Challenges in development and approval: the case of cell based therapeutics

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BBS / PSI 1-Day Scientific Meeting:
Empower the immune system to fight cancer
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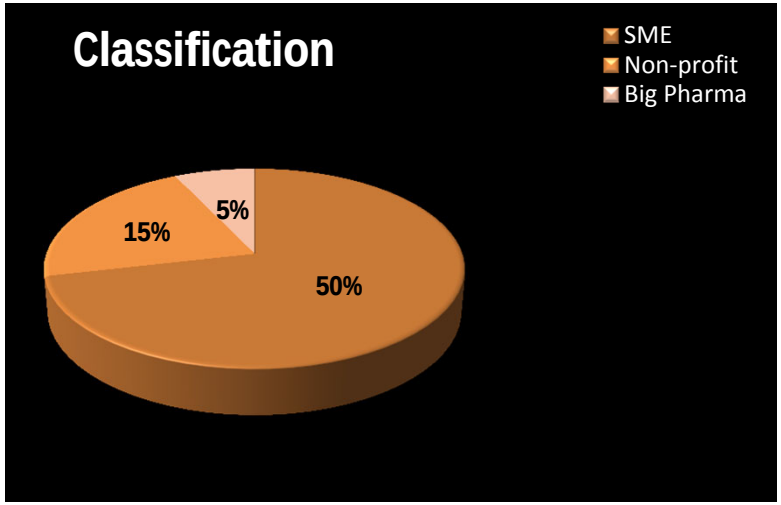
Cotent

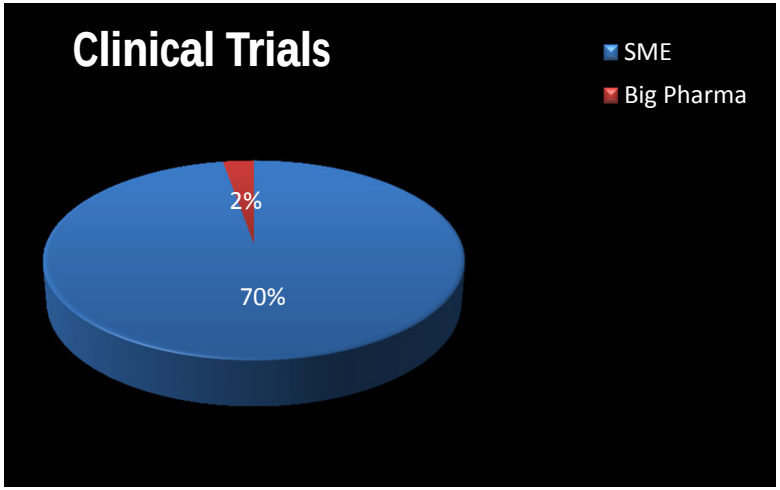
1. Background information of cell based ATMPs
2. General concept and common hurdles in eraly and late stage manufacturing ,non-clinical and clinical development
3. The Zalmoxis case study: suicide genetically modified cells for post-BMT in leukemia patients

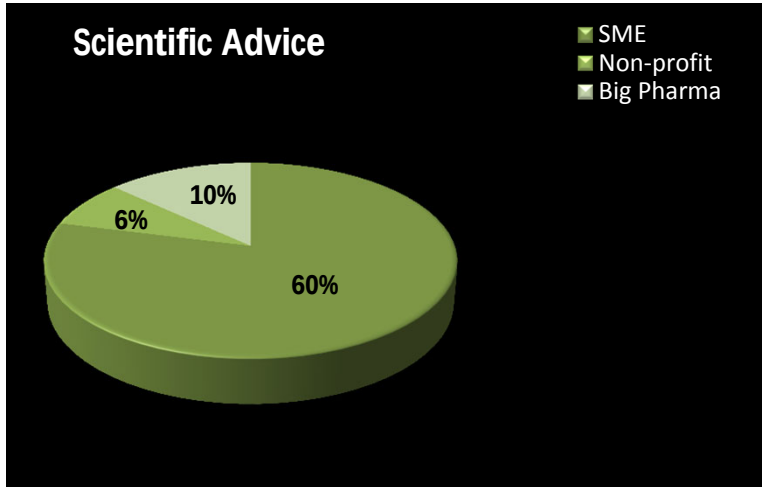
Definitions of Cell based therapeutics

- Contain or consist of a recombinant nucleic acid or Autologous, allogeneic, or xenogenic use living cells
- More than minimally manipulated cells or tissues
- Combined with other components - growth factors, inert matrices, mechanical devices
- Systemically active: effects beyond site of transplantation
- Non-homologous use: application not similar to original tissue function

Organization developing Biologics & ATMPs are different







- Small and medium enterprises (SME)
- Non profit organization (Hospital, Academia and Foundations)
- 40% from SMEs, academia, public bodies and public-private partnerships
- 61% orphan designation drug from SMEs

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Current status for MA of ATMPs in EU

Authorized products

Product		Holder	Date	Therapeutic area
Chondrocelect	TEP	Tigenix	10/2009	Cartilage disease
MACI (R)	Combined	Genzyme	06/2013	Fractures, Cartilage
Provenge (R)	sCBMP	Dendreon UK	10/2013	Prostatic Neoplasms
Glybera (E)	GTMP	UniQure	10/2012	Hyperlipoproteinemia Type (E)
Holoclar	sCBMP	Chiesi	12/2014	Ocular burn
Imlygic (T-Vec)	GTP	Amgen	10/2015	Melanoma
Strimvelis	GTMP	GSK	04/2016	ADA syndrome
Zalmoxis	sCBMP	MolMed	08/2016	ALL
Spherox	TEP	Co.Don.Ag	05/2017	Muscolo-skeletal system

Products under evaluation

Product	Applicant	Application	Therapeutic area
Expanded Mesenchymal Cells	TiGenix	Sept 2015	Perianal Fistulas

