Innovative Therapies for Children with Cancer (ITCC) Pediatric Preclinical Proof-of-Concept Platform (ITCC-P4)

A preclinical filtering platform to prioritize new therapies for children with cancer

Stefan M. Pfister (KiTZ/DKFZ), also on behalf of Louis Stancato (Eli Lilly),

Gilles Vassal (ITCC/IGR) and Hubert Caron (Roche)

Children are not small adults

germ cell tumors; 3,2%
others; 5,0%
kidney tumors; 5,5%
neuroblastoma; 6,9%
bone sarcoma; 4,5%
soft tissue sarcoma; 5,7%
leukemia; 33,0%
CNS tumors; 24,6%
lymphoma; 10,7%

soft tissue sarcoma; 1,2%
others; 6,3%
cns tumors; 1,5%
leukemia, lymphoma, multiple myeloma; 8.3%
ENT cancer; 3,4%
skin cancer; 4,5%
urinary tract cancer ; 6,5%
GI cancer; 24,1%
reprod. system cancer ; 18,3%
lung cancer; 11,3%
breast cancer; 14,7%
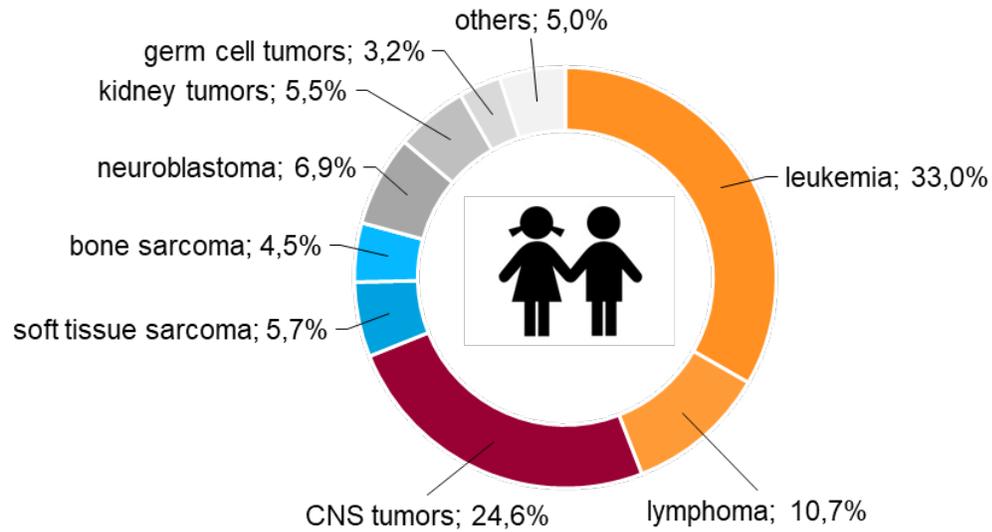
~1%
(yet ~50% of gained years of life!)
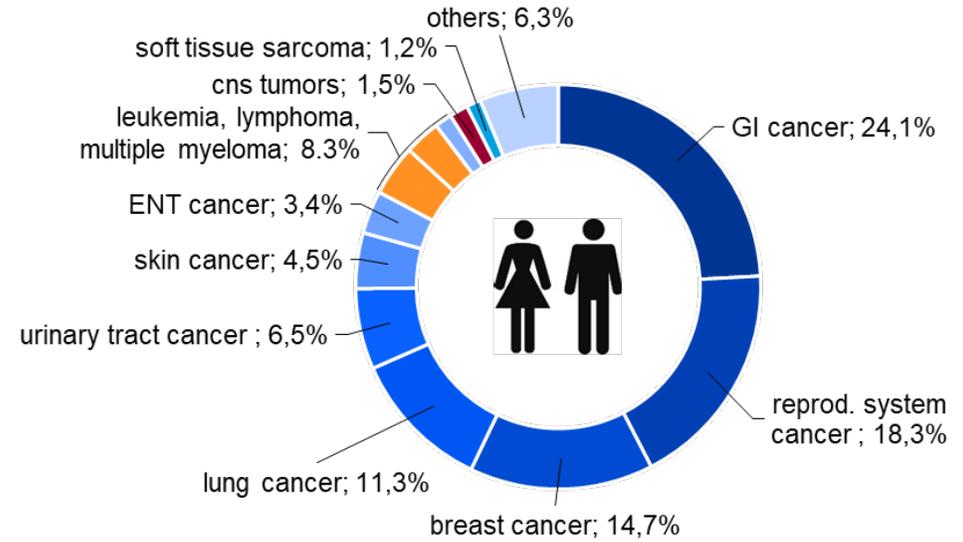
~99%

