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Developing new vaccines
to fight cancer and infectious diseases

Les thérapies du futur : L'immunothérapie

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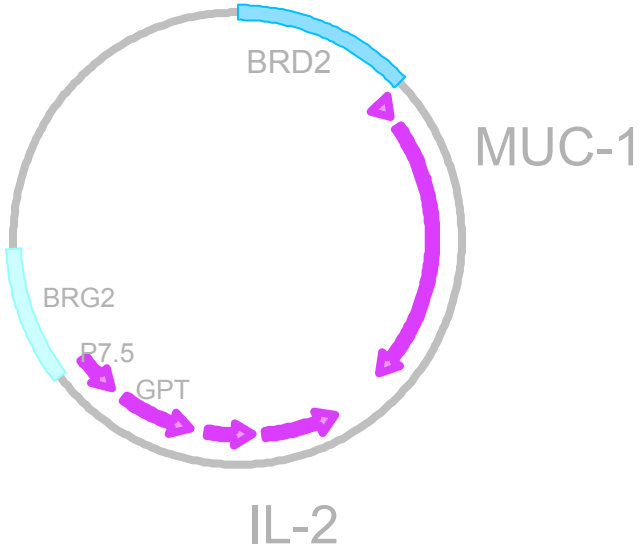
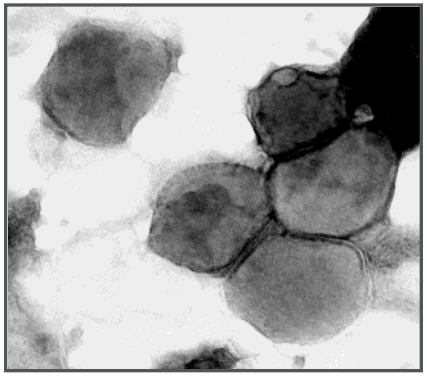
CANCER IMMUNOTHERAPY

- Non specific Immunotherapy
  - Interferon
  - IL2
- Targeted Immunotherapy
  - Passive
    - Monoclonal antibodies (anti-CTLA4, anti-PD1)
  - Active
    - Therapeutic cancer vaccines

TG4010: BACKGROUND

- TG4010 is a targeted immunotherapy
- TG4010 is a recombinant Modified Vaccinia Virus strain Ankara coding for MUC1 tumor-associated antigen and IL-2





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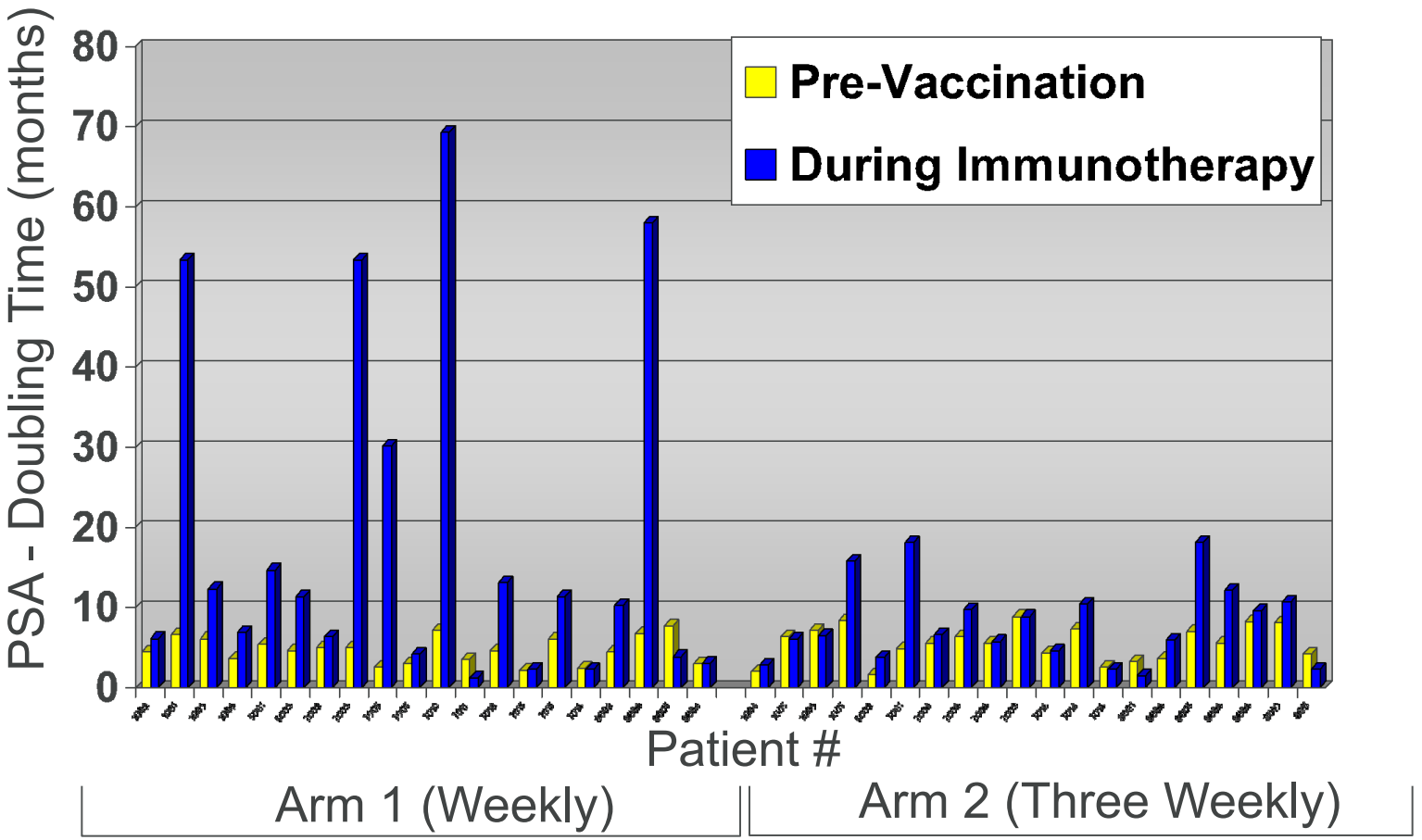
CLINICAL EXPERIENCE WITH TG4010

2 Phase I and 5 Phase II studies, with a total of 345 patients

Study Code	Phase	Country	Indication	Pts No	Status C: completed O: ongoing	
TG4010.01	I	US	Advanced cancers	3	C	2000
TG4010.02	I	CH	Advanced cancers	10	C	1999
TG4010.03	II	US	Prostate cancer (biological failure)	40	C	2002
TG4010.04	II	BE, FR, CH	Metastatic breast cancer	42	C	2002
TG4010.05	II	BE, FR, CH, PL	Advanced NSCLC	65	C	2002
TG4010.06	II	BE, FR	Metastatic renal cell carcinoma	37	C	2003
TG4010.09	IIB	FR, DE, PL, HU	Advanced NSCLC	148	O	2005-