ATMPs & large molecules are different

Manufacturing

Biologics	ATMPs
Produced by host cells	Cell or virus is the product
Process product specific	Patient specific
Large batches	Small batches
Terminal sterilization	No terminal sterilization

Structure and characterization

Biologics	ATMPs
High M.W.	No M.W. defined
Mass activity Balance (µg, IU)	Cell/kg, MOI, Viability
Product degradation	Unwanted cell population

In vivo behavior

Biologics	ATMPs
MABEL	Effective dose
p450 degradation system	Long time resident
PK and TK	Biodistribution
Carcinogenicity, mutagenesis	Tumorigenicity and insertional mutagensis
Developmental toxicity	Vertical transmission

Clinical developemt

Biologics	ATMPs
Large, Blind, randomized pivotal trial	Unblind (non-randomized) pivotal trial
Standard design	Adaptative design
FIM → Ph I → Ph II → Ph III → MA	FIM → (Ph I/II → (Ph III)) → MA
Full MA	Conditional , Exception MA
	PASES , Registry establishment

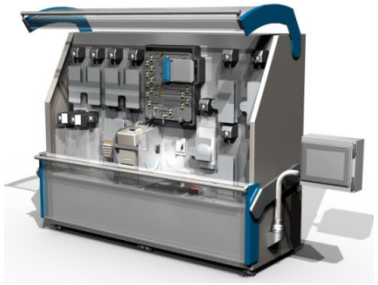
Issues in manufacturing & quality

- Labour intensive
- Non terminally sterilized product
- Process with high rate of changes during development and comparability
- Avaliability of GMP-grade auxilliary material and reagents
- Characterization of the product (and intermediates)
  - Orthogonal design for QC test panel and acceptance limit definition
  - Specific ad hoc test (for potency) to be set up and validated
  - Device and or matrix characterization for combined products
  - Not fully tested MP for patient administration
  - Extent of assay validation
  - Defining / Refining specs
- Traceability as integrated system
- Logistics and overall organization
- Scale up model to accomodate increase numbers in late development post-approval

Scale up and scale out models

VECTOR MANUFACTURING – A SCALE UP MODEL

T CELL TRANSDUCTION – A SCALE OUT MODEL



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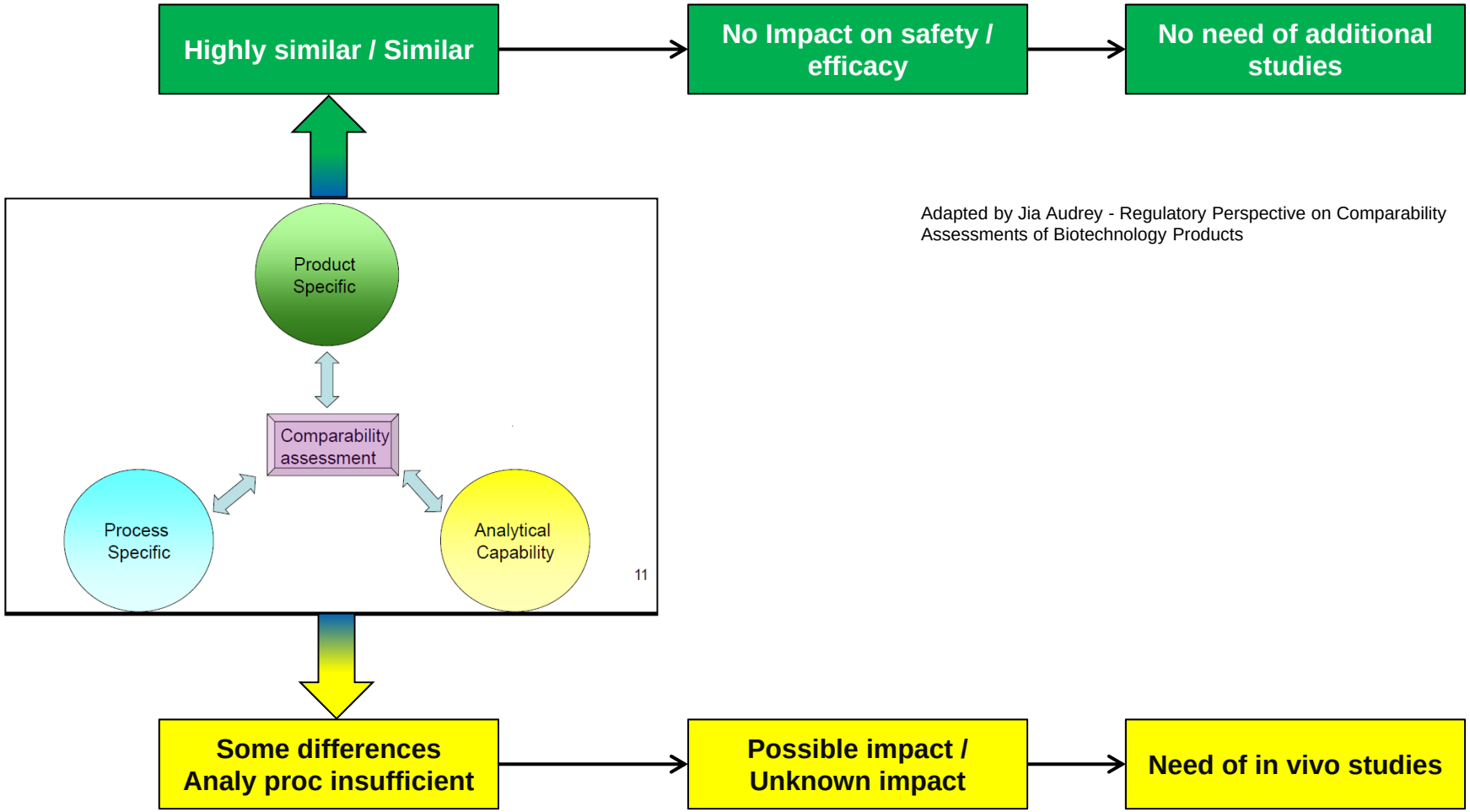
Changes in manufacturing: comparability



