Abstract # 3034

RESULTS OF THE PHASE 2B PART OF TIME STUDY EVALUATING TG4010 IMMUNOTHERAPY IN STAGE IV NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS RECEIVING FIRST-LINE CHEMOTHERAPY

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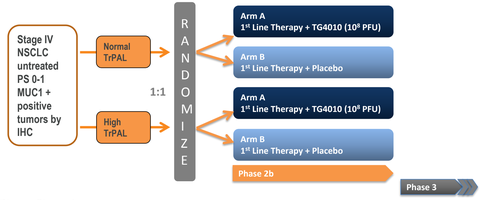
Summary

Background: TG4010 is an immunotherapy using an attenuated and modified poxvirus (MVA) coding for MUC1 and interleukin-2. A previous study showed that the baseline level of Triple Positive Activated Lymphocytes (TrPAL, CD16+CD56+CD69+) might be a predictive biomarker for TG4010 efficacy in NSCLC. **Methods:** TIME is a double blind, placebo-controlled phase 2b/3 study. The phase 2b part compared first-line chemotherapy combined with TG4010 or placebo and further assessed the predictive value of the baseline level of TrPAL. Eligibility criteria included stage IV NSCLC not previously treated, MUC1+ tumor by immunohistochemistry (IHC), PS ≤ 1. TG4010 10^8 pfu or placebo was given SC weekly for 6 weeks (w), then every 3w up to progression in immediate combination with chemotherapy. Primary endpoint was progression-free survival (PFS). **Results:** 222 patients (pts) were randomized 1:1. In pts with normal TrPAL the study met the primary endpoint of a Bayesian probability higher than 95% that HR < 1. PFS was significantly improved in the TG4010 arm in pts with low TrPAL (147pts HR = 0.66 [CI 95% 0.46-0.94] p = 0.01) while there was no improvement in pts with high TrPAL (75 pts HR = 0.90 [CI 95% 0.55-1.48] p = 0.34). PFS was significantly improved in pts with non-squamous tumors (196 pts HR = 0.69 [CI 95% 0.51-0.94] p = 0.009) as well as in pts with non-squamous tumors and low TrPAL (127 pts HR = 0.59 [CI 95% 0.40-0.87] p = 0.003). Overall survival data show an improvement in line with that observed for PFS. Analysis of the effect of PD-L1 expression by IHC on the tumor cells support the activity of TG4010 in patients with low (<5%) PD-L1 expression on tumor cells. Frequency and severity of adverse events were similar in both treatment arms. **Conclusions:** These results provide additional data supporting the efficacy of TG4010, particularly in patients with non-squamous tumors and/or a low level of TrPAL at baseline.

Study Design



Phase 2b part

- Primary Objective: Prospective validation of the predictive value of the TrPAL (CD16+CD56+CD69+) biomarker (Bayesian design) with respect to PFS (primary endpoint)
  - In patients with Normal TrPAL before treatment (baseline) : >95% probability that HR<1
  - In patients with High TrPAL before treatment : >80% probability that HR>1
- Secondary Objectives: ORR, Duration of Response, OS, Safety, Subgroup analyses
- PFS and ORR were assessed using RECIST 1.1

Study Treatments:

- **TG4010 or placebo**: SC injections weekly for 6 weeks and every 3 weeks thereafter until progression
- **Chemotherapy** (4 to 6 cycles):
  - Non-squamous tumors: pemetrexed/cisplatin or paclitaxel/carboplatin
  - Squamous tumors: gemcitabine/cisplatin or paclitaxel/carboplatin
- **Bevacizumab allowed**
- **Maintenance therapy if indicated:**
  - Pemetrexed in non-squamous carcinoma or
  - Erlotinib whatever the histology
  - Bevacizumab if prescribed from start of chemotherapy

PFS Bayesian Analysis

	Normal TrPAL		High TrPAL	
ITT population	TG4010 (n=85)	Placebo (n=85)	TG4010 (n=26)	Placebo (n=26)
No of PFS events	76 (89.4%)	75 (88.2%)	21 (80.8%)	22 (84.6%)
Observed Hazard ratio (HR) [95% CI]	0.75 [0.53;1.02]		0.77 [0.42;1.40]	
Posterior Probability (HR<1)	**98.4%**		68.7%	
Posterior Probability (HR>1)			**31.3%**	

Primary analysis was based on a cut-off for TrPAL value corresponding to upper limit of normal in healthy subjects.

