POSTER #478P

Metronomic oral vinorelbine (MOV) combined with tremelimumab (T) + durvalumab (D): results of the tumor mutational burden-high (TMB-h) and/or microsatellite instability-high (MSI-h) cohort of the MOVIE study.

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BACKGROUND

Both TMB-H and MSI-H result in a high rate of neoantigens, which may favor the efficacy of immune checkpoint inhibitors. Pembrolizumab (an anti- PD1) has been FDA-approved in MSI-H/TMB-H advanced solid tumor (AST) with an agnostic indication (1).

Movie is a multi-cohort phase 1/2 study examining the combination of T+D+MOV in advanced solid tumor. Chemotherapy with vinorelbine is here given with a metronomic regimen, which may produce activation of the immune system and have a synergistic effect with the checkpoint inhibitor combination T+D (2). We report here the results of the TMB-H and/or MSI-H cohort in miscellaneous histologic types of solid tumors.

References

1-Marabelle a, association of tumour mutationalburden with outcomes in patients with advancedsolid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 keynote-158 study. Lancet oncol 2020 oct;21(10):1353-1365 2

2- Kareva I. A Combination of Immune Checkpoint Inhibition with Metronomic Chemotherapy as a Way of Targeting Therapy-Resistant Cancer Cells. Int J Mol Sci. 2017 Oct 13;18(10):2134. doi: 10.3390/ijms18102134. PMID: 29027915; PMCID: PMC5666816.

METHODS

MOVIE is a phase I/II national, multicentre, multiple cohort, prospective open-label, non-randomised study:

- Phase I part: dose escalation. Recommended dose for Phase II (RP2D) was defined (ESMO 2020 – 555P).
- Phase II part: activity study in selected tumor types including cervix cancer.

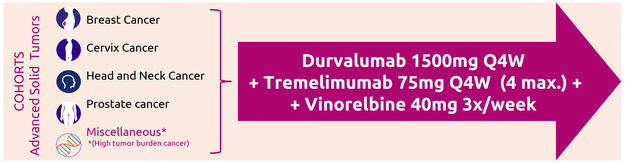


Figure 1: MOVIE study design

Advanced solid cancer patients were eligible in case of resistance to conventional therapies.

Patients were eligible with TMB-h (as determined by a local molecular tumor board), and/or MSI-h (by locally performed PCR and IHC test).

Primary endpoint of phase II part was clinical benefit rate (CBR= CR, PR or SD > 24 weeks) according to RECIST 1.1.

Continuous monitoring of efficacy was based on interim analyses (on the first 10 pts and then every 5 pts) using a Bayesian approach with 3 prior distributions. Secondary objectives included safety, Objective Response Rate (ORR), Duration of response (DOR) and Progression Free Survival (PFS).

RESULTS OF MISCELLANEOUS COHORT

From June 2018 to September 2021, 30 patients with solid tumor bearing high tumor burden and/or MSI high were included and treated at the RP2D (MOV 40mg thrice a week, T 75mg Q4W Cycle1 to Cycle 4, D 1500mg Q4W).

Patients' characteristics at inclusion

	Total patients included in analysis N=30
Age	
Mean years (Standard deviation)	62.7 (12.4)
Median years (min; max)	65 (35 ; 83)
Sex	
Female	5 (17%)
Male	25 (83%)
ECOG	
0	11 (36.7%)
1	19 (63.3%)
Primary tumor site	
Colon	9 (30.0%)
Endometrium	8 (26.7%)
Breast	3 (10.0%)
Ovary	2 (6.7%)
Other (thyroid, Adrenal, Brain, ORL, Cervix, Choloangiocarcinoma, Liposarcoma, Thyroid)	8 (26.7%)
Type of abnormality	
MSI	10 (33.3%)
Mutation Load	13 (43.3%)
MSI and Mutation load	7 (23.3%)
Tumor in place	
Yes	20 (66.7%)
No	10 (33.3%)
Disease status	
Metastatic	28 (93.3%)
Locally advanced	2 (6.7%)
Number of previous metastatic lines	
Median line (min ; max)	1.5 (0; 10)
0	9
1	6
2	5
3	6
4	3
>6	1
Duration between last relapse and inclusion (months)	
Median (min; max)	1.4 (0.1 ; 8.6)