Adapted by Jia Audrey - Regulatory Perspective on Comparability Assessments of Biotechnology Products

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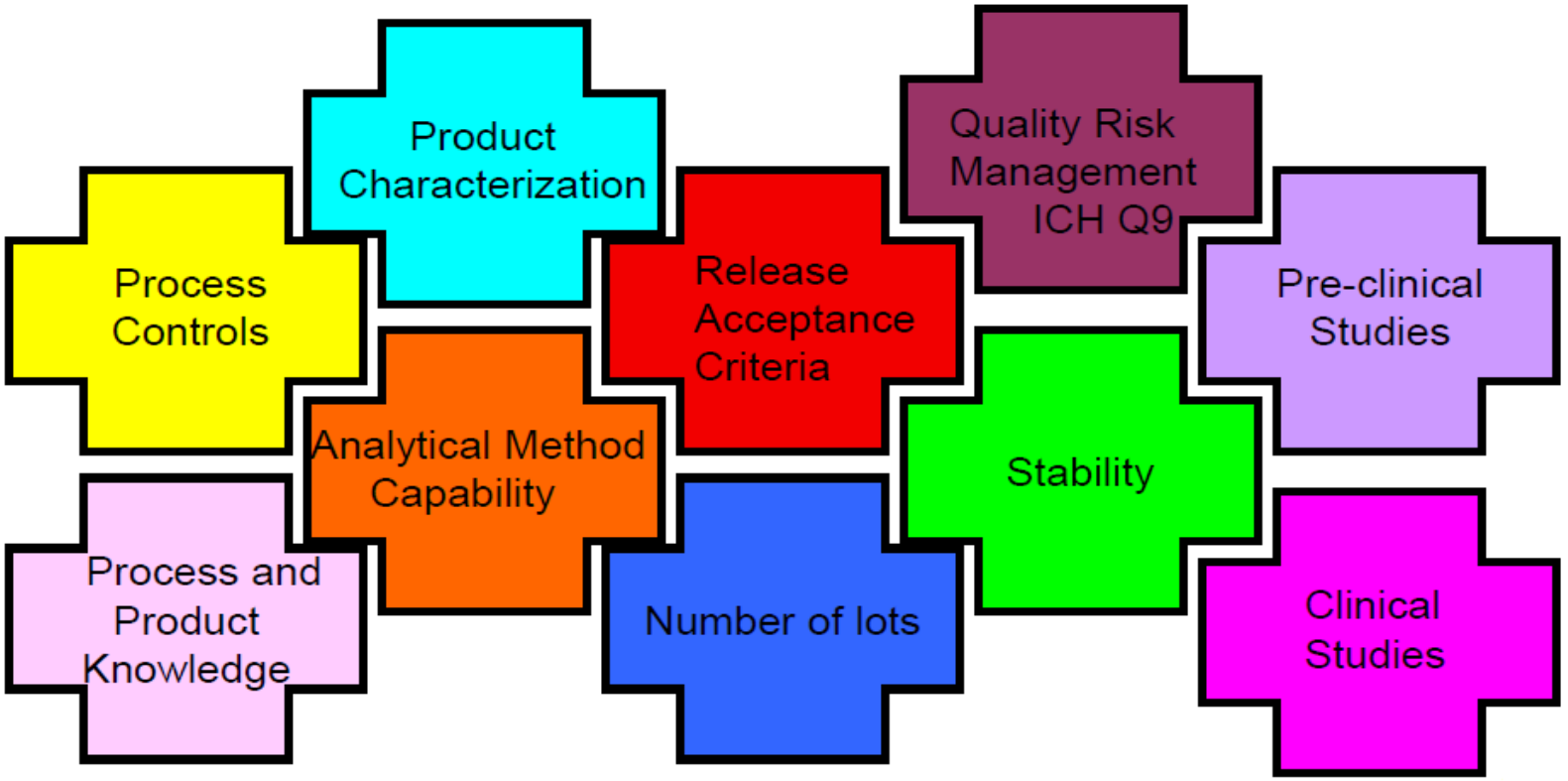
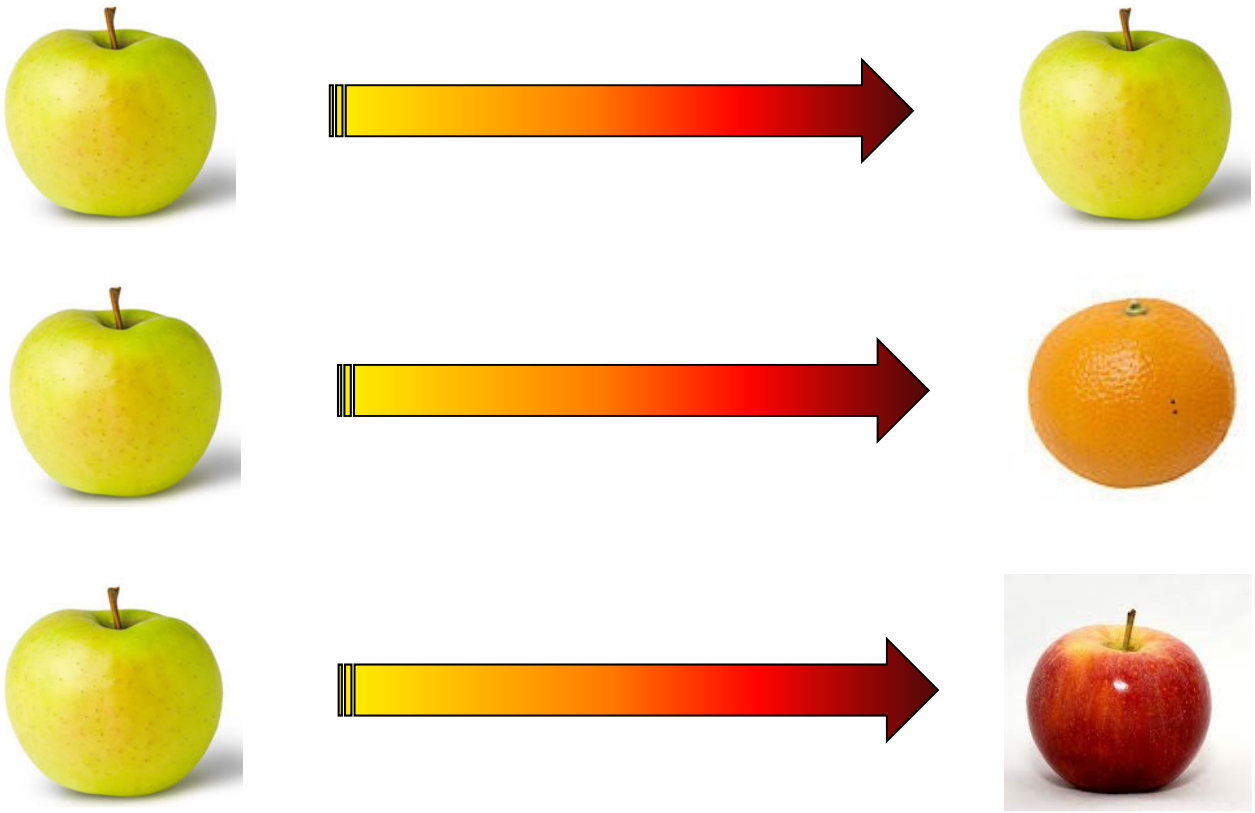
The comparability puzzle



