Early signs of activity of Tedopi (OSE2101), a multiple neoepitope vaccine, in a phase 3 trial in advanced lung cancer patients after failure to previous immune checkpoint inhibitors (ICI) Atalante -1 study trial

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Background

- Several phase II/III trials with cancer vaccines (MAGRIT, START, STOP) have previously failed to demonstrate clinical benefit in Non Small Cell Lung Cancer (NSCLC) patients

- Immune checkpoint inhibitors (ICI) have changed the prognosis of advanced NSCLC achieving 4-year OS of 16% and 27% in previously-treated and treatment naïve patients[1]

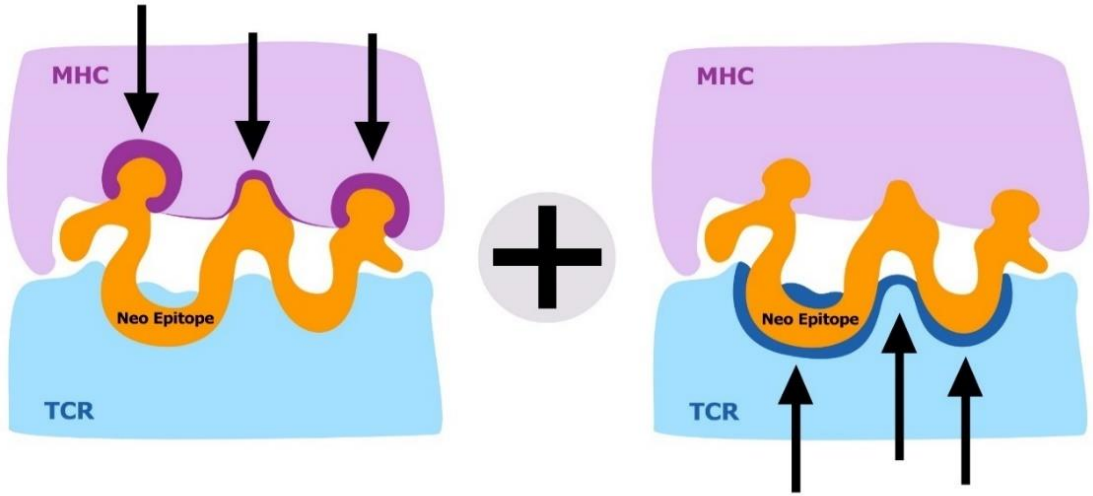
- ICI monotherapy for selected patients or ICI combined with chemotherapy in the whole population[2,3,4] are the new Standard of Care (SoC) in first-line setting. Sequential ICI strategy after first-line chemotherapy is still in use[5]

- Potential enhanced efficacy of vaccines after ICI treatment failure remains unexploited and its biological basis is poorly understood[6]

[1]Felip, ASCO 2018; [2]Gandhi, NEJM 2018; [3]Paz-Ares, NEJM 2018; [4]Reck, JCO 2019; [5]Planchard, Ann Oncol 2018; [6] Jenkins, BJC 2018

Tedopi, a multiple neoepitope vaccine

Formulation of neoepitopes	
5 Tumor Associated Antigens	**9 epitopes**
Carcinoembryonic Antigen (CEA)	(2) Heteroclitic (1) fixed-anchor
p53	(2) Fixed-anchor
Human epidermal growth factor receptor 2 (HER-2)	(1) Fixed-anchor (1) wild-type
Melanoma-Associated Antigen 2 (MAGE-A2)	(1) Wild type
Melanoma-Associated Antigen 3 (MAGE-A3)	(1) Heteroclitic
+ a Pan DR T Helper cell epitope (PADRE) + mineral oil adjuvant	



Tumor eradication by T cells requires high affinity of the targeted peptides for MHC class I

Tedopi neoepitopes are selected and optimized for high affinity to MHC class I (HLA A2 isotype)

