RICERCA E ASSISTENZA NELLA PEDIATRIA CHE CAMBIA:
LA PRESCRIZIONE OFF LABEL
Confronto tra Clinici, Ricercatori e Autorità Legislativa e Giuridica

Trieste
14 Novembre, 2017

Off-label in Onco-Ematologia

Biondi A.
Clinica Pediatrica & Centro M.Tettamanti

Università Milano-Bicocca
FMBBM- Ospedale San Gerardo
Monza
abiondi.unimib@gmail.com

Onco-Ematologia pediatrica: dove siamo?

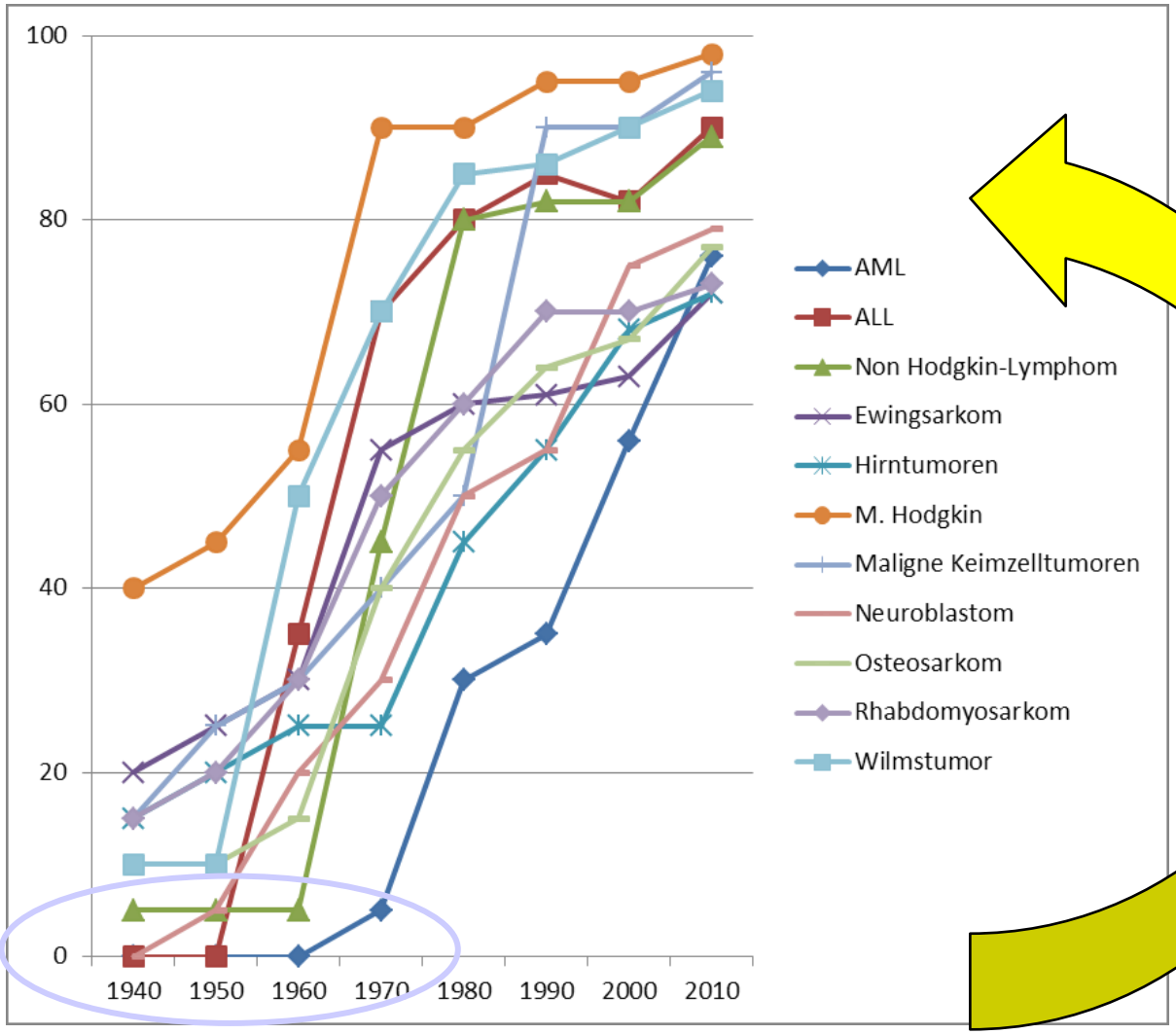
Le ragioni di un successo con qualche sorpresa

Norme e opportunità per off-label: 648/1996

Nuovi farmaci: nuovi paradigmi

Da un successo off-label ad uno scenario sempre più complesso

Dove siamo ?



?

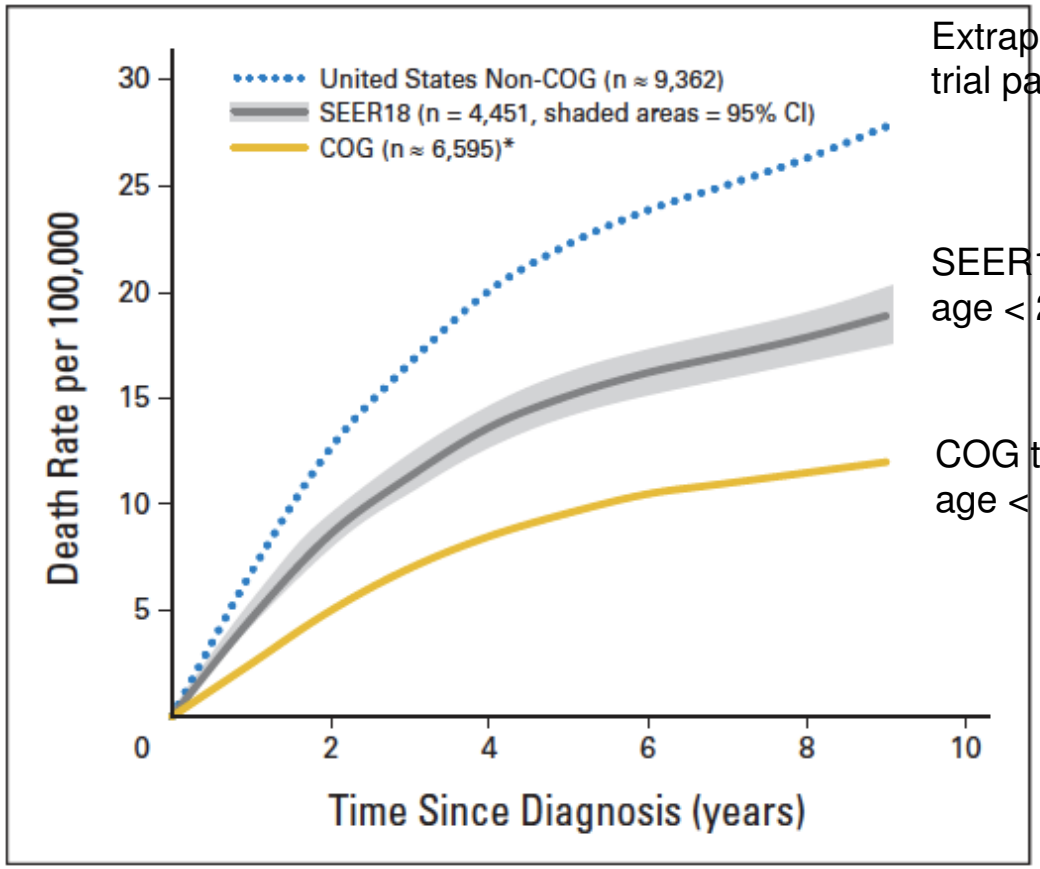
Rossig C et al. Ped Blood Cancer 2013

Principio che ha guidato il successo contro i tumori

The More the Better

Nam June Paik, 1988

Outcome nei pazienti trattati non in studi



Extrapolated survival for non-trial patients age < 20 yrs

SEER18 registry patients age < 20 yrs

COG trial patients age < 22 yrs

Bleyer A et al, JCO (Nov 2012) 30:4037-8, letter to editor
Annual death rate in USA from ALL, 2000-2005

…. con qualche sorpresa!

"About 75% of newly diagnosed children with cancer are expected to be cured.