The clinical need

Cure rates have mostly plateaued over the last >20 years
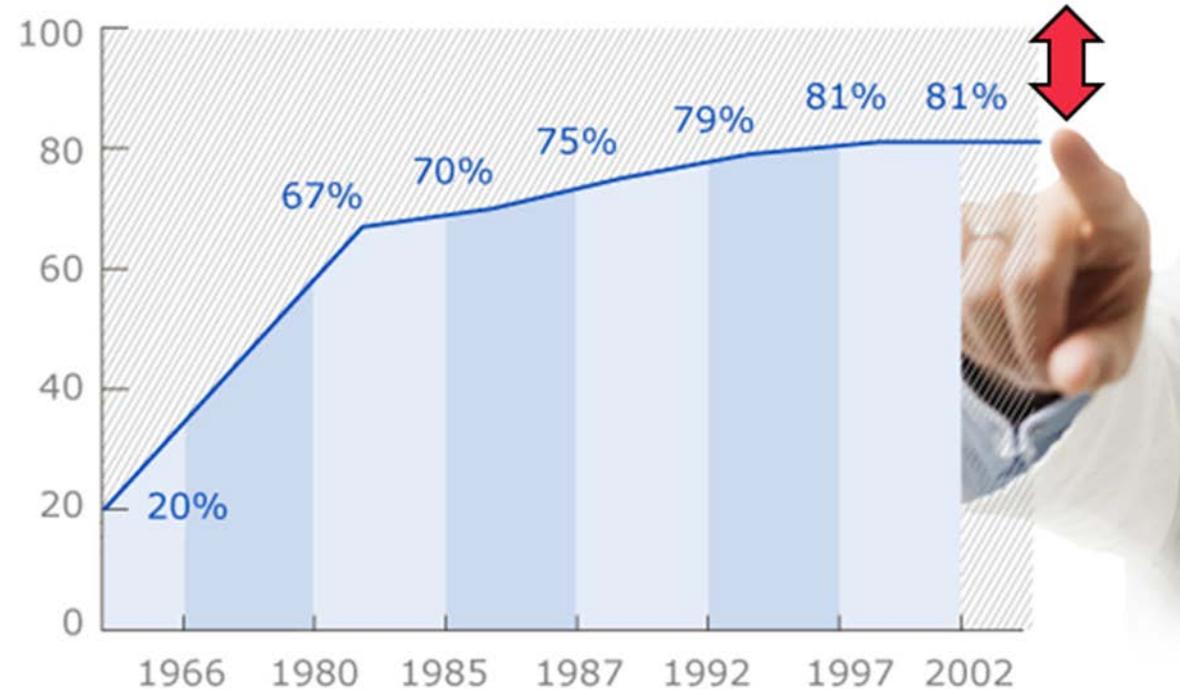
→ the „last 20%" will probably not be cured by „more of the same"!

The regulatory environment is changing

ITCC P4 — PAEDIATRIC PRECLINICAL PROOF OF CONCEPT PLATFORM

FDA REAUTHORIZATION OF 2017

SEC. 504. DEVELOPMENT OF DRUGS AND BIOLOGICAL PRODUCTS FOR PEDIATRIC CANCERS: molecular targets regarding cancer drugs and biological products........ if the drug or biological product is ....

"(i) **intended for the treatment of an adult cancer**;

and

"(ii) **directed at a** <u>molecular target</u> **that the Secretary determines to be** <u>substantially relevant</u> **to the growth or progression of a pediatric cancer.**"

August 2020

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA decision (CW/0001/2015) of 23 July 2015 on class waivers, in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council.

