



XXXIV Congresso Nazionale SIIPS
**Dagli albori della vita ...
un cammino insieme**



Torino
Star Hotel Majestic - Corso Vittorio Emanuele
22-25 Settembre 2022
Presidenti del Congresso:
GIUSEPPE DI MAURO | GIANNI BONA
Presidente Onorario:
PROF. GIANCARLO MUSSA

Il punto sui tumori infantili in Italia e nel mondo. I grandi progressi in ambito diagnostico terapeutico

Prof. Andrea Pession
Cattedra di Pediatria - Università di Bologna

ONCOLOGIA PEDIATRICA

Istotipi

Categoria ICCC in ordine di frequenza (0-18 anni)

I Leucemia	X Tumori a Cellule Germinali
Ia - linfoide	VIII Tumori Ossei
Ib - acuta mieloide	VIIIa – osteosarcoma
III Tumori SNC	VIIIc – sarcoma di Ewing
II Linfomi	IVa Neuroblastoma
Ila - Hodgkin	VIa Tumore di Wilms
Ilb,c,d - non-Hodgkin #	V Retinoblastoma
## Carcinomi	XIb - Tiroide
IX Sarcomi dei Tessuti Molli	XId – melanoma
IXa – rhabdomyosarcoma	Altri NAS

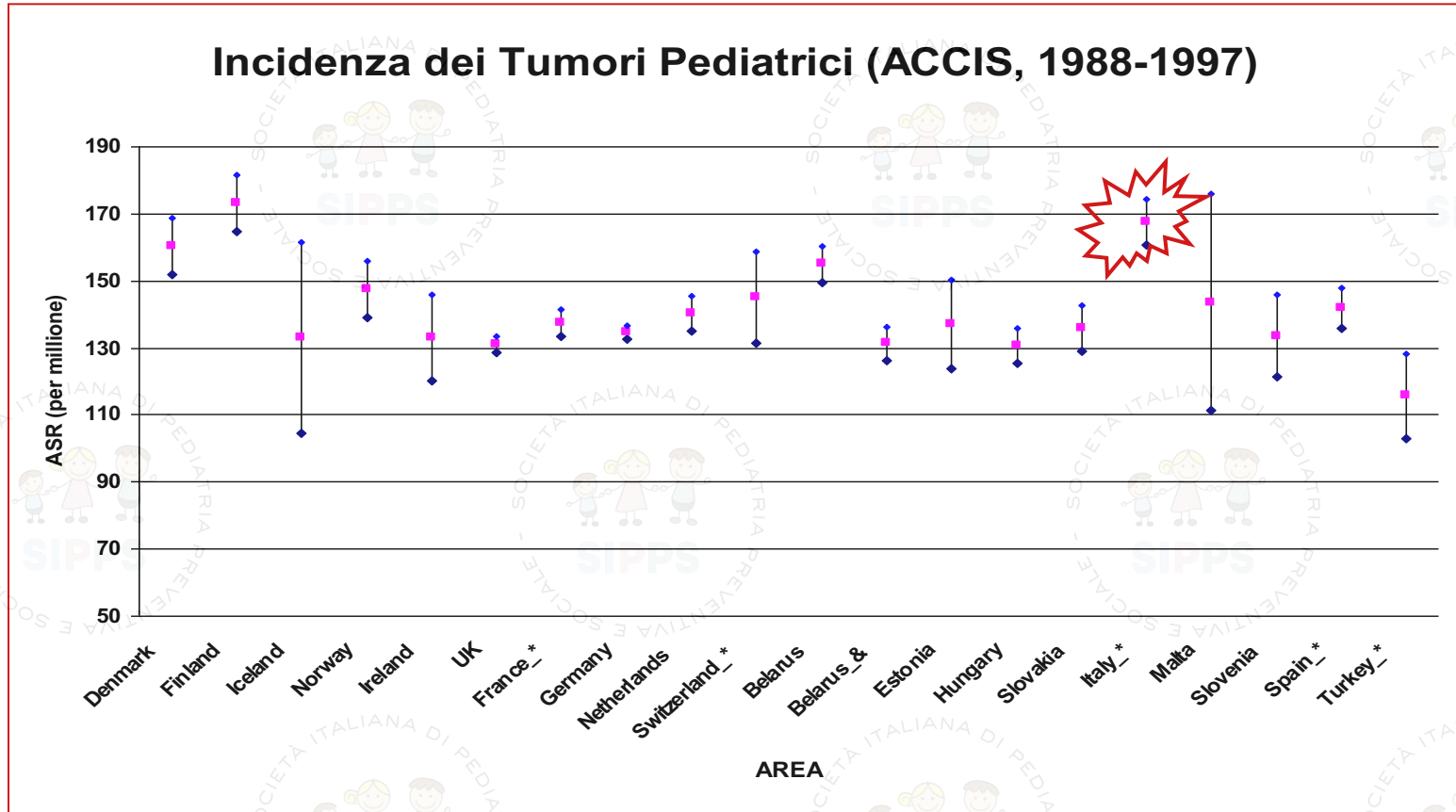
Non-Hodgkin (Ilb), Burkitt's (IIc) e miscellanea (IIId)

Renali (VIb), epatiche (VIIb) e altri (XI)



I TUMORI INFANTILI IN EU

- L'incidenza dei tumori infantili mostra variazioni tra i Paesi EU



<http://accis.iarc.fr/>

ACCIS Automated Cancer Information System // IARC International Agency for Research on Cancer



Premessa

- L'oncologia pediatrica prende avvio **negli anni '40** con i primi studi clinici sulla chemioterapia per la leucemia acuta.
- Ad 80 anni da quei primi fallimentari tentativi, si stima che oggi possa **guarire oltre l'80% dei bambini** con diagnosi di tumore possa guarire.
- L'oncologia pediatrica costituisce certamente **un paradigma di successo della medicina moderna** per via dei notevoli incrementi dei tassi di sopravvivenza che ha riguardato tutte o quasi le patologie neoplastiche infantili.

Agenda

Le ragioni del successo

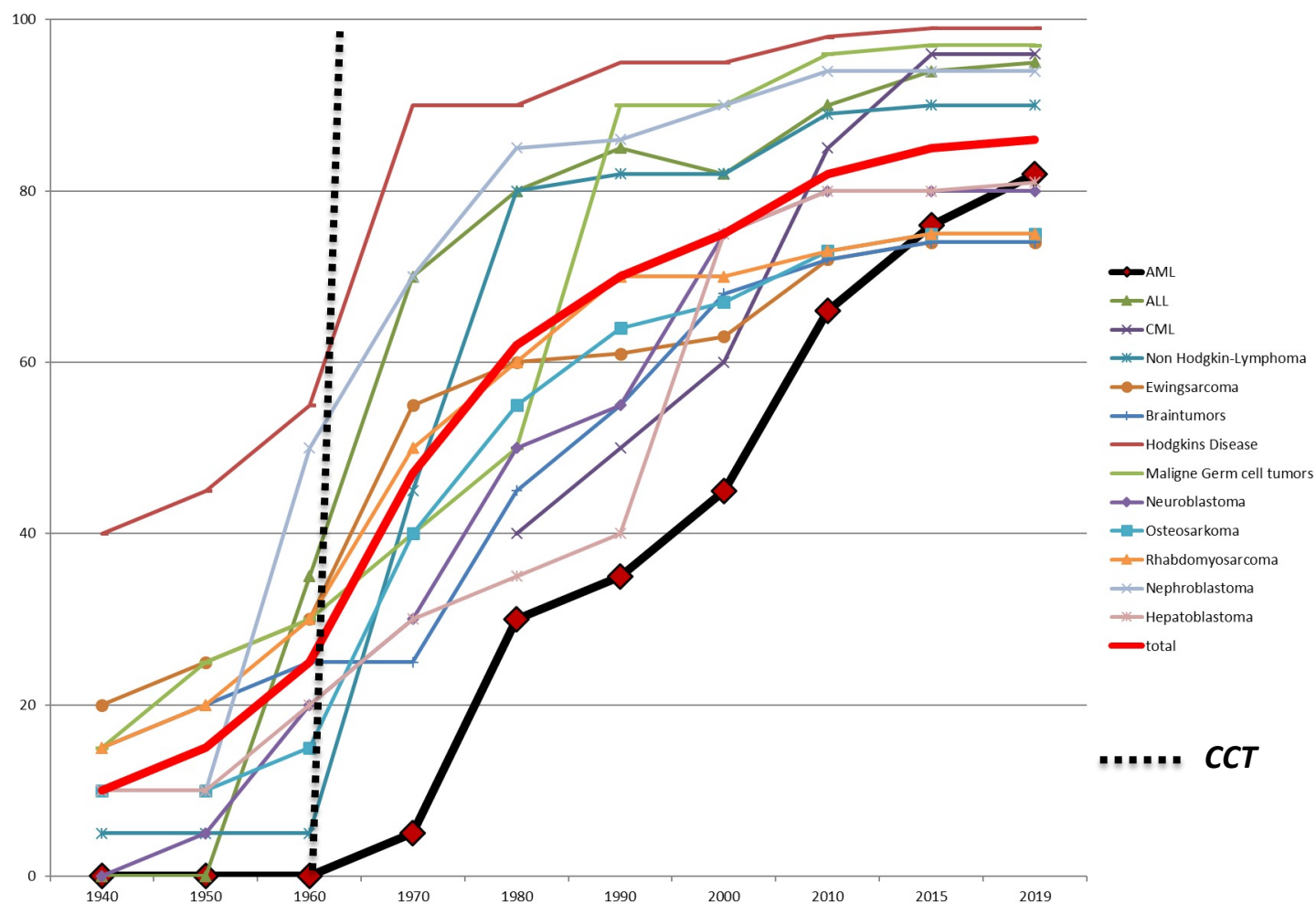
- conduzione di sperimentazioni cliniche controllate
- diagnosi precisa
- predisposizione alla malattia oncologica in età pediatrica
- terapia adattata al rischio
- monitoraggio della malattia residua minima
- terapia multimodale integrata con terapia molecolari mirate, immunoterapia e terapie cellulari ed opportune terapie di supporto
- approccio olistico centrato sul paziente e la sua famiglia.



