TIME: A Phase 2b/3 Evaluating TG4010 in Combination with First-line Therapy in Advanced Non-Small Cell Lung Cancer (NSCLC). Phase 2b results

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Abstract #5152

Summary

Background: TG4010 is an immunotherapy product based on a poxvirus (MVA) coding for the MUC1 tumor-associated antigen and interleukin-2. A previous study showed that a normal baseline level of Triple Positive Activated Lymphocytes (TrPAL, CD16+CD56+CD69+) might be a predictive biomarker for TG4010 efficacy in NSCLC (Lancet Oncol 2011;12:1125-33). The Phase 2b part aims at prospectively validating the baseline TrPAL level as a predictive biomarker.

Methods: TIME is a randomized, double-blind phase 2b/3 study (NCT01383148) comparing the combination of first-line therapy with TG4010 or placebo in stage IV NSCLC patients. Primary endpoint of the Phase 2b part of the study was to compare progression-free survival (PFS, according to RECIST 1.1) between TG4010 and placebo arms using a Bayesian design. Secondary objectives were response rate, safety, survival and subgroup analyses according to stratification factors.

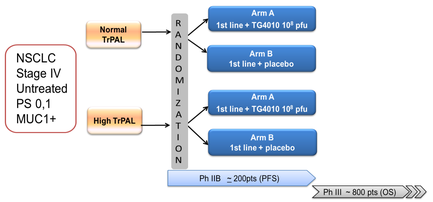
Results: Updated efficacy results presented in this poster are based on a cut-off date of 22 August 2014. 221 patients have been enrolled out of which 170 patients with a normal TrPAL level (pre-determined threshold) and an analysis of PFS was conducted in this cohort after 144 events of progression were recorded. The observed hazard ratio (HR) for PFS is 0.74 (95%CI: 0.53-1.02). This corresponds to a 98.6% Bayesian probability that the true HR is <1, passing the threshold of 95% needed to consider the endpoint met in patients with normal TrPAL. In the high TrPAL subgroup, the required events for analysis is not yet reached. TG4010 related adverse events were limited to mild or moderate fever and injection site reactions. Analysis in patients with the lowest baseline level of TrPAL (three lowest quartiles, n=152) shows a HR for PFS of 0.66 (95%CI: 0.46-0.96; p=0.014) consistent with the observation made in the previous study. Additional pre-planned analyses by subgroup show that patients with non-squamous tumors had a statistically significant improvement in PFS when treated with TG4010 (n=145, HR=0.66; 95%CI: 0.46-0.95; p=0.012) and especially when belonging to the three lowest quartiles (n=131, HR=0.60; 95%CI: 0.41-0.88, p=0.004). First results on OS tend in favor of TG4010.

Conclusions: These data support the concept that baseline TrPAL level is a potential biomarker to identify patients more likely to benefit from TG4010 treatment. They also confirm TG4010 efficacy and safety profile in stage IV NSCLC patients and warrant the continuation of the TIME study Phase 3 part with overall survival as a primary endpoint.

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 : pemetrexed/cisplatin or paclitaxel/carboplatin
  - Squamous : gemcitabine/cisplatin or paclitaxel/carboplatin
- **Maintenance therapy**
  - Pemetrexed in non-squamous carcinoma or
  - Erlotinib whatever the histology
  - Bevacizumab if prescribed from start of chemotherapy

Study Design & Objectives



Phase IIB part: Progression-Free Survival

- Primary Objective: Prospective validation of the predictive value of the TrPAL (CD16+CD56+CD69+) biomarker (Bayesian design)
  - In patients with Normal TrPAL before treatment : probability that HR<1 is >95% (after 89 events)
  - In patients with High TrPAL before treatment : probability that HR>1 is >80% (after 38 events)
- Secondary Objectives: ORR, OS, Safety, Subgroup analyses (according to histology, TrPAL cut-off value based on a quartile approach)
- Efficacy is based on RECIST 1.1

Phase III part: Overall Survival (not yet started)

Patients Characteristics

	All Patients (n=221)		Normal TrPAL (n=170)	
ITT population	TG4010 (n=110)	Placebo (n=111)	TG4010 (n=85)	Placebo (n=85)
Gender : Male (%)	64.5%	63.1%	70.6%	62.4%
Median age (yrs)	63	59	62	58
Former Smoker (%)	93.6%	89.2%	92.9%	87.1%
PS=1 (%)	69.1%	68.5%	68.2%	67.1%
Stage IV at diagnosis (%)	90.9%	93.7%	92.9%	92.9%

Patient subgroups based on Histology and TrPAL level

	N	TG4010 (Arm A)	Placebo (Arm B)
Normal TrPAL	170	85	85
Low TrPAL (<Q3, 3 lowest quartiles)	152	75	77
Non Squamous	195	97	98
Non Squamous – Low TrPAL (<Q3)	131	64	67

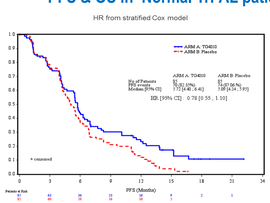
Efficacy in Normal TrPAL patients (n=170)

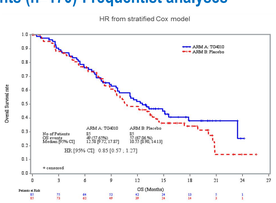
PFS in Normal TrPAL patients- Bayesian Analysis

