Clinical Features Associated with Outcomes and Biomarker Analysis of Dabrafenib plus Trametinib (DT) in Patients with BRAF-Mutant Melanoma Brain Metastases (MBMs)

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Background

- The COMBI-MB phase II clinical trial evaluated the safety and efficacy of dabrafenib + trametinib (DT) in BRAF^{V600}-mutant metastatic melanoma patients (n=125) with untreated and/or progressing melanoma brain metastases (MBMs) [1]
- In Cohort A (BRAF^{V600E} mutation, asymptomatic MBMs, no prior local therapy to MBMs), the largest cohort (n=76) in COMBI-MB, the intracranial response rate (ICRR) was 58% and the intracranial disease control rate (IDCR) was 78%, consistent with high initial anti-tumor activity. However, the median intracranial duration of response was 6.5 months, which was much shorter than previously observed in patients without MBMs
- It is currently unknown why the duration of response with DT was shorter in MBMs. In order to provide insights into this challenge, we performed 2 studies:
  - *Analyzed baseline features of patients enrolled in COMBI-MB to identify significant associations with clinical outcomes*
  - *Performed exploratory biomarker analysis of samples collected in COMBI-BRV, a clinical trial in which BRAF^{V600}-mutant MBM patients (n=6) were treated with dabrafenib (D) for 10-14 days prior to craniotomy*

Methods

- The design, patient characteristics and outcomes of the COMBI-MB study have been reported previously [1]. Summaries for ICRR, progression free survival (PFS), and overall survival (OS) were generated with Kaplan-Meier estimates along with 95% confidence intervals (CIs) and log-rank tests. Univariate and multivariate associations of features with ICRR, IDCR, PFS and OS were assessed using Cox models with Brookmeyer and Crowley method to calculate confidence intervals.
- COMBI-BRV (NCT01978236) was a phase II trial of dabrafenib treatment in patients with BRAF-mutant metastatic melanoma with at least one resectable (1-4 cm) MBM. Patients underwent biopsy of an accessible extracranial metastasis (ECM) prior to pre-operative therapy. In Cohort A, patients were then treated with dabrafenib 150 mg BID for 10-14 days prior to craniotomy; in the planned Cohort B patients were to be treated with dabrafenib + trametinib, but the trial was closed due to poor accrual prior to any patients being enrolled on that arm. On the day of craniotomy patients underwent planned surgical resection of MBM(s) and biopsy or resection of safely accessible ECM. Patient with active disease after surgery received dabrafenib and trametinib until disease progression. Study sites included MD Anderson Cancer Center, Melanoma Institute of Australia, and University of Pittsburgh Cancer Institute.
- COMBI-BRV biospecimen analyses:
  - DNA and RNA were isolated from FFPE tissue sections, and whole exome DNA and RNA sequencing were performed, as previously described [2, 3].
  - Multiplex immunohistochemistry (mIHC) was performed as previously described [4, 5] for P-AKT Ser473, P-ERK1/2, P-P90RSK, P-S6, SOX10, PD1, FOXP3, CD8, CD3, CD20, CD68, PD-L1. Multispectral images were acquired using a Vectra 3 multispectral microscope (Akoya Biosciences). Individual markers were spectrally unmixed and expression in each cell was quantified using the Inform software (Akoya Biosciences). The quantitative data was exported and analysed in Spotfire (Tibco). Samples with less than 100 melanoma (SOX10 positive) cells were excluded from further analysis.
  - Exploratory biomarker data was assessed with a linear mixed-effect model with a random intercept to account for intra-patient correlation. To control the Type I error rate given the small sample size, the models were fitted with the restricted maximum likelihood (REML) method using the lme4 package in R v4.1.0 and p-values derived using the Satterthwaite approximation as provided in the sjPlot R package. No correction for multiple testing was pursued due to the exploratory nature of this analysis and small sample size.
- A p-value less than 0.05 was considered statistically significant for all analyses.

COMBI-MB: Associations with Outcomes

Baseline treatment with steroids was associated with lower ICRR (39% vs 63%, p=0.049) and shorter PFS (HR 1.93, p=0.03) on multivariable analyses. BRAF^{V600E} mutation was associated with longer PFS (HR 0.565, p=0.048). ECOG PS = 0 was the only factor associated with improved OS (HR 0.441, p=0.005).

