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AMERICAN SOCIETY OF CLINICAL ONCOLOGY



TG4010.09: Randomized, controlled phase IIb trial evaluating the therapeutic vaccine TG4010 (MVA-MUC1-IL2) as an adjunct to chemotherapy in patients with advanced non-small cell lung cancer (NSCLC)

Background

- MUC1, a tumor associated antigen, is a potential target for immunotherapy in lung cancer
- TG4010 is a treatment based on active immunotherapy
- TG4010 (MVA-MUC1-IL2) consists a recombinant vector (the highly attenuated Modified Vaccinia Virus Ankara) coding for MUC1 and IL2
- Four phase II trials have tested TG4010 in NSCLC, breast cancer, renal cancer and prostate cancer showing a good safety profile
- In a previous non controlled phase II study in NSCLC patients, TG4010 was combined with chemotherapy (cisplatin + navelbine) in 2 different settings. This study met its primary endpoint (response rate)

Study Design

Screening: 148 patients randomized
Stage IIIB "wet" / IV
PS 0-1;
no previous treatment for advanced disease;
MUC1 positive tumor by IHC

Randomization

ARM 1

Cisplatin: 75mg/m² D1 +
Gemcitabine: 1250mg/m² D1/D8
every 3 weeks, up to 6 cycles

ARM 2

Cisplatin: 75mg/m² D1 +
Gemcitabine: 1250mg/m² D1/D8
every 3 weeks, up to 6 cycles

+

TG4010: subcutaneous injection
weekly for 6 weeks then once every 3
weeks until progressive disease

Objectives

■ Primary Endpoint

- Progression free survival at 6 months (PFS)

■ Secondary Endpoints

- Response Rate ; Time to progression; Overall Survival; Safety; Quality of life; Immunological responses; Proteomics, Transcriptomics, Genomics

■ Fleming design

- Statistical end-point 27/67 patients (40%) non progressor at month 6 in the experimental arm

Statistical Methodology

■ Fleming design

- $H_0=30\%$, $H_A=50\%$
- α and β are set at 5%
- Statistical end-point 27/67 patients (40%) non progressor at month 6 in the experimental arm

■ Stratification for randomization

- ECOG Performance Status
- Stage disease: IIIB “wet” / IV
- Investigator’s site

■ ITT analysis

Efficacy assessments

- Tumor evaluation by CT-scan every 6 weeks until progression
 - Measurements according to WHO criteria
 - Local and independent central review
- Survival evaluated by follow-up documentation on a 3 months basis

Safety assessment

- Physical examination, vital signs and hematology performed weekly for 6 weeks (except D15 and D36 performed only for TG4010 arm) and then every 3 weeks
- Biochemistry evaluation every 3 weeks
- Recording of all adverse events and serious adverse events in order to evaluate the overall incidence for each arm of treatment and for the study as a whole

Results

- 148 patients were enrolled
 - 74 in each arm with a well-balanced distribution for demographics and disease characteristics between both arms

Patient Characteristics (n=148)

	TG4010 + chemotherapy N (%)	Chemotherapy N (%)	Total N (%)
Patients number	74	74	148
<u>Age :</u> median (year) range	58.5 36 - 79	58.5 38 - 79	58.5 35 - 79
<u>Tumor stage at baseline:</u>			
III _B	6 (8%)	6 (8%)	12 (8%)
IV	68 (92%)	68 (92%)	136 (92%)
<u>Tumor histology:</u>			
Adenocarcinoma	45 (61%)	52 (70%)	97 (65%)
Squamous cells carcinoma	18 (25%)	11 (15%)	29 (20%)
Other	11 (15%)	11 (15%)	22 (15%)
<u>Performance status ECOG :</u> distribution N (%)			
0	20 (27%)	20 (27%)	40 (27%)
1	54 (73%)	54 (73%)	108 (73%)
Male/Female N (%)	53 (72%) / 21 (28%)	54 (73%) / 20 (27%)	107 (72%) / 41 (28%)

Safety

- TG4010 was well tolerated and most of related adverse events were injection site reaction, fever and abdominal pain
- 6 SUSARs (Suspected Unexpected Adverse Reactions) were reported in 3 patients: they were possibly related to TG4010 as well as possibly related to chemotherapy