	Normal TrPAL	
ITT population	TG4010 (n=85)	Placebo (n=85)
No of PFS events	70 (82.4%)	74 (87.1%)
No censored	15 (17.6%)	11 (12.9%)
Observed Hazard ratio (HR)	0.74 [0.53;1.02]	
Posterior Probability (HR<1)	**98.6%**	

- Primary endpoint achieved in patients with Nal TrPAL: Probability that HR<1 in patients treated with TG4010 is >95%
- Number of events not yet reached for analysis in patients with High TrPAL

PFS & OS in Normal TrPAL patients (n=170)-Frequentist analyses





Response Rate in Normal TrPAL patients - Frequentist analyses

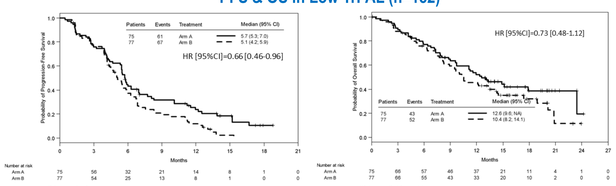
Best Overall Response RECIST 1.1 (local review)	Normal TrPAL (n=170)	
ITT Population (n=170)	TG4010 (n=85)	Placebo (n=85)
Objective Response Rate (all PR)	37.6%	30.6%

Subgroup Analyses

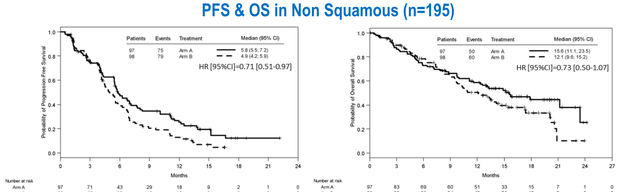
Subgroup analyses were performed based:

- On a Quartile approach for TrPAL value used as a cut-off for analyses:
  - 152 patients with the lowest TrPAL value (<Q3, 3 lowest quartiles) were analyzed as Low TrPAL patients
- On histology

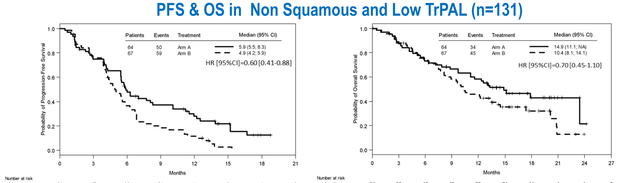
PFS & OS in Low TrPAL (n=152)



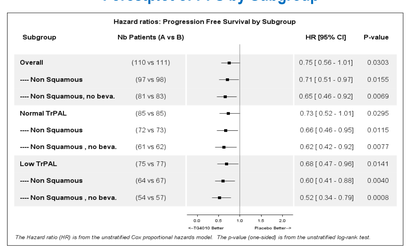
PFS & OS in Non Squamous (n=195)



PFS & OS in Non Squamous and Low TrPAL (n=131)



Forestplot of PFS by Subgroup



Safety

	All Patients		Normal TrPAL	
Safety Population*	TG4010 (n=105)	Placebo (n=100)	TG4010 (n=84)	Placebo (n=81)
Adverse Events (AE)	95%	98%	96%	98%
AE Grade 3/4	57%	64%	62%	63%
Serious AE	42%	47%	41%	44%
AE related to IMP	31%	11%	30%	11%

* Based on cut-off date Sep13 (210 pts)

Most Frequent AE (>20% in either arm)	All Patients		Normal TrPAL	
Safety population*	TG4010 (n=105)	Placebo (n=100)	TG4010 (n=84)	Placebo (n=81)
Fatigue	54%	53%	55%	56%
Nausea	41%	37%	45%	40%
Neutropenia	42%	35%	48%	33%
Anaemia	37%	33%	41%	36%
Injection site reaction	31%	4%	30%	5%
Vomiting	25%	35%	25%	37%
Thrombocytopenia	19%	18%	20%	20%

Most Frequent AE Grade 3/4 (>5% in either arm)	All Patients		Normal TrPAL	
Safety population*	TG4010 (n=105)	Placebo (n=100)	TG4010 (n=84)	Placebo (n=81)
Neutropenia	31%	27%	37%	26%
Thrombocytopenia	11%	16%	11%	6%
Fatigue	11%	11%	11%	15%
Anaemia	8%	14%	8%	16%
Febrile neutropenia	3%	8%	2%	8%
Vomiting	3%	9%	2%	8%

Conclusions

- Primary endpoint is achieved in patients with normal TrPAL before treatment:
  - Bayesian probability that TG4010 improves PFS (HR<1) is >95%
- Good safety profile of TG4010 is confirmed with similar proportion of patients with AEs, Severe AEs and SAEs in both treatment arms. Mild or moderate injection site reactions are the most frequent TG4010 related-AEs
- Subgroup analyses show that TG4010 improves PFS with statistical significance in Non-Squamous carcinoma, both in the overall population and in patients with low TrPAL
- Although still maturing, the Overall Survival, a secondary endpoint of the TIME study, shows an improvement in line with that observed in the Progression Free Survival
- A delayed separation of the Kaplan-Meier curves is observed both for PFS and OS as for other immunotherapeutics
- These results warrant further demonstration of TG4010 efficacy with overall survival as the primary endpoint of the phase III part and in particular in the Non-squamous population.

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