Jia Audrey - Regulatory Perspective on Comparability Assessments of Biotechnology Products

The comparability dilemma: of apples and oranges



The same ?

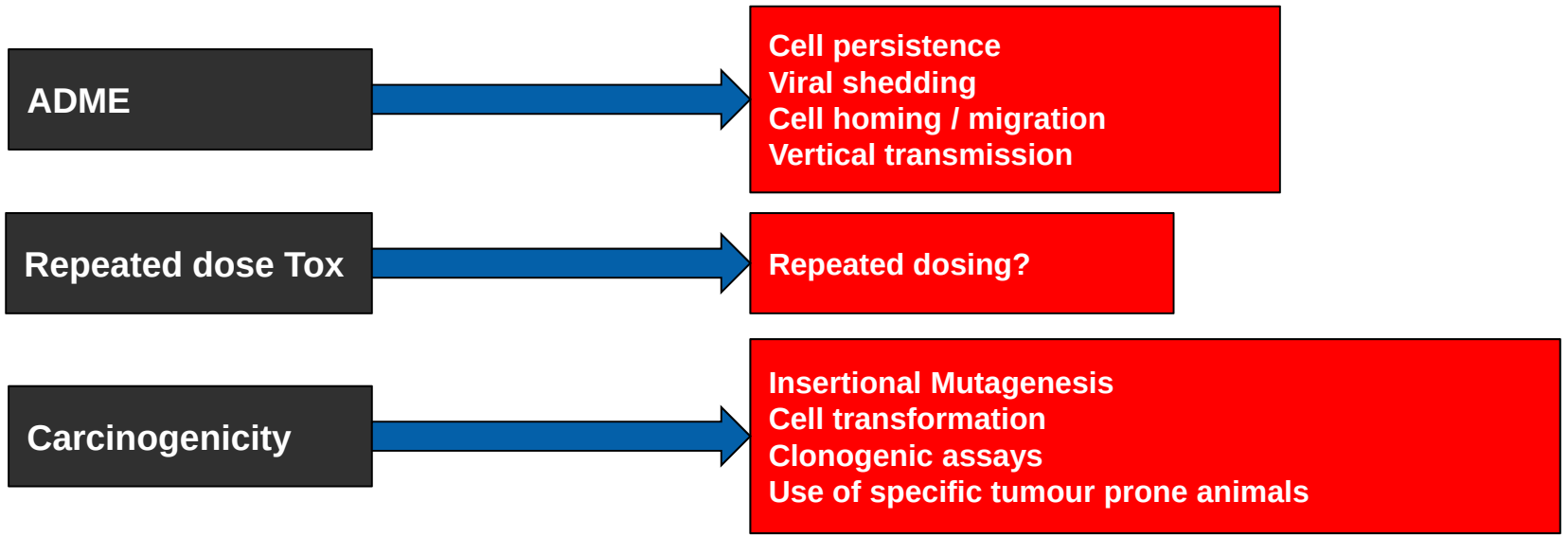
P. Lucas: Implications and regulations of changes during product & process development – TOPRA Msc 2014

Non Clinical development

- Non clinical development of ATMPs follows non-conventional paths
- Non clinical development is designed on a case by case basis
  - Biology of the product
  - Presence of genetic modification
- Non clinical development or toxicology?
- Use of published data supportive of limited non-clinical data set
- Routine QC analysis supportive for safety assessment

Non clinical development

- Standard tox studies and paradigm for safety evaluation hardly applicable to cell based products
- Concurrent efficacy and safety assessement



Issues in non-clinical development

- Extent of non clinical studies
  - Pre-existing clinical data
  - Previous non-clinical data with the same product
- Duration of studies
  - Difficult to establish in long life resident products
  - Dependant to long term expected effects
  - Large animals longer life expectancy than smaller animals
- Choice of relevant animal model
  - Homologous / disease animal model for PoC studies
  - Immunosuppressed animals