This success story has been achieved through ***collaborative***, ***mainly non-commercial clinical trials*** *and* ***improvements in supportive care****.*

Few formal studies have taken place on the pharmacology of these drugs in children, and even fewer trials sponsored by drug companies have aimed to show the antitumour efficacy of these drugs against cancers specific to childhood in order to support a licensed indication"

P.Paolucci et al Lancet Oncol 2008

Active substance	Indications for off-label use in children	Specific priorities	Age group*
Dactinomycin	Rhabdomyosarcoma, Ewing's sarcoma	Pharmacokinetics, safety	..
Carboplatin	Neuroblastoma, low-grade glioma, Wilms' tumour, hepatoblastoma, medulloblastoma, osteosarcoma, germ-cell tumour	Pharmacokinetics, safety, efficacy	<2 years
Cisplatin	Neuroblastoma, low-grade glioma, Wilms' tumour, hepatoblastoma, medulloblastoma, osteosarcoma, germ-cell tumour	Pharmacokinetics, safety, efficacy	>6 months
Cladribine	Acute myeloid leukaemia, chronic lymphoblastic leukaemia, hairy-cell leukaemia	Pharmacokinetics, safety, efficacy	..
Cyclophosphamide	Acute lymphoblastic leukaemia, acute myeloid leukaemia, non-Hodgkin lymphoma, Hodgkin's disease, neuroblastoma, rhabdomyosarcoma, low-grade glioma, Ewing's sarcoma, medulloblastoma, osteosarcoma, hepatoblastoma, germ-cell tumour, haemophagocytic lymphohistiocytosis, bone-marrow transplantation (conditioning regimen)	Age-appropriate formulation; pharmacokinetics	All age groups; <3 years
Cytarabine	Acute lymphoblastic leukaemia, acute myeloid leukaemia, non-Hodgkin lymphoma	Efficacy, safety	<3 years
Daunorubicin	Non-hodgkin lymphoma	Pharmacokinetics, long-term safety	..
Doxorubicin	Ewing's sarcoma, hepatoblastoma	Pharmacokinetics, long-term safety	..
Etoposide	Ewing's sarcoma, rhabdomyosarcoma, Hodgkin's disease	Pharmacokinetics, efficacy, safety	..
Etoposide	Acute lymphoblastic leukaemia, neuroblastoma, rhabdomyoscaroma, low-grade glioma, Ewing's sarcoma, Wilms' tumour, medulloblastoma, ependymoma, osteosarcoma, hepatoblastoma, germ-cell tumour, histiocytosis	Age-appropriate formulation; pharmacokinetics	All age groups; <3 years
Fludarabine	Bone-marrow transplantation (conditioning regimen)	Pharmacokinetics, safety, efficacy	..
Gemcitabine	Acute lymphoblastic leukaemia, acute myeloid leukaemia, Hodgkin's disease, rhabdomyosarcoma, Ewing's sarcoma, osteosarcoma, neuroblastoma, hepatoblastoma, Wilms' tumour, soft-tissue sarcoma	Pharmacokinetics, safety, efficacy	..
Idarubicin	Acute myeloid leukaemia	Pharmacokinetics, long-term safety	..
Ifosfamide	Acute lymphoblastic leukaemia, non-Hodgkin lymphoma, Hodgkin's disease, rhabdomyosarcoma, Wilms' tumour, Ewing's sarcoma, osteosarcoma, germ-cell tumour	Pharmacokinetics, efficacy, safety (and long-term safety)	..
Lomustine	Labelled paediatric use	Age-appropriate formulation	..
Mercaptopurine	Labelled paediatric use	Age-appropriate formulation	..
Methotrexate	Labelled paediatric use	Age-appropriate formulation	..
Mitoxantrone	Acute myeloid leukaemia	Pharmacokinetics, long-term safety	..
Retinoids	Labelled paediatric use	Age-appropriate formulation	..
Temozolomide	Labelled paediatric use	Age-appropriate formulation; Pharmacokinetics, safety, efficacy	All age groups; <3 years
Tioguanine	Labelled paediatric use	Age-appropriate formulation	..
Thiotepa	Bone-marrow transplantation (conditioning regimen) in medulloblastoma, germ-cell tumour	Pharmacokinetics, efficacy, safety	<12 years
Topotecan	Refractory solid tumours	Pharmacokinetics, efficacy, safety	..
Vinblastine	Langerhans-cell tumour	Pharmacokinetics, efficacy, safety	..
Vincristine	Low-grade glioma, medulloblastoma, ependymoma	Pharmacokinetics, efficacy, safety	..
Vindesine	Non-Hodgkin lymphoma	Pharmacokinetics, efficacy, safety	..
Vinorelbine	Labelled paediatric use	Age appropriate formulation	..

*Data required for specific age group according to EMEA[34]

Table 1: **Specific priorities for studies into off-patent medicinal products for children with cancer (Paediatric Use Marketing Authorisation as marketing authorisation requirement)**

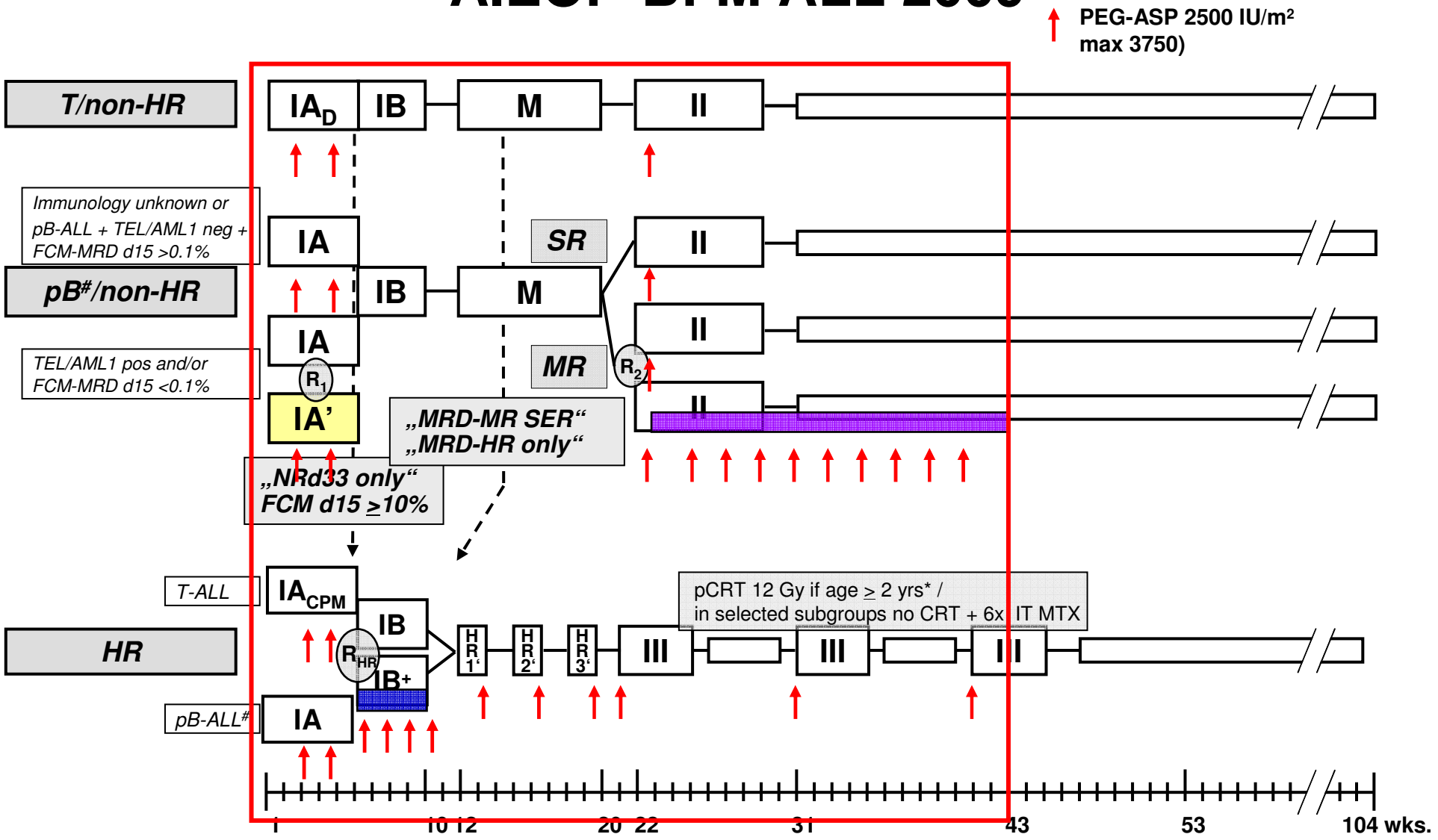
P.Paolucci et al Lancet Oncol 2008

Legge 648/1996 : LLA

- Il prodotto Asparaginasi nelle sue forme pegilata da Escherichia Coli (PEG-ASP) e il suo sostituto cioè quello nativo da Erwinia C. sono ampiamente utilizzati nell'ambito del protocollo concluso nel 2016 in Italia denominato AIEOP-BFM ALL 2009.

- Sono due classici esempi di farmaco rimborsato in base alla legge 648: non registrati in Italia, mancanza di alternative terapeutiche, ritenuti indispensabile, con letteratura consolidata, per patologia grave.

