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Developing new vaccines
to fight cancer and infectious diseases

Regulatory processes & best routes for Drug/ CDx success

CIMT/ Mainz
16 May 2013
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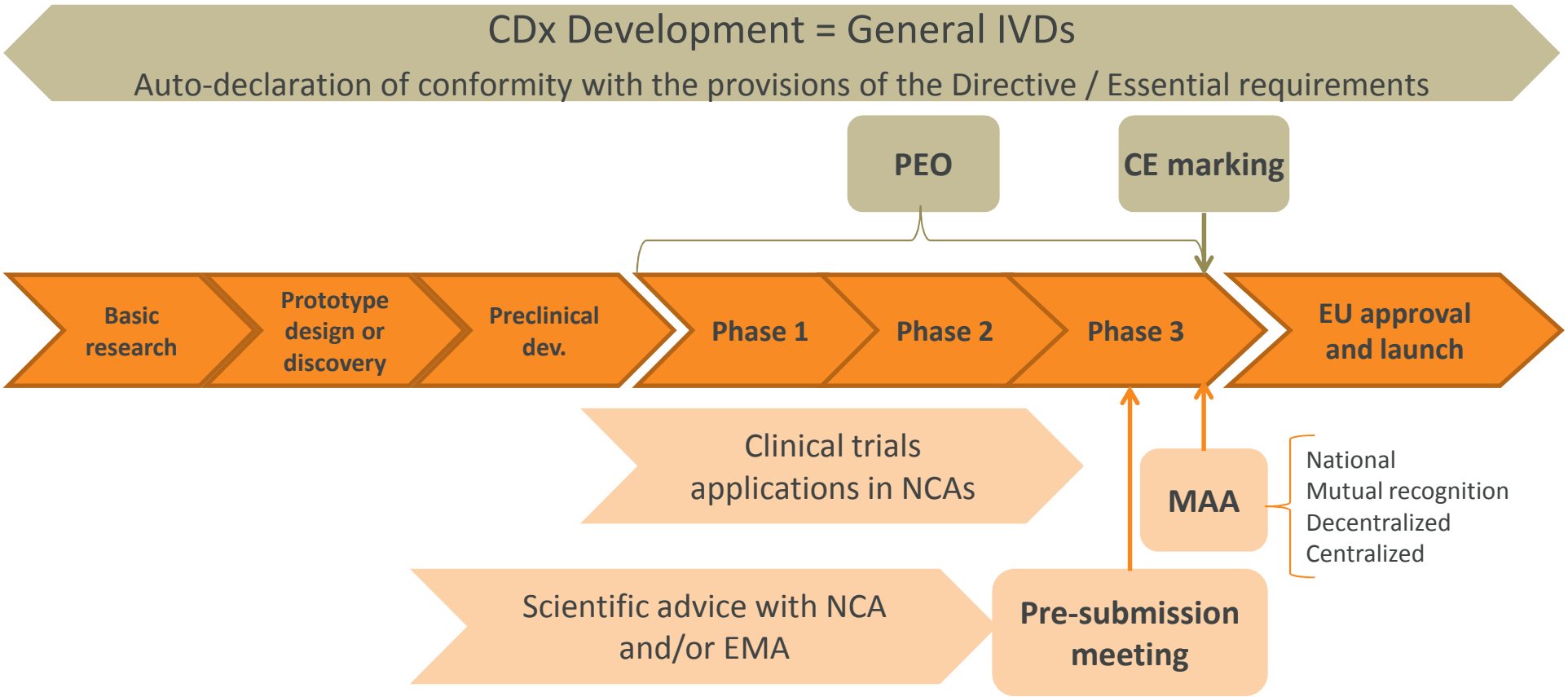
Agenda

- Drug/CDx regulatory processes
- Case study : TG4010/CDx project at Transgene
- Drug CDx co-development challenges
- Best routes for Drug/CDx success

Drug/CDx regulatory process in Europe



Drug/CDx regulatory process in the US

CDx Development = Class III IVDs

Pre-submissions

Pre-IDE meeting

IDE Significant risk trials

PMA application

Basic research

Prototype design or discovery

Preclinical dev.

