



Developing new vaccines  
to fight cancer and infectious diseases

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Approches personnalisées dans le traitement du  
cancer du poumon métastatique

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Transgene

Association Technion France, 12 décembre 2011 - Paris

# AGENDA

**Transgene: a leader in the promising Therapeutic Vaccines Market**

Ongoing revolution towards Biomarkers and Personalized Medicine

Examples of biomarker programs benefit: economic evidence during clinical development

Summary - Conclusion

# Portfolio

CURRENT STATUS & NEXT MILESTONES	INDICATION	PRE-CLINICAL	PHASE I	PHASE II	LATE STAGE CLINICAL TRIALS	PARTNERSHIP STRATEGY		
TG4010 (MVA-MUC1-IL2)	Non Small Cell Lung Cancer ("NSCLC")						<b>Novartis</b>	Phase IIb/III in NSCLC to start <u>Q4 2011</u>
JX594/TG6006	Treatment of Hepatocarcinoma ("HCC") and Other Solid Tumors						<b>Jennerex</b>	Phase IIb in HCC <u>mid-2011</u> and Phase I/II in CRC in <u>H2 2011</u>
TG4001 (MVA-HPV-IL2)	Treatment of pre-cancerous lesions of the cervix (HPV16 virus)						New co-development partnership contingent on Phase IIb results	Phase IIb (CIN2/3) Interim data <u>Q4 2011 / Q1 2012</u>
TG4040 (MVA-HCV)	Chronic Hepatitis C ("HCV")						New co-development partnership contingent on Phase II results	Phase II in HCV Interim data <u>Q4 2011</u>

One of the largest portfolios of mature products in the European bio-space

Biomarker programs

# AGENDA

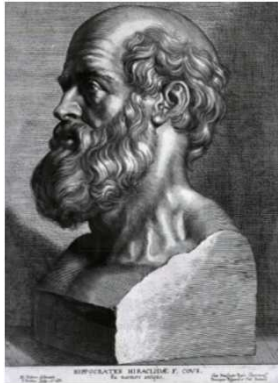
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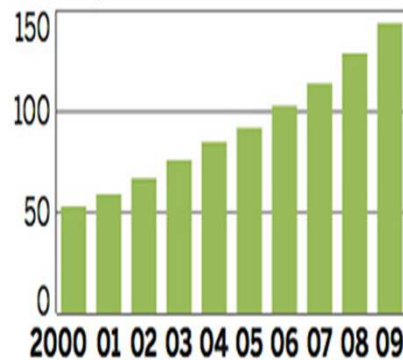
# A Long-Recognized Need with Compelling Drivers



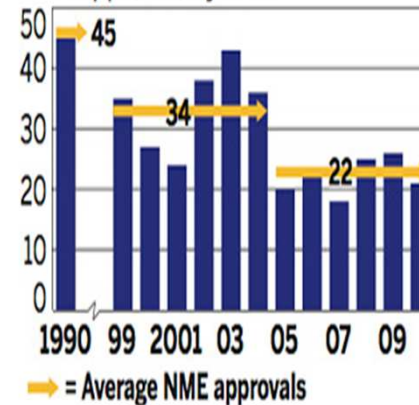
*It is more important to know what sort of person has a disease than to know what sort of disease a person has.*  
 Hippocrates, 460-370 B.C.

## **DIVERGENCE** As R&D spending rises, drug approvals are declining

R&D expenditure, \$ billions



NME approvals by FDA



NME = New molecular entity. SOURCE: CMS Pharma

# Major drugs ineffective for many, with a tremendous burden for Healthcare systems

Hypertension  
Drugs  
ACE Inhibitors

10-30%



Heart Failure Drugs  
Beta Blockers

15-25%



Anti Depressants  
SSRIs

20-50%



Cholesterol Drugs  
Statins

30-70%



Astma Drugs  
Beta-2-agonists

40-70%



Indirect Ineffectiveness  
cost

\$390 million - \$1.2  
billion

\$345 million - \$575  
million

\$2.3 billion - \$5.8 billion

\$3.8 billion - \$8.8 billion

\$560 million - \$1.0  
billion

Source: Spear B, Heath-Chiozzi M, Huff J *Clinical Trends Molecular Medicine* 2001; 7(5):201-4.