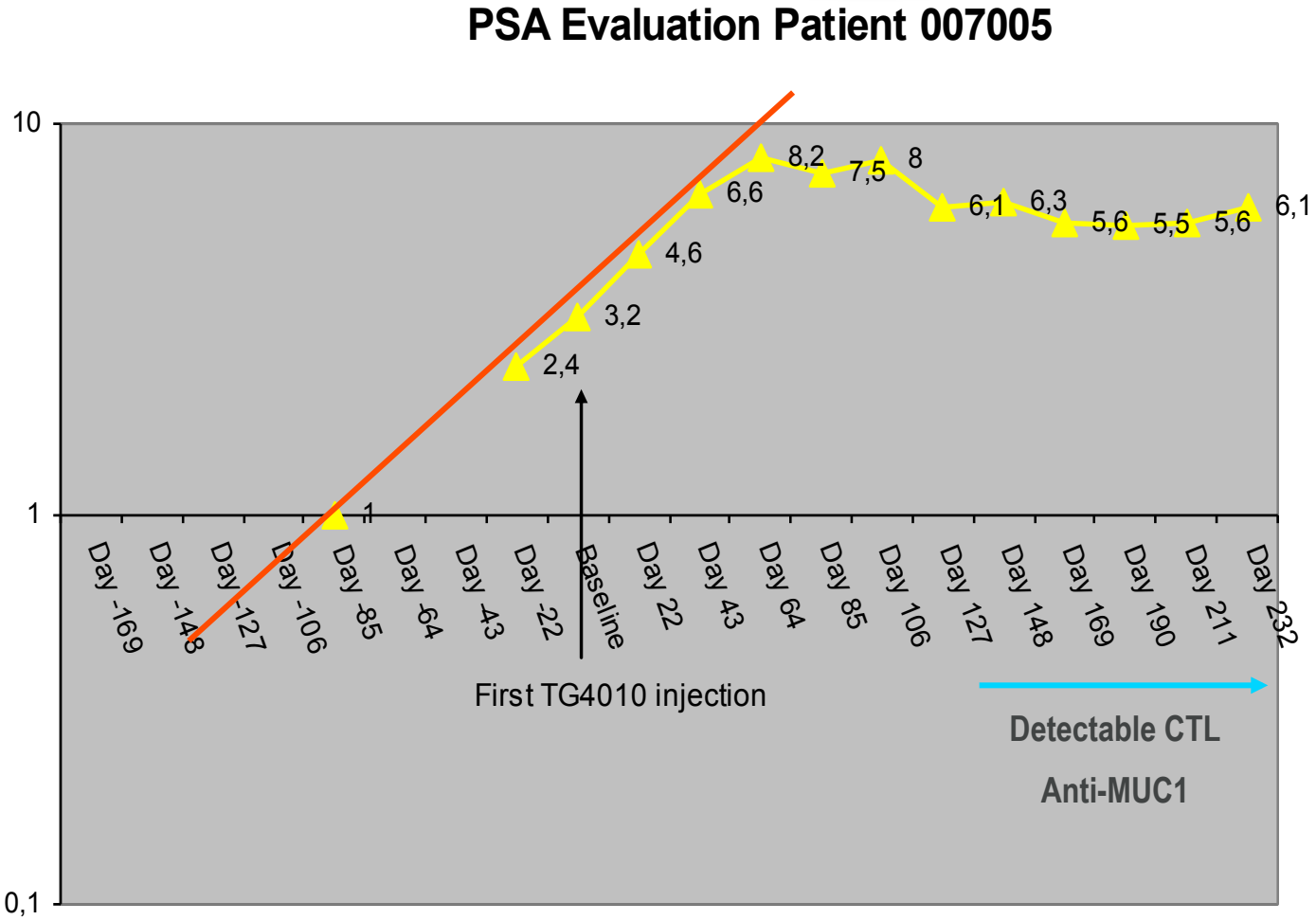
TG4010.03 PATIENT PSA-DT



PSA-DT calculated using the Memorial Sloan-Kettering Cancer Center Website calculator

Interinm data analysis, April 2005

TYPICAL PSA RESPONSE



NSCLC – TG4010 PHASE II STUDY

- ✓ Arm 1 : Combination chemo + TG4010
  35 evaluable patients

- ✓ 11 PD
- ✓ 13/35 (37%) PR (validated by central reading)
- ✓ 12/35 (34%) SD > 12w

→ 25/35 (71%) Disease Control

- ✓ TTP: 6.4 months
- ✓ OS: 13 months

TG4010 : PHASE IIB STUDY TG4010.09 IN ADVANCED NSCLC

148 patients randomized
Stage IIIB "wet" / IV; PS 0-1
No previous treatment for advanced disease
MUC1 positive tumor by IHC (≥25% cells)

Randomization

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

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

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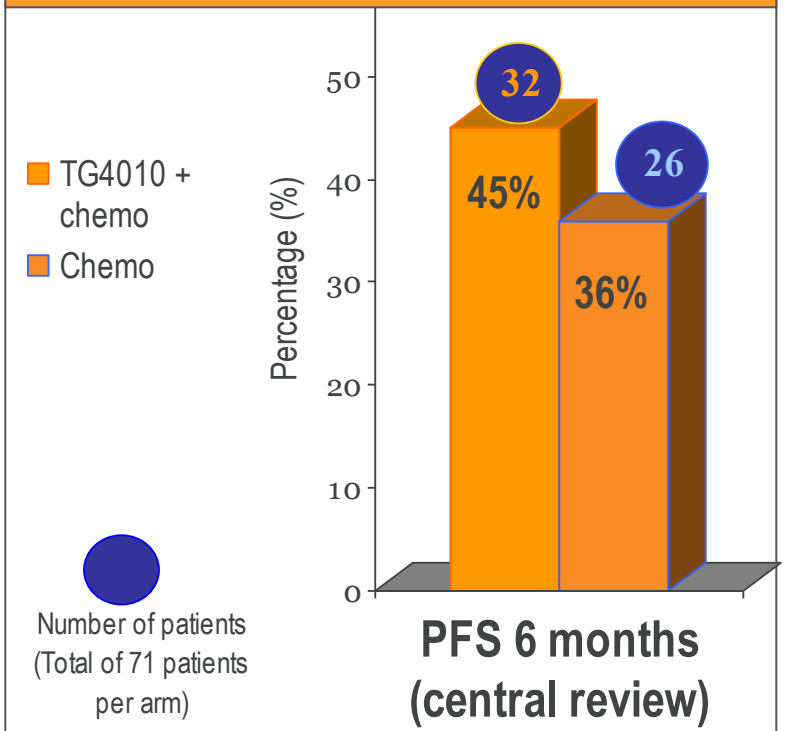
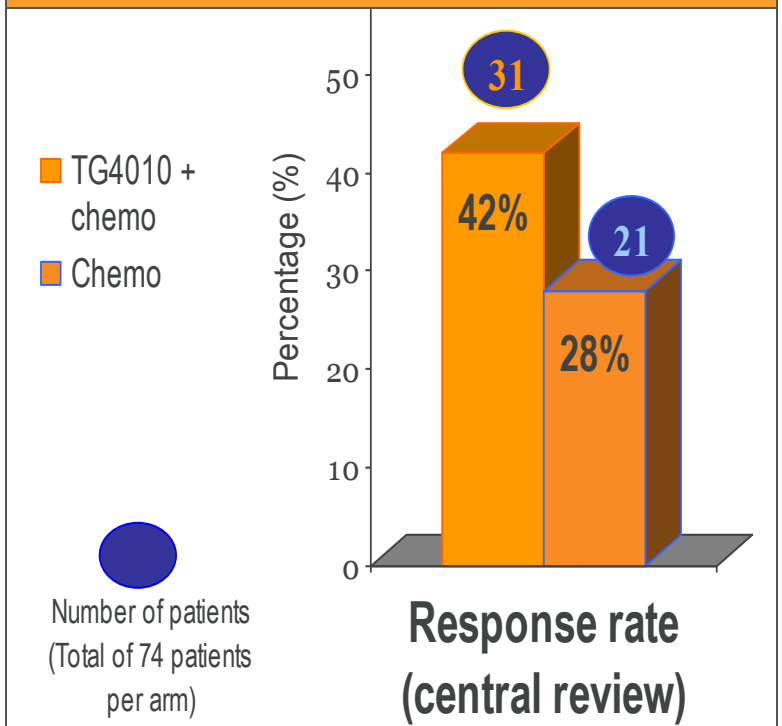
TG4010.09 : EFFICACY RESULTS