AIEOP-BFM ALL 2009



IA Prot. IA with 4 DNR doses (day 8, 15, 22 and 29)

IA' Prot. IA with 2 DNR doses (day 8 and 15)

PEG-ASP 2500 IU/m² every 2 weeks, over 20 weeks in total (1+9 doses)

PEG-ASP 4 x 2500 IU/m² over 4 weeks

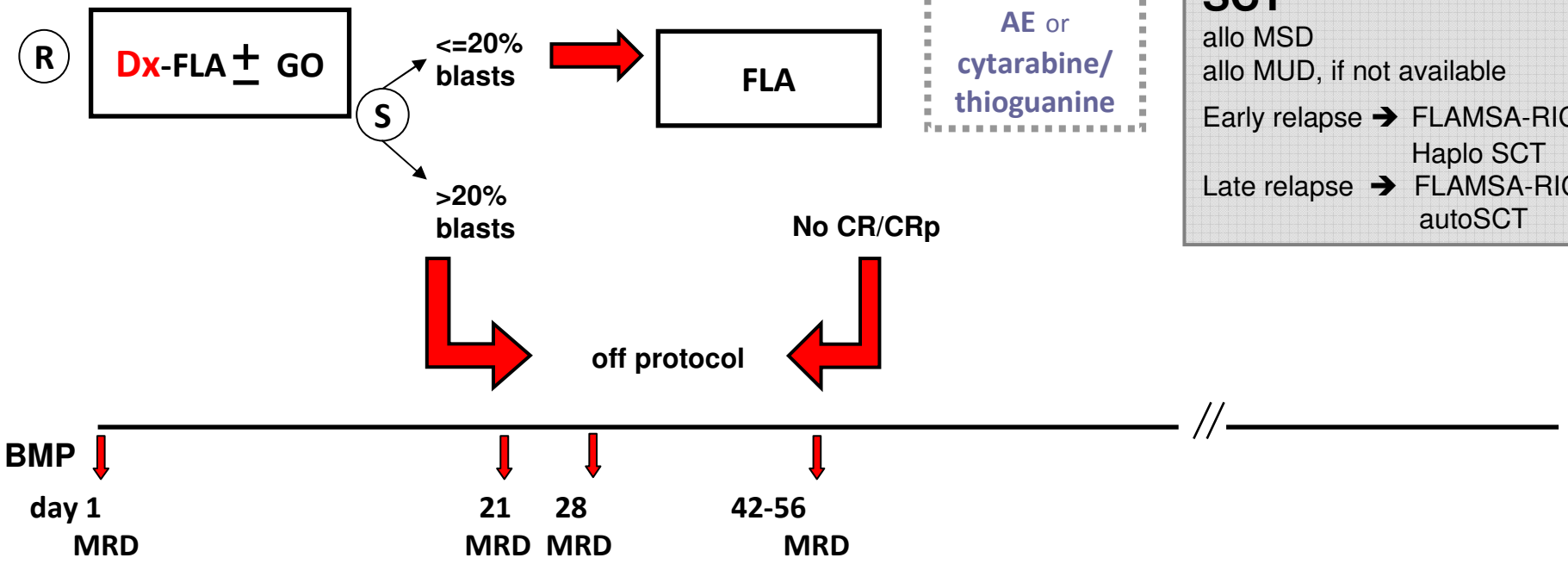
or immunophenotype unknown

* in patients with CNS disease (CNS 3) tCRT with 12 Gy/18 Gy (dose age-adapted))

Legge 648/1996 : LMA

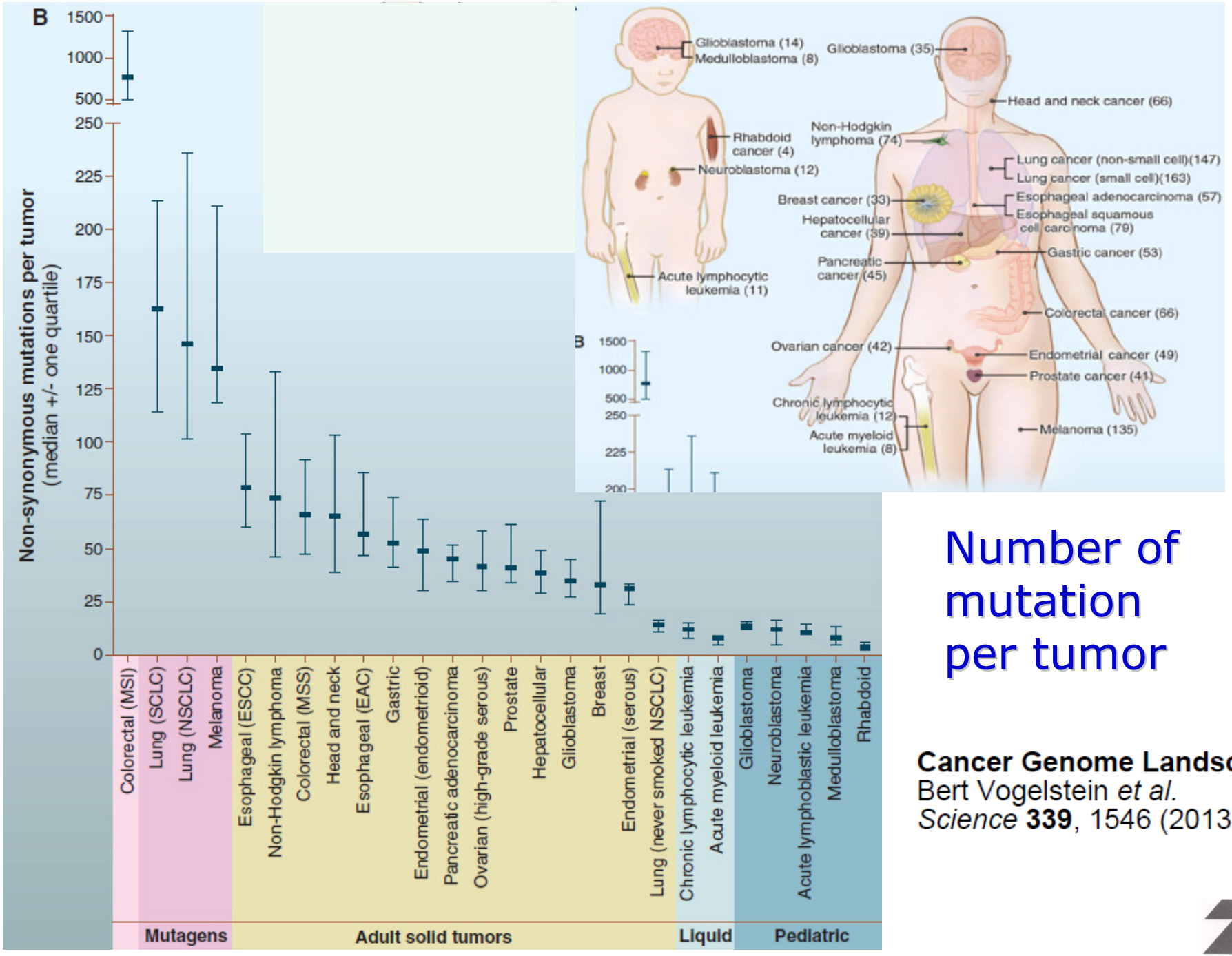
- Il prodotto Daunoxome (Daunomicina Liposomiale) è attualmente l'antraciclina considerata «golden standard» nelle recidive di Leucemia Mieloide Acuta ma anche nella LLA (front-line e recidivata).
- Il suo uso è da sempre off-label nella leucemia dell'età pediatrica perché il farmaco è registrato per i pazienti adulti con "*Sarcoma di Kaposi AIDS-correlato in pazienti con una bassa conta di cellule CD4*".

Relapsed AML 2010/01 I-BFM-SG



R	randomisation
S	stratification
Dx:	**LIPOSOMAL DAUNORUBICIN**
FL:	fludarabine
A:	ARA-C; cytarabine
GO:	gemtuzumab ozogamicin
SCT:	stem cell transplantation

E:	etoposide
AMSA:	amsacrine
RIC:	reduced intensity conditioning
TG:	thioguanine
MRD:	Minimal residual disease
BMP:	bone marrow puncture



Number of mutation per tumor

Cancer Genome Landscapes
Bert Vogelstein *et al.*
Science **339**, 1546 (2013);