Personalized Medicine is a key driver for significant Healthcare savings ...

# General benefits of the biomarkers' approach

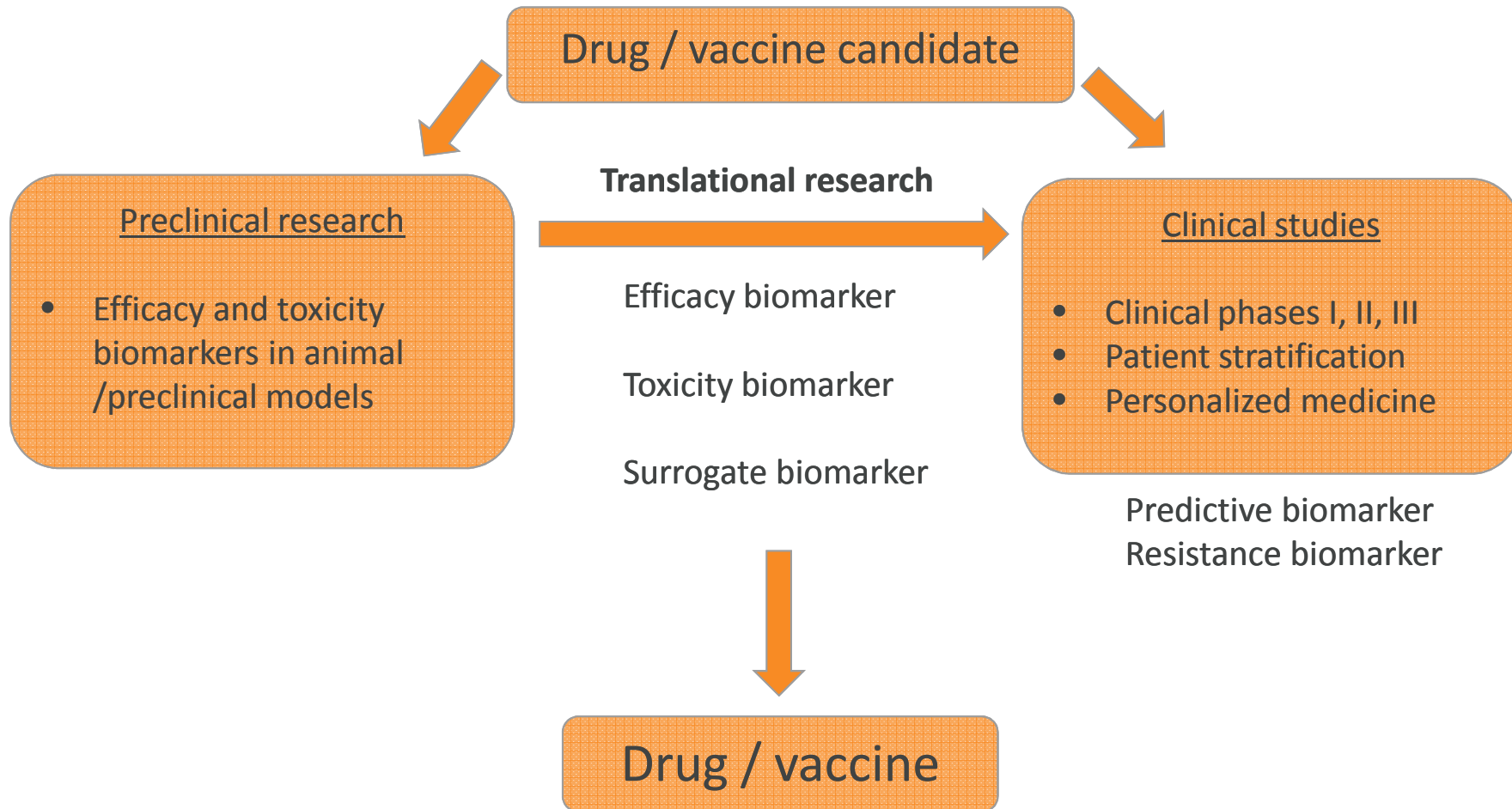
	Today	Tomorrow
Development time	10 to 12 years	5 to 7 years
Development cost	>1000M US\$	<500M US\$
Success rate	5 to 10 %	25 to 50 %
Number of patients/NDA	5175	< 2500