- Primary endpoint was achieved in patients with normal TrPAL: Probability is >95% that HR<1 in patients treated with TG4010
- No detrimental effect was observed in patients with high TrPAL

Significant difference in PFS in the overall study population (HR=0.74 [95% CI: 0.55-0.98]; p=0.019)

Analyses by subgroup were performed :

- Histology: in non-squamous tumors
- Quartile approach for TrPAL value based on 572 patients screened
  - 147 patients with low TrPAL (≤Q3, 3 lowest quartiles)
  - 127 patients with low TrPAL and non-squamous tumors

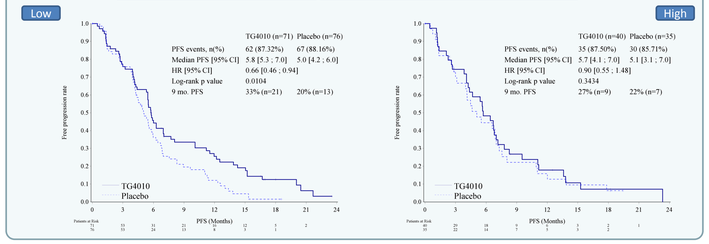
Patients and Baseline Characteristics

	All Patients (n=222)	
ITT population	TG4010 (n=111)	Placebo (n=111)
Gender : Male	64.5%	63.1%
Median age (yrs)	63	59
Current/Ex-smoker	93.6%	89.2%
PS=1	69.1%	68.5%
Stage IV at diagnosis	90.9%	93.7%
Non-squamous tumor	88.3%	88.3%