ONCOGENE/FUSION PRODUCTS

MYCN or C
EWS/ETS

SIGNAL TRANSDUCTION INHIBITORS

EGFR, ALK, IGF1R
PI3K/AKT/mTOR
RAS/RAF/MEK
NOTCH, sHH

CELL CYCLE INHIBITORS

Cdk2/4
PLK-1

IMMUNE-RELATED TARGETS

GD2, IL2, IL6
CTLA-4, PD-1

APOPTOSIS & AUTOPHAGY MODULATORS

Bcl2, IAP
Survivin
TRAIL

DNA REPAIR MODULATORS

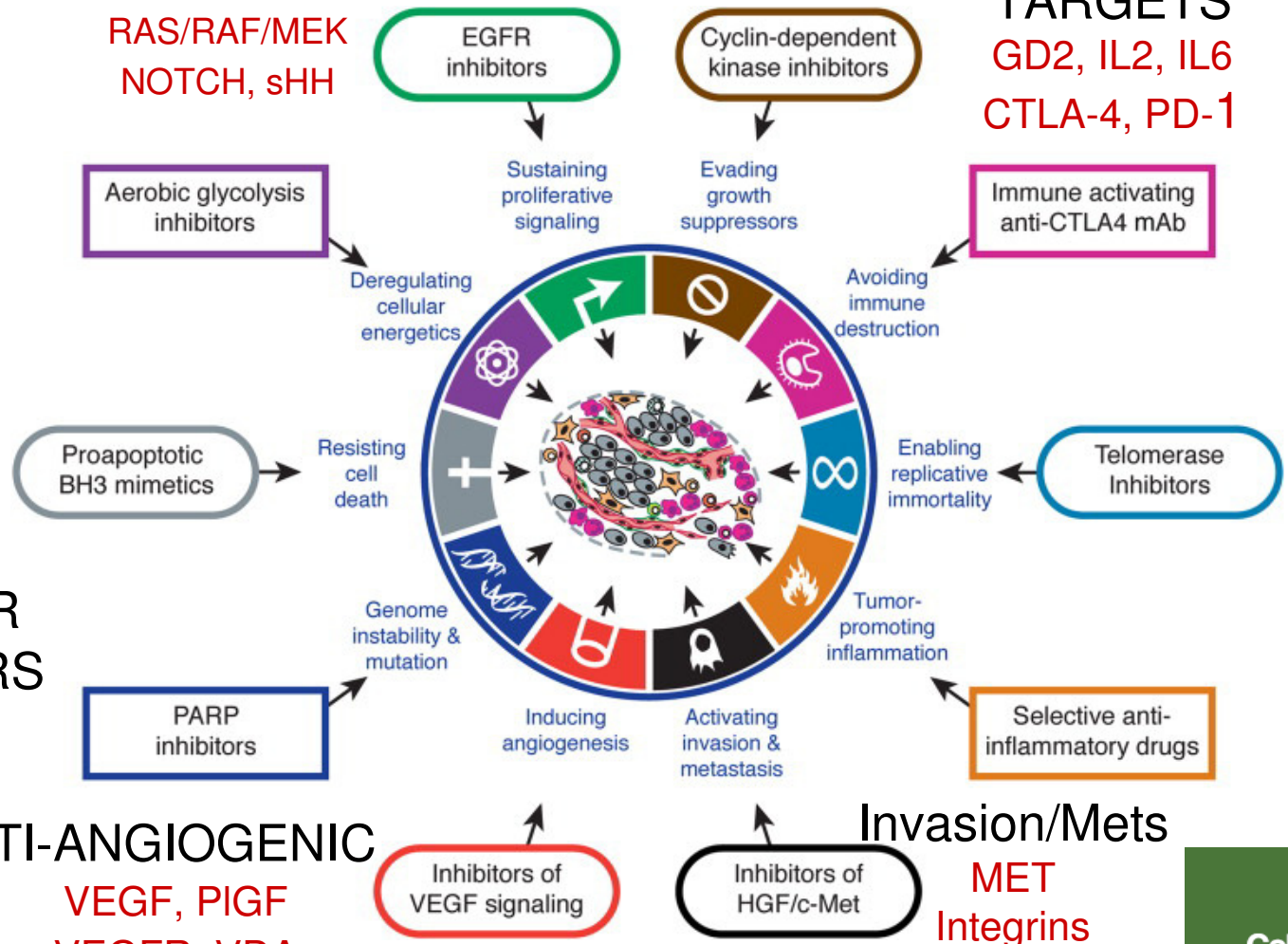
PARP-1
Nutlins

ANTI-ANGIOGENIC

VEGF, PIGF
VEGFR, VDA

Invasion/Mets

MET
Integrins

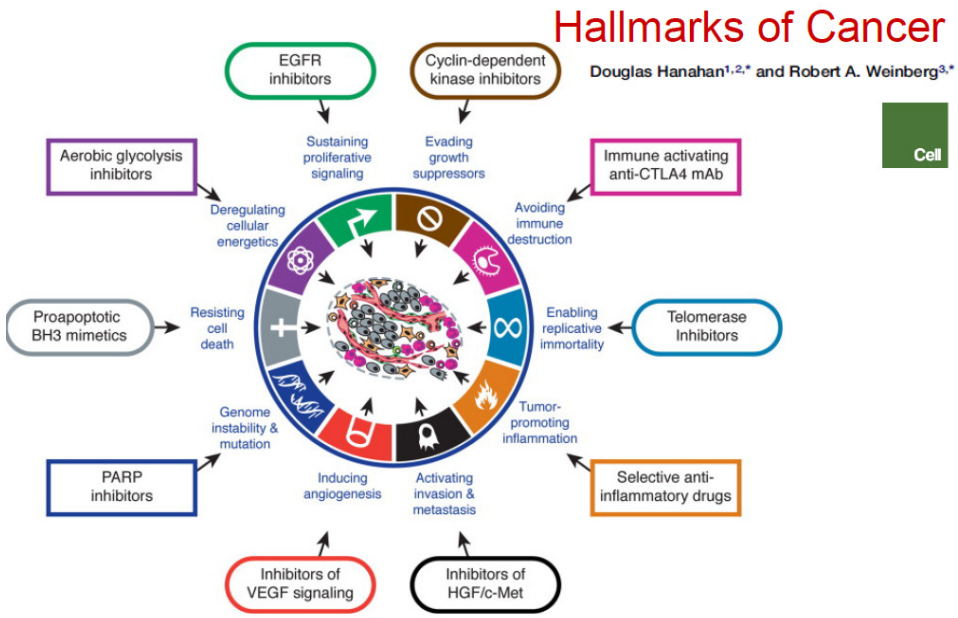


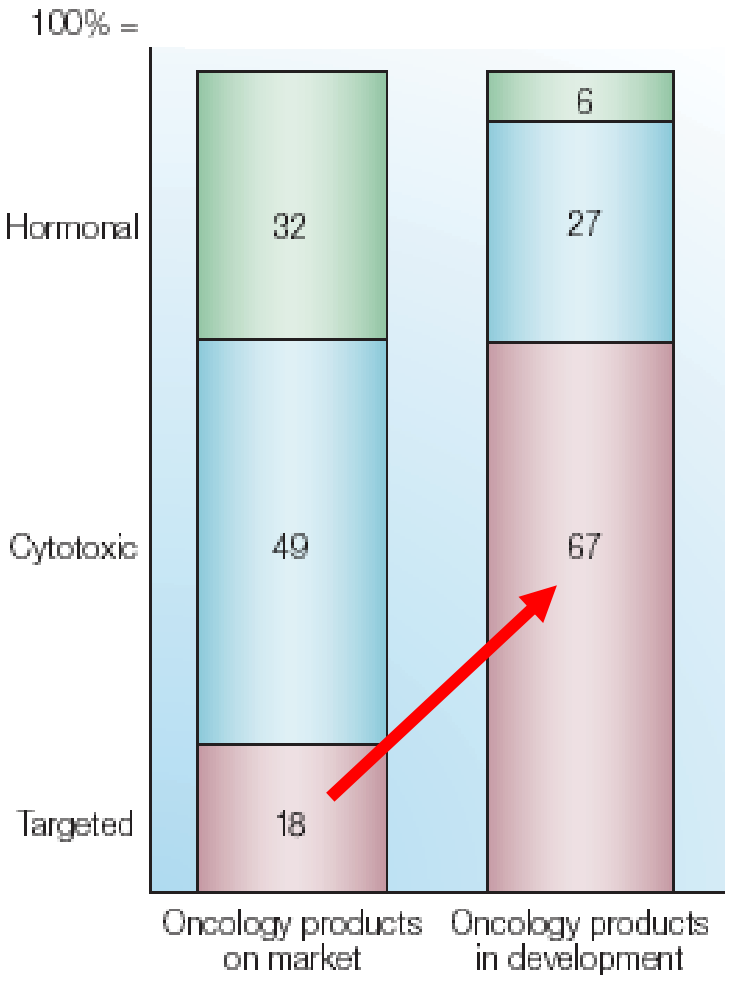
Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]

Molecole differenti/nuovi paradigmi

- > 800 anticancer compounds yearly under development

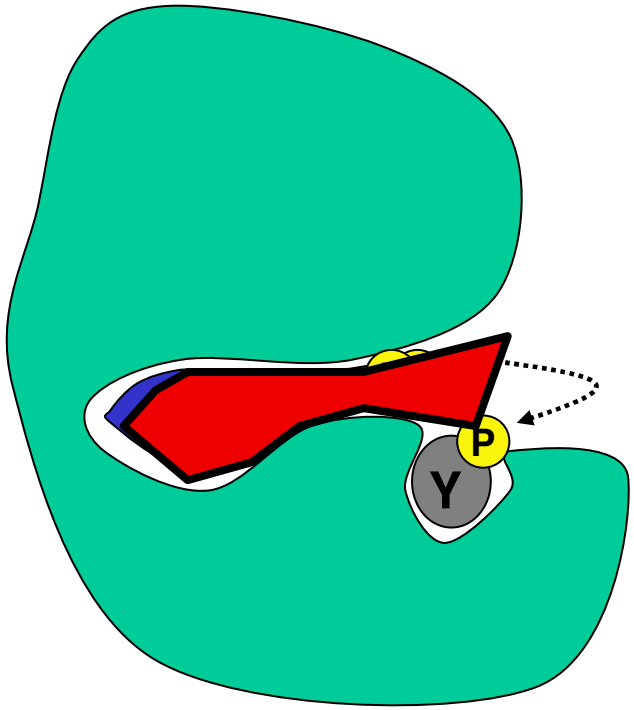
- Mainly targeted compounds
  - New mechanisms of action
  - New profile of activity
  - Distinct profile of toxicity
  - Often oral and prolonged adminstration





