Combined exploratory immunophenotyping and transcriptomic tumor analysis in patients treated with OSE2101 (Tedopi®) vaccine in HLA-A2+ advanced non-small cell lung cancer (NSCLC) from the ATALANTE-1 trial

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Introduction

Tedopi® (OSE2101) is a combination of 10 neoepitopes (including universal Helper T cell epitope) as precision treatment for HLA-A2 positive patients (incidence of 45% in a general population). Tedopi® is composed of 2 wild type and 7 chemically modified peptides to increase HLA-A2 or T cell receptor (TCR) affinity which target five tumor associated antigens (TAA) frequently expressed in solid tumors: carcinoembryonic antigen (CEA), human epidermal growth factor receptor 2 (HER-2/neu), melanoma-associated antigen type 2 and type 3 (MAGE2 and MAGE3), and p53. A pan-DR epitope (PADRE) of helper T-lymphocyte (HTL) has been added to increase Cytotoxic T Lymphocyte (CTL) responses.

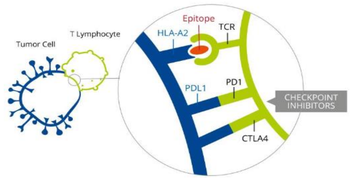
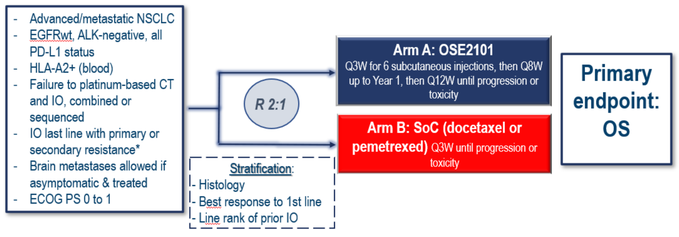


Figure 1. TEDOPI mechanism of action

The phase III, randomized, open-label ATALANTE-1 study showed a statistically survival (OS) improvement of Tedopi® over standard treatment (SoC docetaxel/pemetrexed) with an HR of 0.59 and a meaningful gain of 3.6 months in the population of patients with secondary resistance (Kluger *et al.* 2020) to sequential chemotherapy-immune checkpoint blockers (ICB). Available tumor biopsies at initial diagnosis from some patients treated with Tedopi® have been analyzed to determine the expression of the TAAs and to identify other tumor factors associated with long-term survival (Besse *et al*., ESMO meeting 2021, abstract #1049).

Study design



*Primary resistance: failure within 12 weeks of IO, secondary resistance: failure after minimum 12 weeks of IO; Kluger *et al*., 2020

Figure 2. Study Design (NCT02654587)

- All patients considered for biopsy analysis received sequential CT-ICB (platin based-CT first line, then ICB as second line therapy) before Tedopi® treatment.

Methods

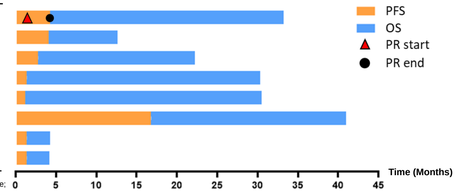
Tumor biopsies at initial diagnosis were available for 8 HLA-A2+ (blood test) stage IV NSCLC patients having received sequential chemotherapy / ICB (Immune Checkpoint Blocker) included in the trial. HLA-class I, PD-L1, CD8 T-cells, HER2, CEA and P53 tumor expression were evaluated by immunohistochemistry (IHC). NanoString gene expression profiling was performed using the Pan Cancer Immune gene set.

Results

Clinical data for 8 patients included in the translational analysis

Table 1. Efficacy data

Patient ID	Prior CT	Prior ICB	Tedopi®	Secondary resistance ICB
1208015	PR	SD	PR	Yes
1215018	SD	-	SD	Yes
1218013	PR	PD	SD	Yes
1218008	PD	PR	PD	Yes
1708007	PR	PD	PD	Yes
1708005	SD	PR	SD	No
1222021	SD	PD	PD	No
1215019	PD	PD	PD	No

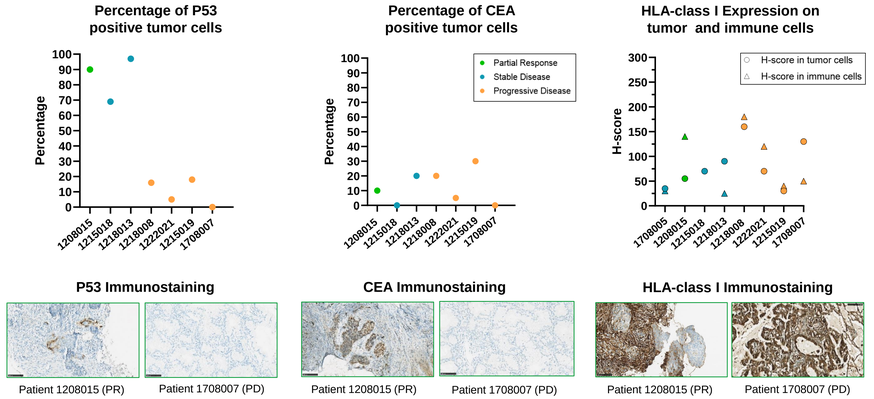


Patient ID: Patient identification; CT: Chemotherapy; ICB: Immune checkpoint blocker; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; FPS: Progression Free Survival; OS: Overall Survival