Tailored, case by case and risk-based approach

Clinical

- The specific requirements are linked to the biologic characteristics of the product
  - Dependency / reactivity to micro-environment
  - Differentiation / de-differentiation processes
  - Migration
- Patient population and indication
  - Orphan and ultra-rare indication
  - Non conventional statistics and design
- FIM and Phase I/II studies
  - Disease patients
  - Concurrent safety / efficacy endpoint
- Logistics issues
  - Delivery and Supply chain
  - Storage at the site

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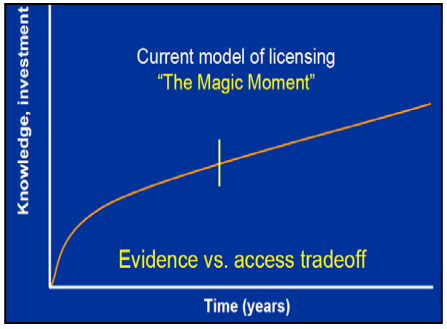
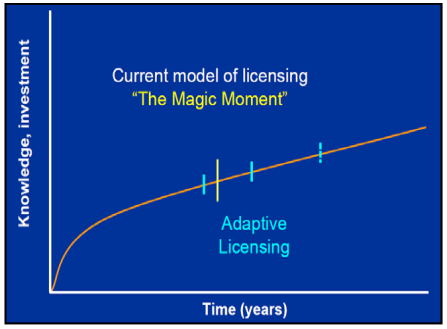
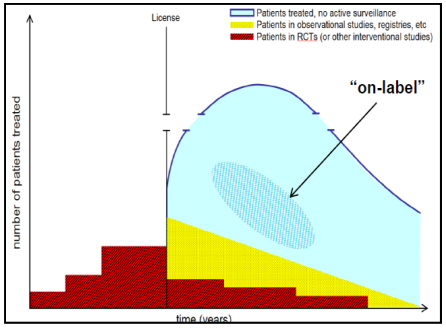
Tools for expedite clinical development and registration: adaptive licensing

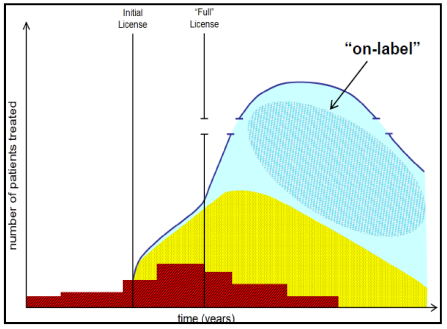
EU	USA
PRIME / Accelerated assessment	Breakthrough therapy
Conditional Marketing Application	Accelerated Assessment
Exceptional circumstances	Fast track
	Priority review

adaptive licensing









ATMPs can be licensed with restrictions and with limited clinical data

Product / clinical devleopment		Holder	Therapeutic area	Post MA Commitments
Chondrocelect	Phase III (n=57/61)	Tigenix	Cartilage disease	NA
MACI (R)	Phase III (m=72/72)	Genzyme	Fractures, Cartilage	NA
Provenge (R)	Phase III (n=333/167)	Dendreon	Prostatic Neoplasms	Registry establishment Results of on-going clinical trial clinical study for distant metastasis
Glybera (E)	3 Phase I/II (n = 27)	UniQure	Hyperlipoproteinemia Type (E)	Registry establishment, Improve viral safety, Assay validation New clinical study on 12 patients
Holoclar	Pivotal study (n=106) Total patients treated (135)	Chiesi	Ocular burn	Educational material Completion of interventional study
Strimvelis	Pivotal Phase I/II (n=12) Total patients treated: 18			
Zalmoxis	CMA Phase I/II (n = 30) Phase III on going (n=17)	MolMed	ALL	Educational material PASS Study with registry Completion Phase III

Clinical challenges

- Pivotal Phase III studies
  - Prospective, randomized CT expected, but difficult to achieve
  - Control arms difficult to establish
  - Multicenter (multinational) vs monocentre studies
  - Dose selection and justification
- Confunding factors
  - Administration procedures (e.g. surgery)
  - Hospital procedures for manufacturing
  - Concomitant, non standardized therapies (immunosuppression)
- Non conventional design & stats
  - Orphan diseases
  - Bayesian statistics and adaptive designs
- Known risks
  - Infections
  - Immune / Inflammatory reactions
  - Tumourigenicity
  - Off-target transduction
- Pharmacovigilance
  - Study duration: long follow up and risk management
  - Safety and efficacy endpoints

Issues in manufacturing & quality

Adapted from Jia Audrey - Regulatory Perspective on Comparability Assessments of Biotechnology Products

FIM	Before Pivotal study	Late phase / post MA
Raw material low quality Validated safety analytical tests Limited process validation data Safety studies including PK Set up of in vivo model PoC studies in homologous model	**Increase product understanding** **Increased raw material quality** **Potency tests set up and initial validation** • **Process changes to accommodate increased production rate** • **Changes in raw materials** • **Formulation changes** • **Development towards a more closed manufacturing process** • **Identify PC and CQA** **Non-clinical data to address** **Repro Tox (if applicable)** **Insertional mutagenesis**	Full analytical validation Formal stability study Complete process characterization and validation Process changes Ensured supply chain Ideal closed manufacturing process Alternate supplier for critical raw materials Complete cell chain identity In use and shipping stability Educational material in place