**Revised Class Waiver List
Enters into force July 28, 2018**

→ **Mandate for pediatric development has changed from „tumor type" to „relevance of the mechanism-of-action"**
→ **Almost all new oncology drugs HAVE to be explored for potential pediatric indications**

innovative medicines initiative

The challenge

Pharma „pipelines": ~1000 new oncology drugs
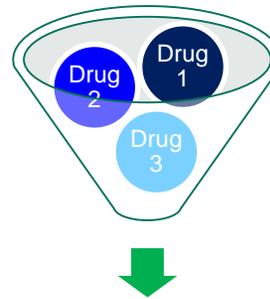
**A (smaller) fraction to be prioritized for clinical trials
with a good rationale in pediatric oncology**

→ Needs: 🔴 Prioritize preclinically effective treatments
🔴 De-prioritize non-effective treatments
🔴 Identify rational combinations
🔴 Identify/validate predictive biomarkers

The potential solution: ITCC-P4
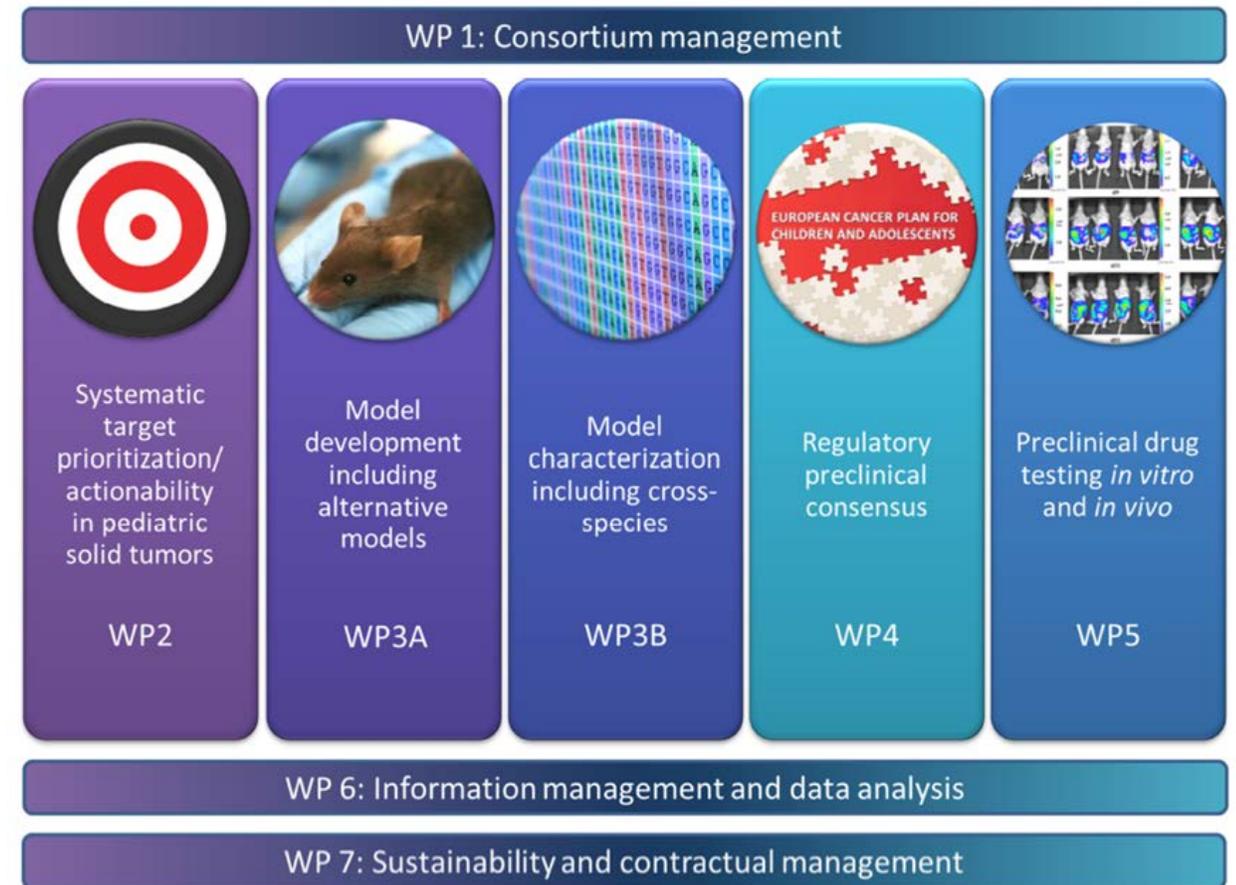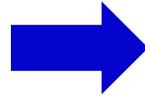
15 academic institutions, 10 EFPIA companies and 3 CROs