Source: Ross et al. Am J Clin Pathol 2003

- Clinical development with higher success rate, associated with no response in patients as potentially all patients tested might be responders
- Companion biomarker approach would change the traditional scales of development
  - the number of patients tested in phase II and III decrease without loss of statistical power
  - the duration of phase II would be reduced
- The elimination of ineffective / dangerous molecules at an earlier stage, would theoretically reduce the cost from ~1B\$ to potentially below 500M\$

Biomarkers' approach may be part of the solution of the intricate equation of Innovation in the pharma industry

# Usefulness of biomarkers in biomedical research



# Biomarker Discovery Strategy in clinical studies

## ➤ Some Key Considerations

- Planned and prepared during the clinical study set-up
  - Consistent with the believed mechanism of action of the investigational drug or intervention...
  - ...but not only focused on it, « think outside the box »
  - Allow for additional complementary analyses
    - ICF wording clear and precise but open to additional analyses « in the field » if useful
    - Sample collection strategy allowing additional testings if needed
- ➔
- Multiple sampling occasions
  - Multiple sample types
  - Multiple technologies

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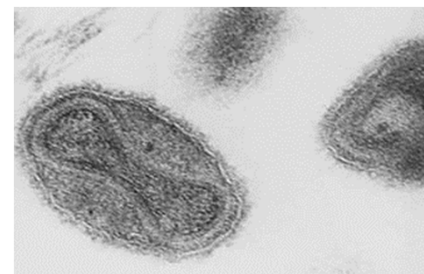
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**Examples of biomarker programs benefit: economic evidence during clinical development**

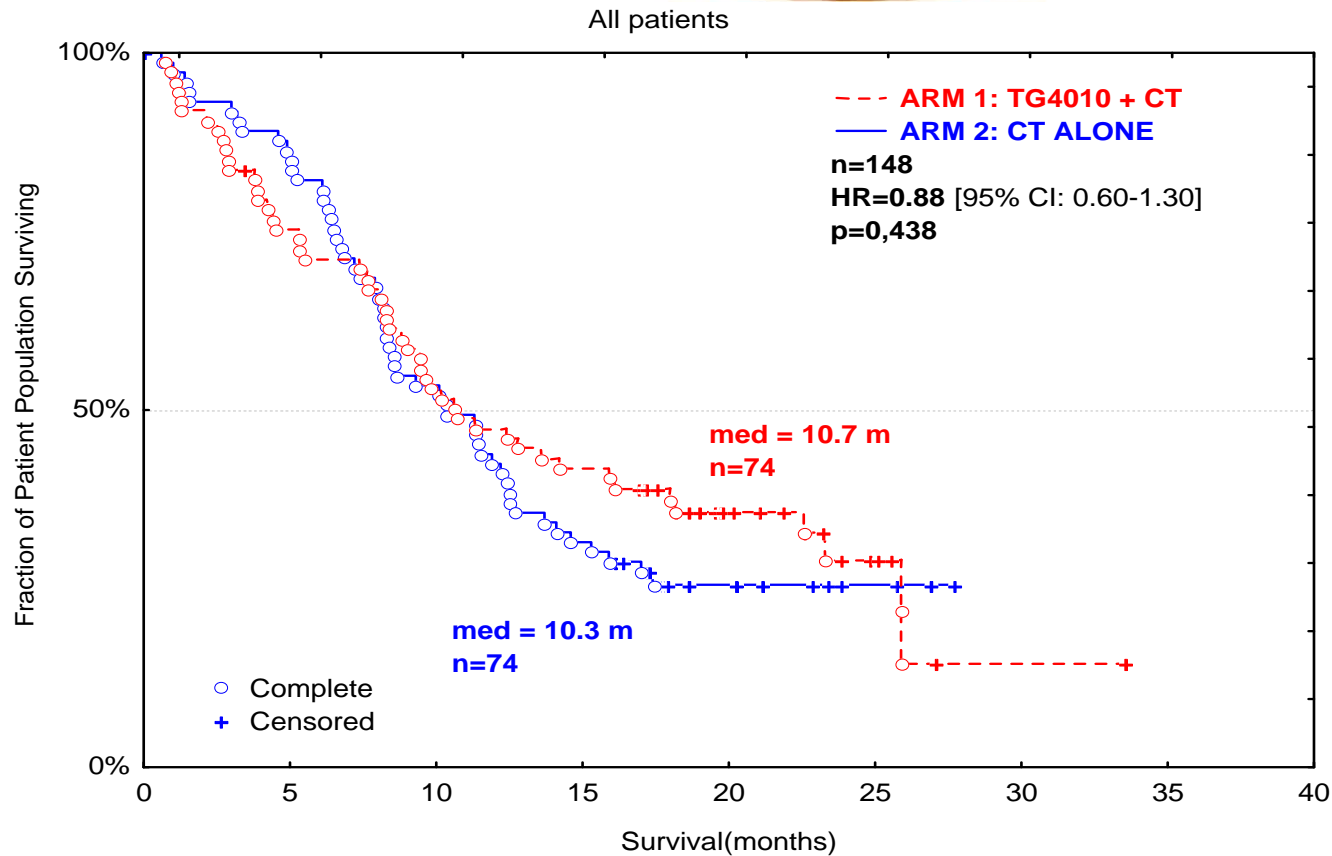
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# Biomarkers in clinical studies: case study