Safety - AE

	TG 4010 + Chemotherapy (n=73) (%)		Chemotherapy (n=72) (%)		P value
	Global incidence (%)	Grade 3 - 4 (%)	Global incidence (%)	Grade 3 - 4 (%)	
Hematology	83	47	79	40	NS
General / site administration	81	37	70	28	NS
Fatigue	57	0	51	0	NS
Fever	23	0	8	0	0.016
Injection site reaction	8	0	0	0	0.015
Gastrointestinal	71	16	65	12	NS
Abdominal pain	16	3	3	1	0.006
Respiratory	51	18	64	23	NS
Metabolism / nutrition	49	15	43	18	NS
Nervous system	44	8	32	5	NS
Skin and subcutaneous	35	5	28	0	NS
Cardiac	7	1.5	12	0	NS

Safety - SAE

	TG 4010 + chemotherapy (n=73) (%)		chemotherapy (n=72) (%)	P value
	Global incidence (%)	Possibly related to TG4010 and to chemotherapy (%)	Global incidence (%)	
% of patients with SAE	51	4	44	NS
Hematology	19	3	18	NS
Anemia	5	1.5	7	NS
Febrile neutropenia	3	1.5	1.5	NS
General /site administration	12	0	14	NS
Respiratory	11	3	11	NS
Acute pulmonary oedema	1.5	1.5	0	NS
Pneumothorax	1.5	1.5	1.5	NS
Pulmonary embolism	1.5	0	3	NS
Pulmonary haemorrhage	3	0	0	NS
Cardiac	3	0	4	NS
Infections and Infestations	1.5	1.5	0	NS
Pyopneumothorax	1.5	1.5	0	NS

Efficacy

- Primary endpoint was met. PFS at 6 months is 44% (33/74) in the TG4010 + chemotherapy arm and 35% in the chemotherapy arm (control arm)
- Response rate was 43% (32/74) in TG4010 arm and 27% (20/74) in the control arm. These results are statistically significant ($p=0.03$)

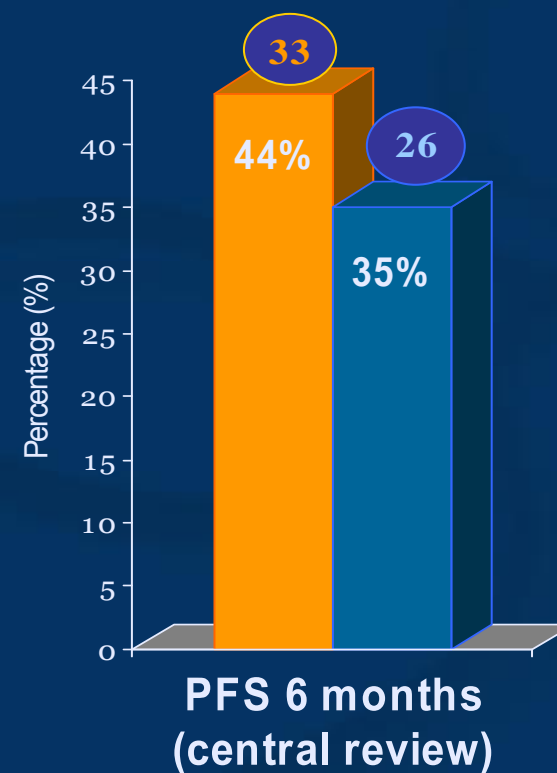
Progression Free Survival at 6 Months (central review)

Evaluation every 6 weeks (WHO criteria)

	TG4010 + chemo N (%)	Chemo N (%)
Patients evaluable	74	74
PFS at 6 months	33 (44%)	26 (35%)

■ TG4010 +
chemo
■ Chemo

● Number of patients
(Total of 74 patients
per arm)



ITT analysis

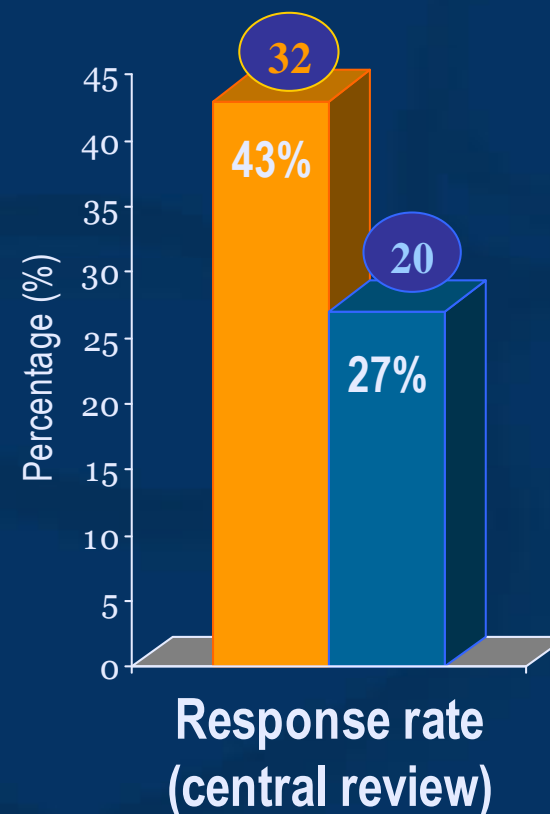
Response Rate (central review)