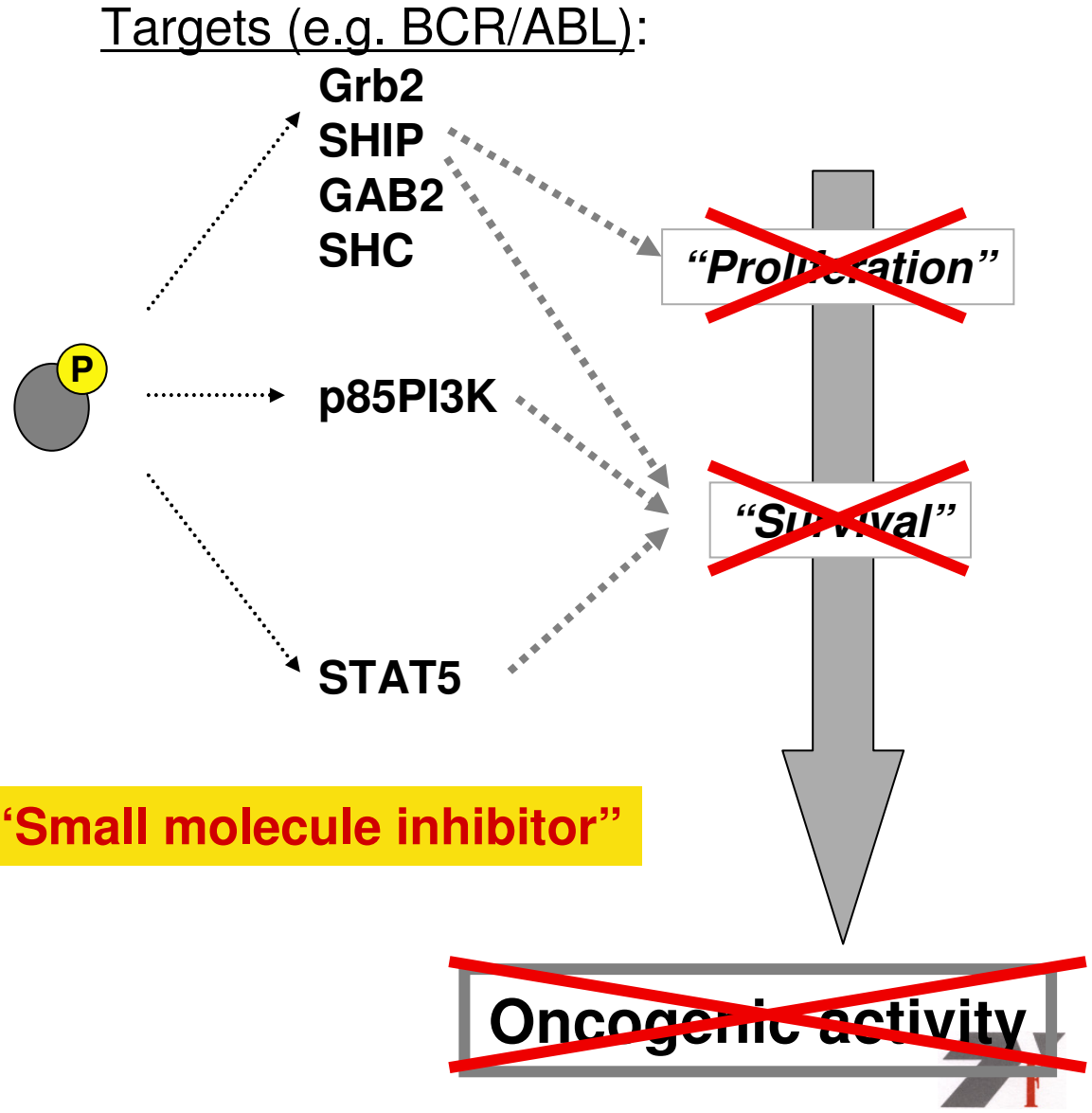
Lengauer et al., Nat Rev Drug Discov 2005

Geni “malati” come bersaglio selettivo di nuovi farmaci



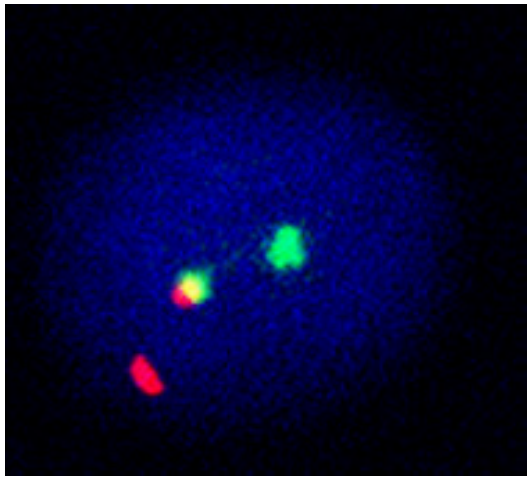
Mutated constitutive-active
or ***over-expressed***
protein kinase

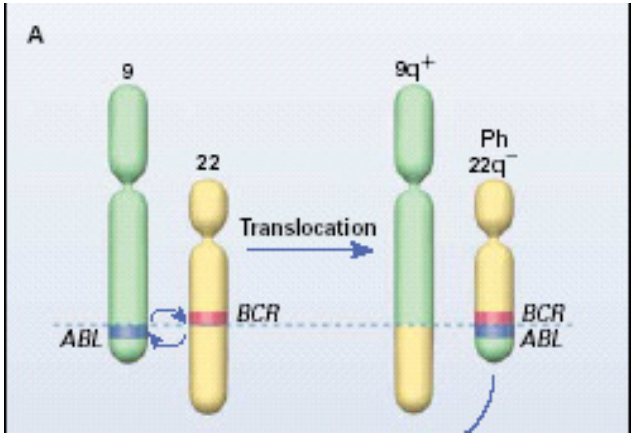
[e.g. *X-ABL*; FLT3-ITD]

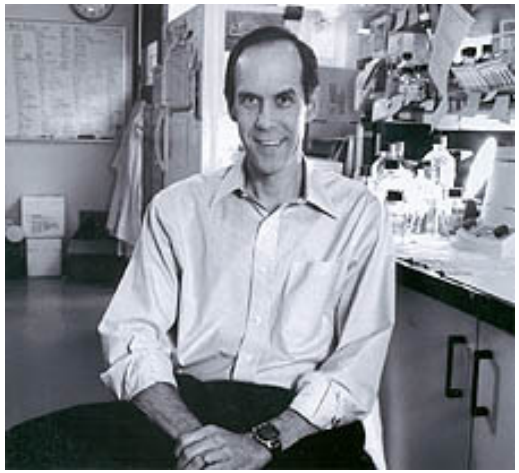


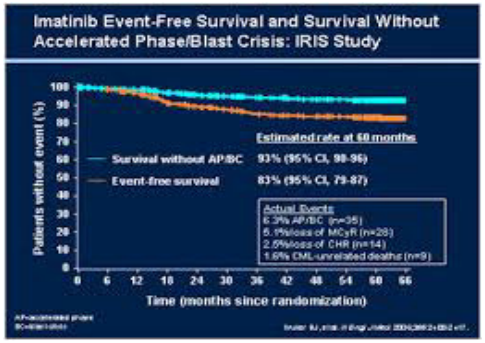
“Small molecule inhibitor”

Le leucemie con il cromosoma Philadelphia









CAR-T cells: the Breakthrough of the Year 2013

A 25 years old history….1989-2014

Proc. Natl. Acad. Sci. USA
Vol. 86, pp. 10024–10028, December 1989
Immunology

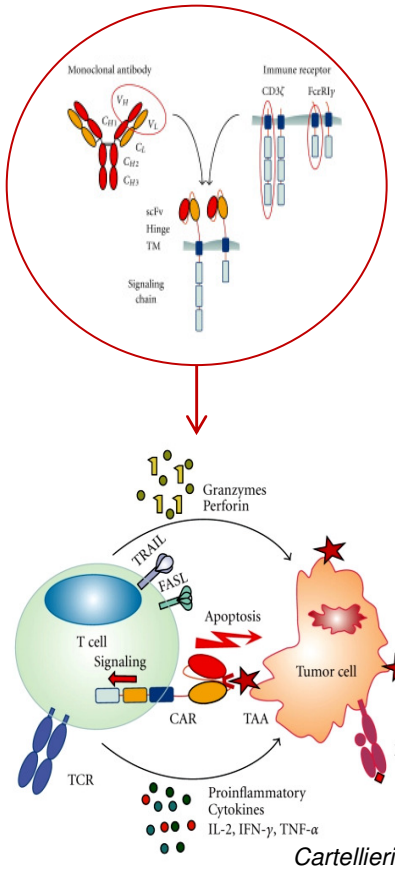
Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity

(chimeric genes/antibody variable region)

GIDEON GROSS, TOVA WAKS, AND ZELIG ESHHAR*

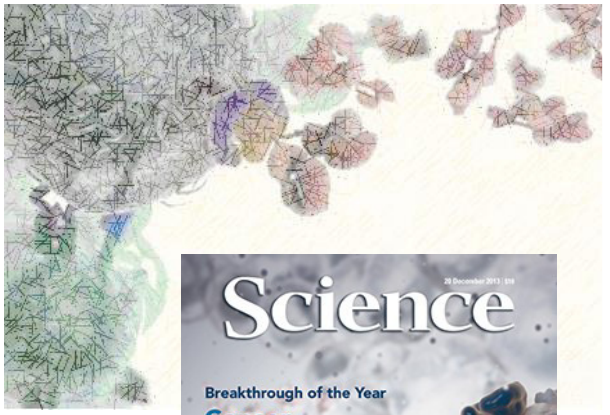
Department of Chemical Immunology, The Weizmann Institute of Science, Rehovot 76100, Israel

Communicated by Michael Sela, July 13, 1989 (received for review June 18, 1989)



