

SUPPLEMENTARY MATERIALS

Table S1. Simplified overview of the pathologic staging of melanoma (American Joint Committee on Cancer 8th edition).

Stage		Tumor	Nodes	Metastases
0		Melanoma in situ	None	None
I	A	≤ 1mm, +/- ulceration	None	None
I	B	1 to 2mm, no ulceration	None	None
II	A	1 to 2 mm, + ulceration 2 to 4mm, no ulceration	None	None
II	B	2 to 4mm, + ulceration >4mm, no ulceration	None	None
II	C	>4mm, + ulceration	None	None
III	A	Up to 1mm +/- ulceration 1 to 2mm, no ulceration	1 to 3 clinically occult nodes	None
III	B	No evidence of primary Up to 2mm +/- ulceration 2 to 4 mm, no ulceration	1 clinically detected node, OR evidence of ILD * Up to 3 tumor-involved nodes, OR evidence of ILD	None
III	C	No evidence of primary Up to 2mm +/- ulceration OR 2 to 4mm, no ulceration 2 to 4mm +/- ulceration OR > 4.0mm, no ulceration > 4.0mm, + ulceration	>2 tumor-involved nodes, OR ILD reaching nearby nodes, OR matted nodes ≥ 4 tumor-involved nodes, OR ILD reaching nearby nodes, OR ≥ 1 matted node ≥ 1 tumor-involved node, +/- evidence of ILD 1 to 3 tumor-involved nodes OR evidence of ILD	None
III	D	> 4.0mm, + ulceration	≥ 4 tumor-involved nodes ILD reaching ≥ 2 nearby nodes ≥ 1 matted node	None
IV		Any	Any	Evidence of distant metastases

*ILD: Intralymphatic disease refers to in-transit, satellite and/or microsatellite metastases.

Table S2. Summary of targeted therapy trials in the treatment of unresected stage III or IV melanoma and resected melanoma. NR: not reported.

RESECTABLE MELANOMA						
Trial Drugs compared N	Patients included	Treatment	Median follow-up (months)	Response rate (%)	Recurrence-free survival (%)	Overall survival (%)
COMBI-AD [1,2] Dabrafenib + Trametinib versus placebo	Completely resected BRAF+ stage IIIA melanoma with LN metastasis ≥1mm, stage IIIB melanoma, stage	Dabrafenib + Trametinib (n=438)	60 months	NA	88% at 1 year 67% at 2 years 58% at 3 years 55% at 4 years 52% at 5 years	97% at 1 year 91% at 2 years 86% at 3 years

N=870	IIIC melanoma (ac- cording to AJCC 7)			Median RFS NR (HR versus pla- cebo = 0.51 [95%CI = 0.42- 0.61])		
		Placebo (n=432)	58 months	NA	56% at 1 year 44% at 2 years 39% at 3 years 38% at 4 years 36% at 5 years Median RFS = 16.6 months	94% at 1 year 83% at 2 years 77% at 3 years
DFS*:						
BRIM 8 [3]	Cohort 1: stage IIC- IIIB melanoma (ac- cording to AJCC 7)	Vemuraf- enib (n=157)	30.8 months	NA	84% at 1 year 72% at 2 years	93% at 2 years
		Placebo (n=157)		NA	Median = NR 66% at 1 year 57% at 2 years Median 36.9 months	87% at 2 years
	Cohort 2: stage IIIC melanoma (according to AJCC 7)	Vemuraf- enib (n=93)	33.5 months	NA	Median DFS = 23.1 months (HR versus pla- cebo = 0.80 [95% CI 0.54- 1.18], p = 0.26)	84% at 2 years
		Placebo (n=91)		NA	58% at 1 year 48% at 2 years Median DFS = 15.4 months	85% at 2 years
UNRESECTED MELANOMA						
Trial Drugs com- pared N	Patients included	Treatment	Median follow- up (months)	Re- spons e rate (%)	Progression- free survival (months) [95% CI]	Overall sur- vival (months) [95% CI]
CoBRIM [4]	BRAF+ melanoma, un- resected stage IIIC or stage IV, previously untreated	Cobi- metinib + Vemuraf- enib (n=247)	14.2	ORR = 70 CR = 16	12.3 [9.5-13.4]	75% at 1 year 48% at 2 years
Cobimetinib + Vemurafenib versus Vemu- rafenib N=495			(18.5 for OS anal- ysis)		0.58 [95% CI = 0.46-0.72] p <0.0001)	Median = 22.3 [20.3-not esti- mable] (HR versus Vemurafenib = 0.70 [95%CI =