Table 1. Baseline characteristics of COMBi-MB patients

Feature	Values	Cohort A (n=76)	Cohort B (n=16)	Cohort C (n=16)	Cohort D (n=17)	Total (n=125)
Age (years)	Median (range)	52·0 (23–84)	54·5 (36–74)	63·0 (44–84)	46·0 (23–68)	
Sex	Male	40 (53%)	10 (63%)	11 (69%)	11 (65%)	72 (58%)
ECOG performance status	0	50 (66%)	11 (69%)	12 (75%)	9 (53%)	82 (66%)
	1	25 (33%)	5 (31%)	4 (25%)	6 (35%)	40 (32%)
	2	1 (1%) *	0	0	2 (12%)	3 (2%)
BRAF genotype	V600E	73 (96%)	16 (100%)	0	15 (88%)	104 (83.2%)
	V600K	3 (4%) †	0	14 (88%)	1 (6%)	18 (14.4%)
	V600R	0	0	2 (13%)	1 (6%)	3 (2.4%)
	V600D	0	0	0	0	0
# Target MBMs	1	41 (54%)	7 (44%)	7 (44%)	7 (41%)	62 (49.6%)
	2	20 (26%)	7 (44%)	6 (38%)	7 (41%)	40 (32%)
	3	7 (9%)	2 (13%)	2 (13%)	1 (6%)	12 (9.6%)
	4	4 (5%)	0	0	1 (6%)	5 (4%)
	5	4 (5%)	0	1 (6%)	1 (6%)	6 (4.8%)
SLD of target intracranial lesions (mm)		20 (6–117)	14 (5–40)	20 (5–61)	33 (10–84)	
ECMs	No	8 (11%)	4 (25%)	0	5 (29%)	17 (14%)
	Yes	68 (89%)	12 (75%)	16 (100%)	12 (71%)	108 (86%)
Serum LDH	Elevated (>ULN)	28 (37%)	3 (19%)	6 (38%)	5 (29%)	42 (34%)
On Steroids	Yes	13 (17%)	3 (19%)	3 (19%)	14 (82%)	33 (26%)
Previous Systemic Tx	Yes	17 (22%)	5 (31%)	3 (19%)	7 (41%)	32 (26%)

Abbreviations: MBM, melanoma brain metastasis; SLD, sum of longest diameters; ECM, extracranial metastasis; Tx, Treatment

Table 2. Intracranial Response Rate (ICRR): Associations

				Univariate		Multivariate	
Category	Group	Patients (N)	N responding (%)	OR (95% CI)	P-value	OR (95% CI)	P=value
Age	<54	59	34 (58)	1.066 (0.524-2.166)	0.8599	1.143 (0.512-2.554)	0.7443
	>=54	66	37 (56)				
Gender	Female	53	28 (53)	0.755 (0.369-1.546)	0.4425	0.735 (0.334-1.618)	0.4447
	Male	72	43 (60)				
ECOG	0	82	50 (61)	1.637 (0.777-3.447)	0.1946	1.034 (0.399-2.681)	0.9456
	>=1	43	21 (49)				
BRAF Mutation	V600E	104	61 (59)	1.56 (0.609-3.999)	0.3541	1.686 (0.574-4.957)	0.3421
	Other	21	10 (48)				
# Target MBMs	1	62	37 (60)	1.138 (0.432-2.997)	0.568	1.287 (0.355-4.668)	0.5891
	2	40	21 (53)	0.85 (0.303-2.386)	0.5717	0.988 (0.286-3.410)	0.7598
	>=3	23	13 (57)				
SLD of target intracranial lesion	<median	62	35 (56)	0.972 (0.479-1.973)	0.9378	0.632 (0.184-2.167)	0.4655
	>=median	63	36 (57)				
Largest MBM	<median	60	35 (58)	1.128 (0.555-2.291)	0.7396	1.177 (0.392-3.530)	0.7717
	>=median	65	36 (55)				
ECMs	Yes	97	55 (57)	0.982 (0.420-2.297)	0.9669	1.212 (0.435-3.379)	0.7135
	No	28	16 (57)				
Elevated Serum LDH	Yes	42	21 (50)	0.660 (0.312-1.394)	0.2761	0.71 (0.302-1.676)	0.436
	No	83	50 (60)				
On Steroids at Baseline	Yes	33	13 (39)	0.381 (0.168-0.862)	0.0206	0.323 (0.105-0.996)	0.0491
	No	92	58 (63)				
Prior Systemic Tx	Yes	32	21 (66)	1.642 (0.712-3.786)	0.2449	1.831 (0.710-4.719)	0.2105
	No	93	50 (54)				
Prior Tx to Brain	Yes	28	14 (50)	0.702 (0.302-1.632)	0.4108	1.186 (0.385-3.654)	0.7669
	No	97	57 (59)				
Prior CNS Radiation	Yes	34	15 (44)	0.493 (0.222-1.096)	0.0827	0.477 (0.156-1.464)	0.196
	No	91	56 (62)				
Prior Craniotomy	Yes	121	69 (57)	1.327 (0.181-9.734)	0.7809	1.487 (0.172-12.850)	0.7182
	No	4	2 (50)				
Uncontrolled Neuro Symptoms	Yes	24	13 (54)	0.876 (0.358-2.143)	0.7721	1.603 (0.479-5.367)	0.4438
	No	101	58 (57)				