Phase 1

Phase 2

Phase 3

US approval and launch

Pre-IND meeting

End of Phase 1 meeting

End of Phase 2 meeting

IND

Amendments

NDA BLA

Pre-NDA/BLA meeting

Drug Development

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TG4010

- Targeted cancer immunotherapy
- Recombinant Modified Vaccinia Virus strain Ankara coding for MUC1 tumor-associated antigen and IL-2
- Indicated for first line treatment in combination with first line therapy in patients with advanced non-small cell lung cancer

TG4010 / CDx models

- Triple positive CD16/CD56/CD69 lymphocytes (aNK phenotype) flow cytometry assay

  - Predictive biomarker
  - Patients with normal aNK level before treatment can benefit from TG4010 treatment
  - Cut-off: upper limit of normal (ULN) in healthy donors

- MUC1 immunohistochemistry (IHC) assay

  - Selection biomarker
  - MUC1 = TG4010 target
  - Cut-off: ≥ 50% of tumor cells expressing MUC1

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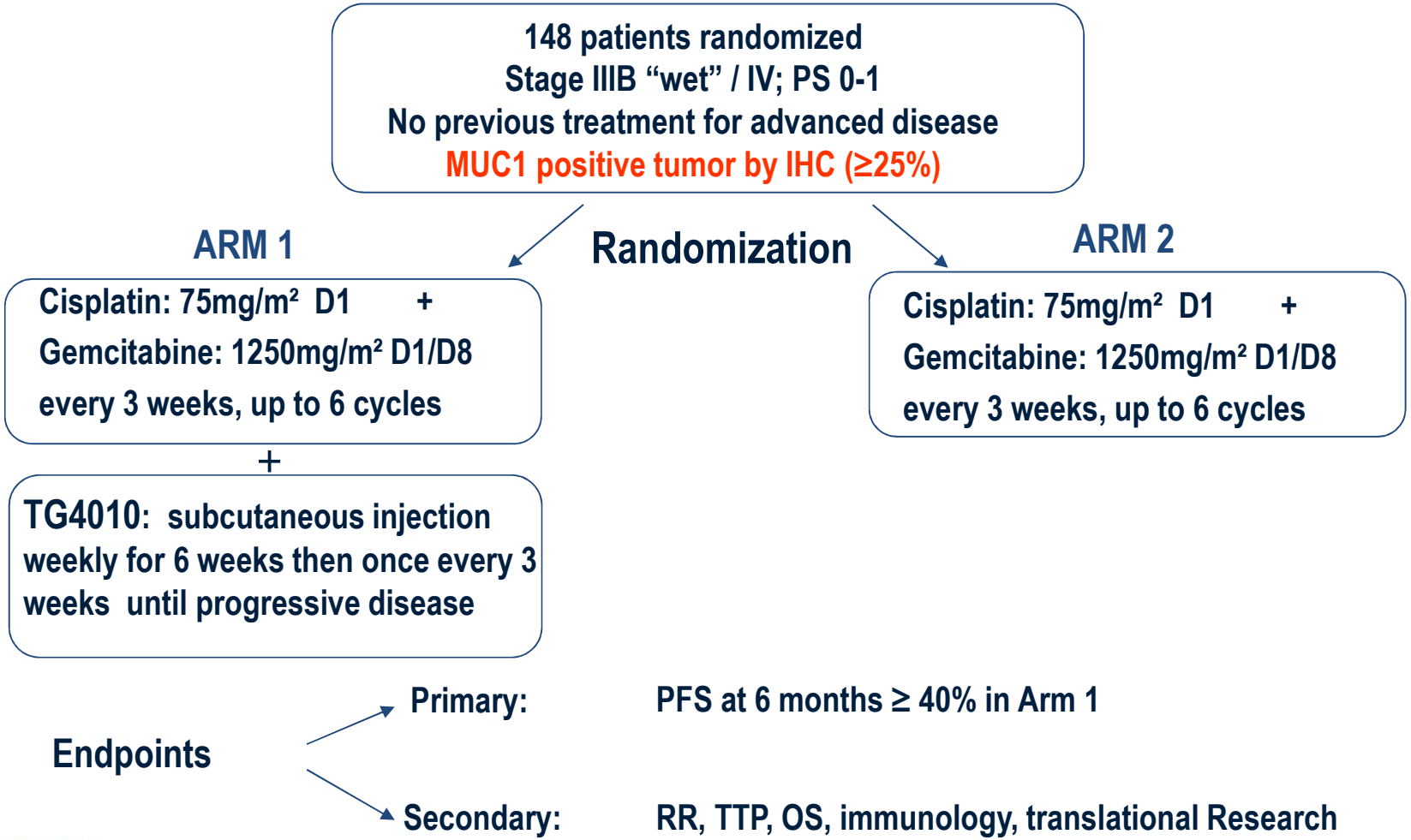
aNK biomarker identification