Cartellieri et al., 2010

From bench to bedside and back



On 1 July 2014, FDA granted '**breakthrough therapy' designation to CTL019**, the anti-CD19 CAR T-cell therapy developed at the University of Pennsylvania

	ADULT DISEASE	PAEDIATRIC/ TYA DISEASE
SAME DISEASE AND SAME TARGET		
BRAF	Melanoma	Melanoma
IGF-1R	Ewing's sarcoma	Ewing' s sarcoma
BCR-ABL	CML, ALL Ph +	CML, ALL Ph +
CD30	HL, anaplastic large cell lymphoma	HL, anaplastic large cell lymphoma
ALK	Anaplastic large cell lymphoma	Anaplastic large cell lymphoma
LDE 225	Medulloblastoma	Medulloblastoma
CD20	NHL	NHL
SAME TARGET BUT DIFFERENT DISEASE		
ALK	Non-small-cell lung cancer	Neuroblastoma
LDE225	Small cell lung cancer	Medulloblastoma
BRAF	Melanoma	Glial tumors
mTOR	Kidney, breast, pancreatic neuroendocrine tumours	Subependymal giant-cell astrocytoma associated with tuberous sclerosis
SPECIFIC PEDIATRIC TARGET AND DISEASE		
N-MYC	-	Neuroblastoma
GD2	-	Neuroblastoma
PAX3/7-FOXO1	-	Rhabdomyosarcoma

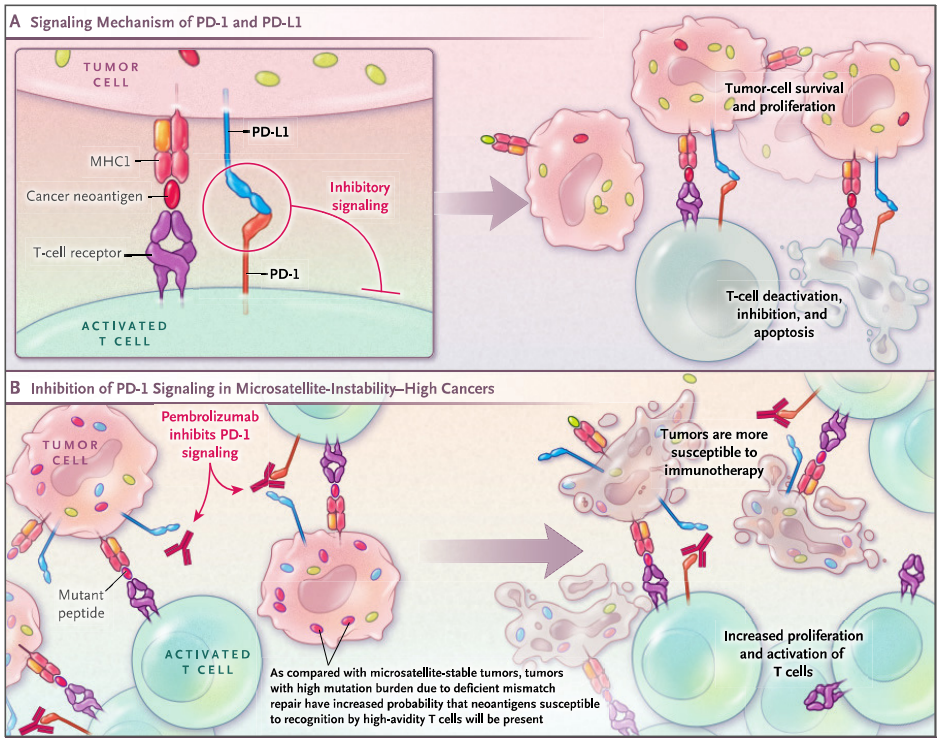
The NEW ENGLAND JOURNAL of MEDICINE

Perspective

OCTOBER 12, 2017

First FDA Approval Agnostic of Cancer Site — When a Biomarker Defines the Indication

Steven Lemery, M.D., M.H.S., Patricia Keegan, M.D., and Richard Pazdur, M.D.



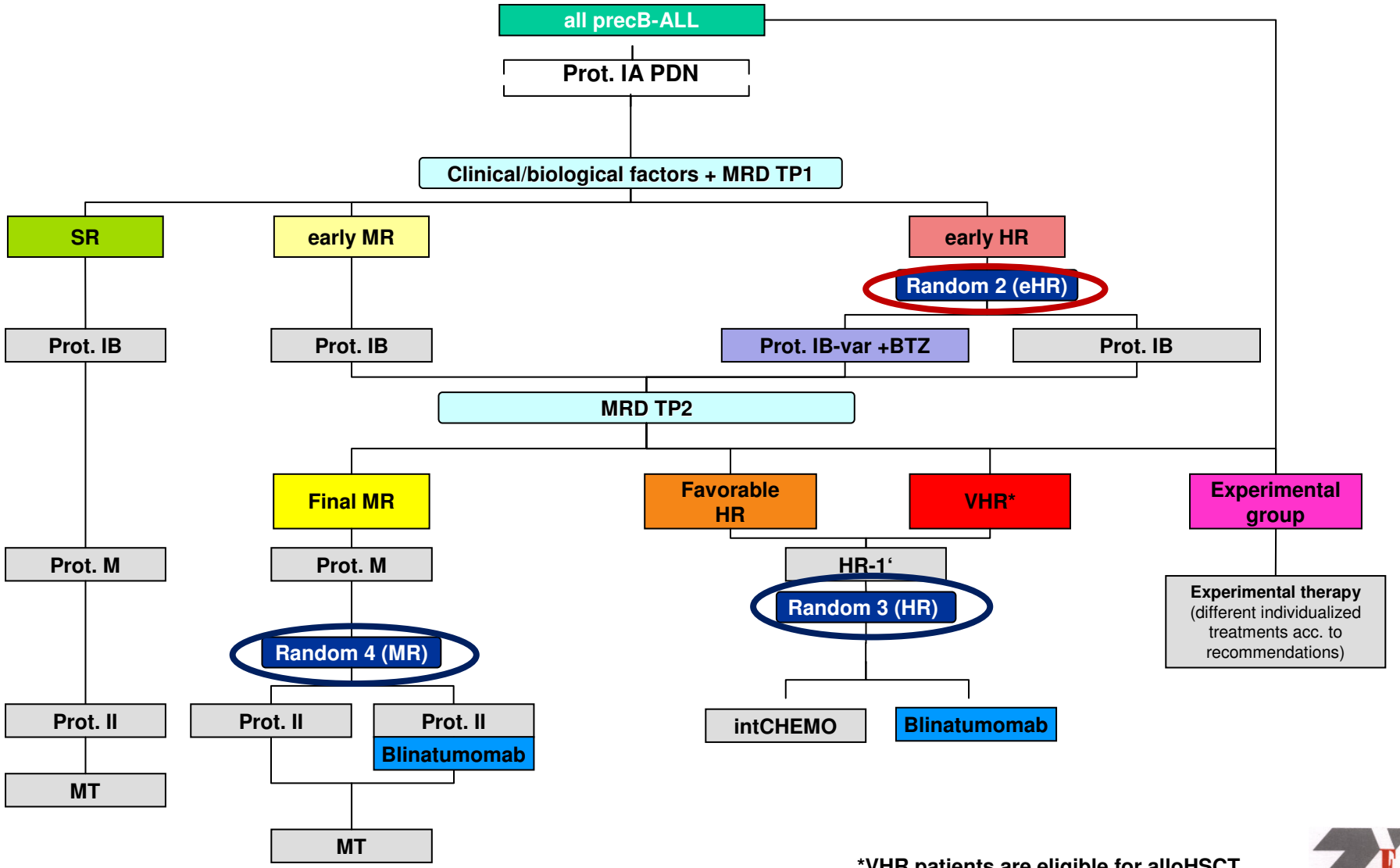
On May 23, 2017, the Food and Drug Administration (FDA) ap- proved pembrolizumab, a pro- grammed death 1 (PD-1) inhibitor, for the treatment of adult and pediatric patients with unresect- able or metastatic, microsatellite- instability–high (MSI-H) or mis- match-repair–deficient (dMMR) solid tumors, regardless of tumor site or histology.

Quali "*unmet clinical needs*"

1. Farmaci nuovi efficaci in studi di fase 2 in pazienti con malattia resistente: come valutarli *upfront* in modo controllato? Chi fornisce il farmaco?
2. Possibilità di utilizzare un farmaco off-label sul singolo paziente ma non all'interno di uno studio clinico;
3. Accesso a nuovi farmaci non solo per patologia ma anche in base al meccanismo d'azione.

