TG4010 immunotherapy plus chemotherapy as first-line treatment of advanced NSCLC: Phase 2b Results of the TIME trial

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Poster #463

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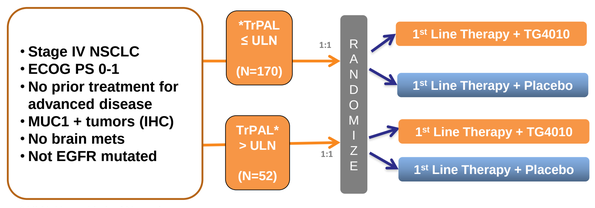
Study Design

Background: TG4010 is an immunotherapy using an attenuated and modified poxvirus (MVA) coding for MUC1 and interleukin-2 to induce a cellular immune response against MUC1 expressing tumors. Previous Phase 2 trials have demonstrated the efficacy and safety of TG4010 in combination with chemotherapy. In addition, level of Triple Positive Activated Lymphocytes (TrPAL; CD16+, CD56+, CD69+) was identified as a potential biomarker predictive of efficacy. TIME is a double blind, placebo-controlled phase 2b/3 study.



* ULN: Upper Limit of Normal

TG4010 (1.0 x 10^8 PFU) or Placebo:
SC injection weekly for 6 weeks and then once every 3 weeks until progression

1st Line Therapy:
Carboplatin + paclitaxel, or
Cisplatin + gemcitabine (for squamous), or
Cisplatin + pemetrexed (for non-squamous)
Up to 6 cycles
Bevacizumab at investigator's discretion
Maintenance therapy (pemetrexed or erlotinib) if eligible at investigator's discretion

Study endpoints

- Primary endpoint: PFS (Bayesian probability)
- Secondary endpoints: Overall response rate (ORR), Duration of response, Overall survival (OS), Safety
- Pre-planned analyses using cut-off value for TrPAL (based on screened patients) defining 2 patients populations: Low or High TrPAL
- Pre-planned analyses in non-squamous patients

PATIENT CHARACTERISTICS

ITT population	TG4010 (n=111)	Placebo (n=111)
Gender : Male (%)	64.5	63.1
Median age (yrs) (range)	63 (38-81)	59 (36-77)
Current or Ex-Smoker (%)	93.6	89.2
ECOG PS=1 (%)	69.1	68.5
Non-squamous tumors (%) Squamous tumors (%)	88.3 11.7	88.3 11.7

RESULTS

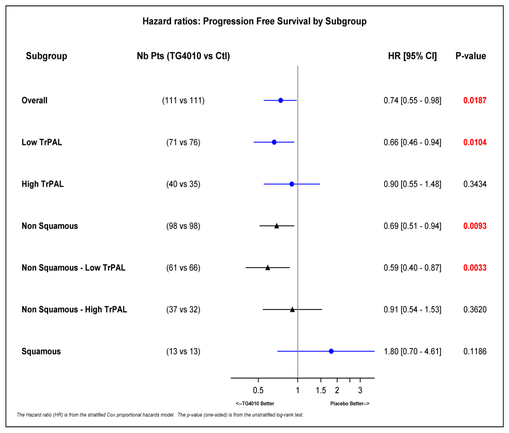
PFS (bayesian analysis)	TrPAL ≤ULN		TrPAL >ULN	
ITT population	TG4010 (n=85)	Placebo (n=85)	TG4010 (n=26)	Placebo (n=26)
Observed HR (CI 95%)	0.75 [0.53;1.02]		0.77 [0.42;1.40]	
Probability (HR<1)	**98.4%**		68.7%	
Probability (HR>1)	1.6%		**31.3%**	

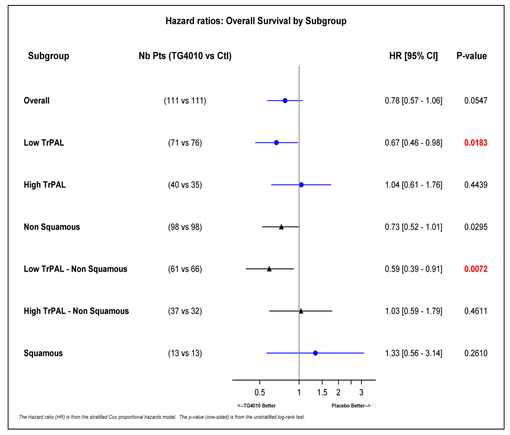
- Primary endpoint achieved in patients with level of TrPAL ≤ ULN with a bayesian probability that HR<1 greater than 95%