HLA.A2 phenotype is present in about 45% of general population

[1] Engels, Cancer Cell 2013; [2] Beebe et al, Human vaccine 2008

Mechanism of action of multiple neoepitope vaccine when resistance to ICI

Multiple neoepitope vaccine[1]

- Increase the tumor associated antigen (TAA) presentation
- Increase the priming and activation of T cell

To increase the recognition of cancer cells by specific T cells

	Mechanism	Examples
Tumor cell-intrinsic	**Absence of antigenic proteins**	Low mutational burden Lack of viral antigens Lack of cancer-testis antigens Overlapping surface proteins
	Absence of antigen presentation	Deletion in TAP transporters Deletion in B2M Silenced HLA
	Genetic T cell exclusion	Oncogenic PD-L1 expression MAPK oncogenic signaling Stabilized b-catenin Mesenchymal transcriptome
	Insensibility to T cells	Mutations in ITNδ pathway signaling
Tumor cell-extrinsic	**Absence of T cells**	**Lack of T cells with tumor antigen-specific TCRs**
	Inhibitory immune checkpoints	VISTA, LAG-3, TIM-3
	Immunosuppressive cells	TAMs, Tregs

Mechanisms of primary & adaptive resistance to immunotherapy[2]

[1] Fikes, EOBT 2003; [2]Sharma, Cell 2017

Previous phase II results in pre-treated NSCLC patients

64 NSCLC patients HLA-A2+ [1]

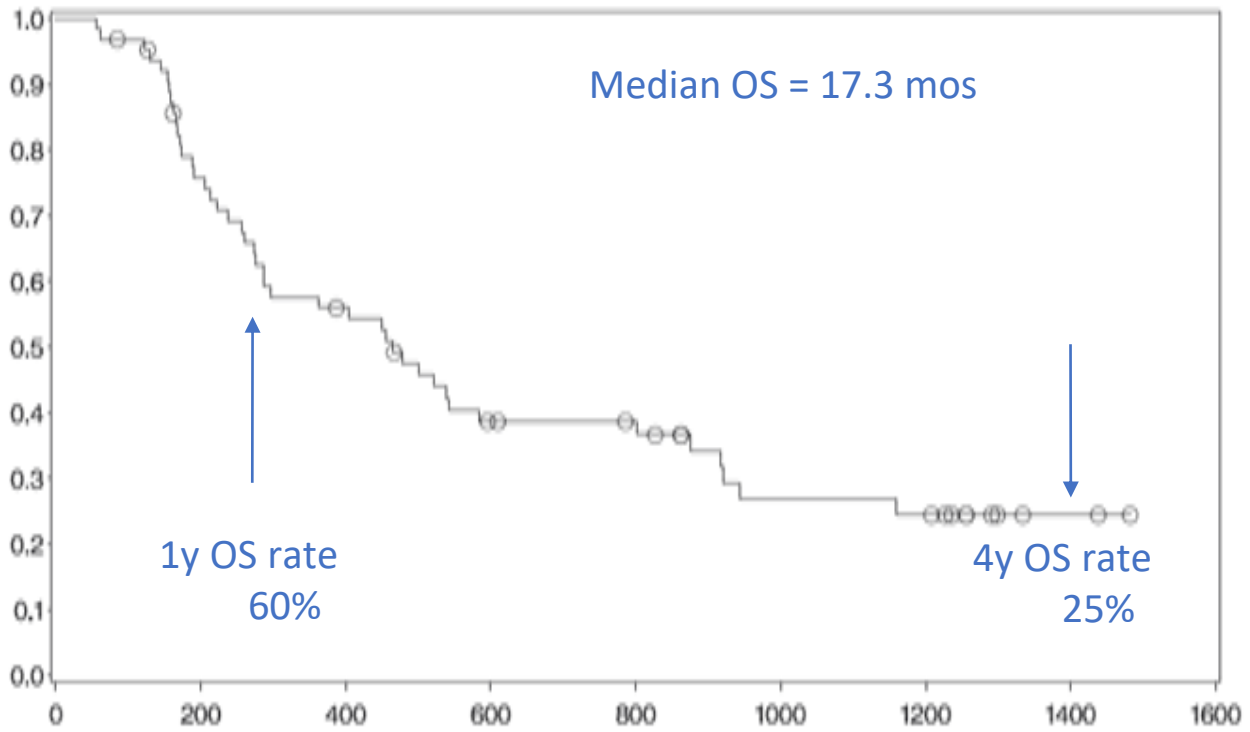
- Failure to platinum CT (92%) and TKIs (34%)
- Stage IV (67%) NSCLC
- 66% in 3rd line systemic treatment
- 9% with stable brain metastasis