- Secondary (≥ 12 weeks) resistance to ICB was observed in 5 (62%) patients and Primary (<12 weeks) resistance was observed in 3 (38%) patients.
- Best response and OS were: 1 partial response (PR) (OS of 33 months), 3 stable disease (SD) (OS of 22, 26 and 41 months) and 4 disease progression (PD) (OS of 3, 4, 30 and 31 months).

Tumor-associated antigen and HLA-class I expression

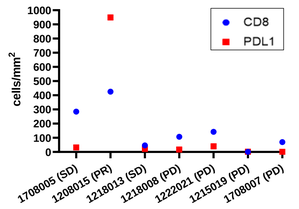
Figure 3.



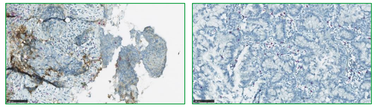
- IHC analysis revealed that P53, CEA and HER2 were expressed in 6/7, 5/7 and 0/7 patients, respectively. P53, CEA, HER2, MAGE2, and MAGE3 were detected at RNA level in 5/5 tested patients (data not shown).
- HLA-class I is expressed in all tumor samples.

Immunophenotyping and transcriptomic tumor analysis

Figure 4. CD8 and PD-L1 cell density in tumor



CD8 / PD-L1 Immunostaining



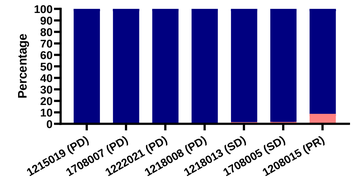
Patient 1208015 (PR) Patient 1708007 (PD)

Table 2. Immunoscore® and CPS data

Patient ID	Immunoscore CD8 / PDL1	PDL1 CPS
1208015 (PR)	High / High	279
1708005 (SD)	High / Low	5
1218013 (SD)	Low / Low	4.5
1218008 (PD)	Low / Low	20
1222021 (PD)	Low / Low	0.3
1215019 (PD)	Low / Low	0
1708007 (PD)	Low / Low	0

Patient ID: Patient identification; CPS: Combined Positive Score

Figure 5. CD8 and PD-L1 cells proximity



- Immunoscore® CD8/PD-L1 showed High/High, High/Low and Low/Low scores for 1/7, 1/7 and 5/7 patients, respectively. High/High Immunoscore®, High PD-L1 CPS score and a pronounced tumor CD8+ T-cell infiltration were observed in the PR patient.
- CD8/PD-L1 cells proximity analysis showed a higher proportion of CD8 cells interacting with PD-L1 cells in the PR patient (8.75%) and lower levels in SD patients (1.41-1.59%).

Table 3. Tumor gene expression profiling

Patient ID	Secondary resistance to ICB	OS Tedopi	TREM2 mRNA	MARCO mRNA	SLC11A1 mRNA	CHIT1 mRNA	SERPINB2 mRNA	IFNγ signature* (ssGSEA)	Expanded Immune Gene Signature* (ssGSEA)
1208015 (PR)	**Yes**	33.2	469	1135	2351	7222	1858	171	102
1708007 (PD)	**Yes**	30.5	132	172	358	235	34	116	54
1218008 (PD)	**Yes**	30.3	59	121	212	80	22	136	55
1218013 (SD)	**Yes**	22.2	227	191	721	250	95	74	-37
1215019 (PD)	**No**	4.2	45	41	275	70	18	29	-49

Samples from patients 1222021, 1708005 and 1215018 were not analyzed

ICB: Immune checkpoint blocker; Patient ID: Patient identification; OS: Overall Survival; ssGSEA: Single-sample Gene Set Enrichment Analysis. Green bars = Gene Signature upregulation; Red bars = Gene Signature downregulation

*Ayers et al., 2017

- High IFN-γ and Expanded Immune Gene Signature (*e.g.* CD3D, CD3E, GZMB, LAG3) scores were observed in long-term survivor patients with secondary resistance to ICB. Overexpression of genes associated with activated macrophages (TREM2, MARCO, SLC11A1, CHIT1, SERPINB2) was observed in PR and SD patients.

Key findings and conclusions

- All HLA-A2+ patients (blood test), expressed HLA class I in the tumors at initial diagnosis.
- The PR patient showed High/High IMMUNOSCORE® associated with high CD8 T-cell tumor infiltration, and a higher proportion of CD8 cells interacting with PD-L1 cells.
- Transcriptomic data in the patients that benefited from Tedopi® showed activated macrophage pathway. High IFN-γ and Expanded Immune Gene Signatures scores were observed in long-term survivor patients with secondary resistance to ICB.
- These data will be validated on larger number of patients treated with Tedopi®

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