Emphasis is primarily on product safety

Emphasis on product safety and efficacy

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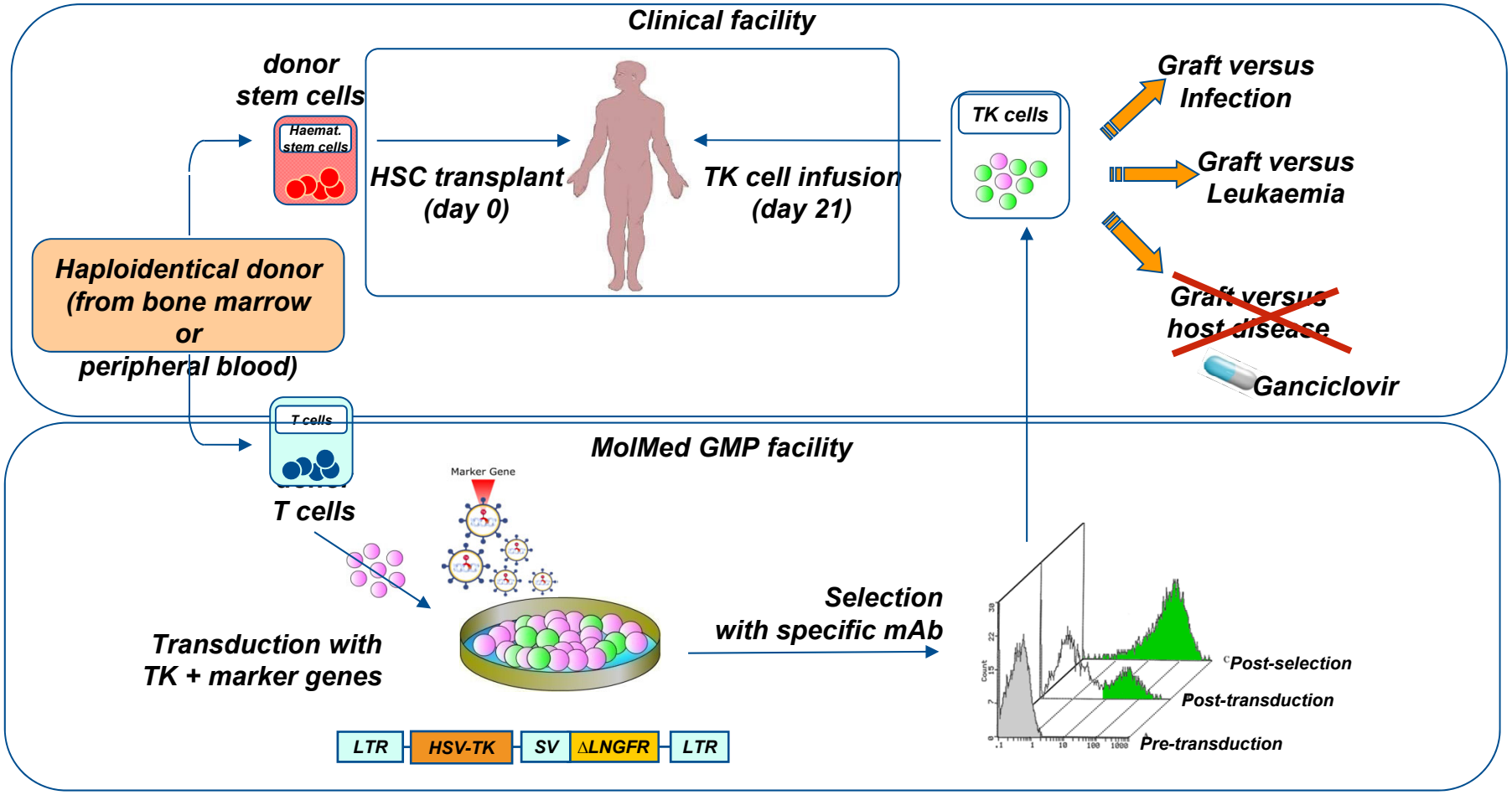
Zalmoxis – a CB therapy for leukemia

Indication: post-BMT adjunctive treatment for HR AML & ALL w/o HLA-matched family or unrelated donor