- **Vaccine candidate design: TG4010 (MVA-MUC1-IL2)**
- **Vector: Modified vaccinia Ankara (MVA)**
  - Belongs to the pox viruses family
  - non propagative virus: safely used in the 70's for pox vaccination (>100,000 people)
  - highly attenuated by over 500 passages in chick embryo fibroblasts
  - Stimulates a strong Th1 CTL response
- **Encoding for MUC1**
  - The Entire MUC1 molecule (N - VNTR - C)
  - All putative antigenic epitopes
- **Encoding for Interleukin-2**
  - Stimulation of T and NK cells



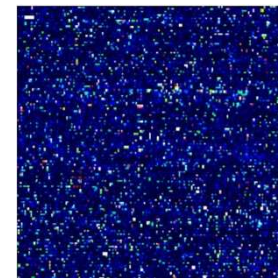
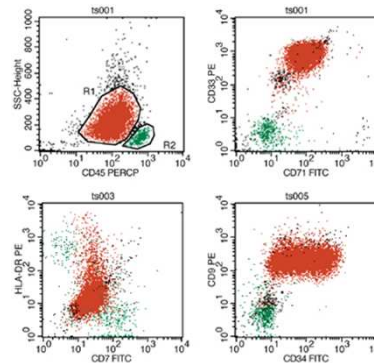
# TG4010.09 (Phase IIb): Overall Survival



Without any patient stratification, OS is very similar in 2 arms, at ~10-11 months