The approach

Patient   PDX/GEMM/organoid   Efficacy across many models single mouse trial approach   Application in **SELECTED** patients
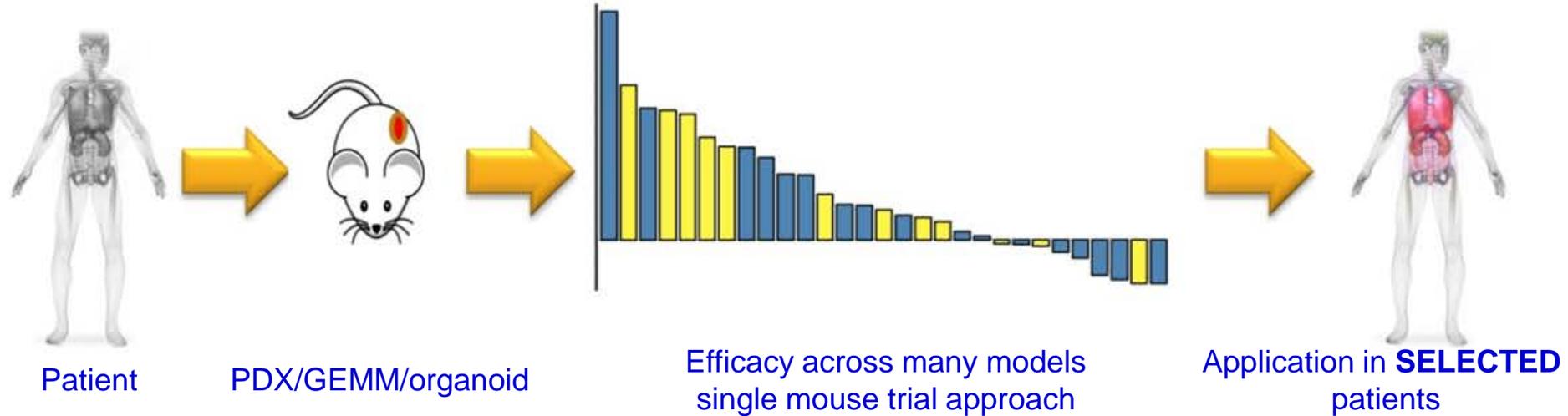
- 400 PDX models/5 years, 2 GEMMs per entity, extension to leukemia & lymphoma in 2020
- Full molecular characterization
- 3 standard-of-care drugs and 6 selected compounds
- Proof-of concept for immunotherapies in humanized models
- Proof-of-concept for organoids

ITCC-P4 Models

ITCC P4 **PAEDIATRIC PRECLINICAL PROOF OF CONCEPT PLATFORM**

Most common solid tumors

Brain tumors are orthotopic; all others flank

- Ependymoma supratentorial [EPD_ST]
- Atypical teratoid/rhabdoid tumor [ATRT]
- High grade glioma other [HGGother]
- High grade glioma K27Mmut [HGG_K27M]
- Ependymoma infratentorial [EPD_IT]
- Medullobastoma WNT [WNT]
- Medullobastoma SHH [SHH]
- Medullobastoma Group3 [GR3]
- Medullobastoma Group4 [GR4]

- Synovial Sarcoma [SS]

- Neuroblastoma [NB]

- Malignant Peripheral Nerve Sheeth Tumor

- Rhabdomyosarcoma [RMS]

- Ewing Sarcoma [ES]
- Osteosarcoma [OS]