AIEOP-BFM ALL 2018: BCP-ALL

Patient stratification and treatment options



*VHR patients are eligible for alloHSCT

Bortezomib

(Messinger Y et al 2012)

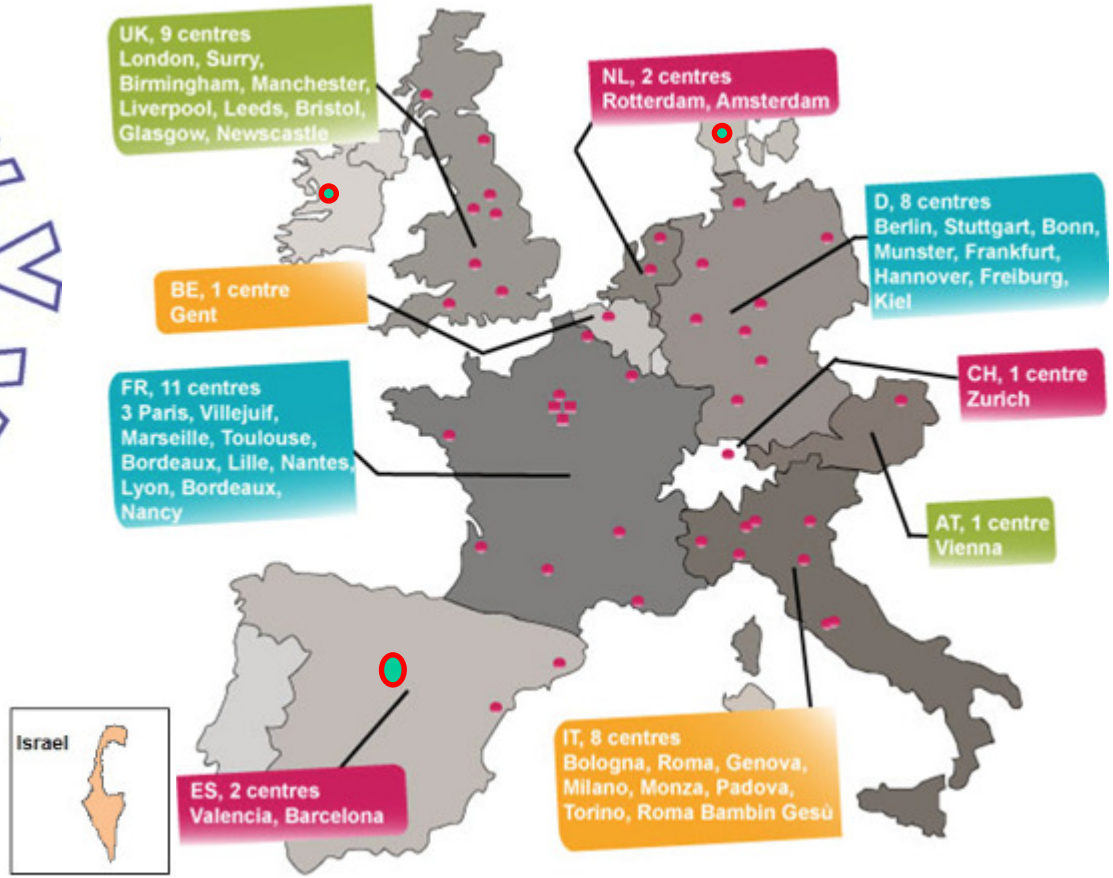
Table 3. Response data

	Total	B	T
n	22	20	2
CR	14 (64)*	14 (70)	0
CRp	2 (9)	2 (10)	0
OR (CR + CRp)	16 (73)†	16 (80)	0
SD/PD	2 (9)	0	2 (100)
Toxic deaths	3 (14)	3 (15)	0
Undetermined‡	1 (4.5)	1 (5)	0
BM response			
M1	17 (77)	17 (85)	0
M2/M3	2 (9)	0	2 (100)
Toxic deaths	3 (14)	3 (15)	0

Innovative Therapies for Children with Cancer

ITCC

European consortium

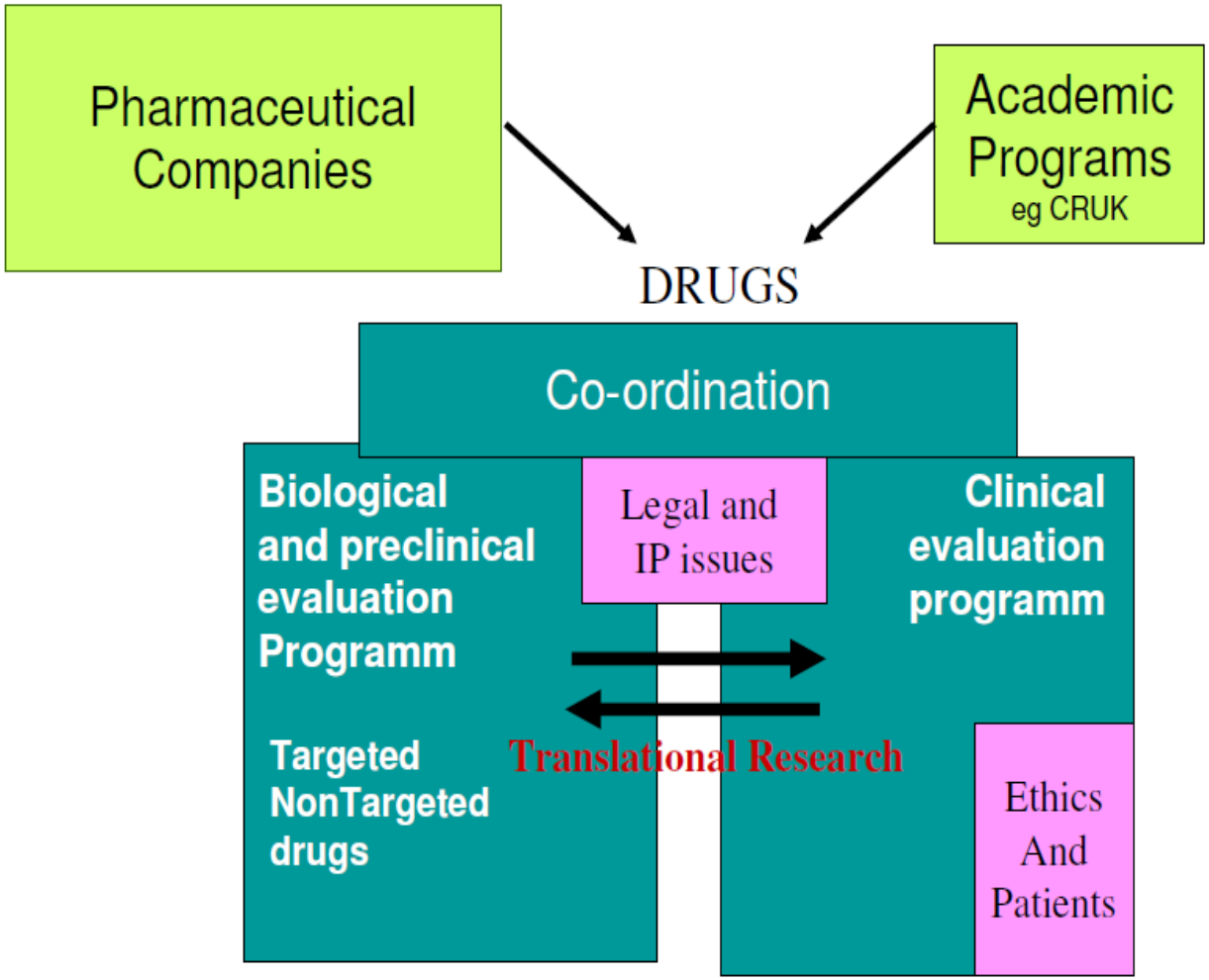


- Created in 2003
- 43 investigation centers
- 9 research labs
- in 11 member states
  Au, Be, Dnk, F, G, I, Ie, NL, Sp, Sw, UK

To conduct a comprehensive preclinical and clinical new drug development program taking into account the unique ethical dimension of investigating new treatments in children with lifethreatening disease