6 months PFS in overall study population (142 evaluable patients at 6 months)



p=0.3

RR in overall study population (ITT population: 148 patients)



p= 0.08

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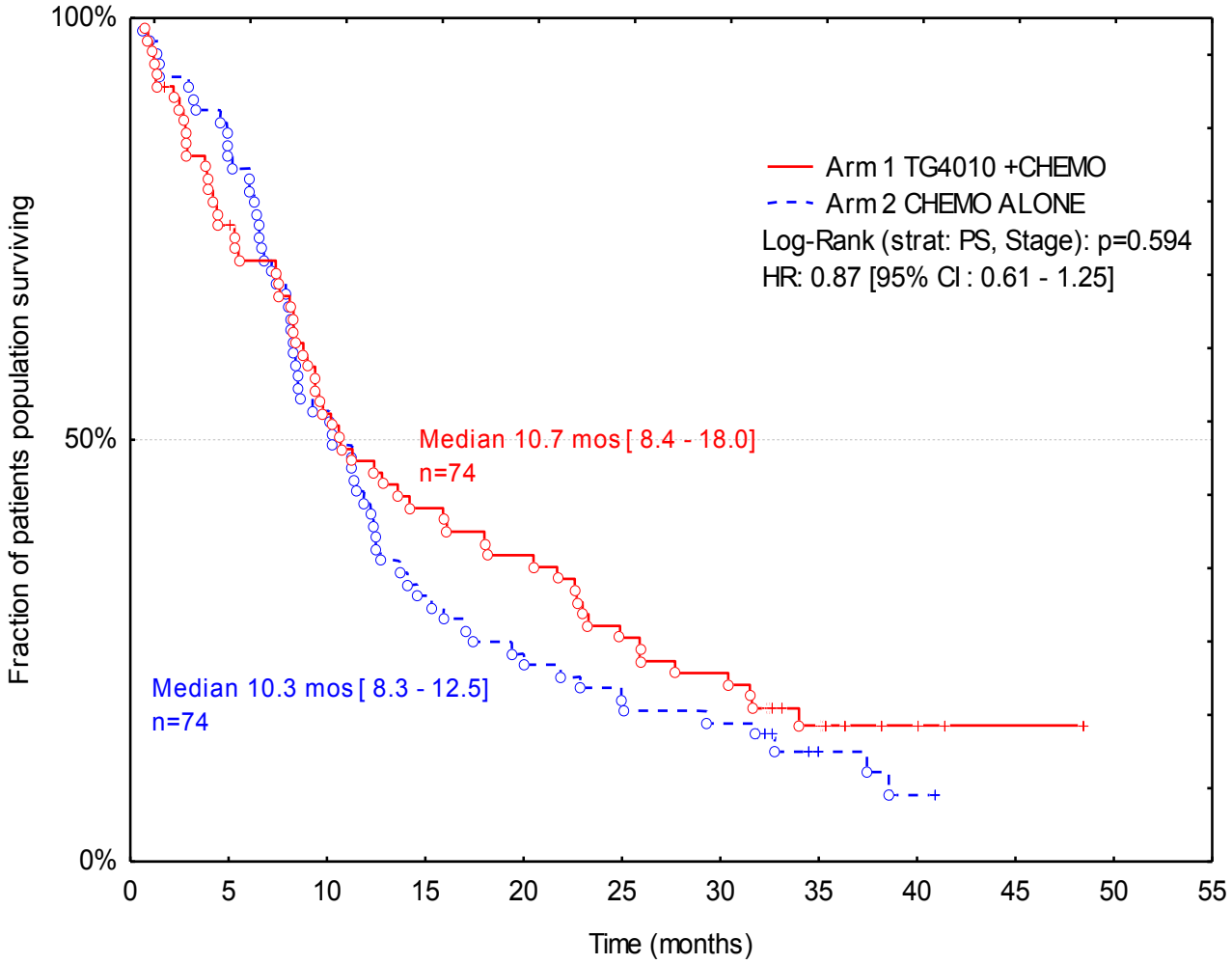
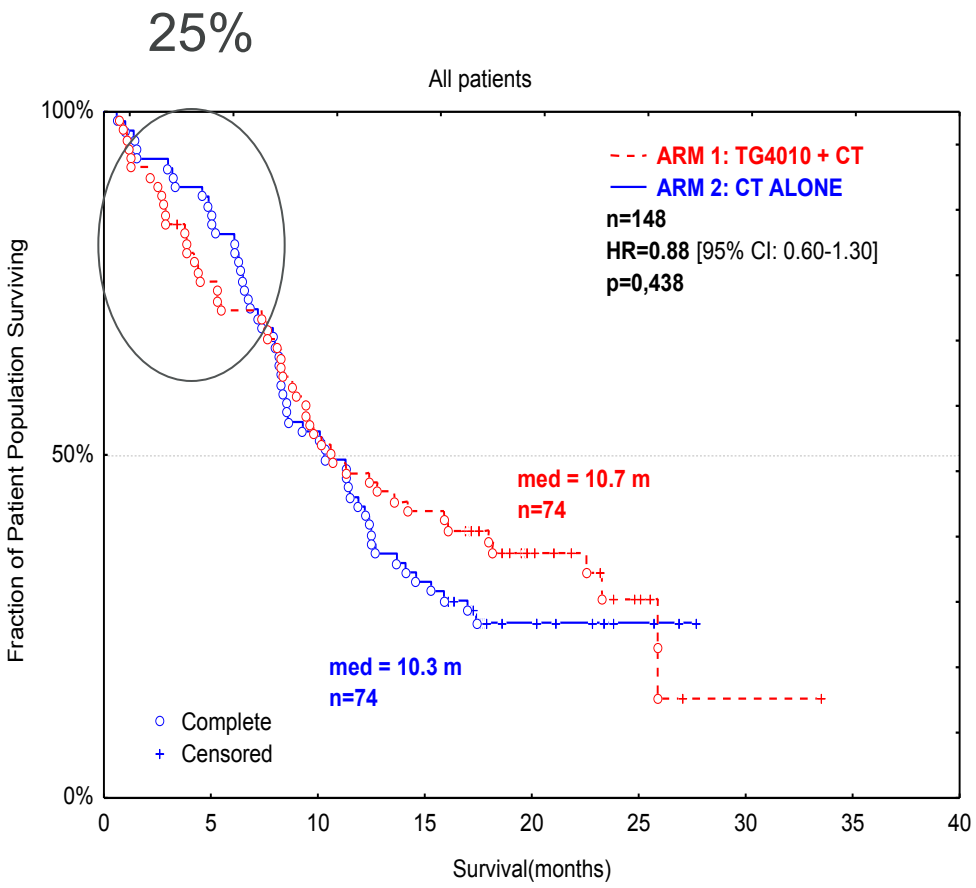
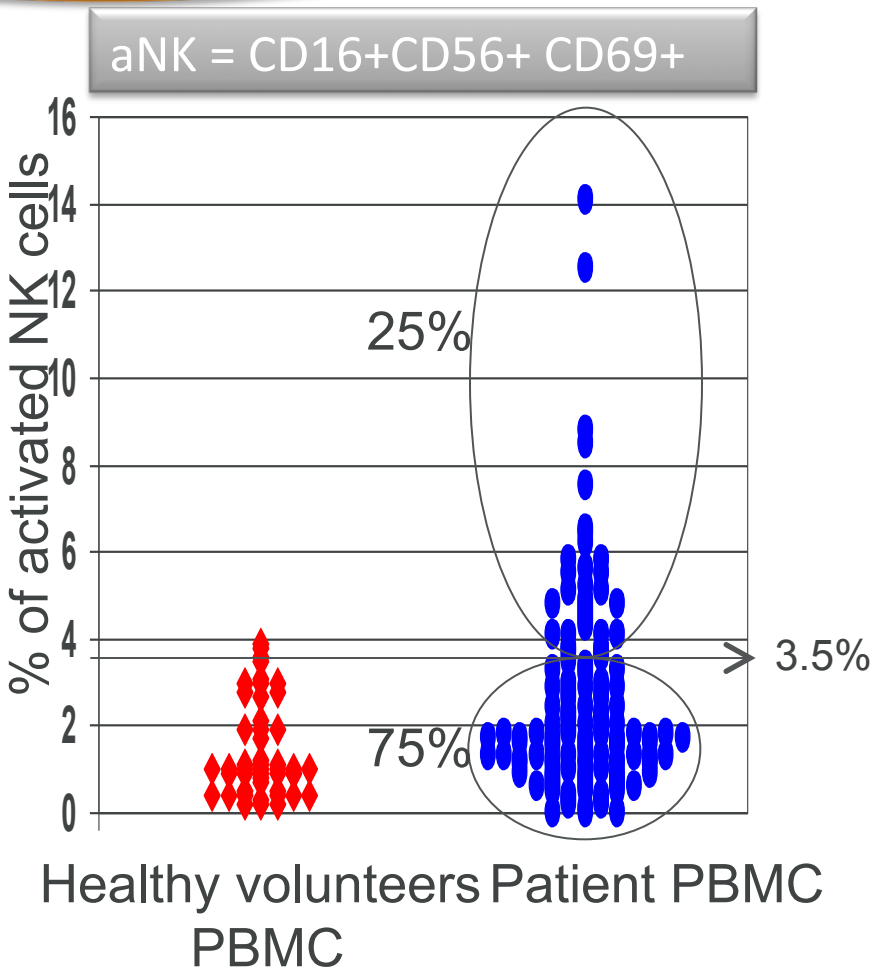
TG4010.09 OVERALL SURVIVAL IN WHOLE STUDY POPULATION