Sperimentazioni cliniche controllate: *la storia di un successo e gli orizzonti sfidanti.*

Sperimentazioni cliniche controllate: RISULTATI

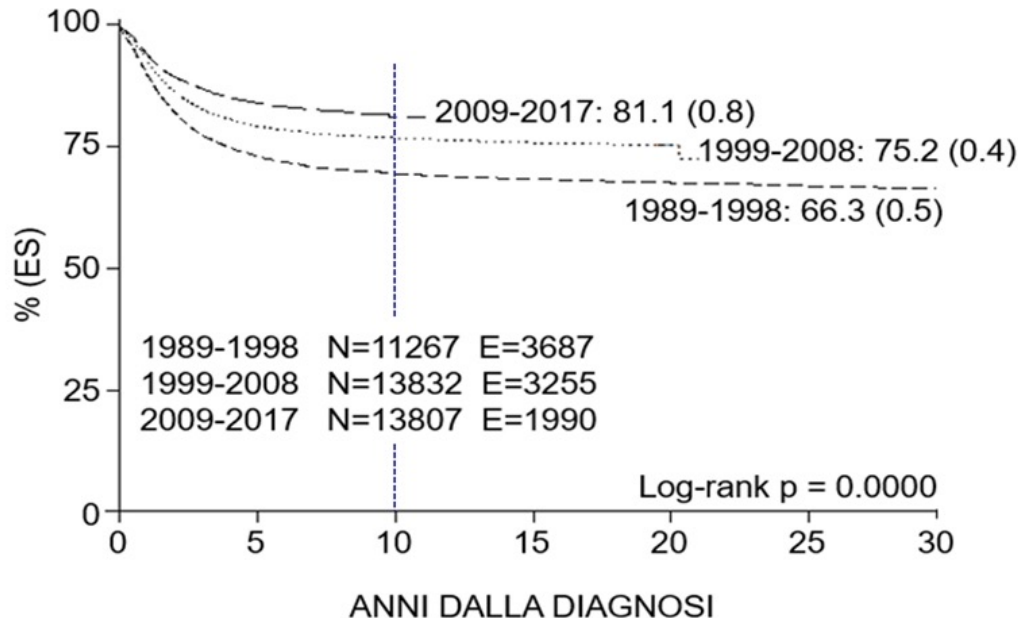
Incremento della sopravvivenza per periodo di diagnosi nei paesi industrializzati





Sperimentazioni cliniche controllate: RISULTATI

Sopravvivenza per periodo di diagnosi di 38907 casi (0-19 anni) residenti in Italia e diagnosticati come neoplasia maligna nel periodo 1 gennaio 1989 – 31 luglio 2017, reclutati attraverso il Mod. 1.01



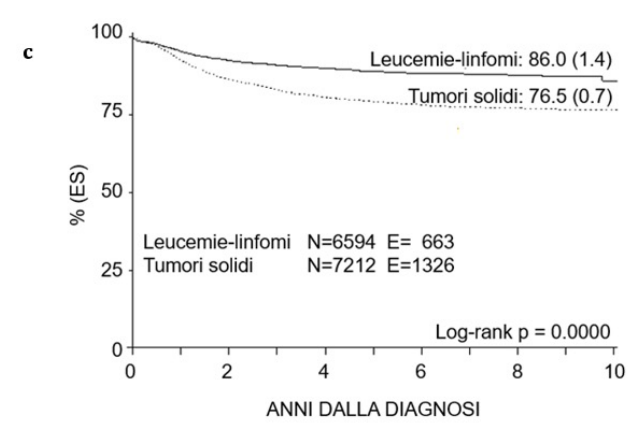
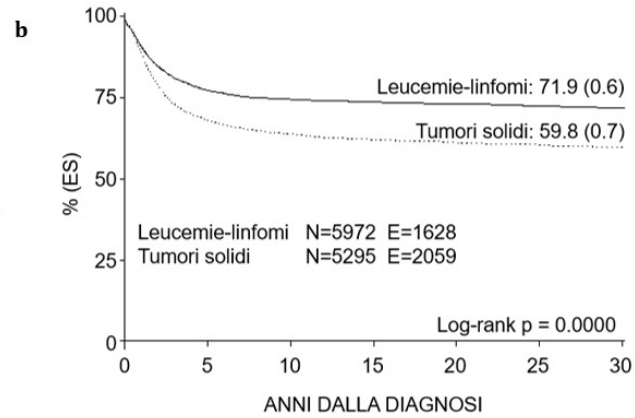
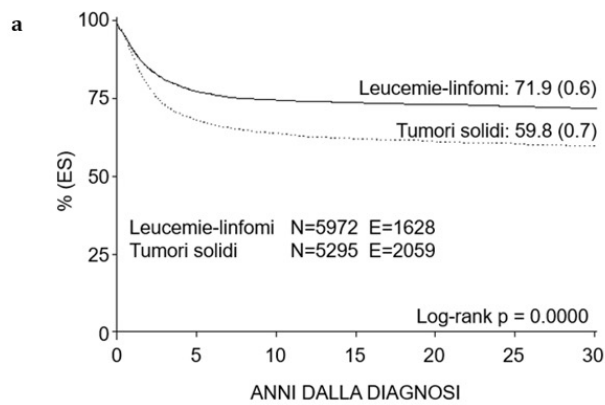
La **sopravvivenza a 10 anni** dalla diagnosi di neoplasia risulta pari a:

- **69.5%** (IC95% 0.4) nel periodo 1989-1998;
- **76.8%** (IC95% 0.4) nel periodo 1999-2008;
- **81.1%** (IC95% 0.8) nel periodo 2009-2017.



Sperimentazioni cliniche controllate: RISULTATI

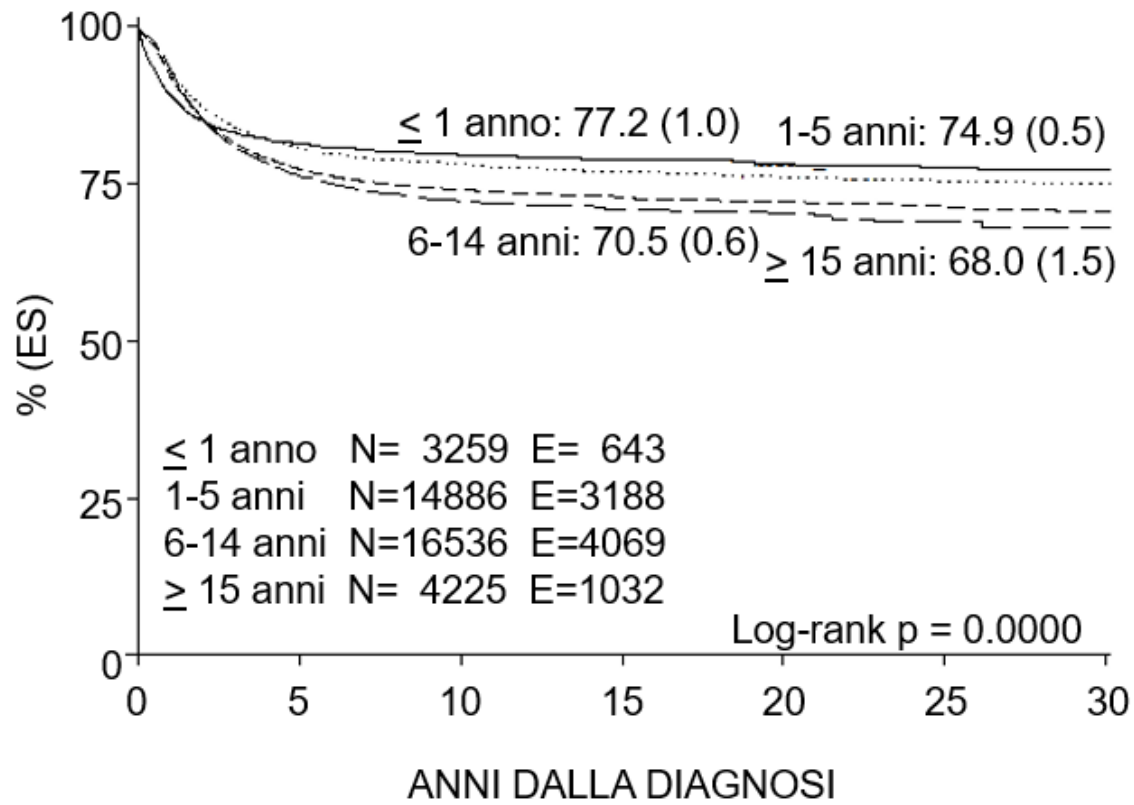
Sopravvivenza per periodo di diagnosi [a) 1989-1998; b) 1999-2008; c) 2009-2017] e categoria diagnostica di 38907 casi (0-19 anni) residenti in Italia e diagnosticati come neoplasia maligna nel periodo 1 gennaio 1989 – 31 luglio 2017, reclutati attraverso il Mod. 1.01.





Sperimentazioni cliniche controllate: RISULTATI

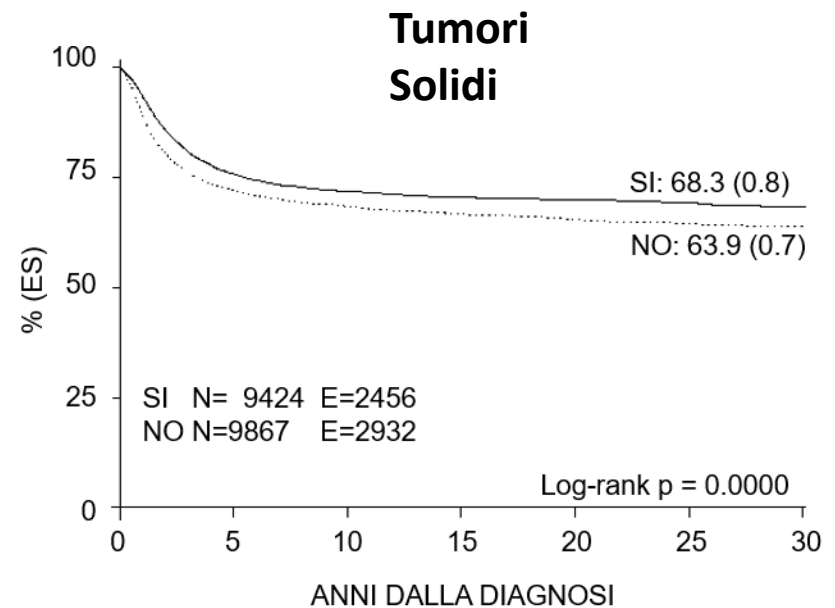
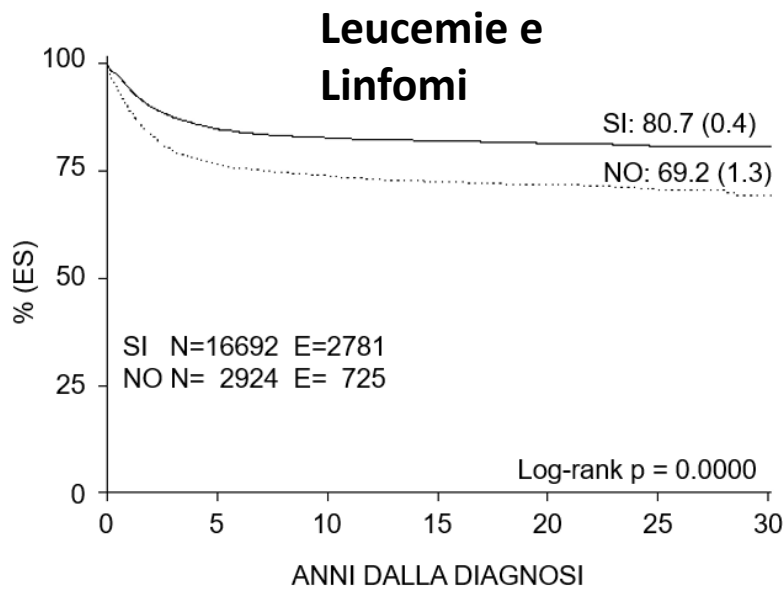
Sopravvivenza per periodo per fascia d'età di 38907 casi (0-19 anni) residenti in Italia e diagnosticati come neoplasia maligna nel periodo 1 gennaio 1989 – 31 luglio 2017, reclutati attraverso il Mod. 1.01.





Sperimentazioni cliniche controllate: RISULTATI

Sopravvivenza per protocollo e AIEOP vs NO-AIEOP e categoria diagnostica di 38907 casi (0-19 anni) residenti in Italia e diagnosticati come neoplasia maligna nel periodo 1 gennaio 1989 – 31 luglio 2017, reclutati attraverso il Mod. 1.01.





Sperimentazioni cliniche controllate: IMPATTO

Migrazione sanitaria in Italia per diagnosi di tumore pediatrico. Dati del registro AIEOP Mod. 1.01.

a) Migrazione per periodo di diagnosi; b) Migrazione per area geografica di residenza;

a

<i>Età (anni)</i>	<i>1989-1998</i> %	<i>1999-2008</i> %	<i>2009-2017</i> %	<i>Totale</i> %
0-14	31.1	27.6	23.2	27.2
15-19	34.2	30.9	26.8	29.2
Totale	31.2	28.0	23.7	27.4

b

<i>Età (anni)</i>	<i>Res. Nord</i> %	<i>Res. Centro</i> %	<i>Res. Sud-Isole</i> %	<i>Totale</i> %
0-14	2.7	11.8	43.1	27.2
15-19	1.9	13.8	56.9	29.2
Totale	2.6	12.1	44.4	27.4



Sperimentazioni cliniche controllate: IMPATTO

Migrazione sanitaria in Italia per diagnosi di tumore pediatrico. Dati del registro AIEOP Mod. 1.01.

c) Indicatori di accesso ai servizi di cure AIEOP: **Keep**: la capacità dei centri locali di mantenere i bambini affetti da patologia tumorale nella stessa macroarea di residenza. **Attract**: la capacità dei centri di attrarre pazienti residenti in macroaree diverse dalla propria. **Burden**: numero di pazienti che vengono trattati in centri al di fuori delle macroaree di loro residenza.