TG4010.09: Phase IIb Study Design



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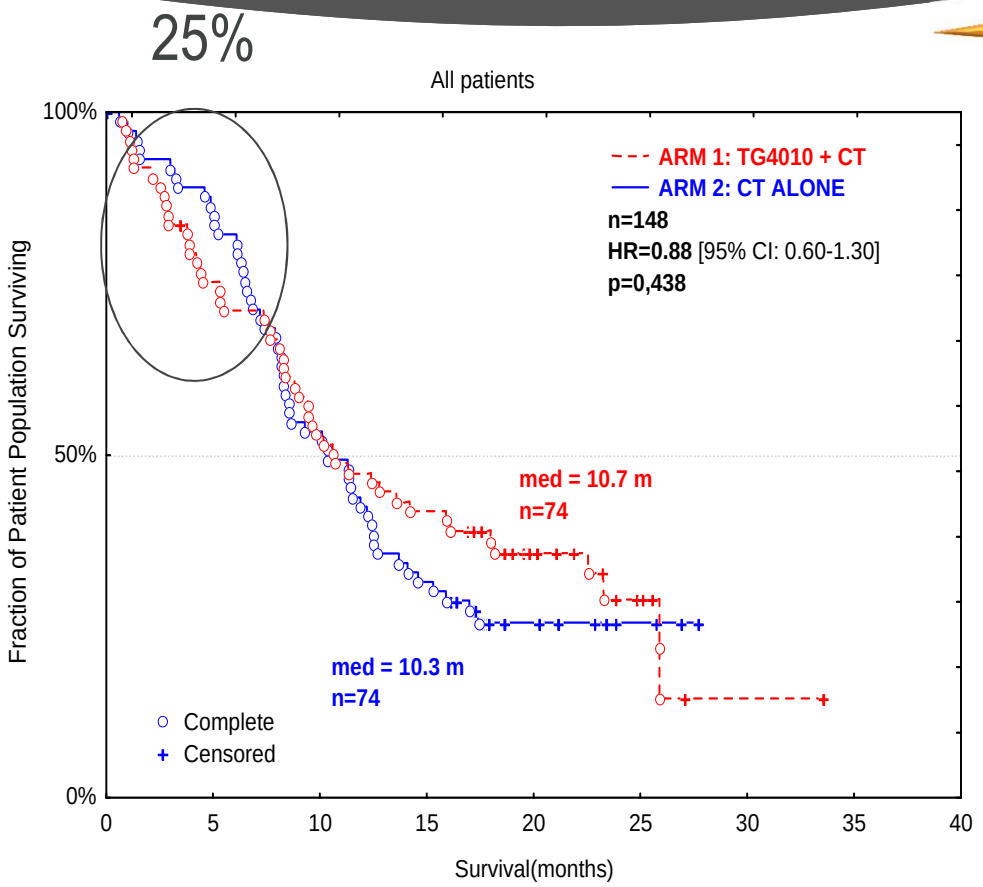