Efficacy

Median duration of follow-up was 9.1 months (1.4 -24.1)

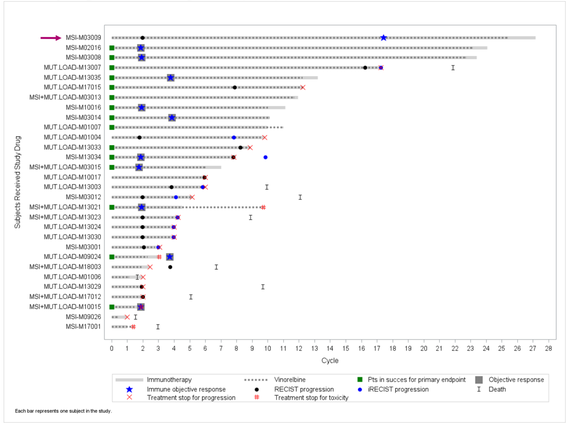
1. **Clinical Benefit Rate (1st objective)**
   - **15 patients were in success : 1 CR, 9 PR and 5 SD >=24 weeks**
   - **15 patients were in failure**

Mean estimated CBR and associated 95%CI, according to the prior distribution considered, are presented in Table bellow

	Prior non-informative prior beta (1,1)	Informative optimistic prior beta (5.7,5.7)	Less informative optimistic prior beta (1.3,1.3)
Mean [95% CI]	50% [33.1% ; 66.9%]	50% [35.0% ; 65.0%]	50% [33.2% ; 66.8%]

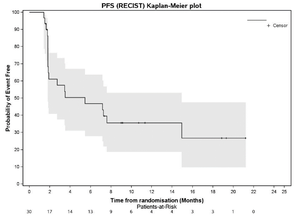
2. **Swimmer plot**

One patient achieved an immune RECIST Partial Response (iPR) after pseudo progression at cycle 2 (→)

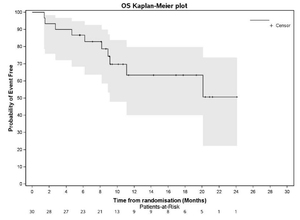


3. **Median progression free and overall survival**

Median PFS: 5.5 m (1.8- 14.9)
19 / 30 events reached



Median OS: not reached (33.3% of pts deceased at the time of analysis)



Safety

Details of toxicity are presented below by grade and type.

TRAE: treatment related adverse event. *i: immune.*

- TRAE grade ≥3: n=9 (30%)
- iTRAE grade ≥3: n=5 (16.7%)

Miscellaneous Cohort n=30

Any grade	Pts with any AE	30	(100.0%)
	Pts with any TRAE related to vinorelbine	24	(80.0%)
	Pts with iTRAE	21	(70.0%)
Grade 2	Pts with any AE	29	(96.7%)
	Pts with any TRAE related to vinorelbine	16	(53.3%)
	Pts with any iTRAE	15	(50.0%)
	Pts with any TRAE	21	(70.0%)
Grade 3	Pts with any AE	16	(53.3%)
	Pts with any TRAE related to vinorelbine	4	(13.3%)
	Pts with any iTRAE	5	(16.7%)
	Pts with any TRAE	9	(30.0%)
Grade 5	Pts with any AE	2	(6.7%)
	Pts with any TRAE	0	(0%)
SAE	Pts with any SAE	15	(50.0%)
	Pts with any SAE related to vinorelbine	3	(10.0%)
	Pts with any SAE immune-related	6	(20.0%)
	Pts with any SAE treatment-related	9	(30.0%)

CONCLUSION

T+D+MOV has promising activity in TMB-h and or MSI-h cohort. Toxicity profile was consistent with previous reports of T+D combination or MOV.

Ancillary analyses are still ongoing to try to identify biomarkers associated with the benefits of immunotherapies in this population,

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