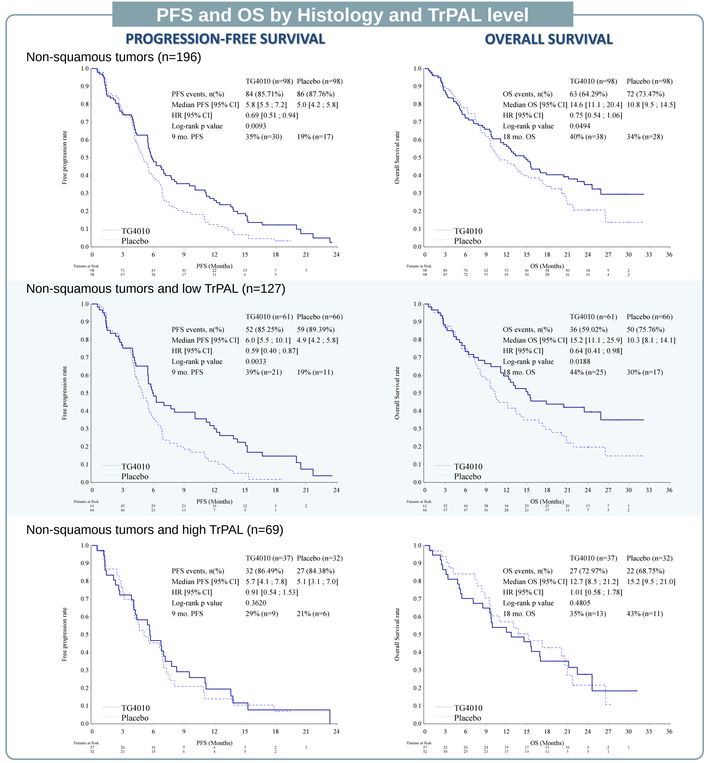
Treatments

Study treatments (n=219)	TG4010 (n=111)	Placebo (n=108)
Platinum-based chemotherapy period		
Pemetrexed + cisplatin	73	65
Paclitaxel + carboplatin	30	33
Gemcitabine + cisplatin	8	10
Bevacizumab	16	15
Maintenance period (after platinum-based chemotherapy)		
Number of patients	75 (67.6%)	61 (56.5%)
with IMP	75	60
with Pemetrexed	38	29
with Bevacizumab	8	9
IMP (TG4010 or Placebo)		
Median nb of injections	12	10

PFS by TrPAL level

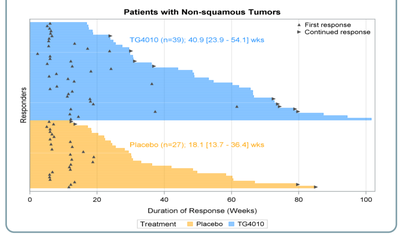


PFS and OS by Histology and TrPAL level



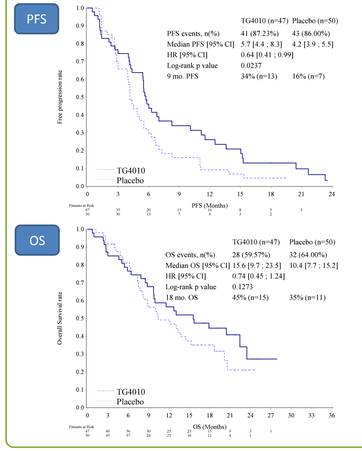
RESPONSE

	TG4010	Placebo
Overall population (n)	111	111
ORR	39.6%	28.8%
Median duration of response (weeks)	30.1	18.7
Non-squamous (n)	98	98
ORR	39.8%	27.6%
Median duration of response (weeks)	40.9	18.1
Non-squamous, low TrPAL (n)	61	66
ORR	39.3%	30.3%
Median duration of response (weeks)	43.1	18.1



TG4010 efficacy and PD-L1 expression

PD-L1 expression was analyzed in 160 patients by IHC staining on tumor slides using E1L3N anti-PD-L1 monoclonal antibody. The cut-off used to determine the level of positive PD-L1 expression was set at 5% of tumor cells. 138 patients had a non-squamous tumor of which 97 patients (70%) had <5% PD-L1 tumor cell expression (PFS & OS shown below).



SAFETY

Frequency of adverse events (AEs)	Safety population*	
	TG4010 (n=110)	Placebo (n=107)
Subjects with at least one AE	**99.1%**	**98.1%**
Serious AEs	46.4%	54.2%
Severe AEs	64.5%	68.2%
AE related to TG4010 / Placebo	32.7%	14%
- Injection site reaction	32.7%	3.7%
Most Frequent AEs, Grade 3/4 (>5%)		
Neutropenia	33.6%	27.1%
Thrombocytopenia	11.8%	5.6%
Anaemia	10.9%	15.0%
Fatigue	10.9%	12.1%
Febrile neutropenia	2.7%	8.4%
Dyspnea	4.5%	6.5%

* Patients having received at least 1 IMP injection

CONCLUSIONS

- TG4010 in combination with chemotherapy has demonstrated clinical efficacy
  - Improved response rate and longer duration of response, including delayed and durable responses
  - Significant improvement in PFS
  - Improvement in overall survival
- TG4010 efficacy is greater in patients with low level of TrPAL
- TG4010 shows efficacy in patients having <5% of tumor cells expressing PD-L1 (70% of patients)
- Excellent safety profile of TG4010 when added to first-line chemotherapy
- Results warrant pursuing further development in NSCLC.
  - Phase 3 study in non-squamous tumors in combination with chemotherapy
  - Phase 2 trials exploring TG4010 in combination with immune checkpoint inhibitors

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