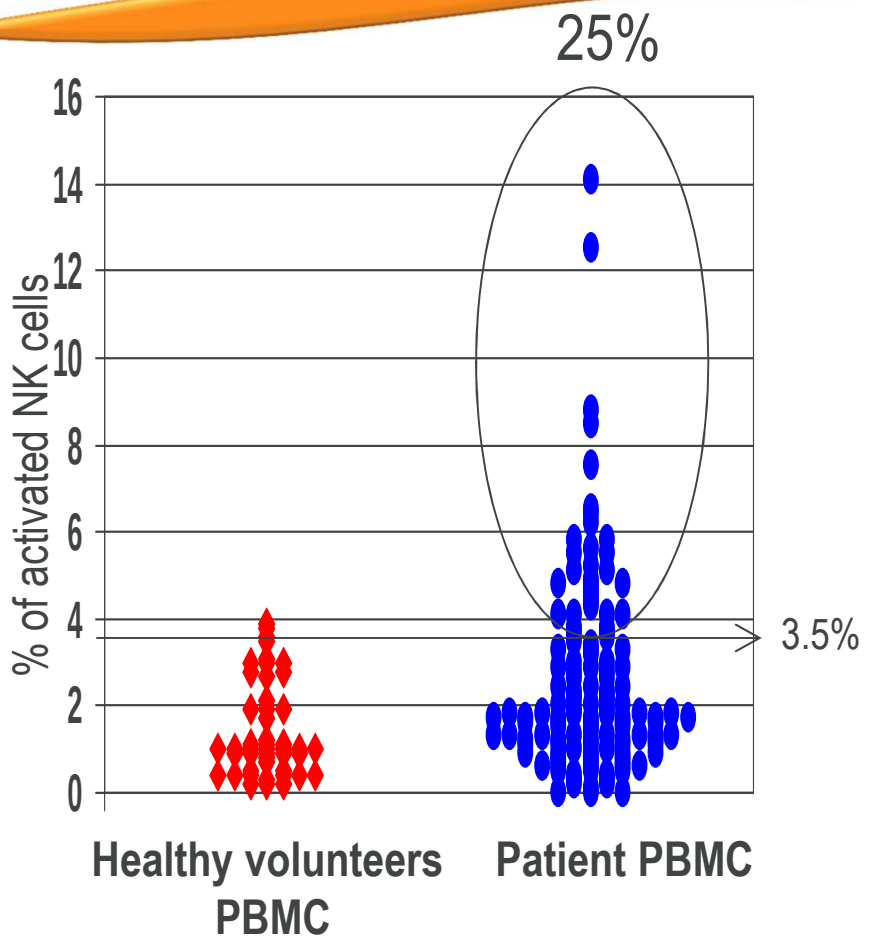
Early Safety Signal: Correlation with aNK Cells Level