Safety data[1,2]:

local injection site reaction in ≈ 1/3 of patients (Grade 1-2 > 95%)

cytokine release syndrome and similar events in ≈ 5% (Grade 1-2 > 90%)

Overall survival at 4 years



High CTL immune responses correlated with OS

Low: 406 days, medium: 778 days, high: 875 days

[1] M. Barve et al, Journal Clin. Oncol. 2008; [2] Integrated safety report-Feb 2019

ATALANTE-1: Phase 3 trial Tedopi vs CT

- **Advanced NSCLC in 2nd or 3rd line**
- **EGRF, ALK- negative**
- **Failure to platinum based CT and ICI**
- **HLA-A2+ (blood)**
- **Brain metastasis allowed if asymptomatic and treated**
- **ECOG 0 to 1**

R
2:1

Arm A: OSE2101 (Tedopi)
Day 1 each 21-day cycle for 6 cycles, then every 8 weeks up to Year 1, then every 12 weeks until progression or toxicity or patient consent withdrawal

Control Arm B: docetaxel or pemetrexed
Day 1 each 21-day cycle until progression or toxicity or patient consent withdrawal

Stratification criteria: histology, best response to 1st line and line rank of prior ICI

Primary endpoint: OS

After independent safety review in Nov 2017, only patients previously exposed to ICI were eligible as ICI become a SoC in 1rst and 2d line NSCLC patients: all patients must have failed to ICI as last treatment before tedopi or control

ClinicalTrials.gov Identifier:NCT02654587

Cases of interest- Clinical Characteristics

	Patient 1	Patient 2	Patient 3	Patient 4 (control)
Gender	Male	Female	Male	Female
Age (years)	54	44	49	52
Histology	Squamous	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma
Metastatic sites	Lung, pleural	Pleural	Brain, lung, Lymph	Lung, Adrenal
Mutation profile	Not done	KRAS G12C	EGFR wt ALK wt	KRAS G12V
HLA A2 phenotype*	A*02, A*01	A*02, A*01	A*02, A*30	A*02,A*03
Previous treatment lines	2	2	2	2
ICI treatment	Anti-PD1	Anti-PD1	Anti-PD1 + anti-CTLA4	Anti-PD1 + AXL Inh
ICI best response	SD	PD	PR	PD
Time lapse ICI/Tedopi	57 d	39 d	51 d	43 d