http://www.ITCC-consortium.org

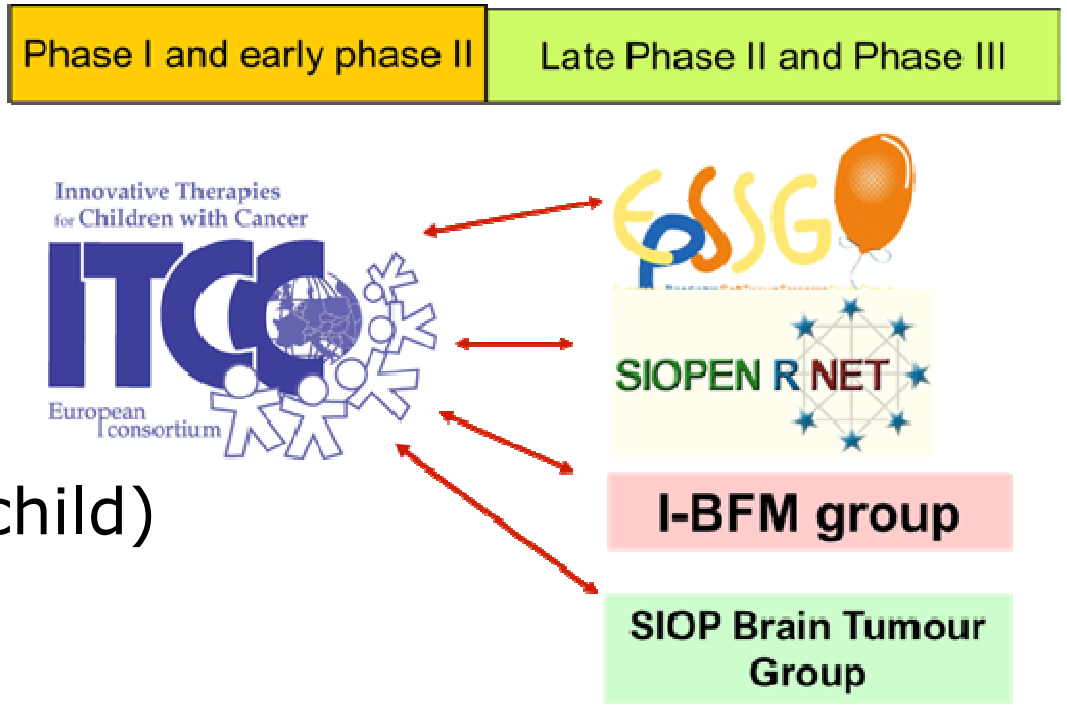
General organization of ITCC



European biology-driven drug development

910 patients
in ITCC trials
Over **10 years**

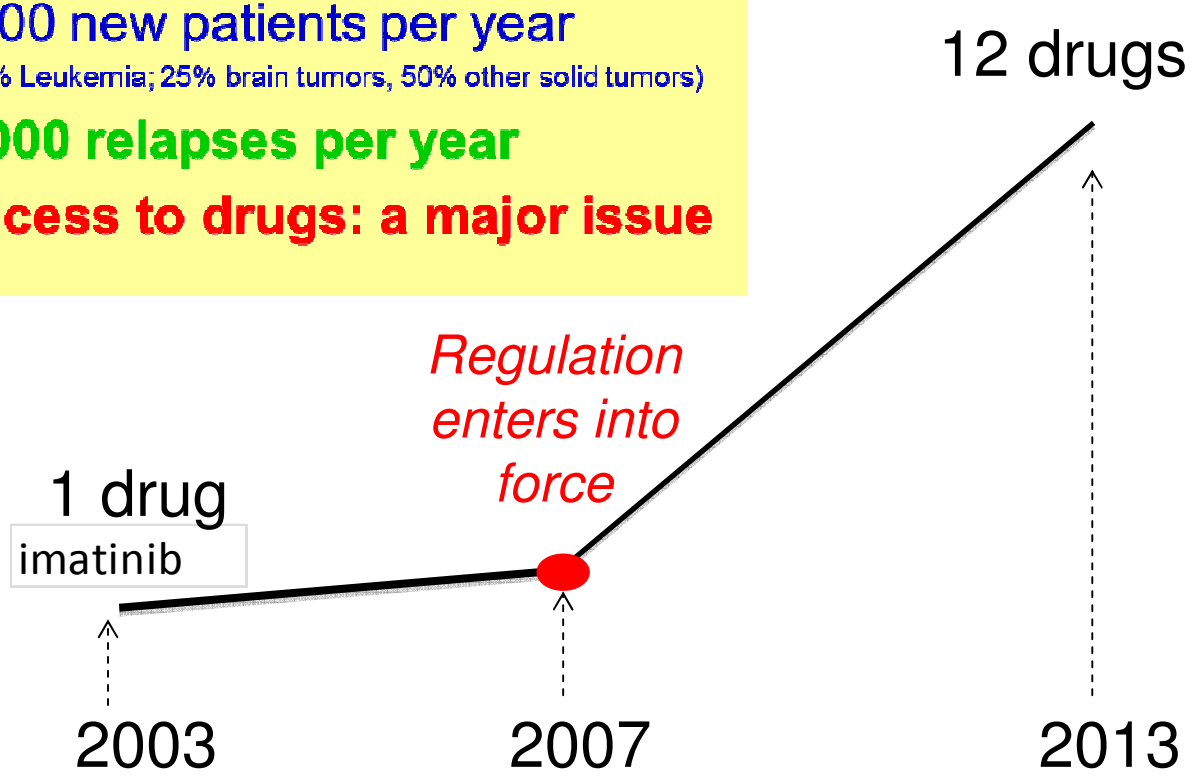
Ongoing:
-12 new drugs
-9 phase I* (7 first in child)
-8 phase 2
-58% single agent



- Joint development programs with EU study Groups
- *Four trials in collaboration with C17, COG phase 1, POETIC and TACL

Drug development in ITCC

- **1000 patients** in ITCC trials
- over **10 years**
- In ITCC centers
- 4000 new patients per year
  (25% Leukemia; 25% brain tumors, 50% other solid tumors)
- **1000 relapses per year**
- **Access to drugs: a major issue**



bevacizumab
blinatumumab
bortezomib
dabrafenib
ipilimumab
LDE225
LDK378
LEE011
nab-paclitaxel
nilotinib
PKC412
vidaza

Within PIP

EU Pediatric Medicine regulation

- Revoke the class waiver list: to design and approve a PIP

  From condition in adults

  To the drug mechanism of action (crizotinib example)

  - Propose new incentives for specific oncology drugs against targets that are specific to childhood cancers

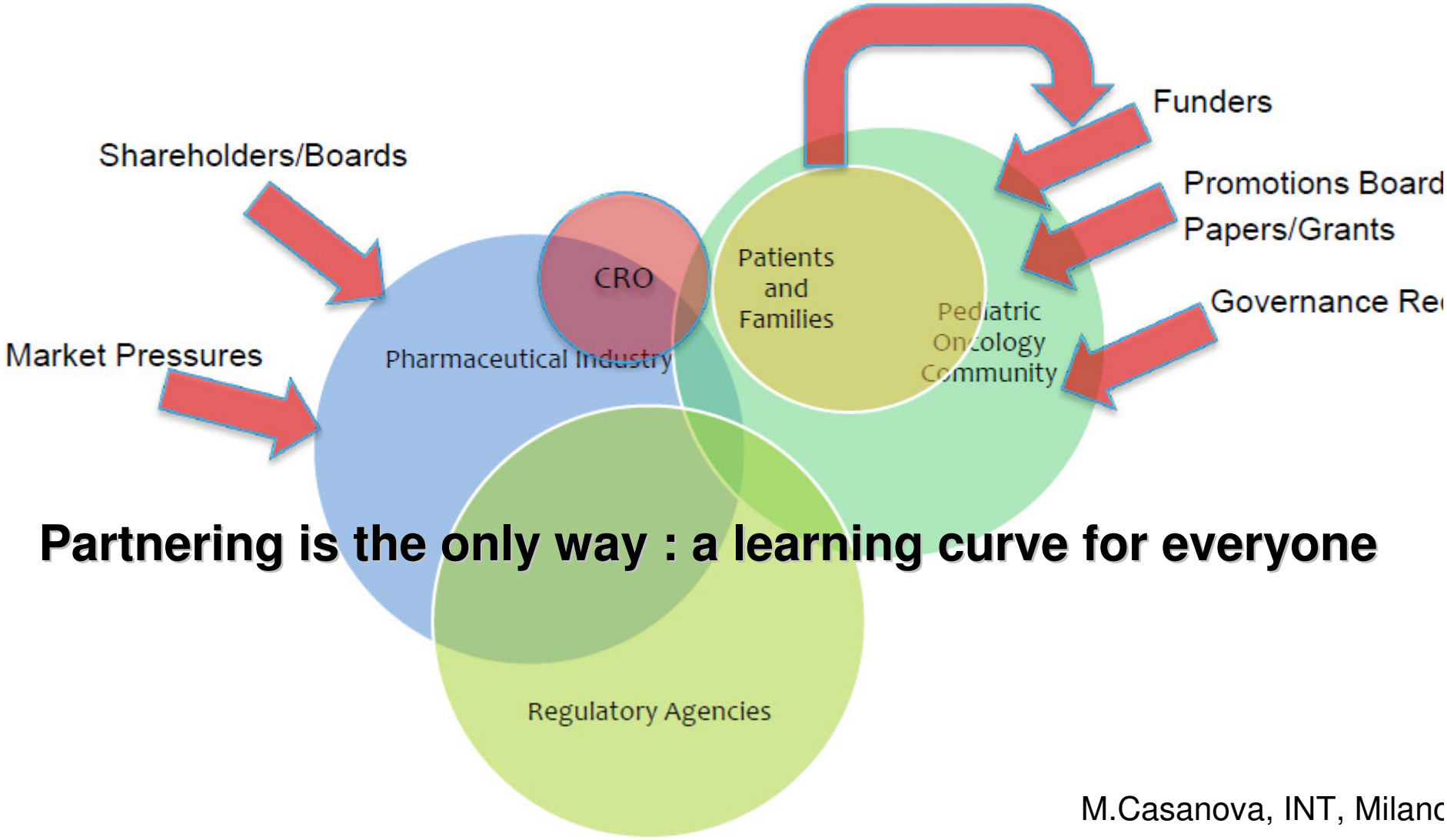
The number of pediatric trials is not the best misure of success of the Pediatric Regulation. Better ultimate metrics are the number of:

- Drugs that have reached phase III trials
- Drugs that have reached clinical use
- First-in-child studies conducted in Europe
- Academic early clinical trials
- Companies that have provided cancer drugs for academic trials (or academic preclinical studies)

Conclusioni

1. Risultati ottenuti in oncologia pediatrica con farmaci off-label;
2. Cambio di paradigma: profilo genetico e nuove molecole con opportunità di farmaci più specifici e con minori effetti a lungo termine;
3. Limiti e vantaggi della EU "*Children Medicine Regulation*";
4. Accesso off-label e accesso ai farmaci per validazione di efficacia;
5. Complessità di gestione di studi internazionali.

The Actors



Partnering is the only way : a learning curve for everyone