The biomarker = level of CD16+CD56+CD69+ lymphocytes, a phenotype of activated natural killer (aNK) cells

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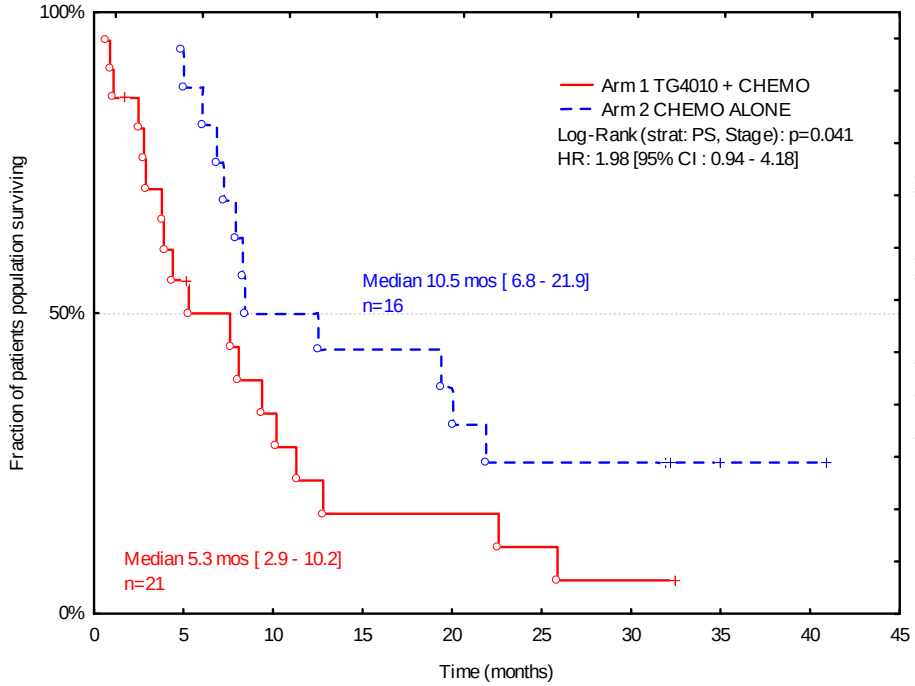
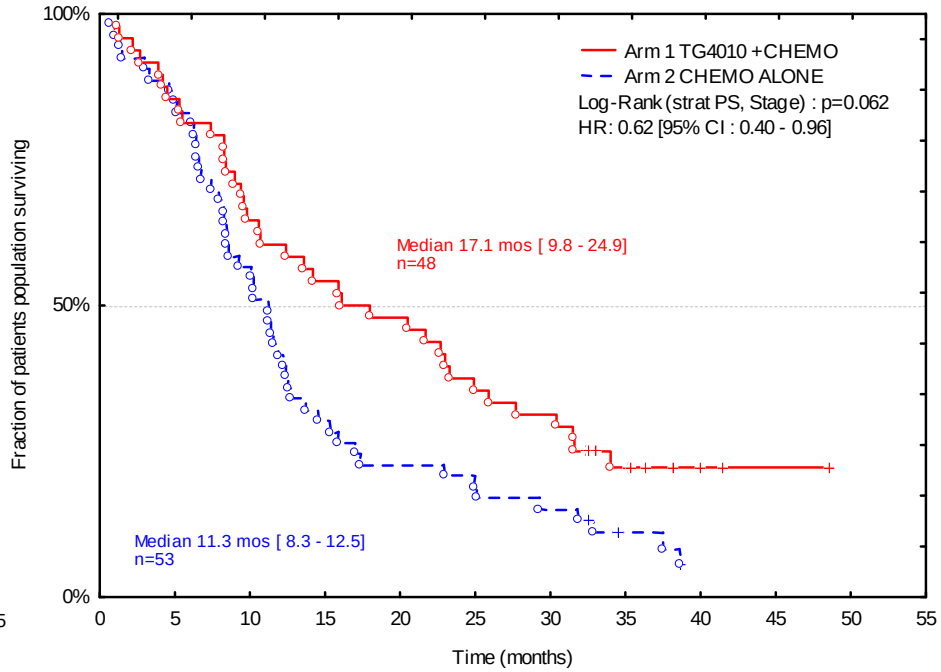
TG4010.09: Safety /Efficacy Consideration

