eighty-six patients underwent PET surveillance according to schedule (IIIA: 11; IIIB: 50; IIIC: 25). In total, 232 PET scans were performed over a median follow-up of 28 months after surgery. Relapses were identified in 25 (29%) patients (IIIA: 4%; IIIB: 56%; IIIC: 40%), of which 20 (80%) were asymptomatic at the time of scanning. Incidental secondary malignancies were found in six (6.5%) patients. Stage IIIA/B relapses were more likely than stage IIIC to be locoregional (IIIA/B: 42%; IIIC: 10%; p = NS). Nine (36%) relapsed patients underwent potentially curative resection (IIIA: 1; IIIB: 6; IIIC: 2), with five (IIIA: 1; IIIB: 4) free of disease after a median 32 months follow-up. The positive and negative predictive values (PPV, NPV) of an individual PET scan for detecting disease relapse at the same time point were: stage IIIB PPV 69% (95% CI: 43-87) and NPV 99% (95% CI: 95-100), stage IIIC PPV 73% (95% CI: 39-94) and NPV 97% (95% CI: 90-100). The PPV and NPV of each surveillance protocol for detecting any disease relapse were: stage IIIB PPV 68% (95% CI: 43-87) and NPV 97% (CI: 83-99), stage IIIC PPV 73% (95% CI: 39-94) and NPV 86% (95% CI: 57-98). The sensitivity and specificity of the overall approach of sub-stage-specific PET/CT surveillance for detecting disease relapse were 88% (CI: 69-97) and 84% (CI: 72-92), respectively. **Conclusions:** fluorodeoxyglucose (FDG)-PET is effective in detecting asymptomatic metastases and thus facilitating early treatment in patients who relapse after resection of stage III melanoma.

9004 Oral Abstract Session

Sat, 1:15 PM-4:15 PM

CLINICAL RESPONSE, PROGRESSION-FREE SURVIVAL (PFS), AND SAFETY IN PATIENTS (PTS) WITH ADVANCED MELANOMA (MEL) RECEIVING NIVOLUMAB (NIVO) COMBINED WITH IPILIMUMAB (IPI) VS. IPI MONOTHERAPY IN CHECKMATE 069 STUDY

First Author: F. Stephen Hodi

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Background: Combined blockade of T-cell checkpoints by nivolumab (NIVO) and ipilimumab (IPI) demonstrated a high objective response rate (ORR), promising overall survival (OS), and a manageable safety profile in patients (pts) with advanced melanoma (MEL) in a phase I study, based on which an appropriate dose was selected for registration trials. We report efficacy and safety of the NIVO + IPI combination vs. IPI alone in treatment-naive pts with advanced MEL, including pts with poor prognostic factors, in a phase II study. **Methods:** Pts (n = 142) with metastatic or unresectable MEL were randomized 2:1 to receive IPI 3 mg/kg combined with either NIVO 1 mg/kg or placebo every three weeks (Q3W) × 4, followed by NIVO 3 mg/kg or placebo every two weeks (Q2W) until disease progression or unacceptable toxicity. The primary endpoint was ORR in BRAF wild-type (WT) pts. Secondary and exploratory objectives included progression-free survival (PFS) in BRAF WT pts, ORR and PFS in BRAF V600 mutation-positive (MT) pts, and safety. **Results:** In BRAF WT pts (n = 109), ORR was 60% (43/72) for NIVO + IPI; 11% (4/37) for IPI alone ($p < 0.0001$); complete responses were reported in 12 (17%) and zero pts, respectively. Median PFS was 8.9 months for the combination vs. 4.7 months for IPI alone ($p = 0.0012$). Higher ORR was observed for NIVO + IPI vs. IPI in predefined pt subgroups with poor prognostic factors, such as elevated baseline lactate dehydrogenase (LDH, 53 vs. 0%) and M1c stage disease (62 vs 25%). Similar ORR and PFS results were observed in 33 BRAF MT pts. Grade 3-4 drug-related adverse events (AE) were reported in 51% of pts receiving NIVO + IPI vs. 20% for IPI alone. The safety profile of NIVO + IPI was similar across pt subgroups, including age. Select AEs related to the combination regimen were consistent with phase I reports, and most resolved with immunosuppressive medication (> 83% across organ categories) with the exception of endocrinopathies. Updated results from a planned data analysis in March 2015 will be presented. **Conclusions:** NIVO + IPI significantly improved ORR and PFS compared with IPI alone and had a manageable safety profile. The efficacy and safety of the combination was similar across pt subgroups and provided a favorable risk-benefit ratio in treatment-naive pts with advanced MEL.

Clinical trial information: **NCT01927419**

9005 Oral Abstract Session

Sat, 1:15 PM-4:15 PM

LONG-TERM EFFICACY OF PEMBROLIZUMAB (PEMBRO; MK-3475) IN A POOLED ANALYSIS OF 655 PATIENTS (PTS) WITH ADVANCED MELANOMA (MEL) ENROLLED IN KEYNOTE-001

First Author: Adil Daud

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Background: The anti-PD-1 antibody pembrolizumab (pembro) is approved in the USA for treating unresectable or metastatic melanoma (MEL) that progressed following ipilimumab (IPI) and, if *BRAF*V600 mutant, a BRAF inhibitor. Pembro has demonstrated robust antitumor activity and manageable toxicity in IPI-treated (IPI-T) and naive (IPI-N) pts. In KEYNOTE-002, pembro significantly prolonged progression-free survival (PFS) over chemotherapy in IPI-refractory MEL. Here we present long-term follow-up data for all pts with MEL enrolled in KEYNOTE-001 (NCT01295827). **Methods:** IPI-T and IPI-N pts received pembro 2 mg/kg every three weeks (Q3W), 10 mg/kg Q3W, or 10 mg/kg every two weeks (Q2W) until unacceptable toxicity, disease progression, or investigator decision. Treatment could continue beyond initial radiographic progression in eligible pts. Response was assessed every 12 weeks. Pts were followed for survival every three months after discontinuation. Primary end point was objective response rate (ORR) per RECIST v1.1 by central review; secondary end points included PFS, overall survival (OS), and duration of response (DoR). **Results:** 655 pts enrolled: 342 IPI-T, 313 IPI-N. Median follow-up duration was 14.8 months (range, 7.5-29.0). Median duration of exposure was 5.6 months (range, 0.03-28.3). At the time of analysis, 217 (33%) pts remained on therapy. The ORR was 34% (29% IPI-T, 38% IPI-N), with a 6% complete response (CR) rate. Median time to response was 2.8 months (range, 1.6-19.3). Of responses, 80% were ongoing at the time of analysis, and median DoR was not reached (range, 6+ to 98+ weeks). Median PFS was 5.2 months (95% CI: 3.6-5.5) (IPI-T, 4.9 months; 95% CI: 3.0-5.5; IPI-N, 5.4 months; 95% CI: 3.1-6.9). The PFS rates at six and 12 months were, respectively, 44 and 34% (41 and 32% IPI-T, 47 and 36% IPI-N). The one-year OS rate was 67% (63% IPI-T, 71% IPI-N); the rate at two years was 50% (46% IPI-T, 53% IPI-N). Overall, 14% of pts experienced grade 3-4 treatment-related adverse events (AE), and there were no treatment-related deaths. In randomized cohorts, there were no significant differences in efficacy and safety between doses/schedules. **Conclusions:** Pembro provides robust and durable antitumor activity, promising long-term survival data, and a manageable safety profile in pts with IPI-T and IPI-N metastatic MEL. These results support the approved indication for pembro and its further exploration in other MEL populations.

Clinical trial information: **NCT01295827**