Stereotactic radiotherapy combined with immunotherapy is safe and effective: Results from a Phase I clinical trial

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Conclusion

SABR combined with immunotherapy is generally safe overall.

We found the optimal therapeutic index may be achieved with 10Gy delivered with the third cycle of immunotherapy

Background

There is growing evidence to suggest synergism between stereotactic ablative radiotherapy (SABR) and immunotherapy against metastatic melanoma. The optimal timing and dosing of SABR for this purpose has not been established nor whether this approach is safe.

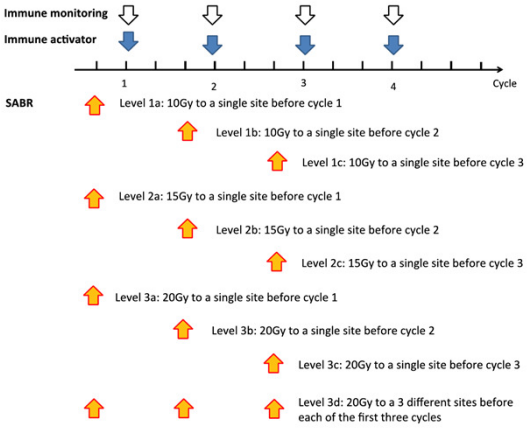
Aim

The objective of this trial is to determine the maximum tolerated dose (MTD) of treatment of metastatic melanoma, and to determine whether the SABR in combination with immunotherapy for the treatment has any clinical efficacy.

Methods

Metastatic melanoma patients with at least two metastases received SABR to a single metastatic site. All patients had standard dose immunotherapy with anti-PD1 and/or anti-CTLA4 at the discretion of their treating clinician.

Following a standard 3+3 design, patients were escalated through three SABR doses (10Gy, 15Gy and 20Gy) delivered at three different time points (at Cycle 1, 2, or 3 of immunotherapy).



Dose limiting toxicity (DLT) were defined as Grade 3 or higher toxicity within three months of first treatment and assessed by an independent data safety monitoring committee (IDSMC).

Results

Patient and Treatment Characteristics

Between April 2016 and August 2018, 24 patients were enrolled.

The median follow-up was 10 months.

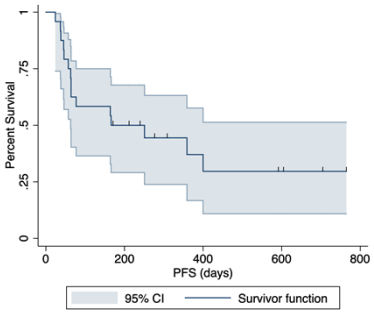
Baseline Patient Characteristics			Treatment Characteristics		
Age at Treatment		66.8	RT Dose	10	10 (42%)
Gender	Male	19 (79%)		15	14 (58%)
	Female	5 (21%)	IT Type	Pembro	15 (62%)
Previous RT		6 (25%)		Nivo	1 (4%)
Previous IT		4 (17%)		Ipi	1 (4%)
Baseline ECOG	0	15 (62%)		Ipi/Nivo	7 (29%)
	1	7 (29%)	Response	PD	14 (58%)
	2	2 (8%)		PR	10 (42%)

Survival Analysis

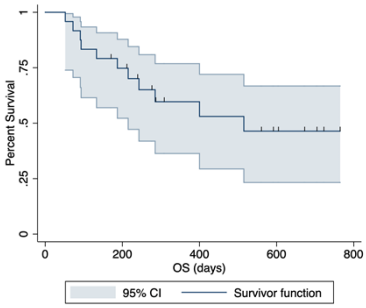
The median PFS and OS were 5.4 months (95% CI 2.1 months - NR) and 16.9 months (95% CI 7.1 months - NR), respectively.

The median PFS for those receiving 10Gy was numerically higher than those receiving 15Gy, 11.8 months vs. 2.6 months (p=0.42).

Progression Free Survival



Overall Survival



Toxicity Analysis

Three patients (12.5%) developed DLTs and these were enterocolitis, hepatitis and liver function derangement. None of these were at SABR treated sites and all occurred in patients receiving 15Gy (one at cycle 1, two at cycle 3). DLTs were not associated with SABR timing (p=0.44) or use of combination immunotherapy (p=0.72). On this basis the IDSMC recommended stopping the trial and the MTD was defined at 10Gy.

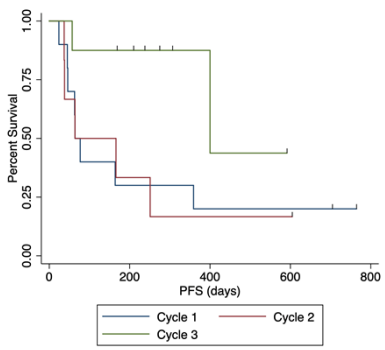
Multivariate Cox Regression Analysis

The only treatment related factor associated with improved PFS (HR=0.14, p=0.02) and OS (HR=0.09, p=0.04) was receiving SABR with Cycle 3. SABR dose (PFS p=0.75, OS p=0.67) and immunotherapy type (PFS p=0.13, OS p=0.06) were not significant.

Variable		Progress Free Survival		Overall Survival	
		HR	P Value	HR	P Value
SBRT Timing	Cycle 1	Ref		Ref	
	Cycle 2	1.47	0.60	1.76	0.45
	Cycle 3	0.14	0.02*	0.09	0.04*
SBRT Dose		1.29	0.75	0.68	0.67
Combination immunotherapy		4.63	0.13	9.00	0.06
Age at Treatment		1.08	0.04*	1.10	0.03*
Gender		6.03	0.04*	6.17	0.06
Baseline ECOG		0.48	0.16	0.59	0.38

Survival by Radiotherapy Timing

Progression Free Survival



Overall Survival