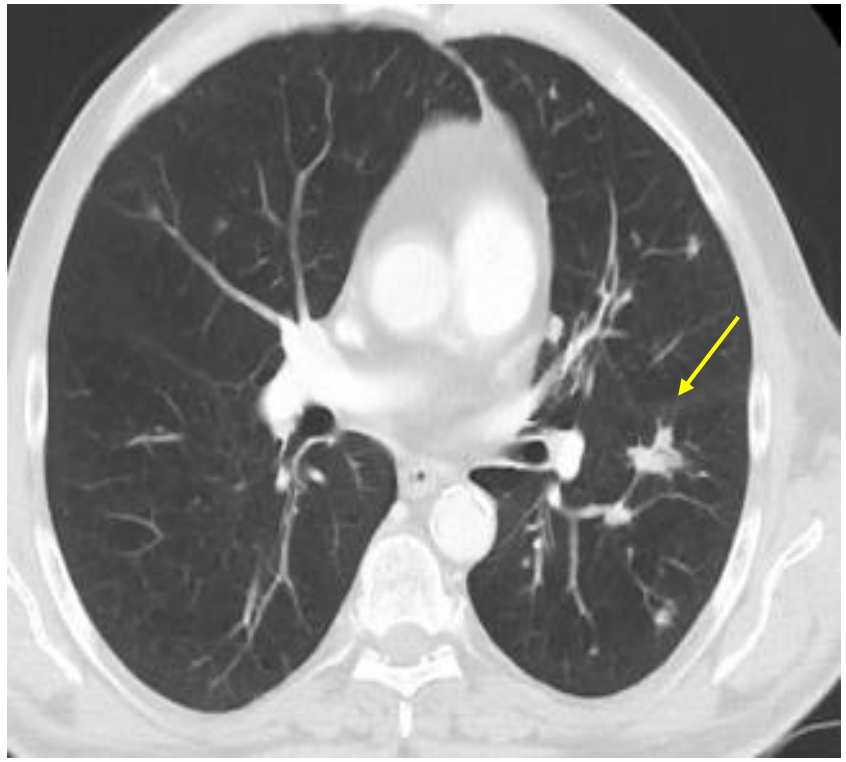
*HLA typing by PCR-SSOP (Luminex)

Case of interest- efficacy & safety

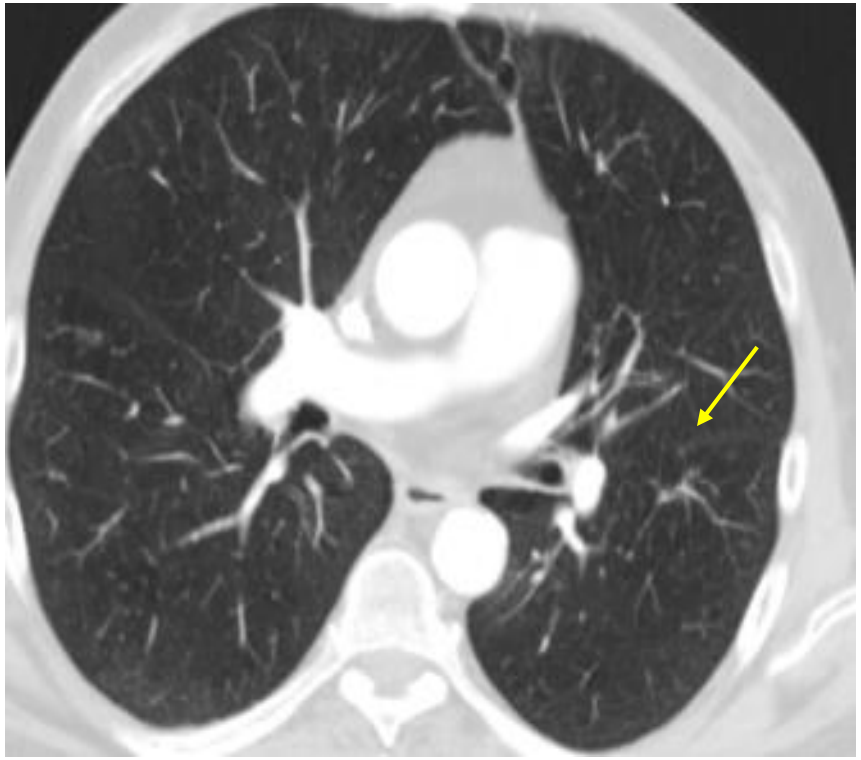
	Patient 1	Patient 2	Patient 3	Patient 4 (control)
Best response to Tedopi	**PR**	**SD > 9 mo**	**SD > 9 mo**	**PD**
Treatment duration	3.7 mo	11.5 mo	16.9 mo	2.8 mo
Progression Free Survival	4.2 mo	11 mo	18.1 mo	2.1 mo
OS after Tedopi initiation	20.6+ mo	22.1+ mo	20.3+ mo	7.1+ mo
Immune–related adverse events	No side effects	Post-injection Cytokine release syndrome x 5; Local site induration; Hyperthyroidism	Hyperthyroidism	Hypothyroidism; Post-injection Fever x 2
Treatment after Tedopi	Yes (CT)	Yes (CT)	Yes (CT)	Yes (CT)