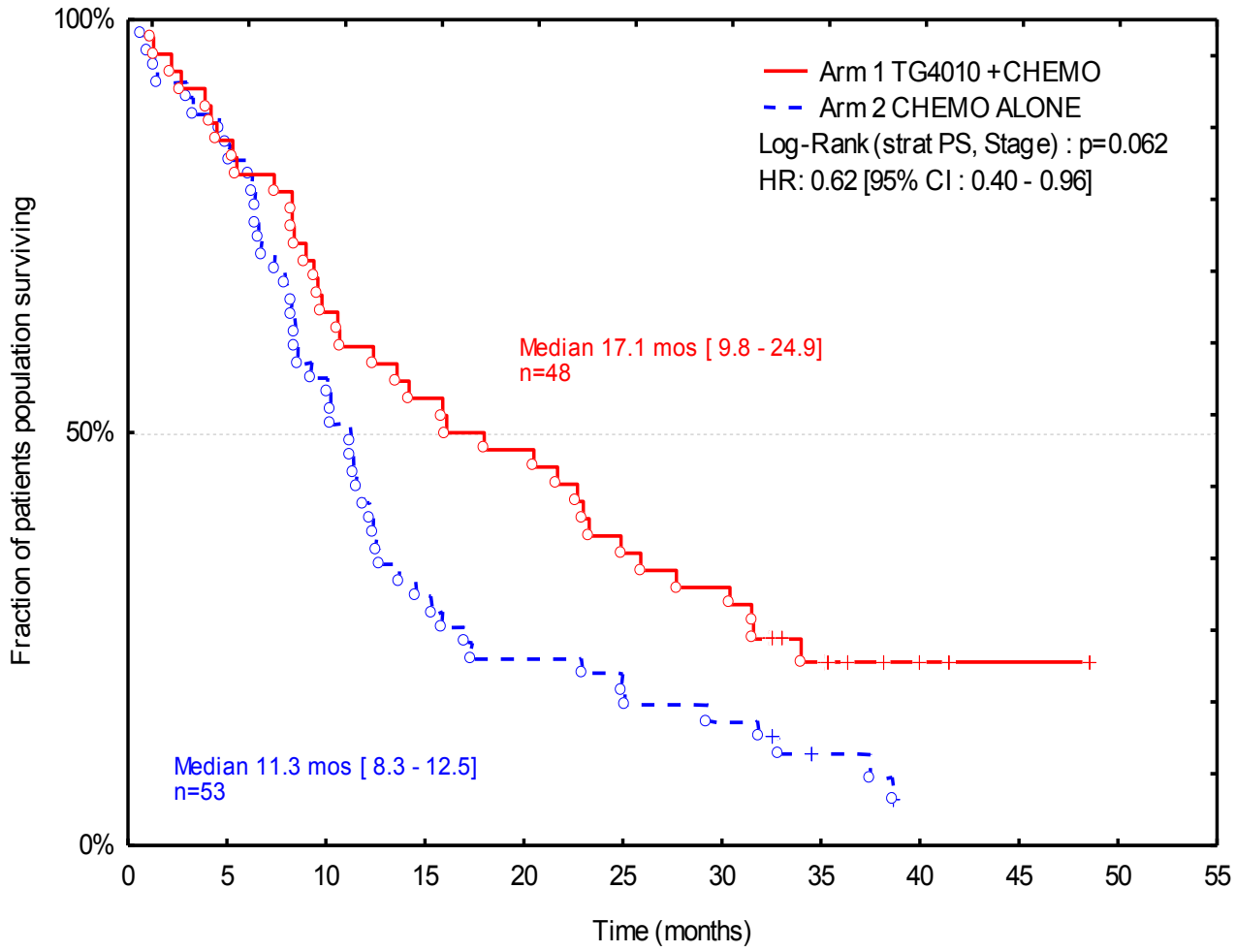


EARLY SAFETY SIGNAL: CORRELATION WITH ACTIVATED NK CELLS



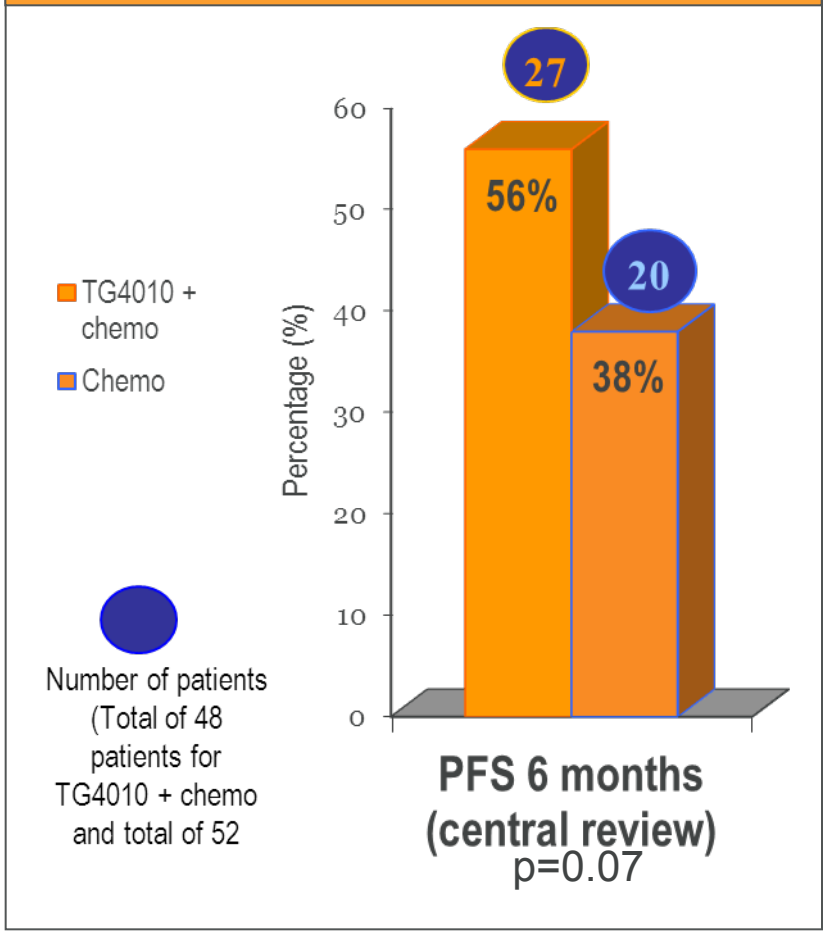


TG4010.09 OVERALL SURVIVAL IN PATIENTS WITH NORMAL LEVEL OF aNK

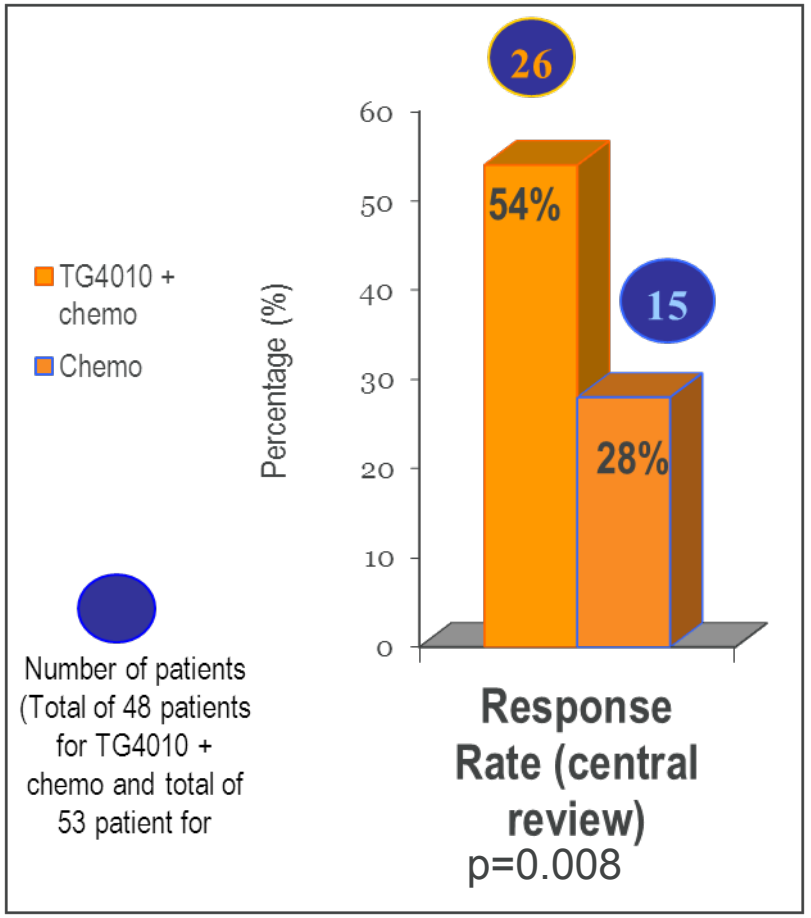


PFS AND RR IN PATIENTS WITH A NORMAL LEVEL OF ANK

6 months PFS in patients with normal level of aNK cells at baseline (101 pts)



RR in patients with normal level of aNK cells at baseline (101 pts)