Evaluation every 6 weeks (WHO criteria)

	TG4010 + chemo N (%)	Chemo N (%)
Patients evaluable	74	74
PR/CR confirmed (2 subsequent evaluations)	32 (43%)	20 (27%)

■ TG4010 +
chemo
■ Chemo

● Number of patients
(Total of 74 patients
per arm)

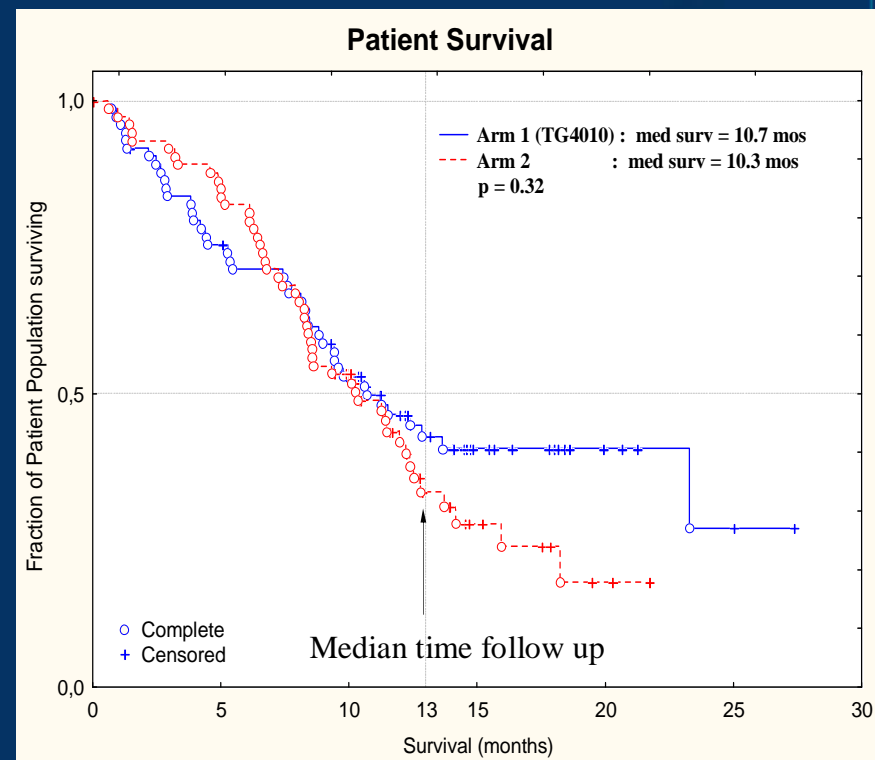
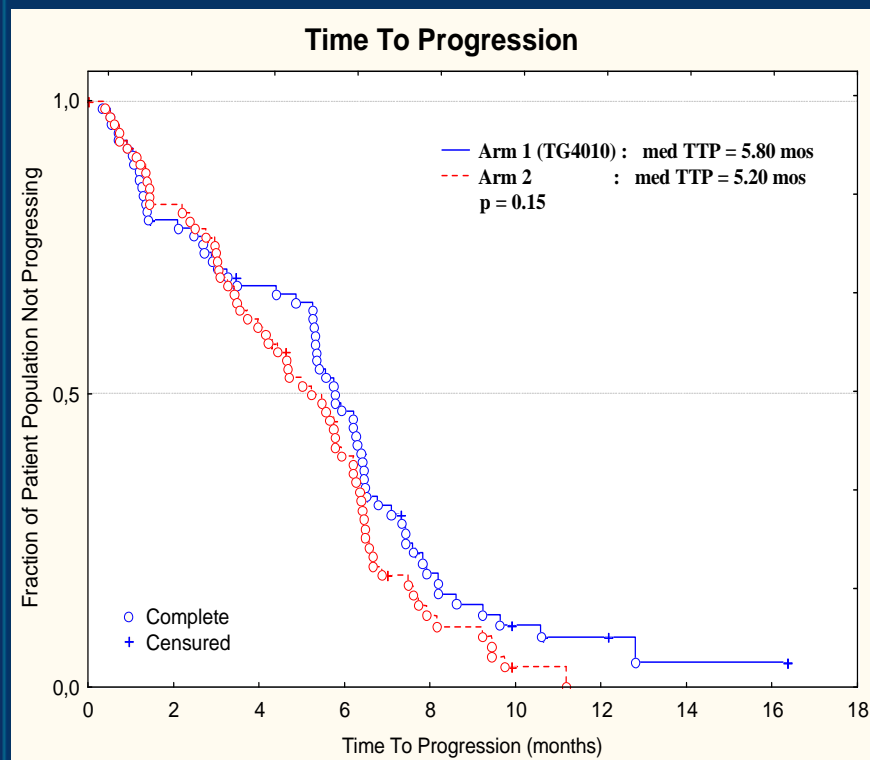