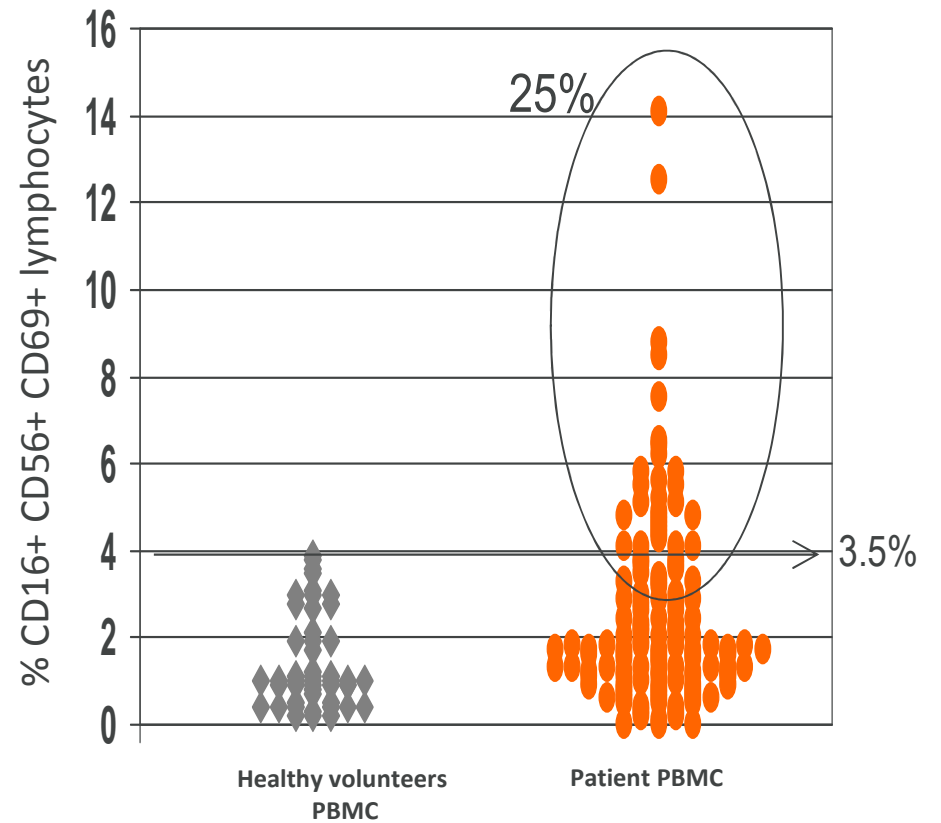
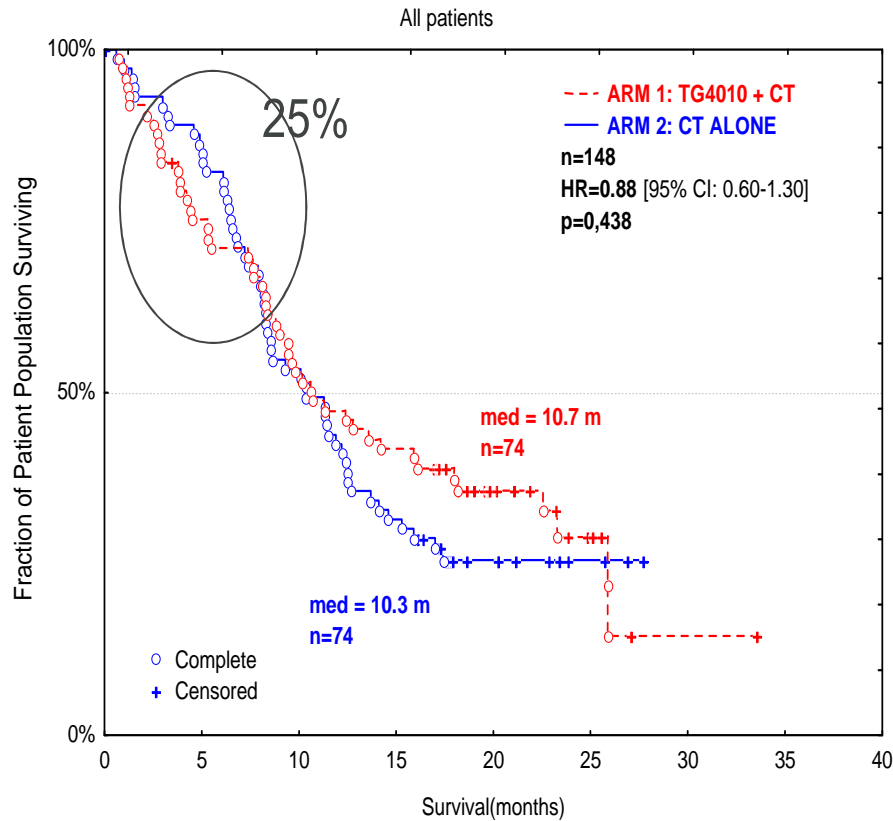
# TG4010 Phase IIb : biomarker program

- Immunohistochemistry
  - MUC1 positive cancers for patient inclusion (>25%)
- Determination of the specific immune response
  - MUC1 specific T cell response (ELISPOT), tetramers, specific antibodies
- Exploratory biomarkers
- Immunophenotyping
  - T Cells, activated T cells, NK, aNK
- Proteomics on plasma
  - Caprion
- Cytokine concentration in plasma
  - RBM
- Transcriptomics on whole blood (days 1, 43 and 85)
  - Affymetrix human U133 plus 2,0 on 69 patients