PRE-PLANNED ANALYSES

- Based on previous study results, definition of 2 populations with TrPAL cut-off according to observed values in patients (low and high TrPAL)
- Analysis also performed according to histology (stratification factor)

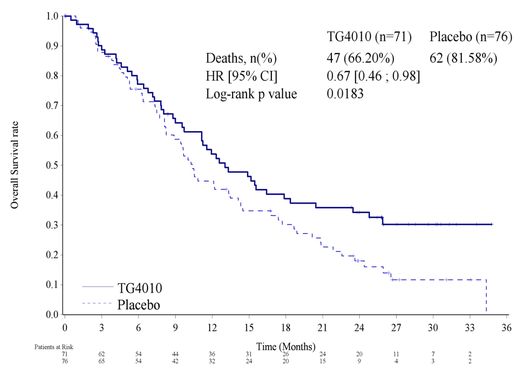
Forest Plot for PFS and OS



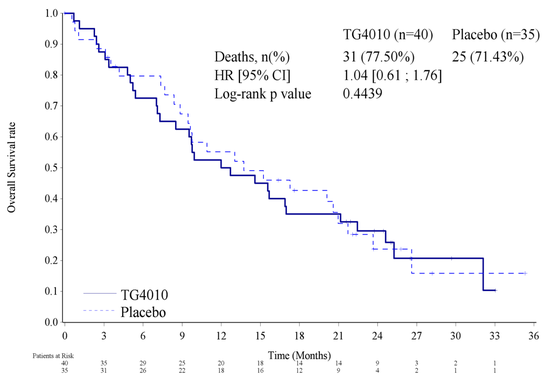


- Results are consistent across endpoints

OS in patients with Low TrPAL (n=147)

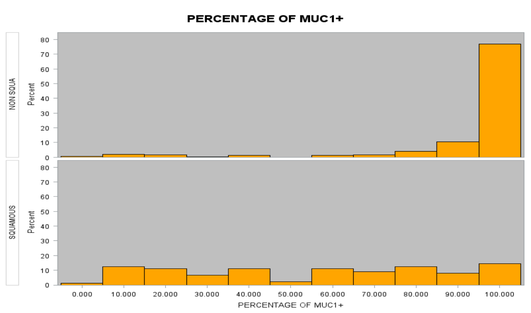


OS in patients with High TrPAL (n=75)

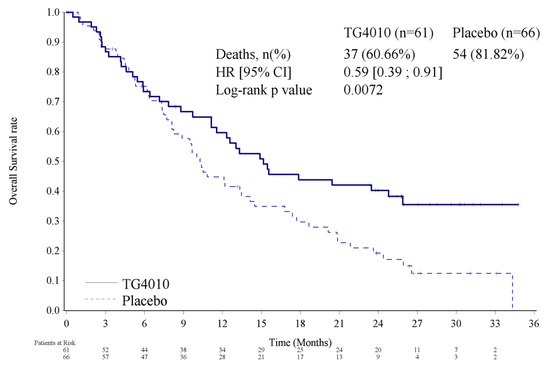


- In patients with low pre-treatment level of TrPAL, TG4010 provides statistically significant benefit whereas no efficacy is demonstrated in patients with high pre-treatment TrPAL level.

MUC1 expression according to histology

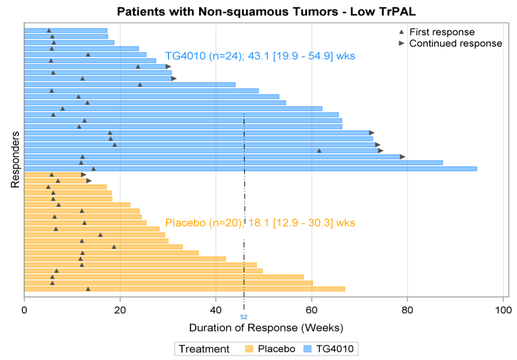


OS Non-squamous tumors & Low TrPAL (N=127)



