1044P - Sequential targeted and immunotherapies in stage IV melanoma

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BACKGROUND

Targeted (TT) and immunotherapies (IT) significantly improved the outcome of stage IV melanoma patients (pts). However, data on the optimal therapy sequence for pts with BRAFV600 mutated melanoma is scarce. [1,2]. Here we analyze if different therapy sequences have different survival outcomes, particularly in patients with BRAF mutated melanoma.

MATERIALS AND METHODS

In this retrospective study, we analyze survival data of pts diagnosed with Stage IV melanoma between January 2011 and December 2018 and treated in the Center for Dermato-Oncology of the University of Tübingen. The date of data cut-off analysis was August 2021. Follow-up time (FUP) was the time between stage IV diagnosis and death or last contact. Patients received IT 1st line (1L) and 2nd line (2L) (IT-IT); IT 1L and TT 2L (IT-TT); TT 1L and IT 2L (TT-IT), and TT 1L and 2L (TT-TT). Here, we present descriptive analyses of the pts characteristics and best overall response to 1L and 2L therapy line, focusing on the subgroup receiving IT-TT or TT-IT. Kaplan-Meier analysis for overall survival (OS) and progression free survival (PFS) are also presented.

RESULTS

We included 1046 stage IV melanoma pts with a median FUP of 53 months [IQR: 34-72]. For the whole cohort (n=1046) the number of systemic therapies received ranged from 0 to 8, and 387 pts received at least two lines of systemic therapy. The number of pts treated with each therapy sequence previously mentioned is as follows: IT-IT 81 pts, TT-IT 79 pts, IT-TT 41 pts and TT-TT 35 pts; 151 pts received other combinations of 1L and 2L. Further information on the pts characteristics and the survival analysis are presented in the tables and graphics next.

PATIENTS CHARACTERISTICS WHOLE COLLECTIVE

Table 1. Patients characteristics and median overall survival according to Kaplan-Meier estimates (n=1046)

		n(%)	mOS* (95%CI)	*p* value
Age groups	≤65 yo	537 (51.3)	27 (20.7-33.3)	**<0.001**
	>65yo	509 (48.7)	18 (14.7-21.3)	
Sex	Female	456 (43.6)	24 (18.0-30.0)	0.371
	Male	590 (56.4)	21 (16.6-25.4)	
Histological subtype	SSM	276 (36.6)	17 (12.7-21.3)	**0.045**
	NM	226 (30)	23 (16.6-294)	
	LMM	38 (5)	81 (N/A)	
	ALM	66 (8.8)	31 (16.8-45.2)	
	Mucosal	49 (6.5)	17 (9.7-24.2)	
	Other	99 (13.1)	19 (7.9-30.1)	
S100 level	Normal	408 (45.9)	40 (29.7-50.3)	**<0.001**
at stage IV diagnosis	Elevated	193 (21.7)	21 (14.5-27.5)	
	2x elevated	288 (32.4)	11 (8.8-13.1)	
LDH level	Normal	569 (62.9)	32 (24.8-39.2)	**<0.001**
at stage IV diagnosis	Elevated	244 (27)	16 (11.4-20.6)	
	2x elevated	92 (10.2)	5 (3.7-6.3)	
BRAF status	Mutated	397 (47.4)	27 (20.1-33.8)	0.350
	WT	440 (52.6)	22 (16.8-27.2)	

Abbreviations: mOS - median overall survival in months; yo - years old; SSM superficial spreading melanoma; NM, nodular melanoma; ALM, acrolentiginous melanoma; LMM, lentigo malignant melanoma; WT – wild-type. Patients for whom the information was not available were excluded from the analysis; significant *p* values are in bold

PATIENTS RECEIVING IT-TT OR TT-IT

Table 2. Patients characteristics for the subgroup receiving immunotherapy followed by targeted therapy or the inverse sequence (n=120)

		IT-TT (n=41)	TT-IT (n=79)	χ2
		n (%)	n (%)	
Age groups	≤65 yo	25 (61)	63 (80)	**0.027**
	>65yo	16 (39)	16 (20)	
Sex	Female	17 (42)	38 (48)	0.489
	Male	24 (58)	41 (52)	
S100 level*	Normal	13 (37)	24 (34)	0.814
at stage IV diagnosis	Elevated	6 (17)	10 (14)	
	2x elevated	16 (46)	37 (52)	
LDH level*	Normal	22 (65)	44 (59)	0.766
at stage IV diagnosis	Elevated	9 (26)	20 (27)	
	2x elevated	3 (9)	10 (14)	

Abbreviations: IT-TT – immunotherapy 1st line followed by targeted therapy 2nd line; TT-IT – targeted therapy 1st line followed by immunotherapy 2nd line. χ2- Pearson Chi-Square. * Patients for whom the information was not available were excluded from the analysis; significant *p* values are in bold.