Kaplan Meier curves for overall survival in patients according to aNK cells level before treatment

High aNK patients



Normal aNK patients



Drug/CDx Regulatory Interactions

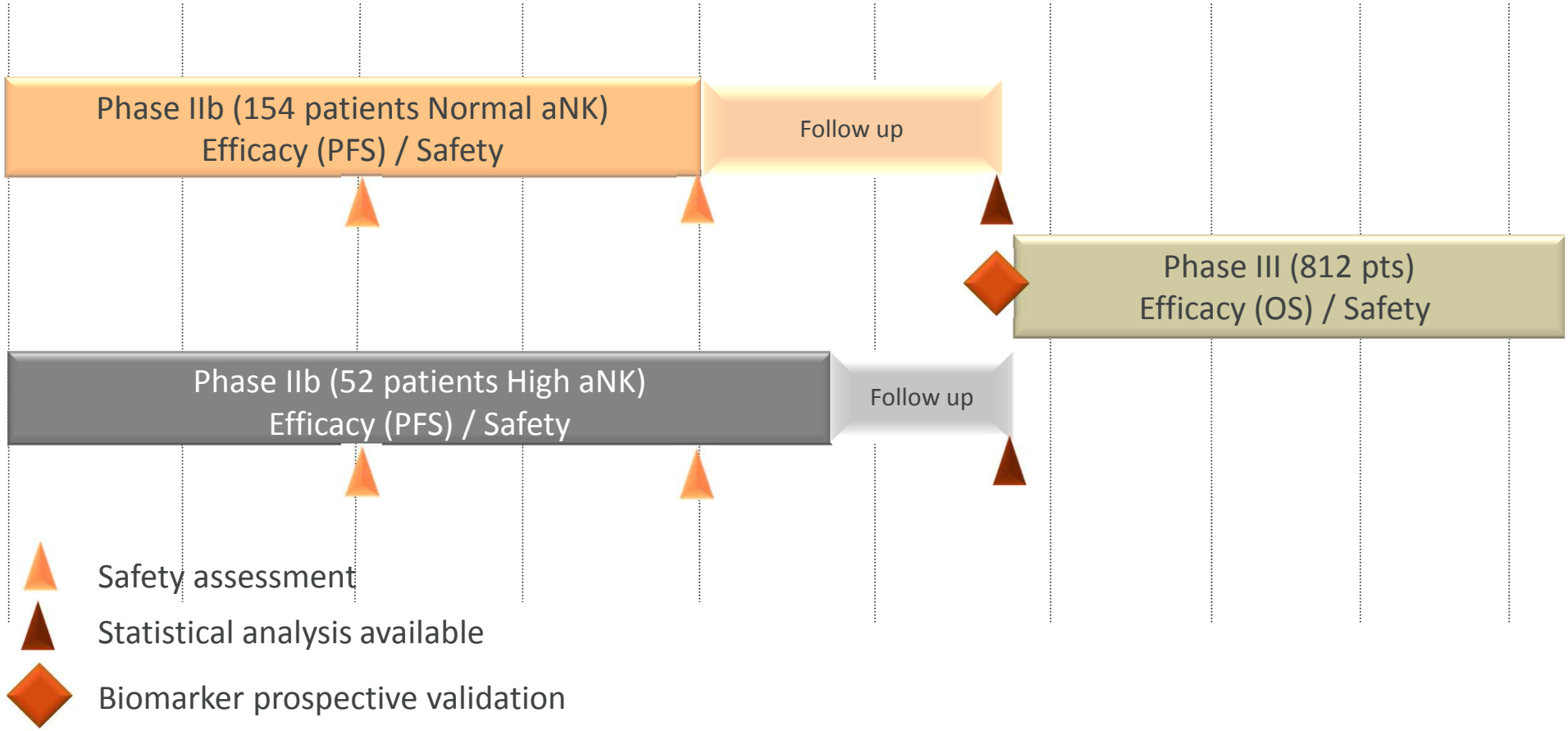
Pivotal Clinical Program

Reg Interaction	Design of pivotal trial	MUC1 IHC Assay	aNK Flow Cytometry Assay
CBER/CDRH **EMA**	Enriched Phase IIb/III study in patients with MUC1 expressing tumors & with normal levels of aNK at baseline	IVD company-developed assay for Phase IIb/III	Phase IIb: Transgene-developed assay Phase III: IVD company-developed assay
	Phase IIb designed to prospectively validate the use of normal baseline level of aNK as predictive biomarker Standard Phase III in patients with MUC1 expressing tumors & with normal levels of aNK at baseline		Phase IIb/ III: IVD company-developed assay

TG4010 project: EMA/ FDA Requirements

EMA	CBER/CDRH
Encourages enrichment trials once the biomarker-related safety/efficacy signal is detected Need prospective confirmation in a adequately defined subset of patients	Requires prospective validation of biomarker predictive value / clinical utility
CDx platform: Final design and validation before pivotal trial	
Biomarker role in the response to treatment for MAA/BLA	

TG4010.14 Design



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TG4010 & aNK CDx Regulatory Route

aNK assays	Research assay flow cytometry	Centralized flow cytometry CDx

Clinical protocols	**TG4010.09** Phase II Biomarker identification	**TIME study** Phase IIb Prospective validation of the use of normal baseline level of aNK cells as a predictive biomarker **In patients regardless of their aNK level**	**TIME study** Phase III Clinical data to support marketing of TG4010 and aNK CDx **Patient baseline aNK status depending on Phase IIb findings**

Pre-IDE (CDRH)
IND "new protocol" (CBER)

IDE (CDRH)

PMA
BLA

Performance evaluation only (CDx NCA)
Clinical trials applications (Drug NCA)