Table 3. Progression free survival (PFS): Associations

					Univariate			Multivariate		
Category	Group	N	PFS events	Median (95% CI) Months	HR	95% CI	p	HR	95% CI	p
Age	<54	59	47	5.6(5.3-7.3)	1.096	(0.740-1.623)	0.6479	1.093	0.705-1.696	0.6908
	>=54	66	54	5.7(5.4-7.3)						
Gender	Female	53	43	5.6(4.2-7.4)	1.056	(0.711-1.568)	0.7884	0.869	0.557-1.356	0.5368
	Male	72	58	5.8(5.5-7.3)						
ECOG PS	0	82	63	6.5(5.6-7.5)	0.617	(0.411-0.927)	0.02	0.692	0.401-1.197	0.1881
	>=1	43	38	3.8(3.5-5.9)						
BRAF Mutation	V600E	104	83	5.9(5.5-7.3)	0.638	(0.381-1.066)	0.0859	0.565	0.321-0.996	0.0483
	Other	21	18	4.2(3.5-9.1)						
# Target MBMs	1	62	48	7.2(5.5-9.1)	0.592	(0.348-1.006)	0.0528	0.673	0.322-1.403	0.2903
	2	40	33	5.5(4.2-6.8)	0.808	(0.463-1.411)	0.4537	1.014	0.503-2.045	0.9685
	>=3	23	20	5.5(3.6-7.4)						
SLD of MBMs	median	62	49	5.9(5.3-7.3)	0.996	(0.674-1.472)	0.9841	1.418	0.667-3.014	0.3637
	>=median	63	52	5.6(4.7-7.3)						
Largest MBM	median	60	46	5.9(5.5-7.3)	0.951	(0.642-1.408)	0.801	1.018	0.523-1.983	0.9572
		65	55	5.6(4.3-7.3)						
ECMs	Yes	97	82	5.6(4.7-6.7)	1.45	(0.879-2.391)	0.1452	1.249	0.722-2.162	0.4261
	No	28	19	7.3(5.6-14.6)						
Elevated serum LDH	Yes	42	35	5.6(3.7-7.5)	1.159	(0.768- 1.749)	0.4821	0.811	0.514-1.280	0.368
	No	83	66	5.7(5.5-7.2)						
Steroid use at baseline	Yes	33	29	4.3(3.5-6.4)	1.788	(1.152-2.774)	0.0095	1.931	1.061-3.513	0.0312
	No	92	72	6.2(5.6-7.3)						
Prior Systemic Tx	Yes	32	27	7.4(5.6-12.0)	0.72	(0.768- 1.749)	0.1485	0.716	0.435-1.179	0.1895
	No	93	74	5.5(4.7-6.2)						
Prior Tx to Brain	Yes	28	21	7.2(5.5-13.4)	0.778	(0.481- 1.260)	0.3077	0.796	0.441-1.435	0.4473
	No	97	80	5.6(5.3-6.7)						
Prior CNS Radiation	Yes	34	26	5.3(4.3-12.2)	0.781	(0.497- 1.227)	0.2838	0.766	0.422-1.390	0.3804
	No	91	75	5.9(5.5-7.2)						
Prior Craniotomy	Yes	121	99	5.6(5.4-7.2)	1.795	(0.441- 7.302)	0.4141	1.817	0.420-7.859	0.4243
	No	4	2	9.1(6.2-9.1)						
Uncontrolled Neuro Symptoms	Yes	24	21	5.3(3.7-7.5)	1.504	(0.921- 2.456)	0.103	1.141	0.611-2.241	0.6346
	No	101	80	5.8(5.5-7.2)						