^c Residenti	Centri AIEOP Nord (%)	Centri AIEOP Centro (%)	Centri AIEOP Sud-Isole (%)	Totale (%)
Nord	15930 (97.3)	402 (2.5)	31 (0.2)	16363 (43.4)
Centro	916 (11.2)	7167 (88.0)	66 (0.8)	8149 (21.6)
Sud-Isole	3815 (28.9)	2057 (15.5)	7349 (55.6)	13221 (35.0)
Totale	20661 (54.8)	9626 (25.5)	7446 (19.7)	37733 (100)



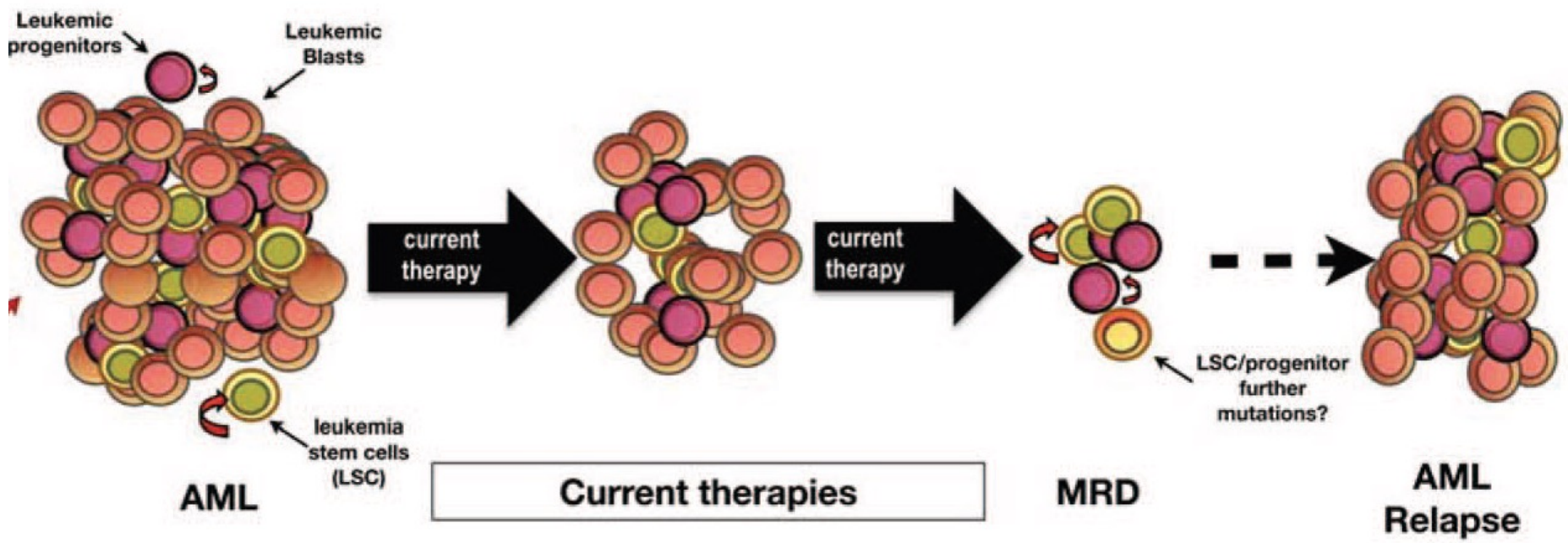
Sperimentazioni cliniche controllate: IMPATTO

Migrazione sanitaria in Italia per diagnosi di tumore pediatrico. Dati del registro AIEOP Mod. 1.01.

c) Indicatori di accesso ai servizi di cure AIEOP: **Keep**: la capacità dei centri locali di mantenere i bambini affetti da patologia tumorale nella stessa macroarea di residenza. **Attract**: la capacità dei centri di attrarre pazienti residenti in macroaree diverse dalla propria. **Burden**: numero di pazienti che vengono trattati in centri al di fuori delle macroaree di loro residenza.

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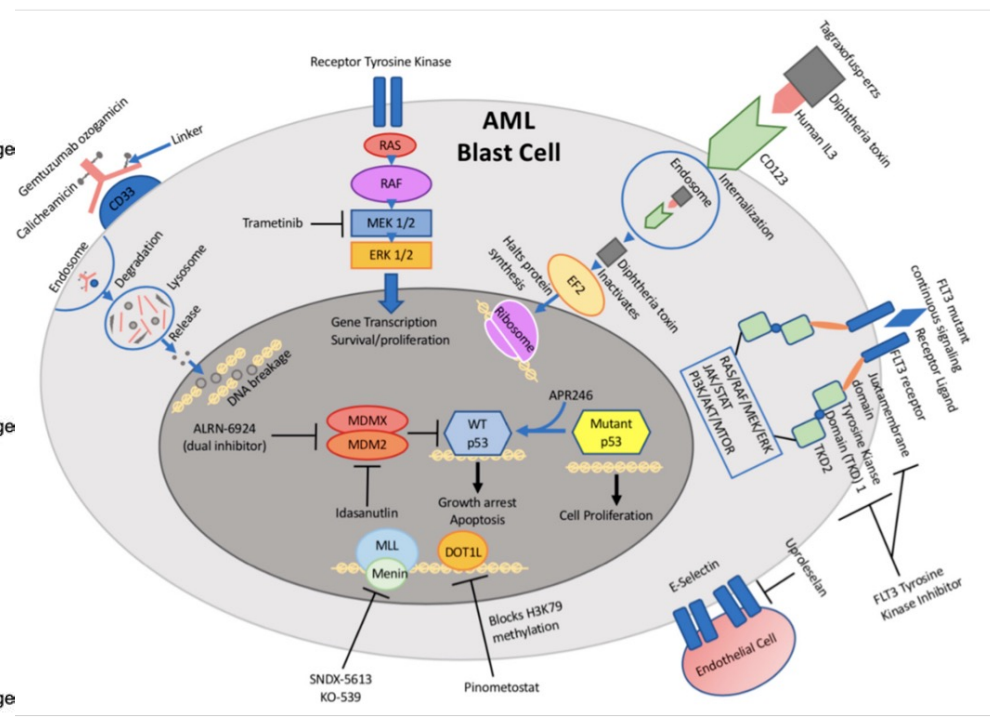
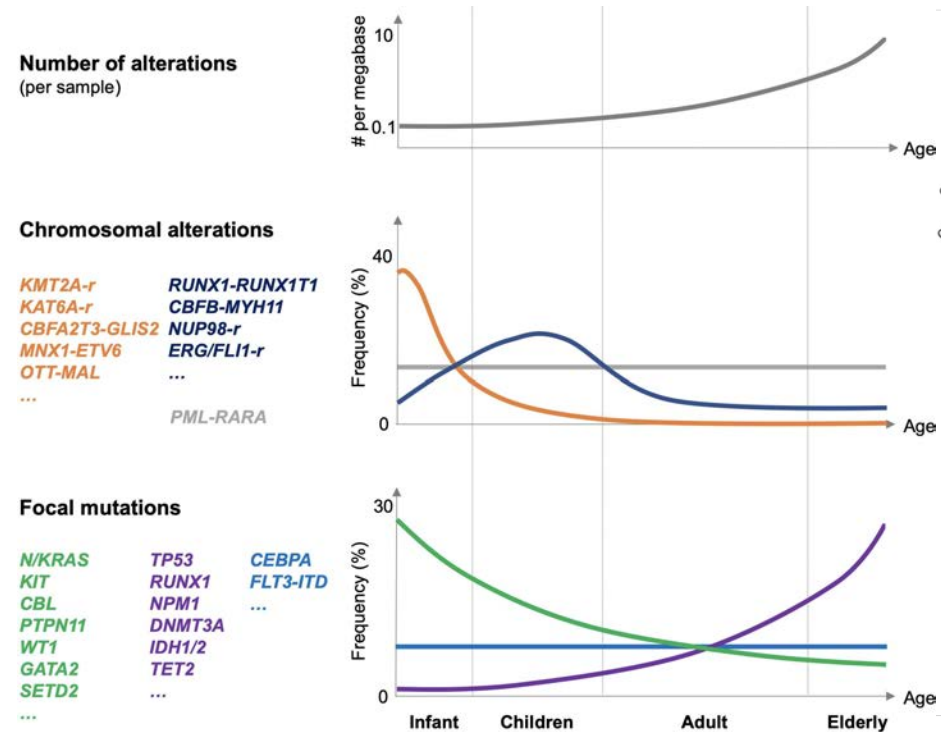
Sperimentazioni cliniche controllate: LIMITE



I limiti di una chemioterapia non sono solo gli effetti collaterali a breve e lungo termine, ma anche il mancato controllo della crescita dei cloni resistenti.

Sperimentazioni cliniche controllate: OPPORTUNITA' ?

Terapie molecolari mirate per il trattamento delle leucemie mieloidi acute



Mercher T, Schwaller J. *Front Pediatr.* 2019 Nov 13;7:466.

Lonetti A, Pession A, Masetti R. *Front Pediatr.* 2019 Nov 15;7:463.



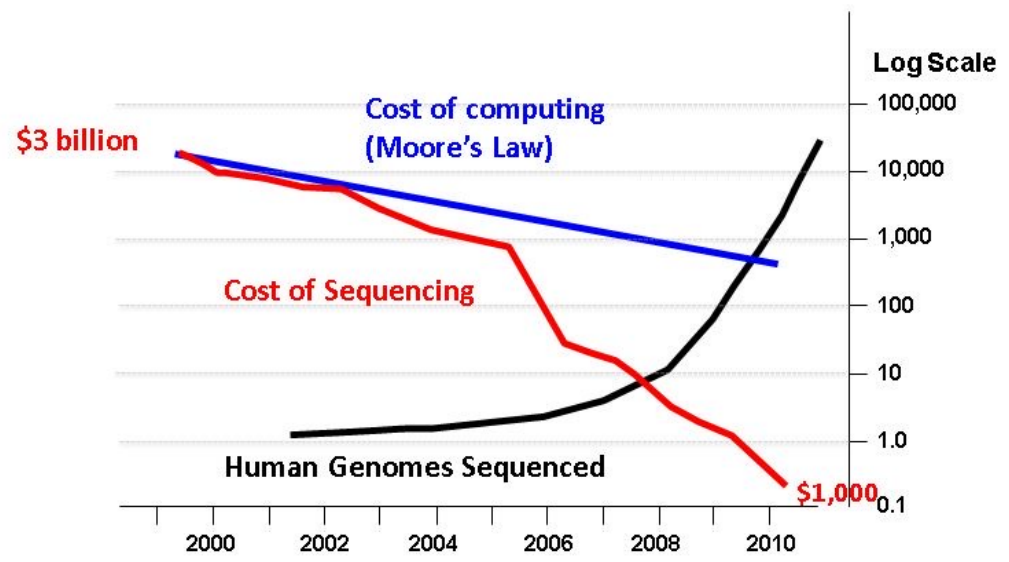
Diagnosi precisa: *la rivoluzione nosologica dell'era post-genomica.*



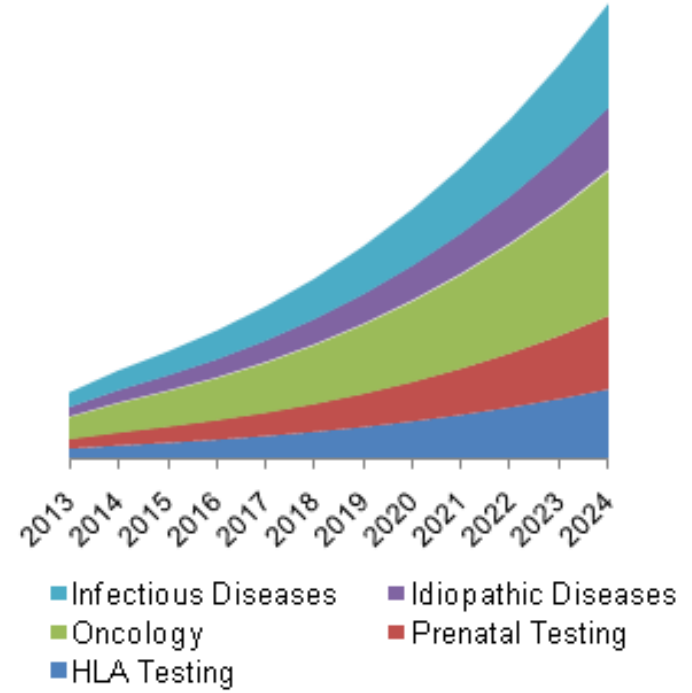
Diagnosi precisa: NUOVE TECNOLOGIE

Adapted from
The Economist

The Sequencing Explosion



U.S. Next Generation Sequencing Market, By Application, 2013-2024 (USD Million)



Diagnosi precisa: NUOVA NOSOLOGIA

Classificazione biologico molecolare dei medulloblastomi.