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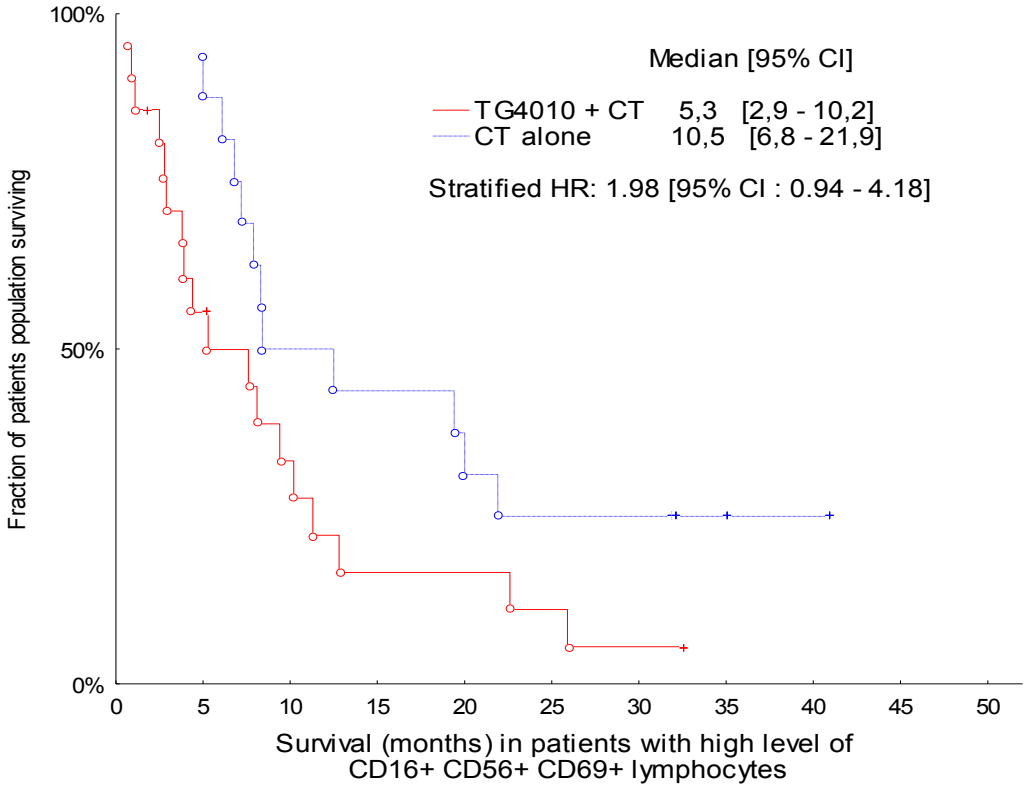
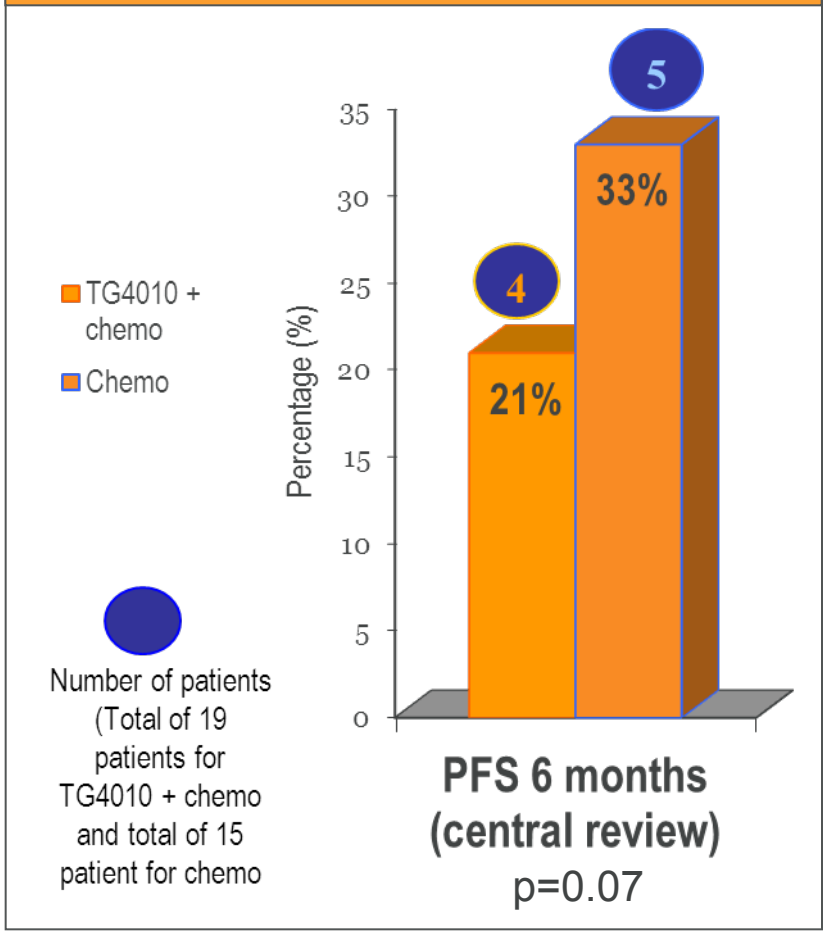
TG4010.09 OVERALL SURVIVAL IN PATIENTS WITH HIGH ANK

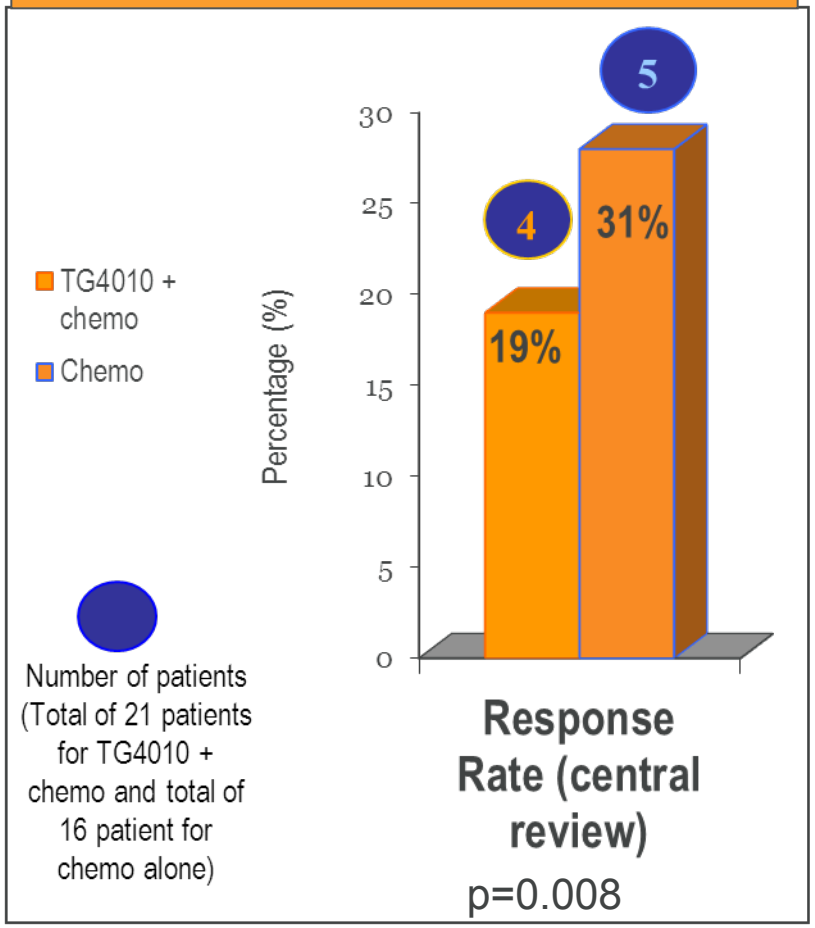


PFS and RR in patients with a high level of aNK

6 months PFS in patients with high level of aNK cells at baseline (37 pts)



RR in patients with high level of aNK cells at baseline (37 pts)