ITT analysis

Time to Progression and Survival

- Time to progression is 5.8 and 5.2 months in TG4010 + chemotherapy arm and chemotherapy arm, respectively
- Median survival is 10.7 and 10.3 months in TG4010 + chemotherapy arm and chemotherapy arm, respectively
- The median-time follow-up is 13 months:
 - 43% of patients are still alive in TG4010 arm
 - 33% of patients are still alive in control arm

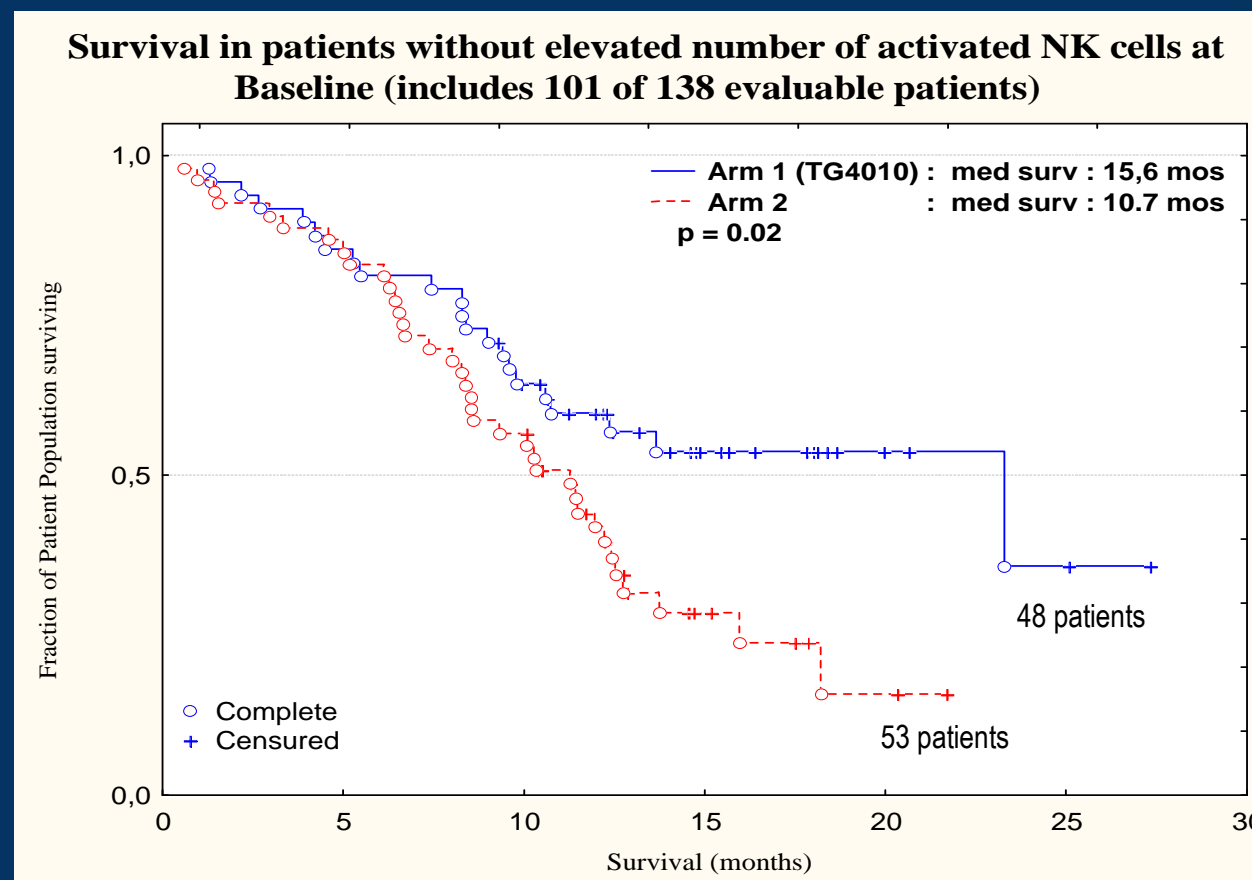
Kaplan-Meier curves



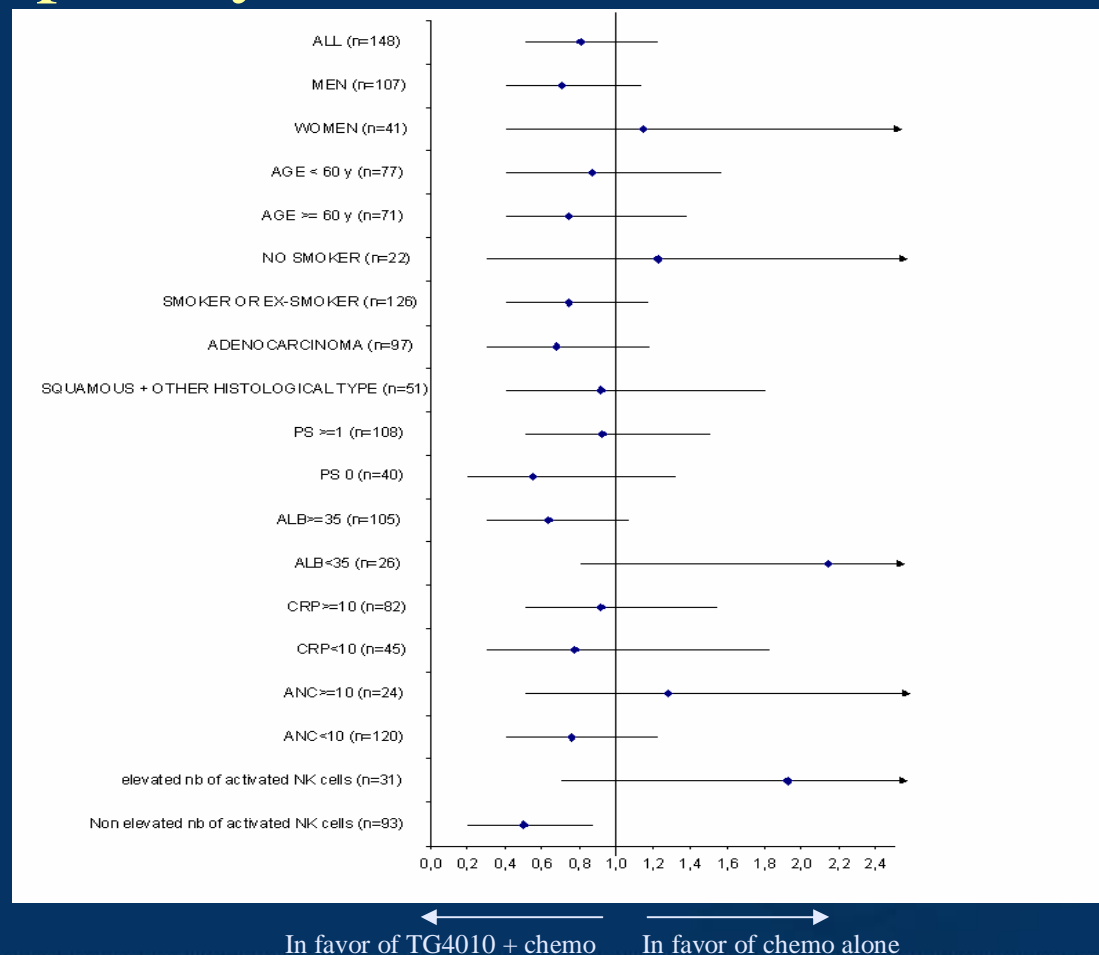
Exploratory subgroup analyses

- Exploratory research program is on-going.
 - First data show a statistically significant correlation between the number of activated NK cells and the survival, observed only in TG4010 + chemotherapy arm

Example of on-going exploratory research program: Predictive immunologic biomarker of patients' survival



Subgroup analyses Forest-Plot for Overall Survival



Key conclusions

- The primary endpoint was achieved (PFS at 6 months \geq 40% in TG4010 + chemotherapy arm)
- Response rate was significantly increased with TG4010
- TG4010 was well tolerated. Most of related adverse events were injection site reactions, fever and abdominal pain
- The data for overall survival are not yet mature, but there is a **trend in favor of the TG4010** combined with chemotherapy for long-term survival
- Preliminary data indicate a significant correlation between the level of activated NK cells prior therapy and survival in the TG4010 + chemotherapy arm only

Next steps

- Interim results warrant further development in Phase III
- **A large biomarker program** is in progress (Immunology, Proteomics, Transcriptomics and Genomics), allowing further characterization of TG4010 mechanism of action and design of Phase III