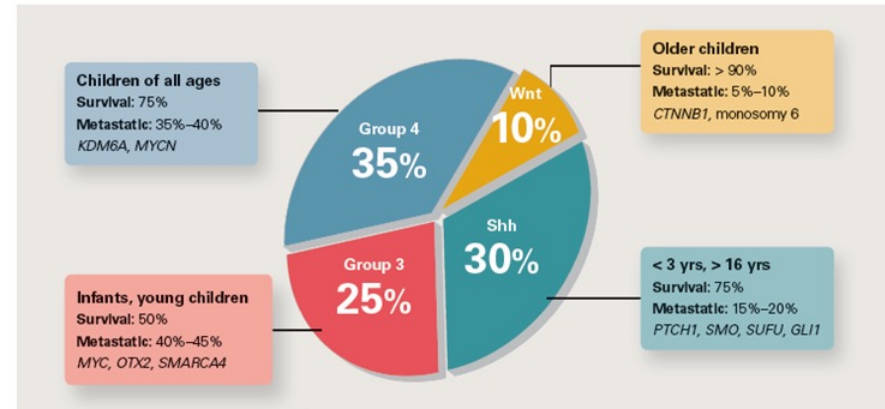
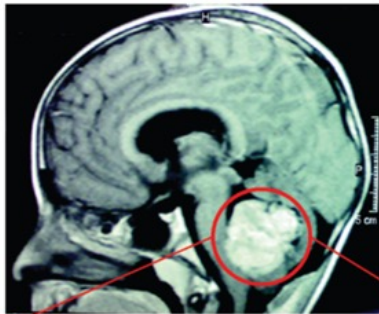


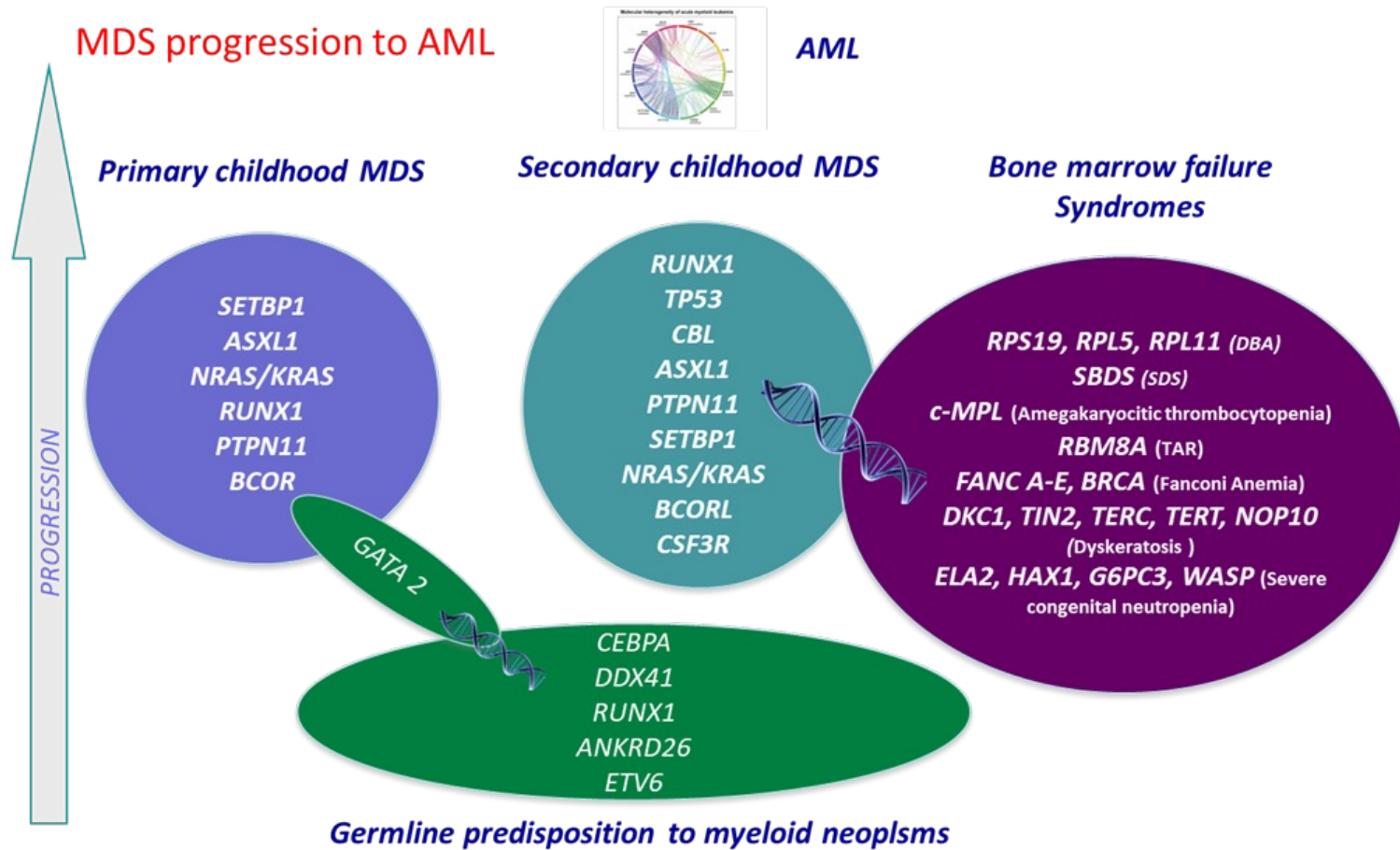
Figure 1. Molecular Subtypes of Medulloblastoma—Medulloblastoma has four molecular subtypes, each with distinct biologic and clinical characteristics. Metastatic = at time of diagnosis; Shh = Sonic hedgehog; survival = overall survival at 5 years; Wnt = Wnt/Wingless.

WNT (10%)	SHH (30%)	Group 3 (25%)	Group 4 (35%)
CTNNB1 mutation Monosomy 6	PTCH1/SMO/SUFU mutation MYCN amplification	MYC amplification PVT1-MYC fusion	CDK6 amplification Isochromosome 17q SNCAIP duplication
WNT signaling	SHH signaling PI3K signaling	Photoreceptor/GABAergic signaling TGF-β signaling	Neuronal/Glutamatergic signaling NF-kB signaling
MYC +	MYCN +	MYC +++	Minimal MYC/MYCN
5y OS 94%	5y OS 87%	5y OS 32%	5y OS 76%
Rare M+	Uncommon M+	Very frequent M+	Frequent M+



Diagnosi precisa: NUOVA NOSOLOGIA

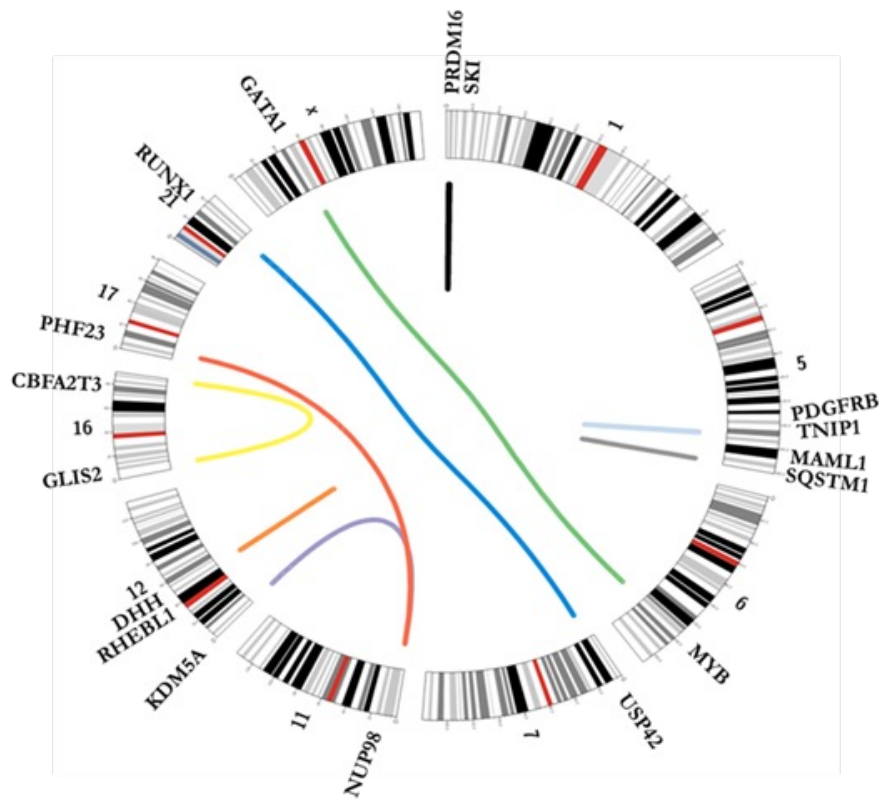
Profilo genetico dei disordini mieloproliferativi.





Diagnosi precisa: NUOVE ENTITA'

Nuovi trascritti in soggetti con leucemia mieloide acuta d'età < 1 anno, con citogenetica normale.