CE
MAA

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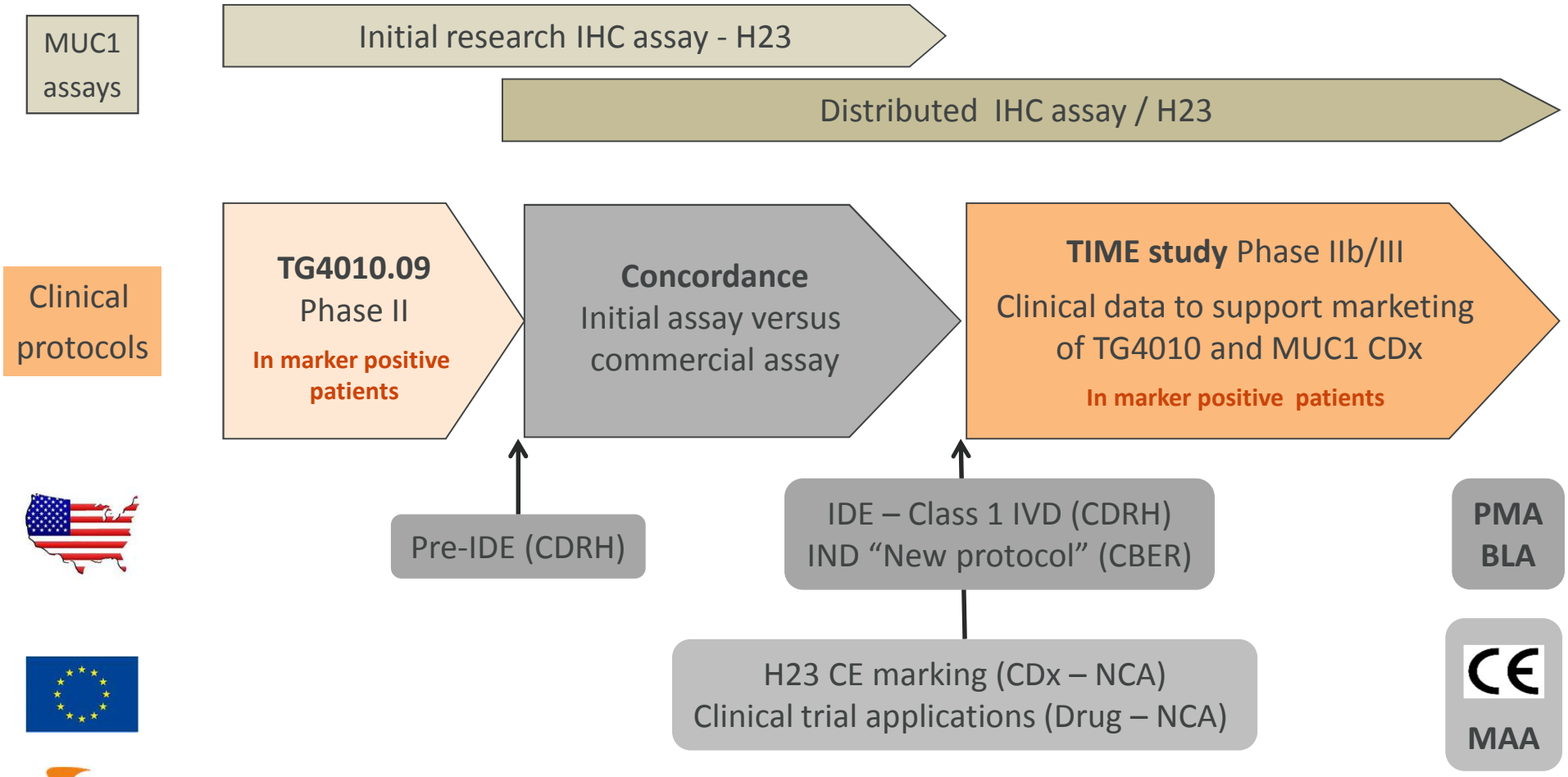
TG4010 & MUC1 CDx Regulatory Route



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Technical Challenges

- Right CDx results for the right treatment decision while patients, laboratories, processing variables
- Difficult access to samples (from positive and negative patient populations)
- Best level of validation at the best time during clinical development

Regulatory challenges

- Regional differences in regulatory requirements for CDx
- CDx and drug companies have different cultures and languages
- Coordination between drug and CDx development
- Randomized clinical study design
  - To answer drug and CDx regulatory requirements for MAA/BLA & CE marking/PMA
- Assay versions during clinical development
  - Need bridging studies ideally on at least 95% of clinical samples

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Best Routes for Drug/CDx success

- Early interactions with drug and CDx authorities
  - Regulatory pathways
  - Clinical trial designs to support drug and CDx marketing authorization
- Systematic collection/storage/accountability of samples in clinical trials for bridging studies
- Good collaboration between Drug & CDx companies: CRUCIAL!
  - Discuss regulatory experience & Drug/CDx development approaches
  - Agree on an integrated Drug /CDx regulatory strategy
  - Contribute to regulatory activities in the partnership
  - Common team model: joint strategic and tactical committees

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Questions?

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