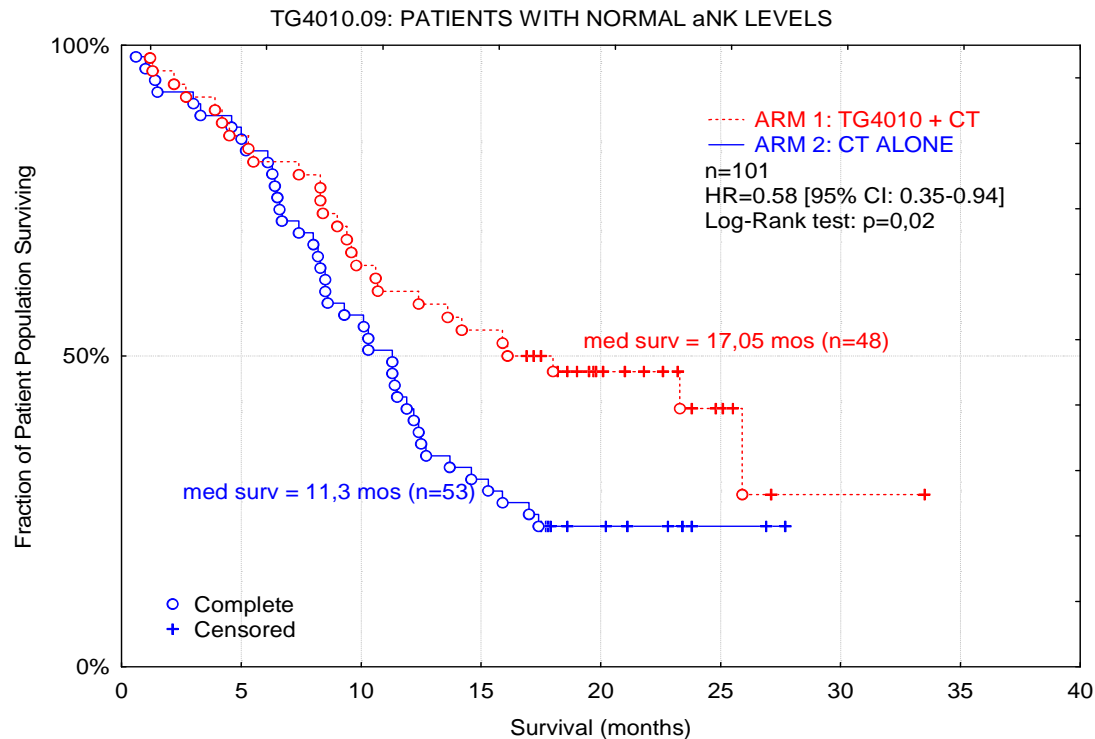
# Early safety signal

## Correlation with the level of activated NK cells in the experimental arm



aNK : CD16+ CD56+ CD69+ lymphocytes

# Results in normal aNK subgroup patients



- Safety issue identified in subgroup of patients with high levels of aNK cells at baseline
- Superior efficacy in normal level of aNK cell patients
- Benefit / risk favors exclusion of patients with high aNK in Phase III study

Identification of a candidate predictive biomarker for patients treated with TG4010 + chemotherapy: level of activated NK cells at baseline