CBFA2T3-GLIS2

Masetti R et al. Blood 2013

DHH-RHEBL1

Masetti R et al. Oncotarget 2013

RUNX1-USP42

Masetti R et al. BJH 2014

PRDM-SKI

Masetti R et al. BJH 2014

NUP98-PHF23

Journal of Hematology Oncology 2015

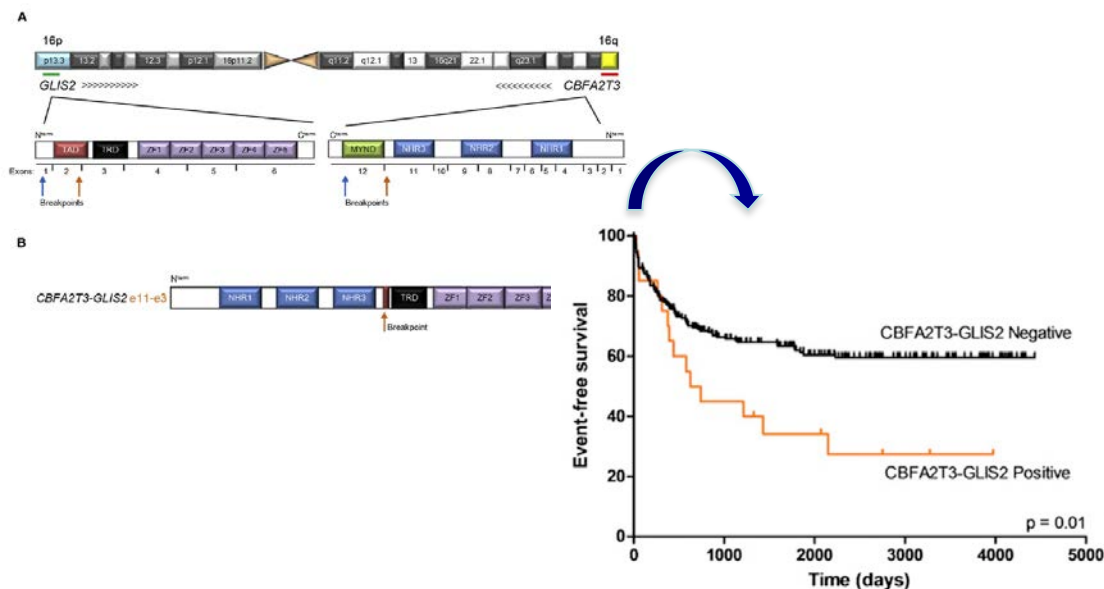
Diagnosi precisa: NUOVE ENTITA'

MYELOID NEOPLASIA

CBFA2T3-GLIS2 fusion transcript is a novel common feature in pediatric, cytogenetically normal AML, not restricted to FAB M7 subtype

Riccardo Masetti,¹ Martina Pigazzi,² Marco Togni,¹ Annalisa Astolfi,³ Valentina Indio,³ Elena Manara,² Rita Casadio,⁴ Andrea Pession,¹ Giuseppe Basso,² and Franco Locatelli⁵

AIEOP AML 2013 Protocol



<p>STANDARD RISK (SR) 20-22%</p>	<p>Anomalie CBFb (senza altre anomalie citogenetiche) e MRD < 0.1% al TP1 -t(8;21)(q22;q22)/[inv(16)(p13q22)]/t(16;16)(p13;q22)</p>
<p>INTERMEDIATE RISK (IR) 50-55%</p>	<p>Cariotipo normale t(9;11)(p22;q23) senza altre anomalie citogenetiche t(1;11)(p32;q23) t(11;19)(p13;q23)</p>
<p>HIGH RISK (HR) 25-30%</p>	<p>Anomalie citogenetiche associate ad <i>outcome</i> sfavorevole: FLT3-ITD Pazienti con LAM citogeneticamente normale e con il trascritto di fusione CBFA2T3-GLIS2 FAB M0, M6, M7 Pazienti con criteri non-SR e WBC >100.000/mL</p>

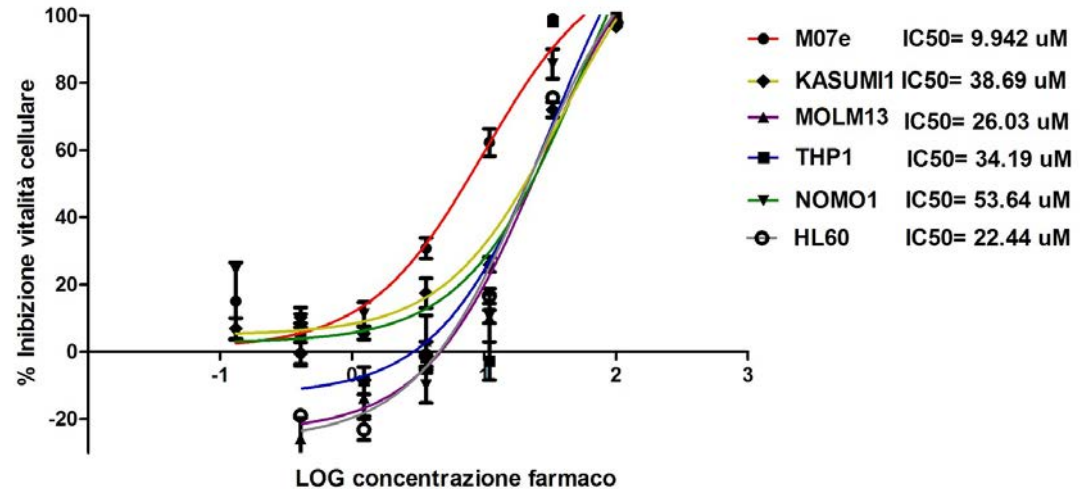
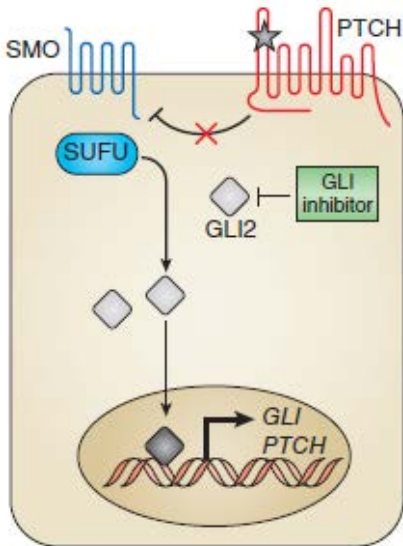
Diagnosi precisa: NUOVE ENTITA' EQ NUOVI FARMACI

TARGETED CANCER THERAPIES

nature
medicine

Unraveling the therapeutic potential of the Hedgehog pathway in cancer

Dereck Amakye¹, Zainab Jagani² & Marion Dorsch³



M07e cell lines harbouring **CBFA2T3-GLIS2** show a lower IC50 compared to the other **GLIS2** wt cell lines

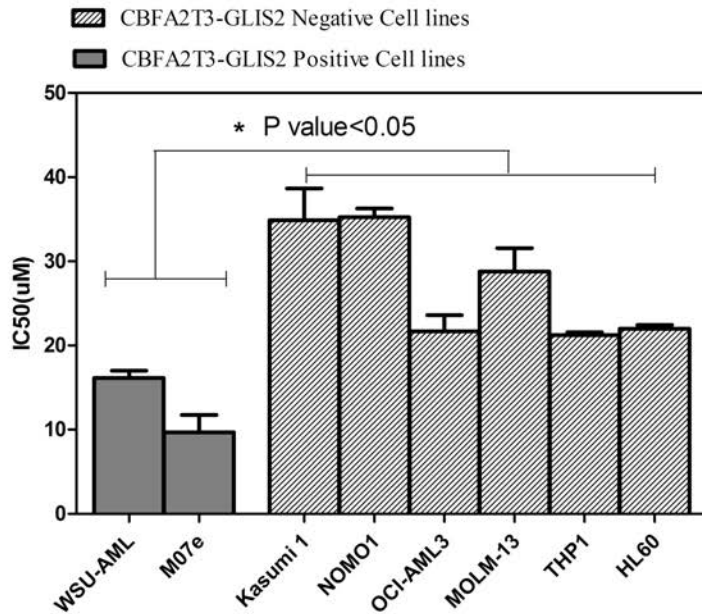
Masetti R, Bertuccio SN, Astolfi A, Chiarini F, Lonetti A, Indio V, De Luca M, Bandini J, Serravalle S, Franzoni M, Pigazzi M, Martelli AM, Basso G, Locatelli F, Pession A. Hh/Gli antagonist in acute myeloid leukemia with CBFA2T3-GLIS2 fusion gene. *J Hematol Oncol.* 2017 Jan 21;10(1):26.



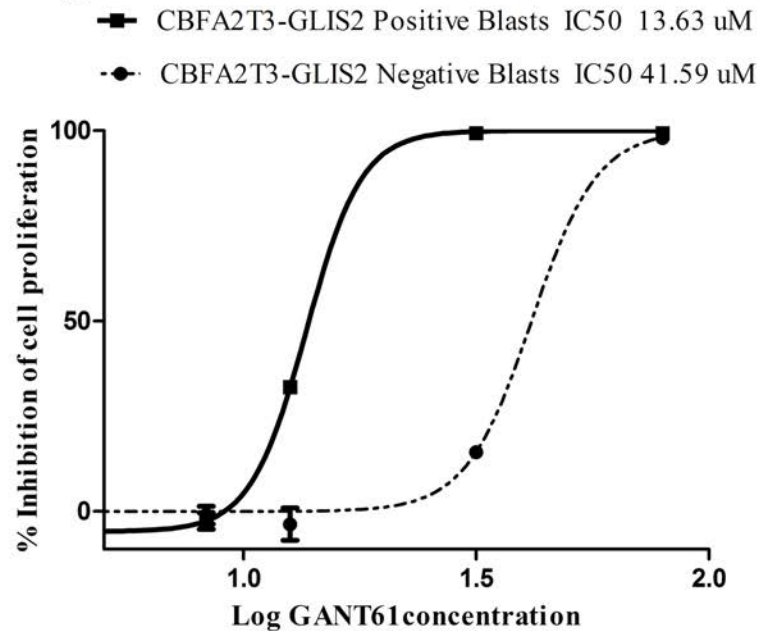
Diagnosi precisa: NUOVE ENTITA' EQ NUOVI FARMACI

Our findings indicate that the GLI inhibitor GANT61 may be used to specifically target the CBFA2T3-GLIS2 fusion gene in pediatric AML.

A



B



Masetti R, Bertuccio SN, Astolfi A, Chiarini F, Lonetti A, Indio V, De Luca M, Bandini J, Serravalle S, Franzoni M, Pigazzi M, Martelli AM, Basso G, Locatelli F, Pession A. Hh/Gli antagonist in acute myeloid leukemia with CBFA2T3-GLIS2 fusion gene. *J Hematol Oncol.* 2017 Jan 21;10(1):26.



**Nuovi concetti di predisposizione alla
malattia oncologica in età pediatrica:
*mai considerare veri per sempre gli insegnamenti
dei Maestri.***



Predisposizione genetica al cancro: DATI EMERGENTI

N ENGL J MED 373;24 NEJM.ORG DECEMBER 10, 2015

ORIGINAL ARTICLE

Germline Mutations in Predisposition Genes in Pediatric Cancer

Jinghui Zhang, Ph.D., Michael F. Walsh, M.D., Gang Wu, Ph.D., Michael N. Edmonson, B.A., Tanja A. Gruber, M.D., Ph.D., John Easton, Ph.D., Dale Hedges, Ph.D., Xiaotu Ma, Ph.D., Xin Zhou, Ph.D., Donald A. Yergeau, Ph.D., Mark R. Wilkinson, B.S., Bhavin Vadodaria, B.A., Xiang Chen, Ph.D., Rose B. McGee, M.S., Stacy Hines-Dowell, D.N.P., Regina Nuccio, M.S., Emily Quinn, M.S., Sheila A. Shurtleff, Ph.D., Michael Rusch, B.A., Aman Patel, M.S., Jared B. Beckfort, M.S., Shuoguo Wang, Ph.D., Meaghan S. Weaver, M.D., Li Ding, Ph.D., Elaine R. Mardis, Ph.D., Richard K. Wilson, Ph.D., Amar Gajjar, M.D., David W. Ellison, M.D., Ph.D., Alberto S. Pappo, M.D., Ching-Hon Pui, M.D., Kim E. Nichols, M.D., and James R. Downing, M.D.