- Non-squamous tumors most constantly express MUC1, the cellular target of TG4010
- TG4010 has greater efficacy in patients with non squamous carcinoma

DURATION OF RESPONSE

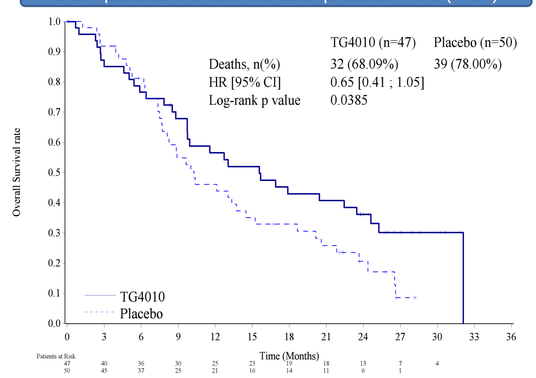


- In patients with non squamous tumors and low TrPAL, the Overall Response Rate was 39.3% in the TG4010 arm versus 30.3% in the placebo arm.
- Delayed responses (≥18 weeks) were observed more often in the TG4010 arm
- Duration of response was more than 2-times longer in the TG4010 arm with 45.8% (11/24) of patients still responder at 1 year versus 15% (3/20) in the placebo arm

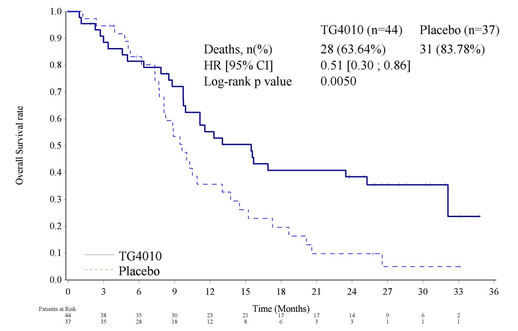
TG4010 EFFICACY IN LOW PD-L1 EXPRESSION

PD-L1 expression was analyzed 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%. In patients with non-squamous carcinoma, 97 patients had <5% PD-L1 expression in tumor cells (TC) and 81 patients had <5% PD-L1 expression in tumor infiltrate immune cells (IC) (Updated OS data shown below).

OS in patients with low PD-L1 expression in TC (n=97)



OS in patients with low PD-L1 expression in IC (n=81)



- TG4010 shows efficacy in patients with low PD-L1 expression

SAFETY

Most Frequent AEs (>20% in either arm)	Safety Population**	
	TG4010 (n=110)	Placebo (n=107)
Fatigue (%)	57.3	56.1
Nausea (%)	49.1	42.1
Anaemia (%)	47.3	37.4
Neutropenia (%)	44.5	35.5
Injection site reaction (%)	32.7	3.7
Vomiting (%)	30.0	33.6
Decreased appetite (%)	21.8	25.2
Constipation (%)	20.0	27.1
Diarrhea (%)	24.5	20.6
Thrombocytopenia (%)	24.5	18.7

** Patients having received at least 1 IMP injection

Frequency of Serious Adverse Events and Most Frequent Grade 3/4 AEs	Safety Population**	
	TG4010 (n=110)	Placebo (n=107)
Serious AEs (%)	46.4	54.2
Grade 3 / 4 AEs (%)	64.5	68.2
• Neutropenia (%)	33.6	27.1
• Anaemia (%)	10.9	15.0
• Thrombocytopenia (%)	11.8	5.6
• Fatigue (%)	10.9	12.1
• Vomiting (%)	3.6	9.3
• Febrile neutropenia (%)	2.7	8.4
• Dyspnea (%)	4.5	6.5

- Most frequent adverse events in TG4010 arm were injections site reactions. All were of low grade severity
- TG4010 was well tolerated. In particular, there was no increase in frequency of severe adverse events or serious adverse events

CONCLUSION

- TG4010 has demonstrated efficacy in combination with first-line chemotherapy. The greatest improvement is seen in patients who have both a low level of TrPAL at baseline and a non squamous tumor
- Delayed and durable responses were observed
- TG4010 shows efficacy in patients with low PD-L1 expression (either in tumor cells or tumor infiltrate immune cells)
- Further development is planned in combination with chemotherapy and checkpoint inhibitors

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