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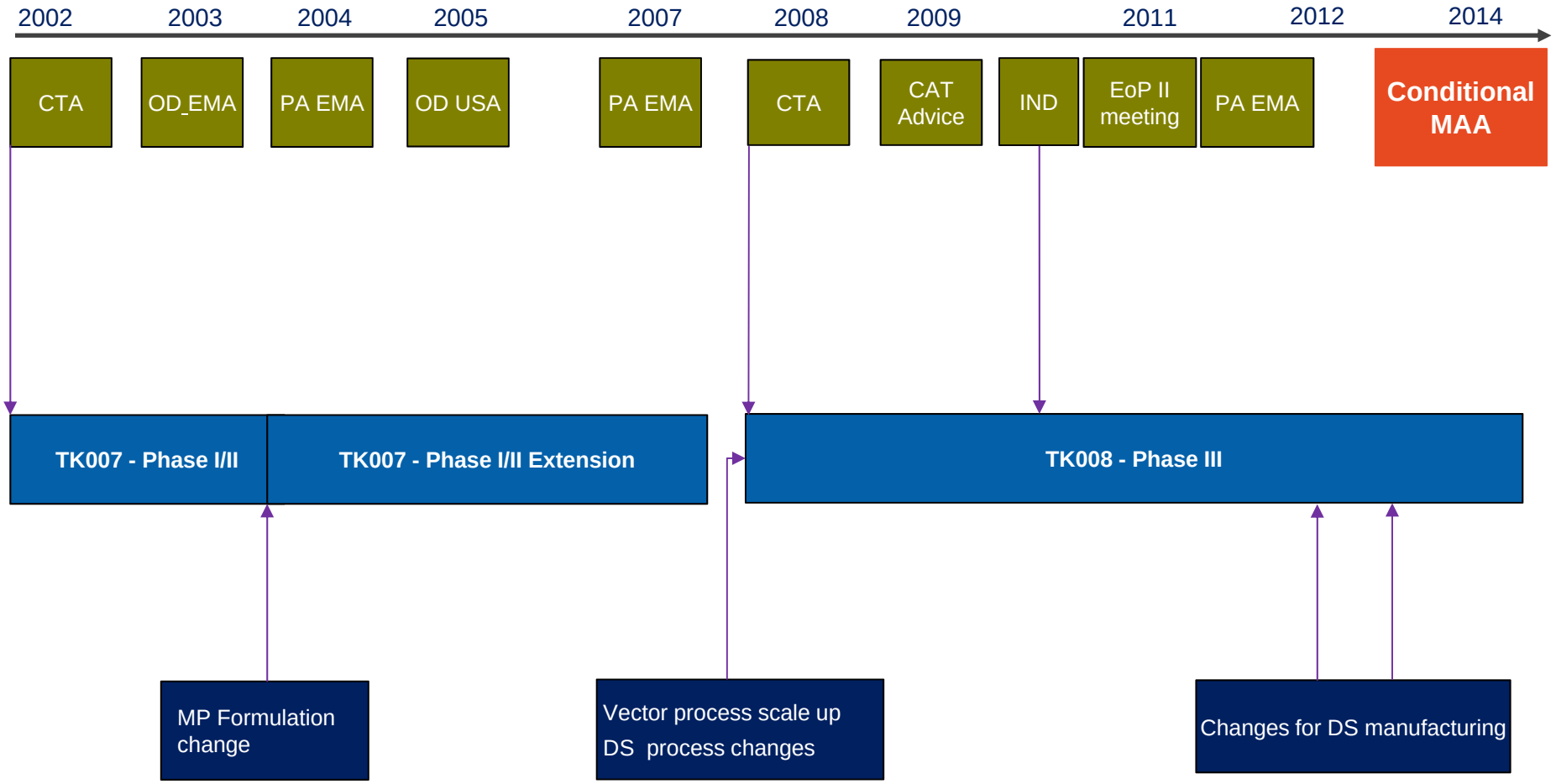
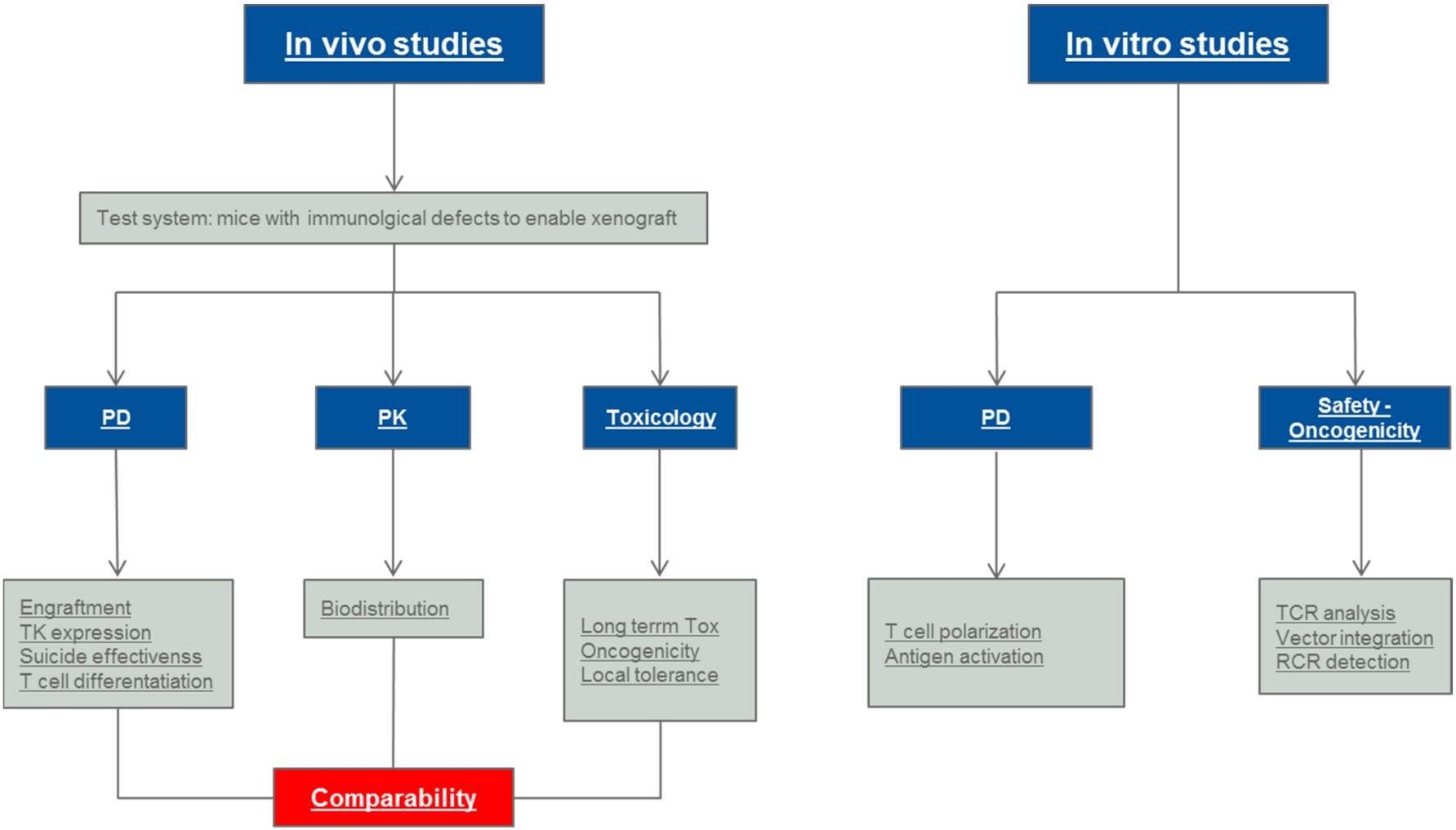
Regulatory and clinical development