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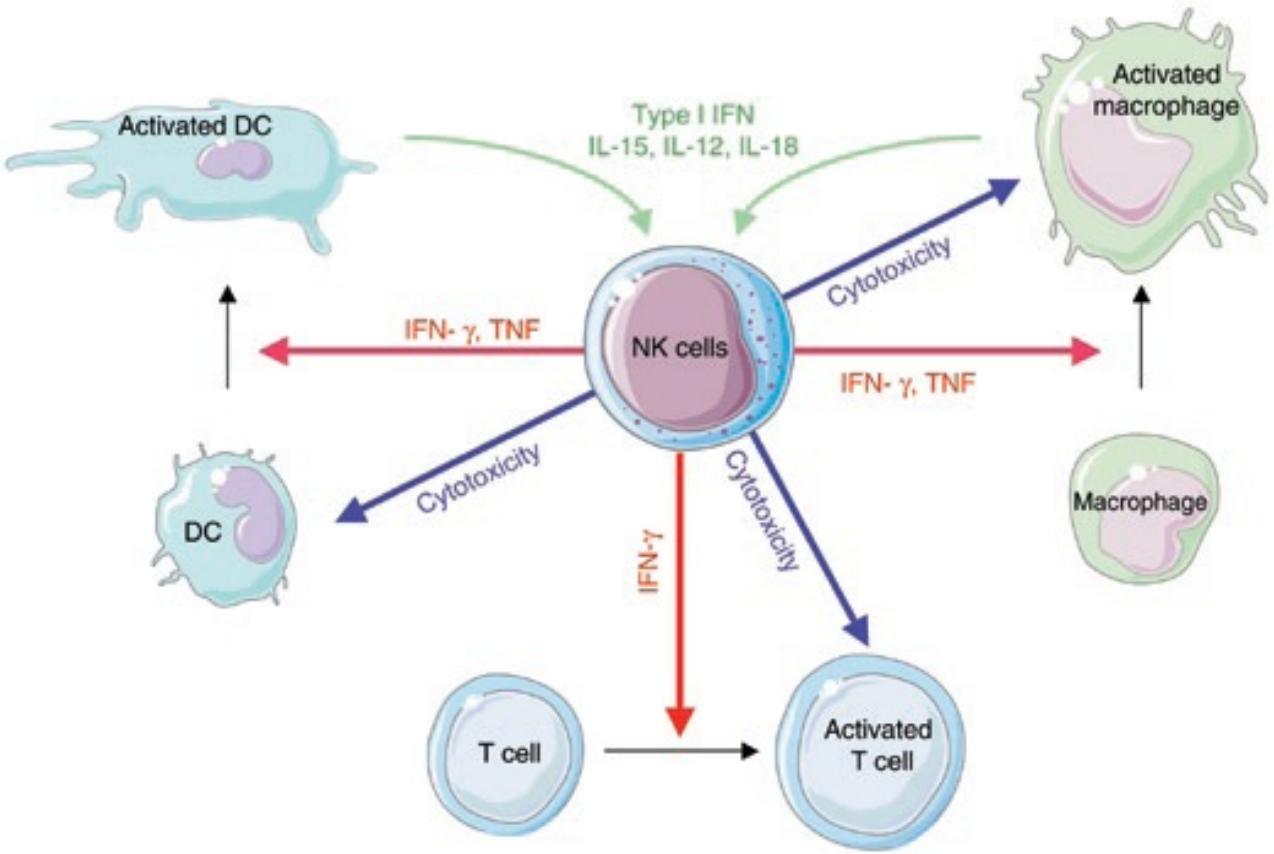
NK CELL IMMUNOREGULATORY ACTIVITIES



From: Vivier *et al*, Nature Immunology 9 (5), 503:10 (2008)

PLASMA PROTEINS BEFORE TREATMENT

Day 1 Plasma Protein	Study Arm	Median Survival (months) Patients with NORMAL Plasma Content	Median Survival (months) Patients with ABOVE Normal Plasma Content	Log-rank p-value
sCD-54	TG4010 + CT	24.5	8.5	0.0001
	CT alone	12.3	8.9	0.07
IL-6	TG4010 + CT	22.6	9.4	0.009
	CT alone	17.0	8.6	0.018
M-CSF	TG4010 + CT	22.7	9.1	0.03
	CT alone	11.8	8.5	0.22

Better survival is associated with normal levels of several inflammatory-associated proteins before treatment especially in patients treated with TG4010

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ON-GOING PHASE IIB/III « TIME »

- Phase IIB part 200 patients
  - Primary endpoint = PFS
  - Prospective validation of the TrPAL biomarker (triple positive activated lymphocytes)
  - Assessment of TG4010 in combinations of chemotherapy not yet tested
- Phase III part 800 patients
  - Primary endpoint = OS
  - Pivotal
- Study launch: April 2012

Background on TrPAL cut off determination

- In the previous clinical study **TG4010.09** the potential predictive value of the TrPAL biomarker was observed with a **quartile approach**, and the limit between Q1-3 and Q4 was observed to be close to the **upper limit of normal (ULN)** determined on a set of healthy volunteers.
- In the study TG4010.09 the determination of TrPAL was performed in batches on **frozen PBMCs** while in the TIME study the analyses have to be performed real-time on **whole blood samples** in order to enable randomization. **A new method** was developed.
- The new method has required the definition of a **cut-off value** for the classification of the patients in the study TIME
- ULN was used to classify in both genders the patients at randomization. The ULN was determined with blood from US and EU healthy donors using the new method.
- An **analysis by quartiles was pre-specified** in the statistical analysis plan
- FDA raised the possibility that the cut-off might need to be tweaked before phase III part based on phase IIb part results

PRELIMINARY RESULTS ON PRIMARY ENDPOINT – PFS

- With the cut-off based on Upper Limit of Normal phase IIB part of the TIME study, the study has not met its primary endpoint in normal TrPAL patients
- The ULN based cut-off used for classifying the patients in the phase IIB part of the study TIME, was too high (<20% classified as high TrPAL)
- The predictive value of the biomarker is to be assessed with a different cut-off.

PRELIMINARY RESULTS ON PRIMARY ENDPOINT – PFS

- A pre-planned analysis with a quartile approach was also used to classify patients in 2 subgroups, <Q3 TrPAL and >Q3 TrPAL at baseline.

- Stratified Log-rank test on PFS shows:
  - **A >25% reduction in the risk of progression in patients with <Q3** TrPAL (75% of the patients)
  - The benefit is even higher in the group with non-squamous tumors having not received bevacizumab
  - **A lack of benefit in the patients with >Q3 TrPAL (25% of the patients)**

- Those observations are consistent to what was observed in study TG4010.09
- Further sub-populations analyses will help to better define phase III study population

PRELIMINARY CONCLUSIONS AND NEXT STEPS

- TG4010 confirms its activity in NSCLC in combination with chemotherapy
- The TrPAL biomarker defines a population of patients benefitting from TG4010
- The safety of the vaccines confirms to be good
- Data of phase Iib part of TIME have been provided to Novartis
- Interactions with FDA regarding the technical and medical validation of the TrPAL biomarker
- Preparation of the phase III part of the TIME study, enrolment in this part of the study expected to be started by end of summer

THE NSCLC IMMUNOTHERAPY LANDSCAPE

Other therapeutic vaccines, main candidates

product	setting	status
Stimuvax (MUC1 peptide) Merck Serono	Maintenance of unresectable stage III after CT-RT	19 December 2012 : primary endpoint not met (START) Improved outcome in the subgroup of 806 patients with concurrent CT-RT (OS 30.8 vs 20.6m HR=0.78) => START2
Lucanix (cellular vaccine) NovaRx	Maintenance in stage IV after Ist line chemo	26 September 2013 : primary endpoint not met Improved out come in the subgroup of 305 patients with vaccination started before 12w after chemo (OS 20.7 vs 12.3m HR=0.75)
MAGE A3 + AS15 GSK	Adjuvant to surgery	20 March 2014 : 1st ans 2nd co-primary endpoints not met (MAGRIT) 3rd co-primary endpoint on patients with immune signature assessed in 2015

THE NSCLC IMMUNOTHERAPY LANDSCAPE

Immune checkpoint blockers

product	setting
Yervoy (anti-CTLA4) BMS	Phase III combo with 1st line chemo in squamous tumors
MK-3475 (anti-PD1) Merck	Phase I 21% RR Phase II/III in second line vs docetaxel
Nivolumab (anti-PD1) BMS	Phase I 18% RR Phase II second line vs docetaxel
BMS-936559 (anti-PDL1) BMS	Phase I 10% RR
MPDL3280A (anti-PDL1) Roche Genentch	Phase I 23% RR Phase II second line vs docetaxel