Patient 1- Partial Response

Decrease of 41% in the sum of target lesions (from 39 mm to 23 mm)
Progression Free Survival of 4.2 months and survival of 20.6+ months (FUp ongoing)



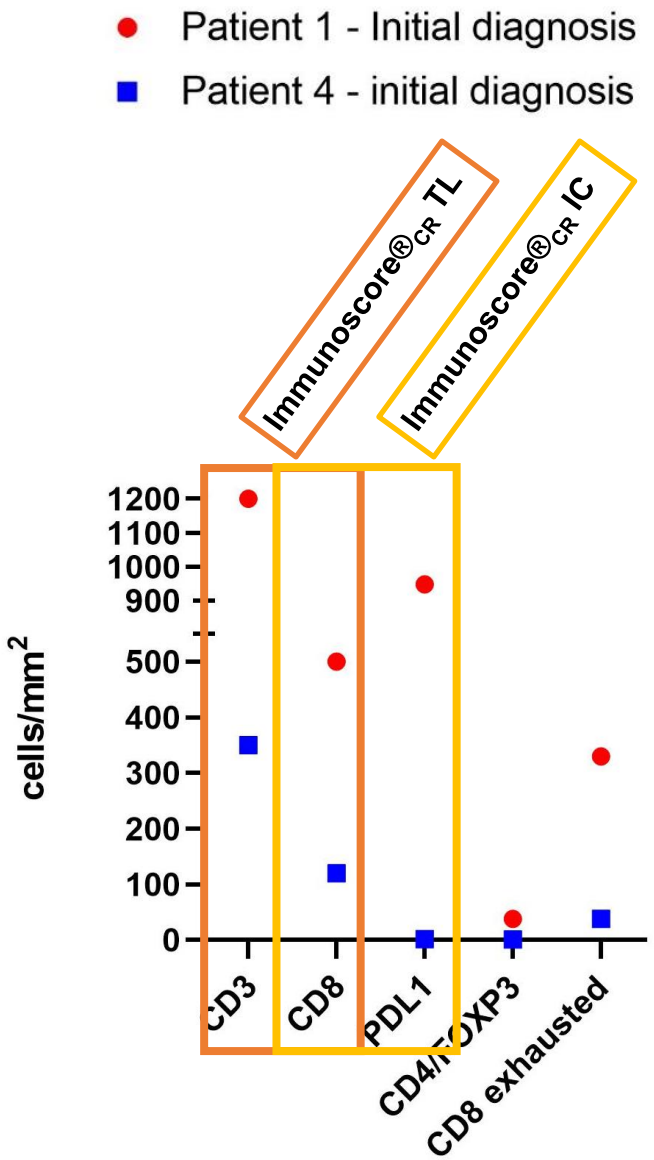
Baseline Chest CT
May 2017

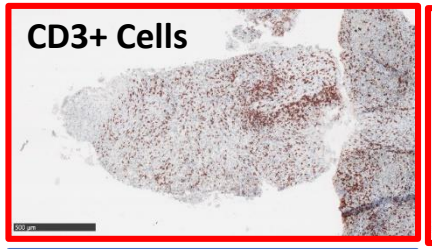


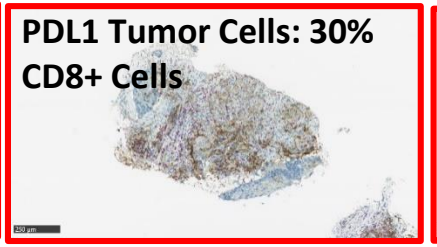
On treatment after 5 injections of Tedopi
August 2017