IMP development

	Pre-Phase I/II	Phase I/II	Phase III	Future developments
Vector Manufacturing	SFCMM3 #16	SFCMM3 #35	SFCMM3 Mut2 #48	
	Cell Factories	Roller bottle	30 Lt fermentor	
	Roche 82.1 Anti-LNGFR MoAb	MM Anti-LNGFR 20.4		Anti-LNGFR 20.4 SFM
Lymphocytes manipulation	PHA	OKT-3		
	Co-Culture	Spinoculation	Retronectin	
		Open Sysytem	CMS	Fully automated system
		14 Day process	10 day process	
		Viable cells adm	Frozen formulation	

Non clinical development for Zalmoxis



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Zalmoxis design for in vivo studies

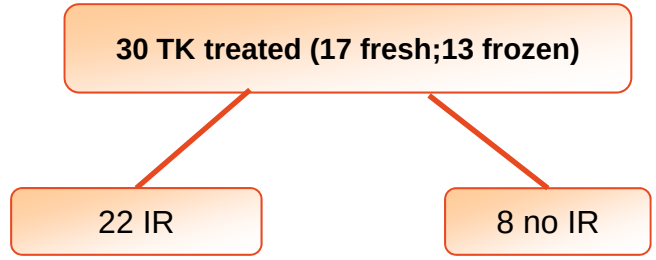
Study	Animal Model	Endpoints	Controls
Study 1	NOD-SCID	Mortality Engraftment GvHD Long term safety GvHD rescue	PBMC / PBL Saline
Study 2	Humanized NOD-SCID	Mortality Engraftment GvHD Biodistribution	PBL Saline
Study 3	NSG	Comparability • Engraftment • GvHD • Mortality	PBMC Mock transduced Saline

Clinical Development – Phase I/II

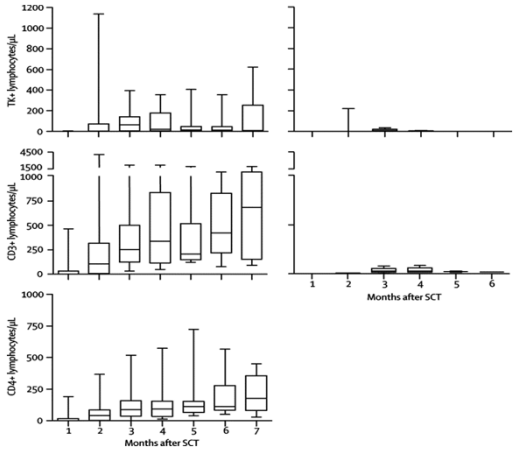
Single arm, non randomized open label study

Patients with haematological malignancies

aGvHD: 10 out 30 pts (33%), 1 cGvHD

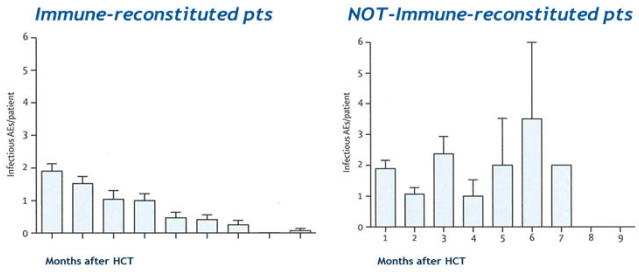


TK cells engraftment

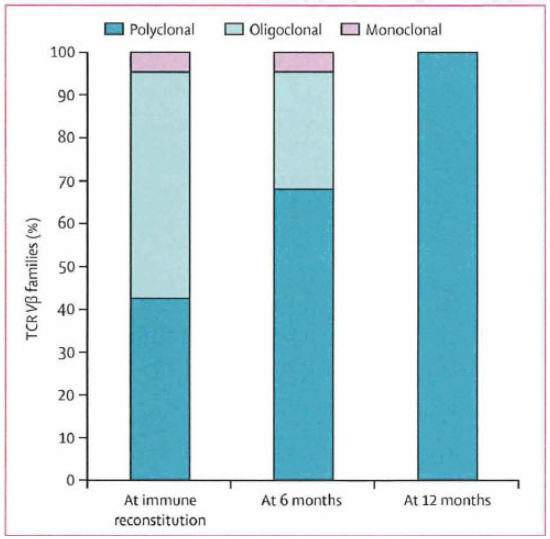


22 pts IR and 6 non-IR

Infectious AE



T cell repertoire by spectratyping



Source *: Ciceri F.,Bonini C. et al. Lancet Oncol. 2009 May;10(5):489-500*

Business or Operating Unit/Franchise or Department

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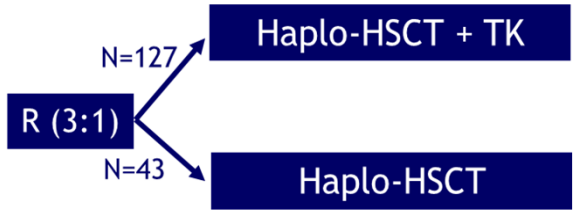
Clinical: Pivotal Phase III Study

- Primary endpoint: Leukemia-free survival
- Secondary endpoints:
  - NRM, overall survival, relapse, disease-free survival
  - immune-reconstitution, engraftment,
  - aGvHD, cGvHD,, infectious, safety,
  - quality of fife, pharmacoeconomics
- Control Arm
  - T-cell depleted haplo +
  - Un-manipulated haploidentical BMT with post-BMT cyclophosphamide (Luznik 2010)



- N=170 patients
- 91 events (death + leukemia relapse)
- 1-year NRM standard haplo:60%
- 1-year NRM ph II study TK: 37%
- Relapse rate standard haplo 25%
- Relapse rate ph II study TK 18%
- Power = 80%; HR= 0.55
- LFS 30% in standard haplo
- LFS 52% expected in exp arm

Source: EMA EPAR for Zalmoxis CMA approval

Thank you

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