Rarer entities

ETMR
Desmoplastic small round cell tumor
HGNET-BCOR
CNS neuroblastoma (FOXR2)
Inflammatory myofibroblastic tumor
Renal cell carcinoma
Hepatocellular carcinoma

2020: Liquid Tumors

1.	BCP-ALL	ETV6-RUNX1
		Hyperdiploid
		Hypodiploid
		TCF3-HLF
		TCF3-PBX1
		Ikaros+
		BCR-ABL/BCR-ABL-like
		iAMP21
2.	T-ALL	ETP
		Early cortical (TLX1/TLX3-mut)
		Late cortical (TAL1, LMO2-mut)
3.	AML	RUNX1-RUNX1T1/ CBFB-MYH11
		RUNX1-mut, TP53-mut, ASXL1-mut
		DEK-NUP214
		MLLr (t[9;11]; t[10;11])
		complex karyotype
		monosomal karyotype
		NPM1 mut
		NUP98r
		Other
4.	Infant AML/ALL	MLLr (t[4;11]; t[9;11]; t[10;11])
		Others

~250 models with full molecular characterization to date
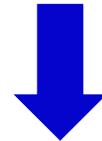
Derivation of organoids from all these + selection of controls

innovative medicines initiative

ITCC-P4 Testing: An example

Testing in one (neuroblastoma) model:

MV17458_ITCC:P4_NB0026

- vehicle — control
- Etoposide ⎫
- Topotecan ⎬ Standard of care
- Cisplatin + Cyclophosphamide ⎭
- Idasanutlin — MDM2
- JQ-1 — BET/BRD4
- Prexasertib — CHK1
- Cobimetinib — MEK
- Lorlatinib — ALK
- Copanlisib — PI3K
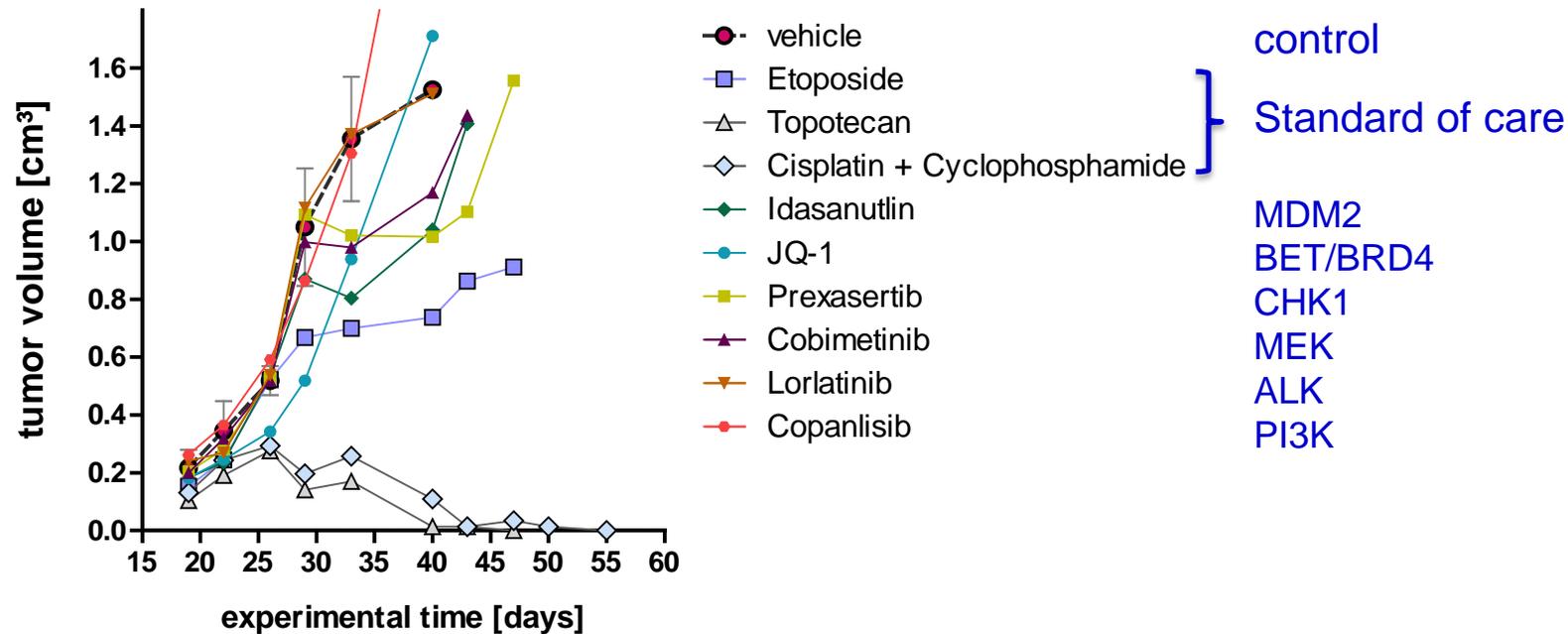
x40 for each tumor type for 9 selected treatment conditions