COMBI-MB: Impact of Steroids

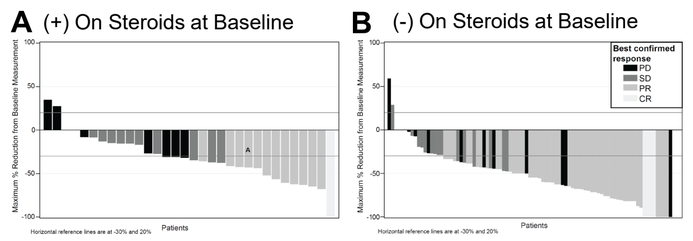

Figure 1. COMBi-MB outcomes by baseline steroids. Maximum change in intracranial tumor burden with dabrafenib + trametinib in (A) patients on steroids, and (B) patients not on steroids at baseline. Kaplan-Meier analysis show shorter PFS for patients on steroids (Orange line) versus not (Black line).

COMBI-BRV: Pre-Operative Dabrafenib in Resectable MBMs

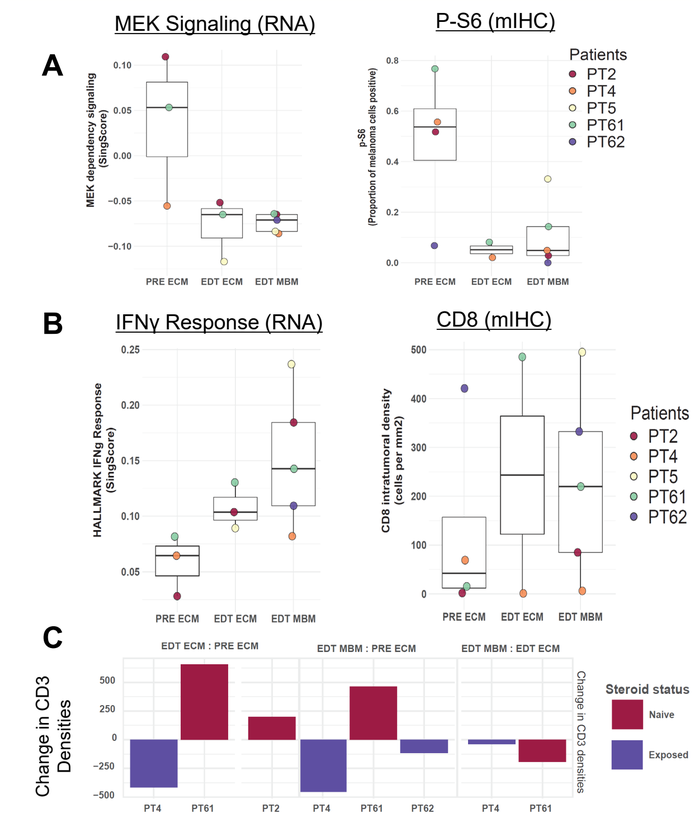

Figure 2. Exploratory molecular and immune analyses of MBMs vs ECMs in COMBI-BRV. *A,* Molecular markers. *B,* Immune markers. *C,* Changes in CD3 ratios by steroid status. Abbreviations: Pre, Baseline; EDT, Early During Treatment (Craniotomy); MBM, Melanoma Brain Metastasis; ECM, Extracranial Metastasis

Summary

- Concurrent treatment with steroids at start of treatment correlated with worse ICRR and shorter PFS in COMBI-MB
- Exploratory analysis of biospecimens collected in COMBI-BRV (pre-operative dabrafenib) showed similar inhibition of MAPK signaling and increase in immune markers in MBMs vs ECMs, albeit with small numbers of samples and with significant heterogeneity. Steroid treatment may blunt immune infiltration in both MBMs and ECMs.
- The results support avoidance of steroids in MBM patients when possible and the need for more effective treatments for patients that require steroids to control MBM symptoms.

References & Support

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3. PMID 33664264. 4. PMID 33664264.
5. PMID 30753825

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