Autosomal dominant cancer-predisposition genes (60) + Autosomal recessive cancer-predisposition genes (29) + Tyrosine kinase genes (23) + Tumor-suppressor genes (58) + Other cancer genes (395) = Total (565)

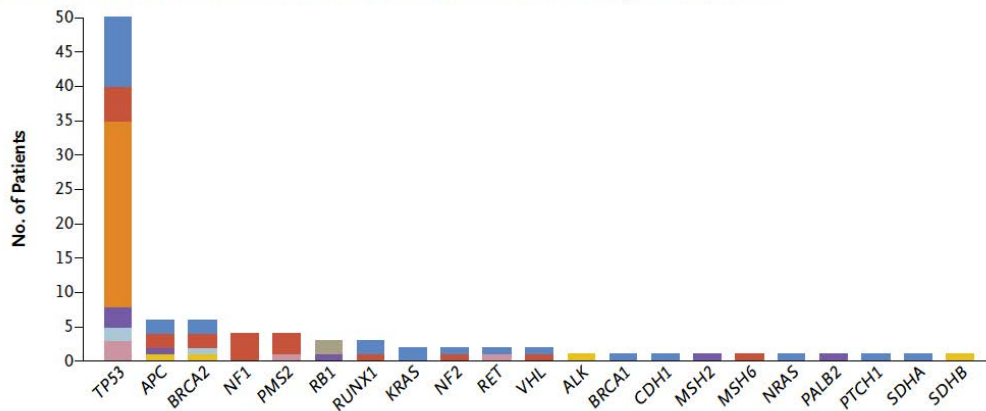
Cancer Predisposition									RASopathy	
ALK	CDC73	DICER1	MLH1	PAX5	RB1	SDHC	SUFU	WT1	BRAF	NRAS
APC	CDH1	EPCAM	MSH2	PHOX2B	RET	SDHD	TMEM127		CBL	PTPN11
BAP1	CDK4	FH	MSH6	PMS2	RUNX1	SMAD4	TP53		HRAS	RAF1
BMPR1A	CDKN1C	GATA2	NF1	PRKAR1A	SDHA	SMARCA4	TSC1		KRAS	SHOC2
BRCA1	CDKN2A	MAX	NF2	PTCH1	SDHAF2	SMARCB1	TSC2		MAP2K1	SOS1
BRCA2	CEBPA	MEN1	PALB2	PTEN	SDHB	STK11	VHL		MAP2K2	

Figure 2. Categories of the 565 Cancer Genes Analyzed for Germline Mutations.

The number of genes in each category is shown in parentheses. Genes that have overlapping categories are listed only once. Gene names in the other categories are shown in Figure S9 in Supplementary Appendix 1. RASopathies are genetic syndromes that include the cardiofaciocutaneous syndrome, Costello's syndrome (also called the faciocutaneouskeletal syndrome), Noonan's syndrome, and the multiple lentiginos syndrome.

Leukemia, CNS tumor, Retinoblastoma, ACT, Osteosarcoma, Rhabdomyosarcoma, Ewing's sarcoma, Neuroblastoma

A Mutations in 21 Genes Associated with Autosomal Dominant Cancer-Predisposition Syndromes



Germline mutations in cancer-predisposing genes were identified in 8.5% of the children and adolescents with cancer.

Family history did not predict the presence of an underlying predisposition syndrome in most patients.



Predisposizione genetica al cancro: DATI EMERGENTI

The Updated WHO Classification of Hematological Malignancies

Blood 2016 127:2391-2405; doi:10.1182/blood-2016-03-643544

Addition of a section for “myeloid neoplasms with germ line predisposition”

Myeloid neoplasms with germ line predisposition without a preexisting disorder or organ dysfunction

AML with germ line *CEBPA* mutation

Myeloid neoplasms with germ line *DDX41* mutation

Myeloid neoplasms with germ line predisposition and preexisting platelet disorders

Myeloid neoplasms with germ line *RUNX1* mutation

Myeloid neoplasms with germ line *ANKRD26* mutation

Myeloid neoplasms with germ line *ETV6* mutation

Myeloid neoplasms with germ line predisposition and other organ dysfunction

Myeloid neoplasms with germ line *GATA2* mutation

Myeloid neoplasms associated with *BM failure syndromes*

Myeloid neoplasms associated with *telomere biology disorders*

JMML associated with *neurofibromatosis, Noonan syndrome or Noonan syndrome-like disorders*

Myeloid neoplasms associated with *Down syndrome*



Terapia adattata al rischio: *semplicemente geniale.*



Terapia adattata al rischio: IL PARADIGMA

Fattori prognostici della leucemia acuta linfoblastica del bambino e dell'adolescente

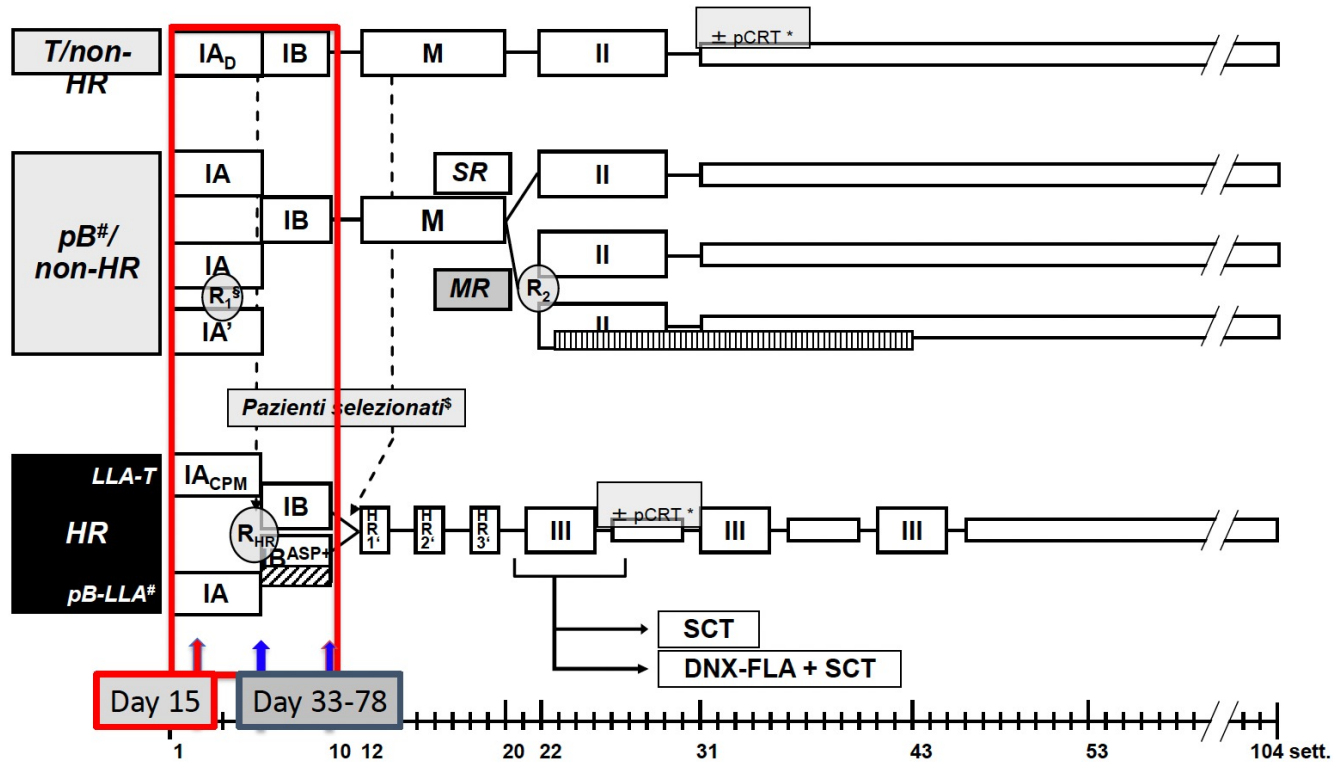
Fattore		Positivo-meglio	Negativo-peggio	
Relativi al paziente	Età alla diagnosi	1-9 anni	< 1 o ≥ 10 anni	
	Sesso	Femmina	Maschio	
	Etnia	Caucasica, asiatica	Afroamericana, ispanica	
	Sindrome di Down	No	Si	
Relativi la malattia alla diagnosi	Numero dei GB circolanti	< 50 x 10 ⁹ /L	≥ 50 x 10 ⁹ /L	
	Immunofenotipo	B	T	
	Interessamento SNC	Assente	Presente o sospetto	
	Interessamento testicolare	Assente	Presente o sospetto	
	Citogenetica e genetica	Ploidia	Iperdiploidia alta (51-65 cr.)	Ipodiploidia < 44 cr.
		Traslocazioni	t(12;21)(p13.2;q22.11) <i>ETV6-RUNX1</i>	t(9;22)(q34;q11.2) <i>BCR-ABL</i> Ph+ <i>BCR-ABL</i> Ph-like t(17;19)(8q22;p13) <i>TCF3-HLF</i>
		Riarrangiamenti	<i>NUMT1</i>	<i>KMT2A</i> <i>MEFD2</i> <i>BCL2</i> o <i>MYC</i>
Amplificazioni			<i>iAMP21</i>	
Risposta alla terapia	Malattia residua minima	Negativa In diminuzione fino a negativa	Positive Persistente o in incremento	



Terapia adattata al rischio: LA COMPLESSITA'

Terapia della leucemia acuta linfoblastica per fascia di rischio

PROTOCOLLO AIEOP-BFM LLA 2009



- | | | | |
|-------------------------|--|-----------------------|---|
| IA | Prot. IA (con Pred e 4 dosi DNR nei giorni 8, 15, 22 e 29) | IA_D | Prot. IA _D (con Dexa e 4 dosi DNR nei giorni 8, 15, 22 e 29) |
| IA' | Prot. IA' (con Pred e 2 dosi DNR nei giorni 8 and 15) | IB-ASP+ | Prot. IB-ASP+ (con 4 x 2500 E PEG-L-ASP) |
| IA_{CPM} | Prot. IA _{CPM} (con Pred, 4 dosi DNR e 1 dose CPM al giorno 10) | PEG-ASP data | PEG-ASP data per 20 settimane |

o immunofenotipo non noto
 * pCRT 12 Gy se età ≥ 2 aa / in sottogruppi selezionati non pCRT + 6x IT MTX / in pazietin con malattia SNC (SNC 3) tCRT con 12 Gy o 18 Gy (dose età-dipendente)
 § per eleggibilità alla randomizzazione vedi protocollo



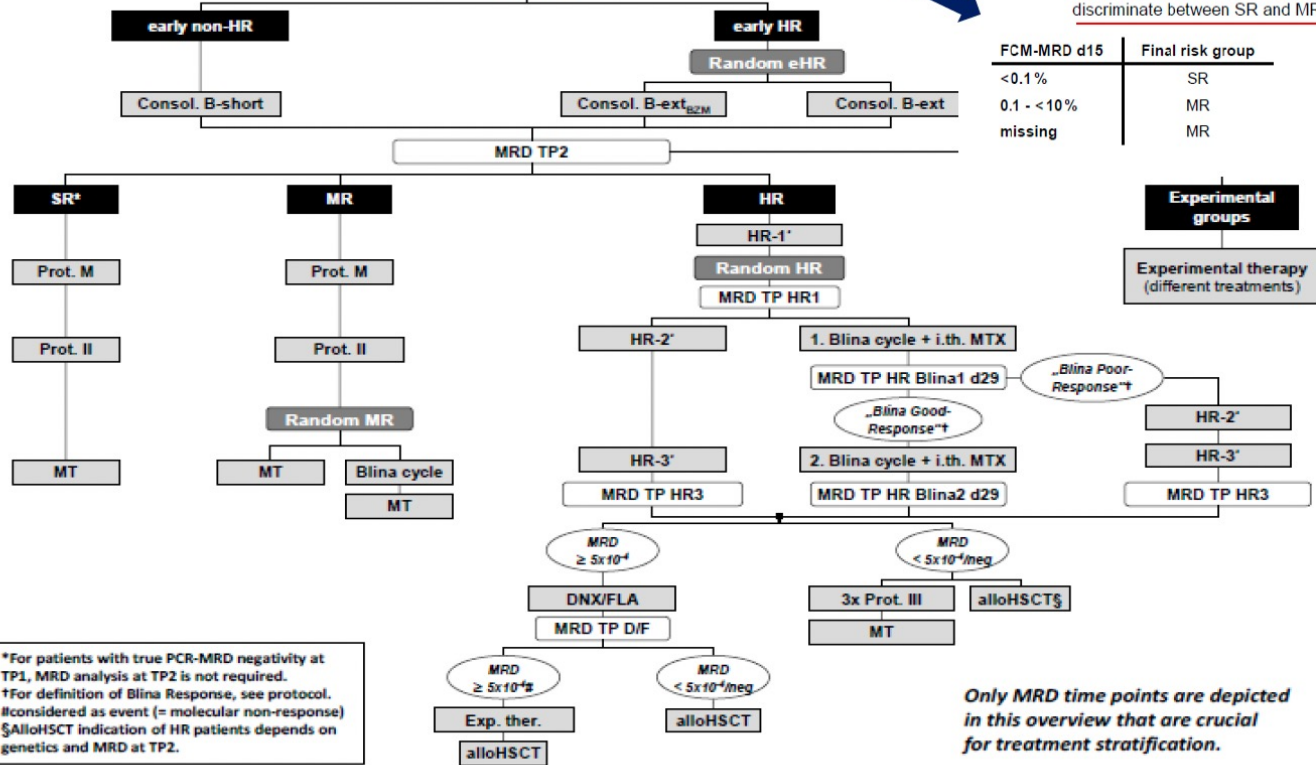
Terapia adattata al rischio: LA COMPLESSITA'