www.itccp4.eu
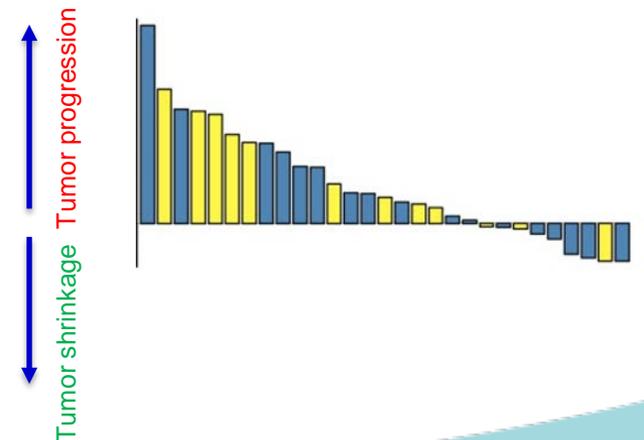
ITCC-P4 Recommendations

…to be submitted
to regulatory authorities
(EMA +/- FDA)
for endorsement

ITCC-P4 Sustainability

Goal: Build a sustainable post-IMI2 infrastructure that will provide the biological and preclinical data to identify and prioritize new oncology drugs for children and adolescents with cancer

Progress to date:
- Preferred model defined
- Service, not models will be sold
- Will serve the needs of both academic and industrial customers
- Plan to ensure the platform and the science carries on
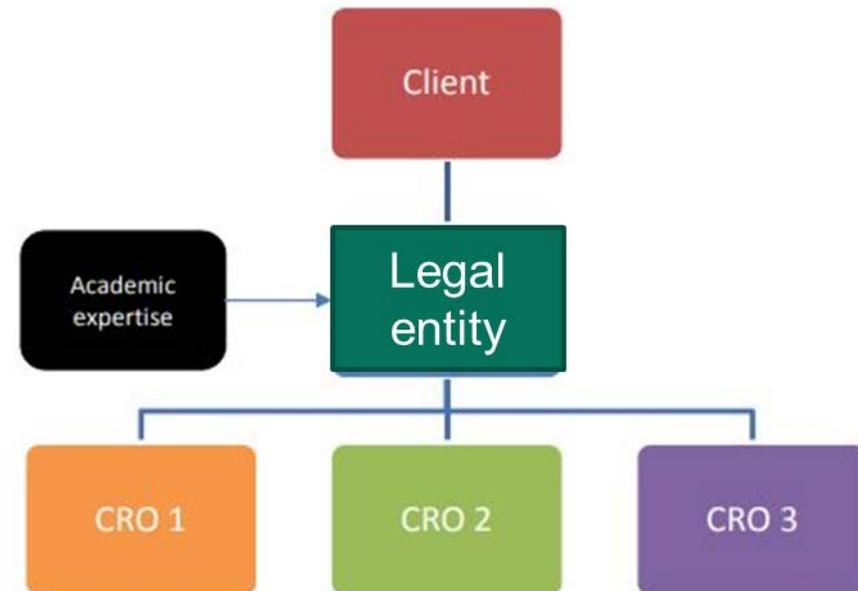
The ITCC-P4 Managing Board

…a great team effort!

www.itccp4.eu
re-launched today!

www.itccp4.eu

Questions?