# Costs and savings during clinical development

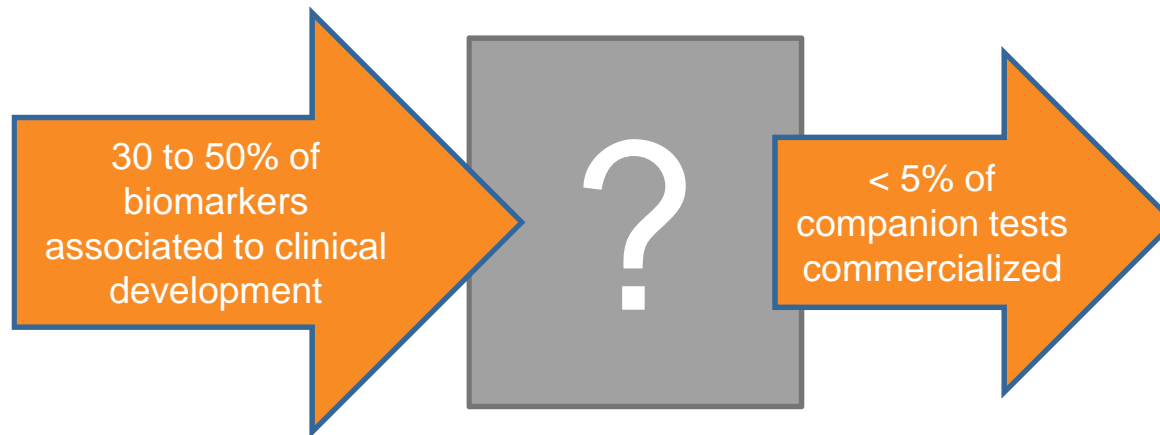
- Costs linked to the biomarker analyses & companion tests
- Companion tests development and validation : 5-10 M€ per CDx
  - MUC1 IHC test (Ventana) : IDE filled before beginning of phase IIb
  - aNK cells assay (BC) : IDE filed before beginning of phase III
- Testing on patients: 6675 US\$ per biomarker analysis in phase I oncology studies(\*)
- Set up of a dedicated team
  - Specialists in specific technologies, assay validation, regulatory affairs
  - Staff hiring and training
- Costs saved due to the companion tests
- Reduced trial size and duration
  - Better efficacy by selecting the responders population
  - Demonstrating a similar efficacy (HR – OS) without the CDx would necessitate > 1300 vs 800 patients
  - Reduced toxicity

(\*)Goulart et al (2004) *J Clin Oncology*, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 22, No 14S (July 15 Supplement), 2004: 6012

# Key factors for stratified medicine applicability

- **Three Key Factors**
  - Therapeutic effect across the population
  - Biomarker prevalence in the patient population
  - Companion Diagnostic Clinical Performance: power to separate high responders from low responders
- **Impact on the:**
  - Enrollment rate
  - Clinical study duration and cost
  - Diagnostics development duration and cost
  - Probability of technical and regulatory success
- **Several analytical tools exist:**
  - Pharmacogenomics Clinical Study Design tool (PCSD tool)
  - IMS Health personalized medicine strategy analysis tool
  - MIT model

# Attrition rate of biomarkers within the pipeline of pharma industry



- Utility/specificity in phase III
- Clinical performance of the biomarker
- Regulatory issues – intra-european and transatlantic harmonization
- Partnership model with Diagnostics companies