BEST OVERALL RESPONSE ACCORDING THERAPY SEQUENCE

Table 3. Best overall response 1st and 2nd line therapy in patients receiving immunotherapy followed by targeted therapy or the inverse sequence

	BOR to 1st line systemic therapy		BOR to 2nd line systemic therapy	
	IT-TT (n=40)	TT-IT (n=75)	IT-TT (n=37)	TT-IT (n=74)
	n (%)		n (%)	
CR	2 (5)	5 (7)	3 (8)	3 (4)
PR	9 (22.5)	39 (52)	23 (62)	9 (12)
SD	8 (20)	18 (24)	7 (19)	5 (7)
PD	21 (52.5)	13 (17)	4 (11)	57 (77)

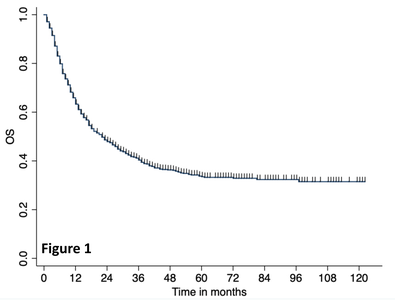
Abbreviations: BOR – best overall response; IT- immunotherapy; TT – targeted therapy; CR – complete response; PR – Partial response; SD – stable disease; PD – progressive disease. RECIST 1.1 [3] was used to access BOR. BOR was defined as the best response achieve during the whole duration of the therapy course.

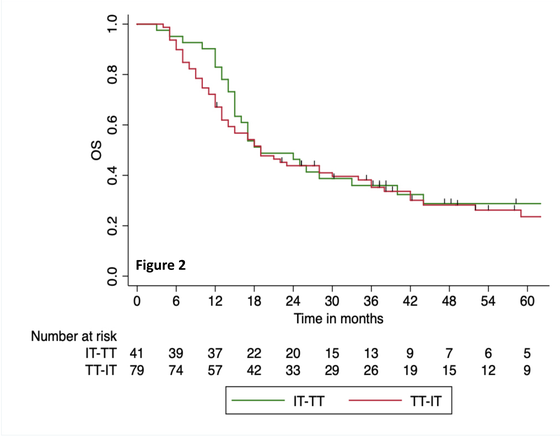
SURVIVAL ANALYSIS

Table 4. Overall survival, progression free survival and survival rates

	OS (95%CI)			
	mOS (months)	1y OS rate	2y OS rate	5y OS rate
All patients	22 (19-25)	63 (60-65.9)	48 (45-51)	33.5 (30-37)
IT-TT	19 (11-27)	82.9 (77-94)	46.3 (31-62)	28.8 (14-44)
TT-IT	19 (12-26)	67.1 (57-77)	43.8 (33-55)	23.6 (13-34)
	PFS1 (95%CI)			
	mPFS (months)	1y PFS rate	2y PFS rate	
IT-TT	3 (2-4)	8.6 (0.6-18)	-	
TT-IT	5 (4-6)	13 (4-21)	6.1 (0.9-13)	

Abbreviations: IT-TT – immunotherapy 1st line followed by targeted therapy 2nd line; TT-IT – targeted therapy 1st line followed by immunotherapy 2nd line. Y – years; OS – Overall survival; mOS – median overall survival; PFS – progression free survival; mPFS – median progression free survival





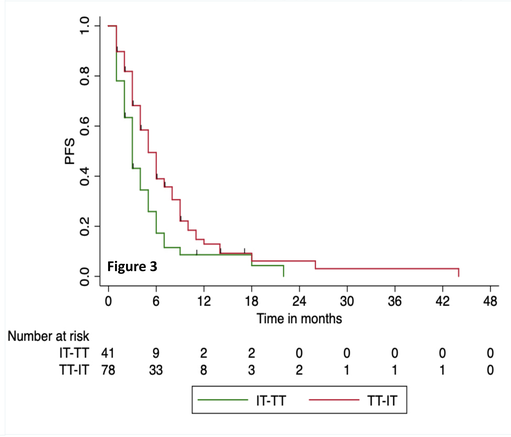


Figure 1: Overall survival for the whole collective **(n= 1046)**
Figure 2: Overall survival for pts receiving IT-TT or TT-IT; **(n= 120; p=0.561)**
Figure 3: Median progression free survival for 1st line therapy; **(n= 119; p<0.010)**. As shown here, there is a statistically significant benefit in terms of mPFS for pts with BRAF mutation receiving 1st line targeted therapy, but this doesn't translate into statistically significant OS benefit, as there is no difference in OS between the two sequences.

DISCUSSION

In this retrospective analysis focused on survival of stage IV melanoma pts, the mOS for the whole collective was 22 months and the 5y OS rate was 33.5% (**Table 4**). These survival rates highlight the progress made in the last decade in terms of effective therapeutic options for stage IV melanoma patients. For pts with BRAF mutated melanoma, there seems to be an advantage in terms of PFS for those receiving 1st line TT, but this does not translate into statistically significant OS benefit in our cohort.
There were no statistically significant differences in terms of pts characteristics between the groups receiving 1st line IT or 1st TT, except for the patients' age, i.e., a higher percentage of younger patients with BRAF mutation where treated with 1st line TT (**Table 2**). This aspect speaks for the subgroups homogeneity at the time of 1st therapy selection. The fact that the pts included in this subgroup analysis received at least two different therapies denotes a negative selection, as the majority of the pts received a 2nd line therapy due to disease progression under 1st line therapy. This worse prognosis is confirmed by the high percentage of pts with elevated S100 and LDH at baseline (**Table 2**). 63% of the pts receiving 1st line IT had elevated S100, while this was true for 66% of pts receiving 1st TT. Regarding LDH level, 35% of the pts receiving 1st line IT had elevated LDH compared to 41% of the pts receiving 1st line TT.

CONCLUSION

Immunotherapy followed by targeted therapy or the inverse sequence can be considered for the treatment of patients with BRAF mutated melanoma, as neither sequence was superior in terms of OS benefit.

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