NIVOLUMAB PLUS IPILIMUMAB IN ADVANCED NSCLC

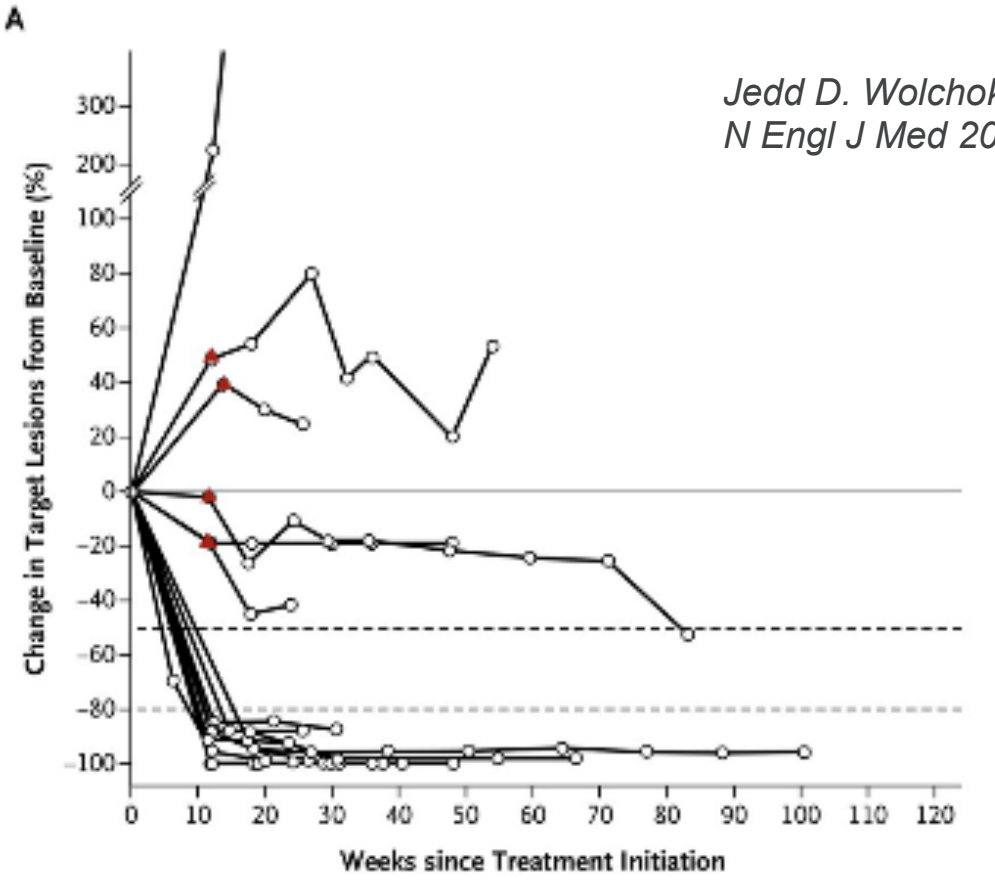
MARCH 05, 2014

BMS jumps to Ph.III lung cancer study

Bristol-Myers Squibb surprised analysts at the Cowen Health Care Conference Tuesday when it announced it was backing a Phase-III study that combines Yervoy and nivolumab for non-small cell lung cancer.

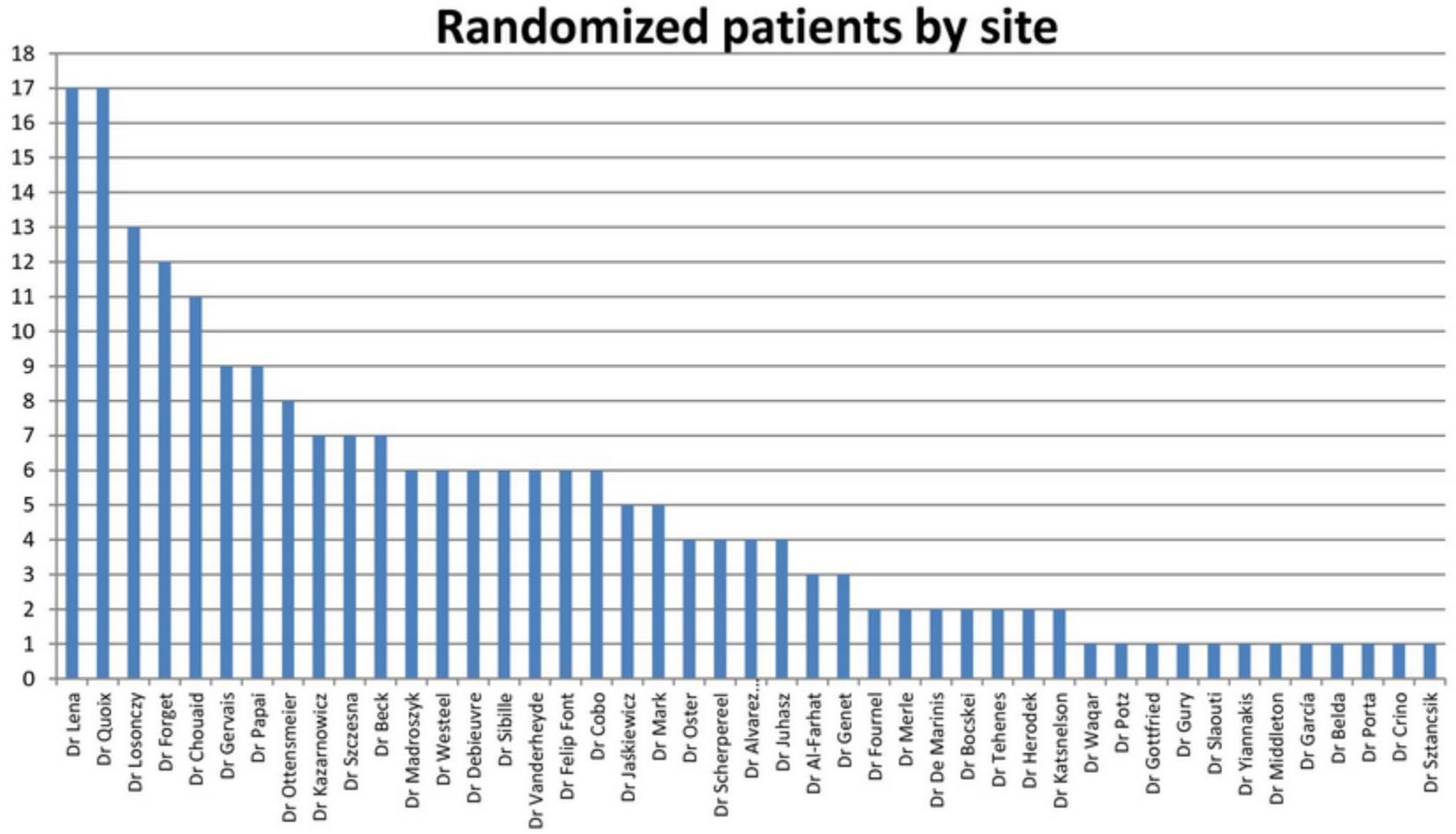
Analysts put weight on BMS in oncology

NIVOLUMAB PLUS IPILIMUMAB IN ADVANCED MELANOMA



Jedd D. Wolchok et al
N Engl J Med 2013; 369:122-133July 11, 2013

ACKNOLEDGEMENTS



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