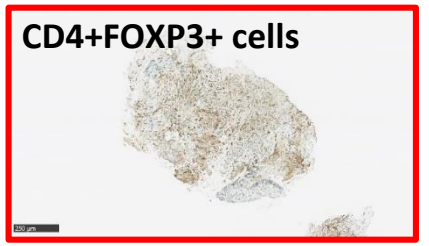
Source: Patient Case Report 1208015

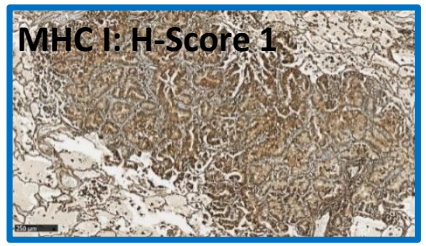
Immune profiling Patient 1 vs Patient 4

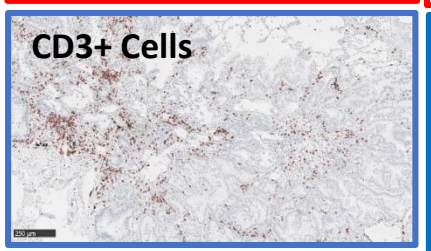


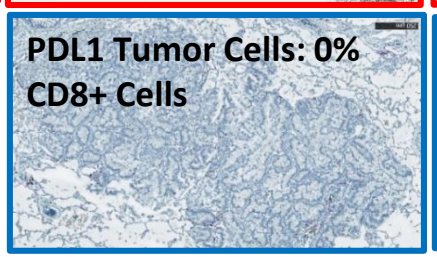


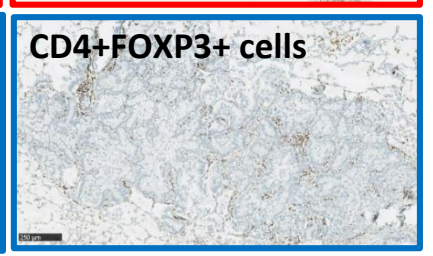












	Patient 1	Patient 4 (control)
Archival tumor biopsy	At initial diagnosis	At initial diagnosis
Last ICI treatment before Tedopi	Anti PD1	Anti PD1 + AXL inh
Best response to Tedopi	PR	PD
Immunoscore® $_{CR}$ TL*	**Hi**	**Low**
Immunoscore® $_{CR}$ IC*	**Hi /Hi CD8/PDL1**	**Hi /Low CD8/PDL1**
% CD8 Exhausted Cells At least PD1+/ TIM3+/LAG3+	**66%**	**34%**

* HalioDx Clinical Research Services

Patient 1 in PR is characterized by a **Hi Immunoscore® TL** and **Hi/Hi Immunoscore® IC** at initial diagnosis suggesting a favorable pre-existing immunity**

**Jérôme Galon & Daniela Bruni - Nature Reviews Drug Discovery 2019

Conclusions

- Survival of about 2 years (including 1 PR) has been observed in 3 NSCLC patients who progressed after ICI before receiving Tedopi as stand alone in 3rd line treatment suggesting efficacy in this setting.
- A possible synergy between previous ICI and Tedopi is hypotesized
- A comprehensive translational program is planned to explore mechanisms of response/resistance in this population
- 2 Ongoing Prospective studies:
  - Atalante-1[1]: Tedopi as sequential strategy after failure to ICI in NSCLC patients
  - TEDOPaM – D17-01 PRODIGE 63 study-GERCOR[2] :Tedopi ± nivolumab as maintenance treatment in pancreatic adenocarcinoma patients responding to standard chemotherapy

[1]ClinicalTrials.gov Identifier:NCT02654587; [2]ClinicalTrials.gov Identifier: NCT03806309