							0.55-0.90], p = 0.005)
							64% at 1 year 38% at 2 years
		Vemurafenib (n=248)		ORR = 50 CR = 10	7.2 [5.6-7.5]		Median = 17.4 [95% CI = 15.0-19.8]
						56% at 1 year 37% at 2 years 29% at 3 years	76% at 1 year 58% at 2 years 47% at 3 years
		Encorafenib + Binimetinib (n=192)	32.1 (PFS) 48.8 (OS)	ORR = 64 CR = 13	Median = 14.9 [11.0-20.2] (HR versus Vemurafenib = 0.51 [95% CI = 0.39-0.67])		Median = 33.6 [24.4-39.2] (HR versus Vemurafenib = 0.61 [95% CI = 0.48-0.79])
COLUMBUS [5]	BRAF+ melanoma, unresected stage IIIB, IIIC or IV, treatment naïve or had progressed after previous first-line immunotherapy,	Vemurafenib (n=191)		ORR = 41 CR = 8	32% at 1 year 20% at 2 years 14% at 3 years Median = 7.3 [5.6-7.9]		63% at 1 year 43% at 2 years 31% at 3 years Median = 16.9 [14.0-24.5]
	N=577	Encorafenib (n=194)		ORR = 52 CR = 7	Median = 9.6 [7.4-14.8]		Median = 23.5 [19.6-33.6]
						74% at 1 year 51% at 2 years	
						Median 11.0 [8.0-13.9]	
						(HR versus Dabrafenib = 0.67 [95% CI = 0.53-0.84], p = 0.0004)	
COMBI-d [6]	BRAF+ melanoma, unresected stage IIIC or stage IV melanoma, no prior systemic therapy	Dabrafenib + Trametinib (n=211)	20 (time on study)	ORR = 69 CR = 16%		Median = 25.1 [19.2-not reached] (HR versus Dabrafenib = 0.71 [95% CI = 0.55-0.92], p = 0.0107)	
	N=423						
		Dabrafenib (n=212)	16 (time on study)	ORR = 53% CR = 13%	Median = 8.8 [5.9-9.3]		68% at 1 year 42% at 2 years Median = 18.7 [15.2-23.7]
						Median = 11.4	72% at 1 year
						(HR versus Vemurafenib = 0.56 [95% CI = 0.46-0.69], p <0.001)	
COMBI-v [7]	BRAF+ melanoma, unresected stage IIIC or stage IV melanoma, no prior systemic therapy	Dabrafenib + Trametinib (n=352)	11	ORR = 64 CR = 13%		Median = not reached (HR versus Vemurafenib = 0.69 [95% CI = 0.53-0.89], p = 0.005)	
		Vemurafenib (n=352)	10	ORR = 51 CR = 8%	Median = 7.3		65% at 1 year Median = 17.2
COMBI-d and COMBI-v	BRAF+ melanoma, unresected stage IIIC or stage IV melanoma,	Dabrafenib +	22	ORR = 68%	31% at 2 years 24% at 3 years 21% at 4 years		52% at 2 years 44% at 3 years 37% at 4 years

(pooled analysis) [8] no prior systemic therapy	apy	Trametinib (n=563)	CR = 19%	19% at 5 years	34% at 5 years
			Median = 11.1 months		

Because of the prespecified hierarchical testing of cohort 2 before cohort 1, and because the primary endpoint was not met in cohort 2, the analyses in cohort 1 cannot be regarded as significant.

Overall Response Rate (ORR) = overall response rate; CR = complete response rate; Duration Free Survival (DFS) measured in BRIM8.

References:

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2. Dummer R et al. Five-Year Analysis of Adjuvant Dabrafenib + Trametinib in Stage III Melanoma. *NEJM*. 2020. 383: 1139-1148.
3. Maio M et al. Adjuvant vemurafenib in resected, BRAFv600 mutation-positive melanoma (BRIM8) : a randomized, double-blind, placebo-controlled, multicentre, phase 3 trial. *Lancet Oncology*. 2018. 19: 510-520.
4. Ascierto PA et al. Cobimetinib combined with vemurafenib in advanced BRAFv600-mutant melanoma (coBRIM) : updated efficacy results from a randomized, double-blind, phase 3 trial. *Lancet Oncology*. 2016. 17: 1248-1260.
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6. Long GV et al. Dabrafenib plus trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicenter, double-blind, phase 3 randomised controlled trial. *The Lancet*. 2016. 386 (9992): 444-451.
7. Robert C. et al. Improved Overall Survival in Melanoma with Combined Dabrafenib + Trametinib. *NEJM*. 2015. 372: 30-39.
8. Robert C et al. Five-year Outcomes with Dabrafenib plus Trametinib in Metastatic Melanoma. *NEJM*. 2019. 381: 626-636.