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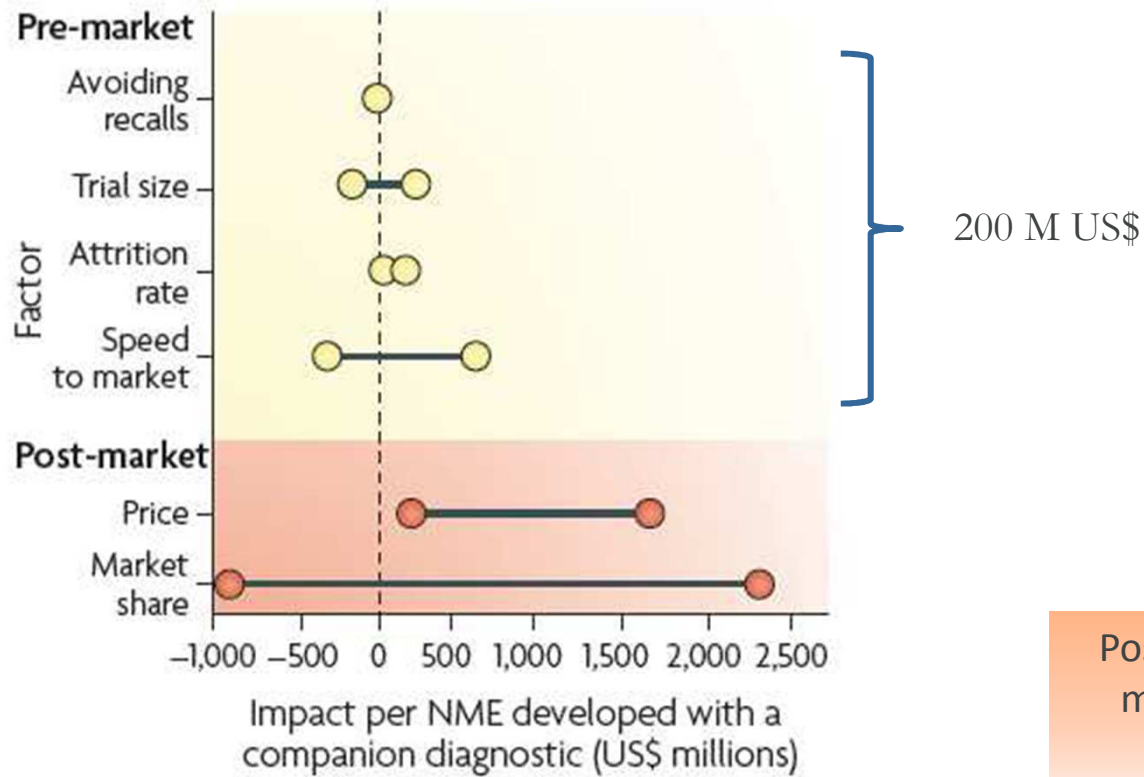
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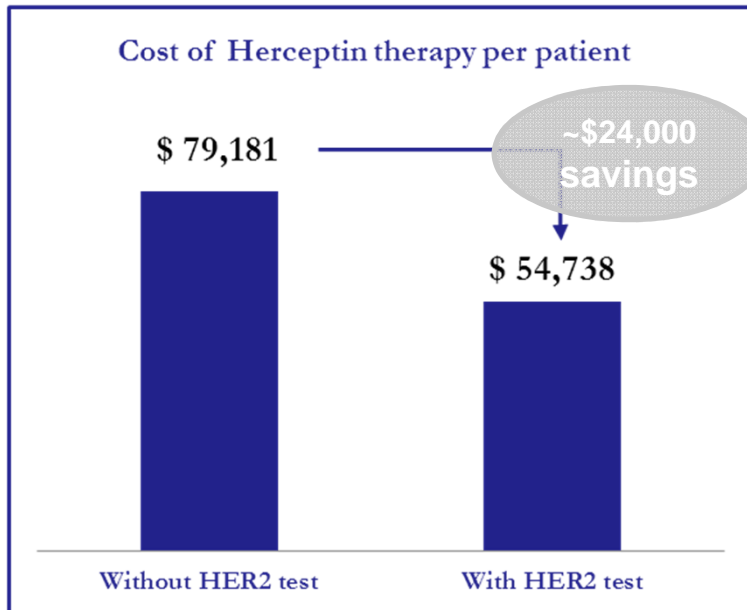
# Impact of CDx co-development



Davis et al (2009) Nature Rev Drug Disc 8: 279

# Herceptin – HER2 test - case study (US)

## Value based on health outcomes and savings



## Reimbursement based on CPT-codes

Price of HER2 testing per patient

CPT	Description	Fee
88368	Morphometric analysis, in situ hybridization (probe #1)	\$183
88368	Morphometric analysis, in situ hybridization (probe #2)	\$183
<b>Total</b>		<b>\$366</b>

\*As measured by FISH and reimbursed by CMS, Los Angeles, 2007 rates  
 Source: Elkin et al. HER-2 Testing and Trastuzumab Therapy for Metastatic Breast Cancer: A Cost-Effectiveness Analysis. J Clin Oncol (2004) 22: 854-863; Genzyme analysis

**HER2 test delivers healthcare savings that are ~65x its costs**

# Conclusion

- **During drug development, biomarkers can be used to:**
  - Improve the safety/efficacy profile of the drug candidates
  - Reduce the number of patients to include (stratification)
  - Reduce the attrition rate
- **The benefit is strongly dependent on:**
  - The therapeutic effect across the population
  - The biomarker prevalence in the patient population
  - The biomarker clinical performance
- **The most important benefit is obtained post-approval**
  - Improve market access condition
  - Extend the market



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