La sola risposta al cortisone al g+8 non è più criterio di alto rischio nelle pB-LLA

AIEOP-BFM ALL 2017

pB-ALL

Overview of treatment





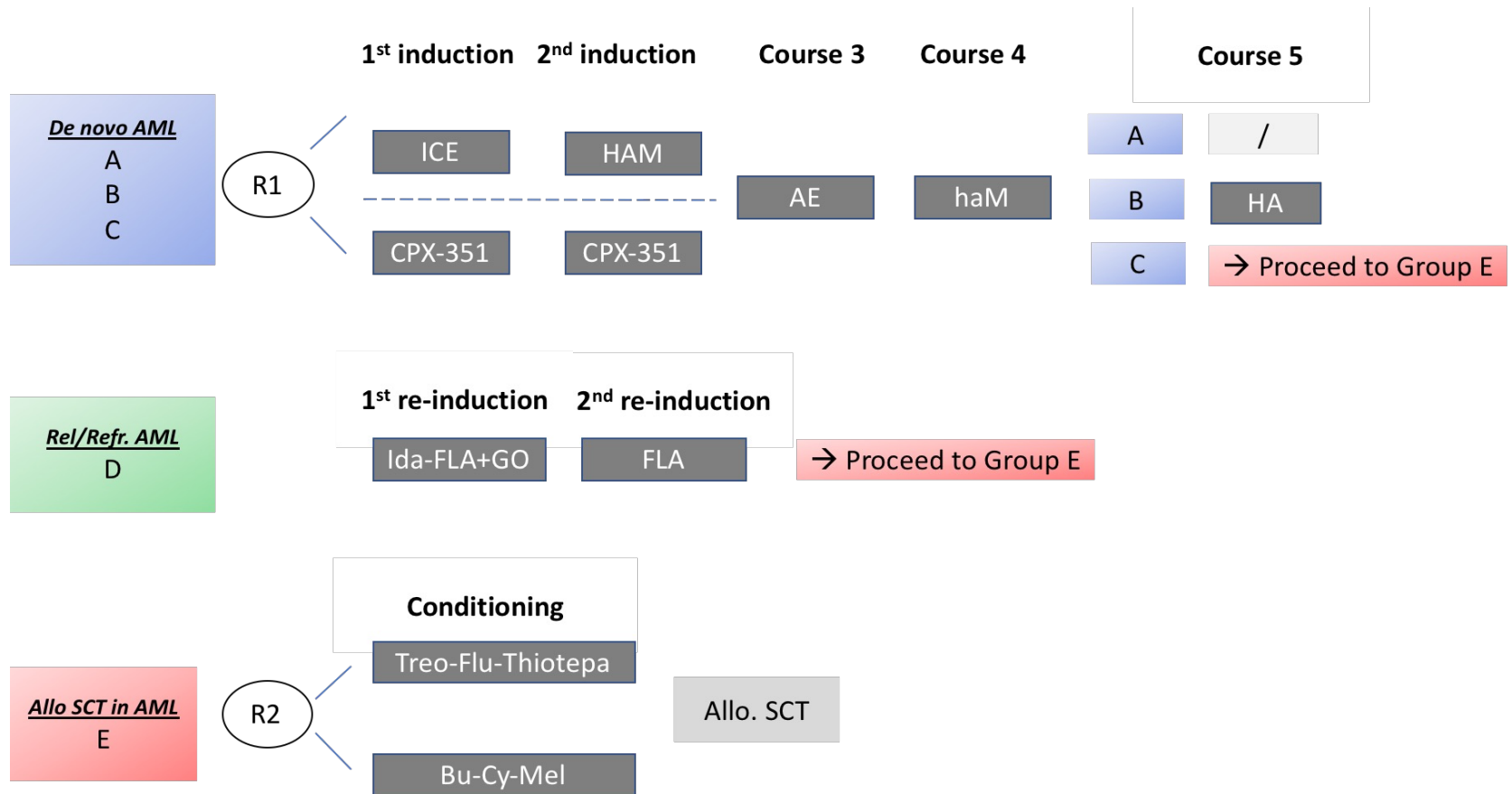
BFM LAM 2020

RISK GROUP	GENETIC RISK CRITERIA	RESPONSE CRITERIA
STANDARD RISK (SR)	<ul style="list-style-type: none"> CBFβ abnormalities <ul style="list-style-type: none"> t(8;21)(q22;q22) with adequate (≥ 2 log) reduction by qPCR at IND 2 inv(16)(p13q22)/t(16;16)(p13;q22) Biallelic CEBPα aberrations t(16;21) <i>CBFA2T3/RUNX1</i> <p>and FLT3-ITD negative</p>	<p>Genetic standard risk and</p> <ul style="list-style-type: none"> MRD <0.1% at IND 1 <p>t(8;21) and</p> <ul style="list-style-type: none"> MRD > 2 log reduction at IND 2 (qPCR)
INTERMEDIATE RISK (IR)	<ul style="list-style-type: none"> NON SR and NON HR patients 	<p>Genetic standard or intermediate risk and</p> <ul style="list-style-type: none"> MRD at IND 1 $\geq 0.1\%$ and < 1% and MRD at IND 2 < 0.1%
HIGH RISK (HR)	<ul style="list-style-type: none"> Complex karyotype (≥ 3 aberrations including at least one structural aberration) <i>excluding those with recurrent translocations</i> Monosomal Karyotype, i.e. -7, -5/del(5q) 11q23/<i>KMT2A</i> rearrangements involving: <ul style="list-style-type: none"> t(4;11)(q21;q23) <i>KMT2A/AFF1</i> t(6;11)(q27;q23) <i>KMT2A/AFDN</i> t(10;11)(p12;q23) <i>KMT2A/MLLT10</i> t(16;21)(p11;q22) <i>FUS/ERG</i> t(9;22)(q34;q11.2) <i>BCR/ABL1</i> t(6;9)(p22;q34) <i>DEK/NUP214</i> t(7;12)(q36;p13) <i>MNX1/ETV6</i> inv3(q21q26)/t(3;3)(q21;q26) <i>RPN1/MECOM</i> 12p abnormalities <i>FLT3-ITD</i> with AR ≥ 0.5 not in combination with other recurrent abnormalities or <i>NPM1</i> mutations <i>WT1</i> mutation and <i>FLT3-ITD</i> inv(16)(p13q24) <i>CBFA2T3/GLIS2</i> t(5;11)(q35;p15.5) <i>NUP98/NSD1</i> and t(11;12)(p15;p13) <i>NUP98/KDM5A</i> Pure Erythroid leukemia 	<ul style="list-style-type: none"> MRD $\geq 1\%$ at IND 1 or $\geq 0.1\%$ at IND 2 or (only if FLOW-result not available/informative) blast count $\geq 5\%$ at IND 1

- If Isolated t(8;16) and/or t(11;16) occur in patients below 1 month of age a watch and wait strategy is recommended
- GATA 1 screening will be performed in all patients and if mutations leading to exclusive GATA1s expression are found, these patients will be treated according to the Down Syndrome AML Protocol



BFM LAM 2020



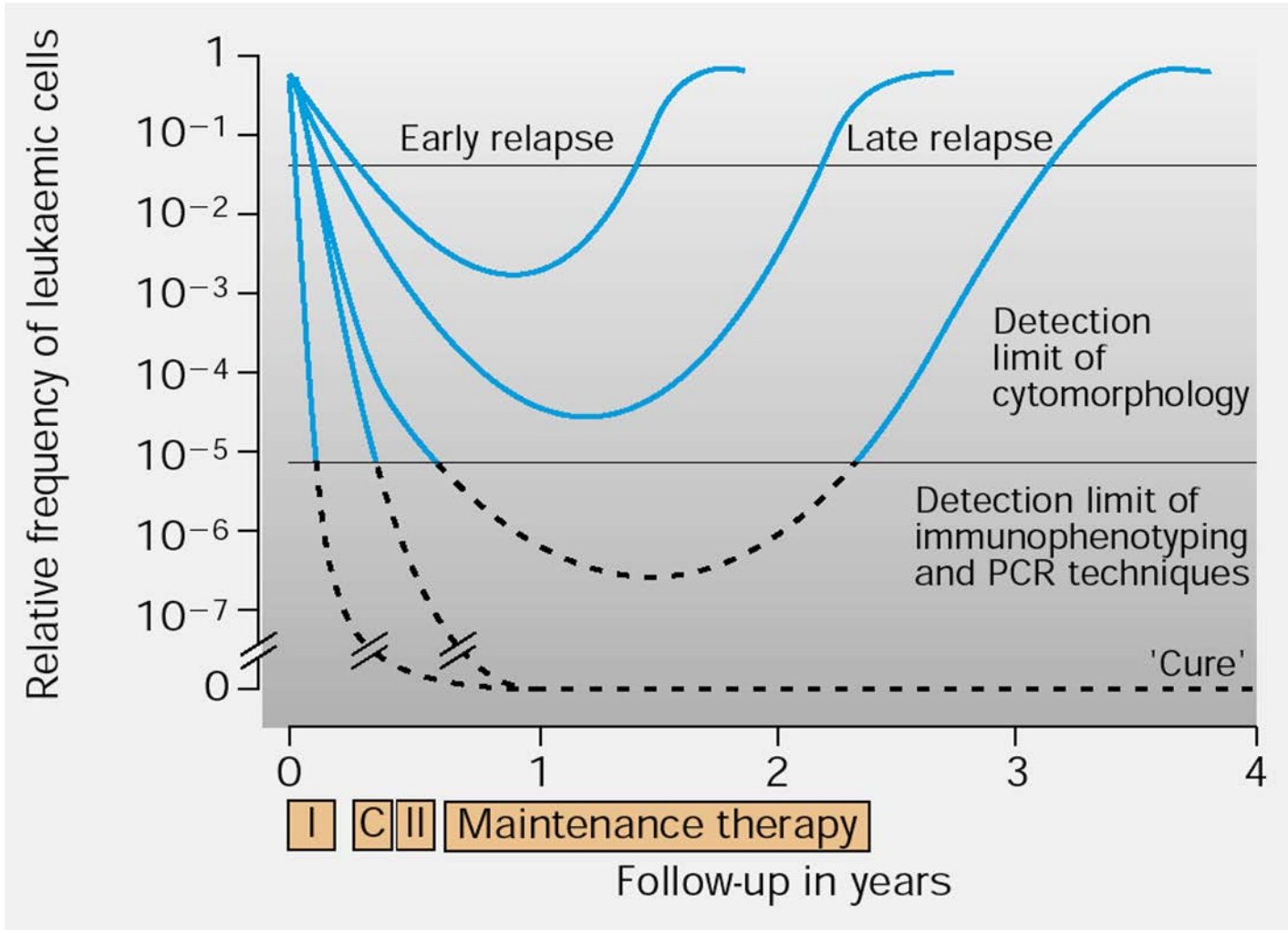


Malattia residua minima e la biopsia liquida:

l'importanza di vedere al di là del proprio naso.

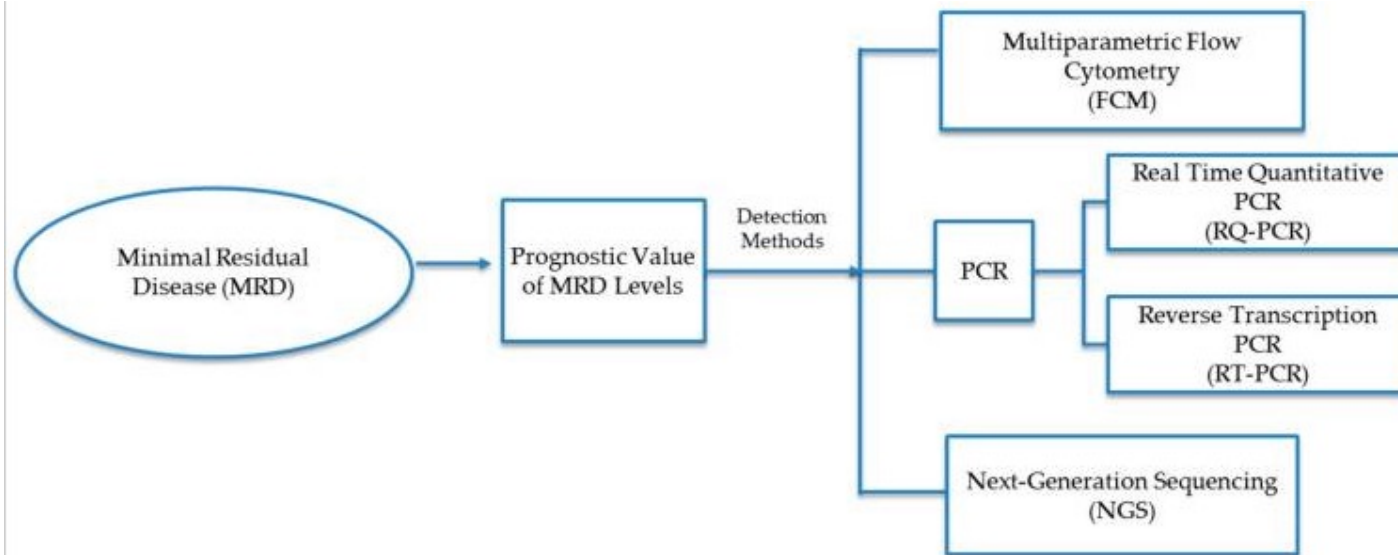


Malattia Residua Minima: LA CERTEZZA





Malattia Residua Minima: LA CERTEZZA



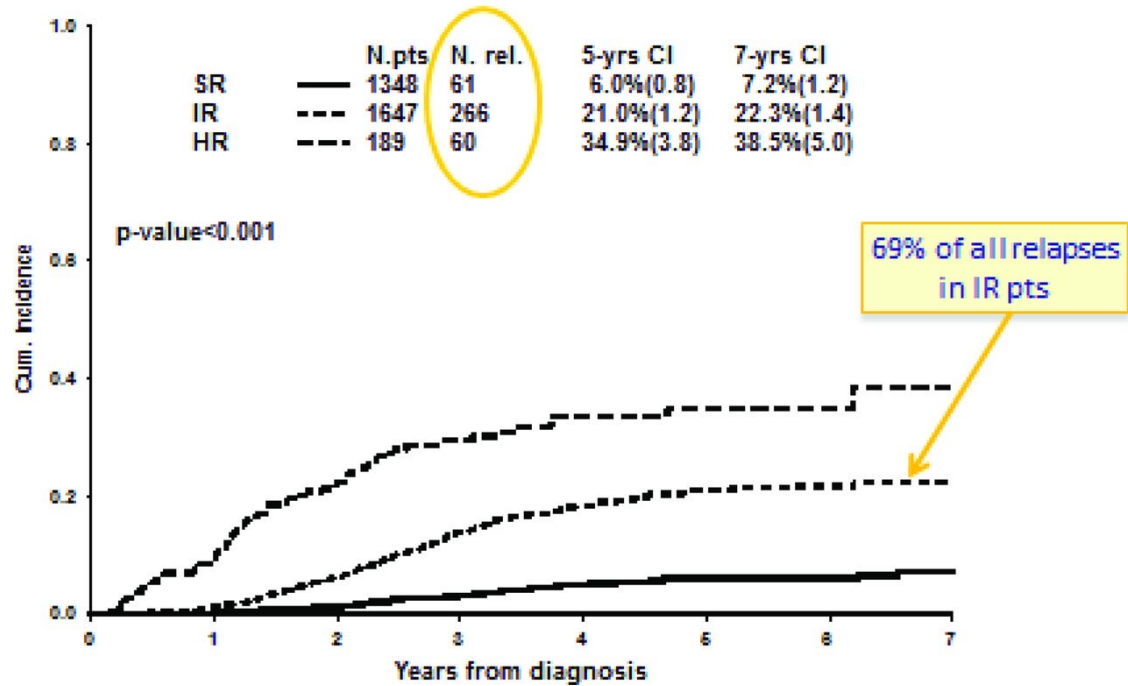
	Strengths	Weaknesses
FCM	<ul style="list-style-type: none"> - Fast - Inexpensive 	<ul style="list-style-type: none"> - Limited standardization - Variable sensitivity - Requires significant expertise
RQ-PCR	<ul style="list-style-type: none"> - Sensitive quantifications - Accurate 	<ul style="list-style-type: none"> - Limited standardization - Not applicable in every case - Complex methodology - Requires significant expertise
RT-PCR	<ul style="list-style-type: none"> - Rapid procedure - Good readout accuracy 	<ul style="list-style-type: none"> - mRNA instability - Quantification errors
NGS	<ul style="list-style-type: none"> - Sensitive quantifications - Relatively fast procedure - Can identify unique genetic patterns and small subclone populations 	<ul style="list-style-type: none"> - Limited standardization - Expensive - Limited clinical evaluations to date



Malattia Residua Minima: LA CERTEZZA

Detection and management of minimal residual disease in acute lymphoblastic leukemia

Relapses in pcB ALL by MRD risk groups AIEOP-BFM ALL 2000



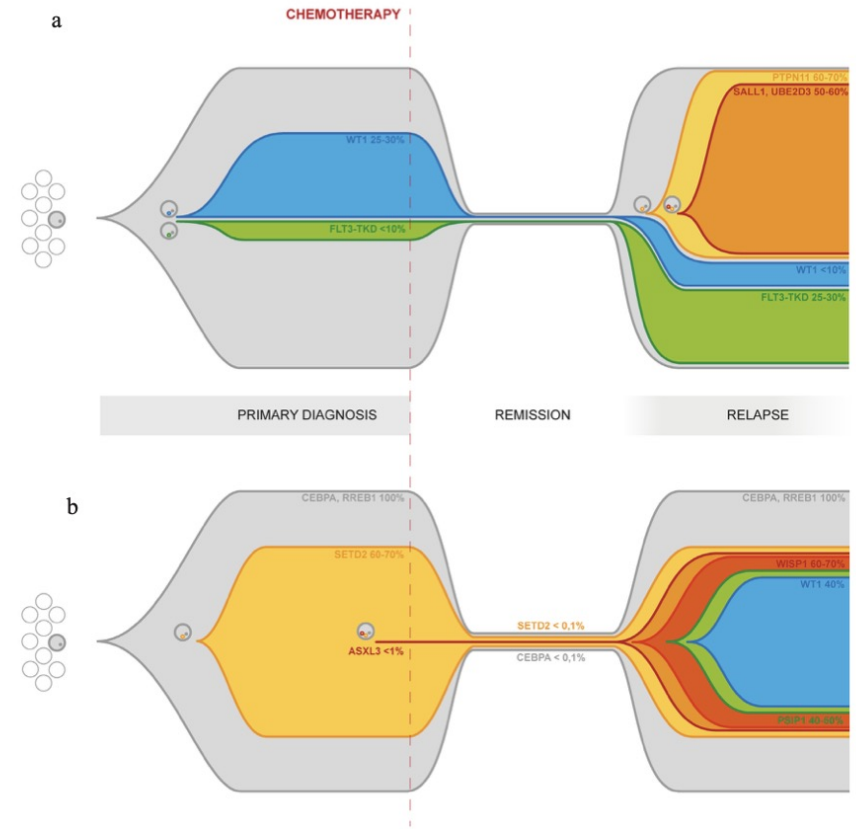
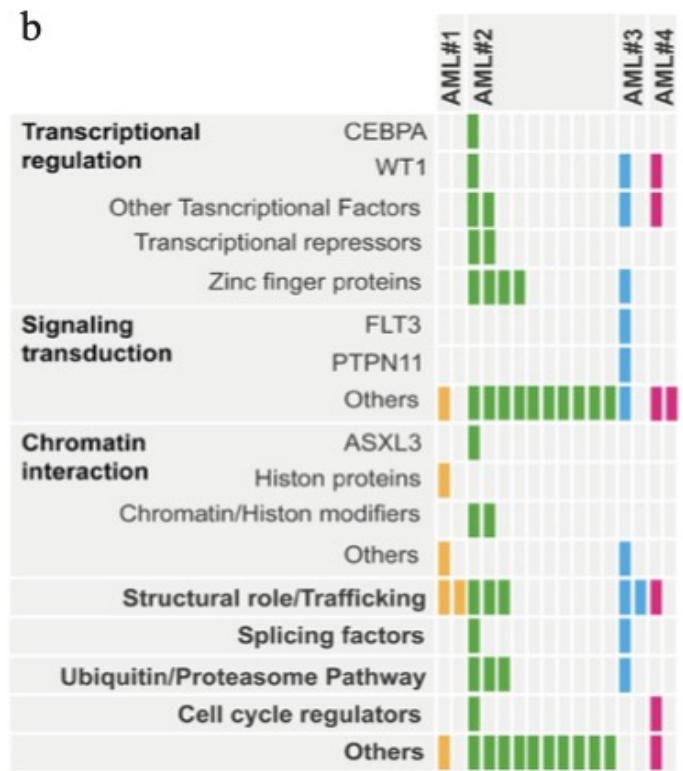
Martin Schrappe, Detection and management of minimal residual disease in acute lymphoblastic leukemia, Hematology Am Soc Hematol Educ Program, 2014.





Malattia Residua Minima: LA CERTEZZA

AML



Masetti, R., Castelli, I., Astolfi, A, Pession, A.(2016). Genomic complexity and dynamics of clonal evolution in childhood acute myeloid leukemia studied with whole-exome sequencing. *Oncotarget*, 7(35), 56746–56757. <https://doi.org/10.18632/oncotarget.10778>



La biopsia liquida: LA NOVITA'



Original Research

Circulating tumour DNA sequencing to determine therapeutic response and identify tumour heterogeneity in patients with paediatric solid tumours



Cell free DNA (cfDNA) is fragmented genomic DNA that is present in blood or CSF. In cancer patients, circulating tumour-derived DNA (ctDNA) is present in blood as a subset of total cfDNA.

The method was found to be highly sensitive (0.96 for SNVs and 0.97 for INDEL), specific (0.82 for SNVs and 0.978 for INDEL), repeatable (>0.93 [95% CI: 0.89e0.95]) and reproducible (>0.87 [95% CI: 0.87 e0.95])

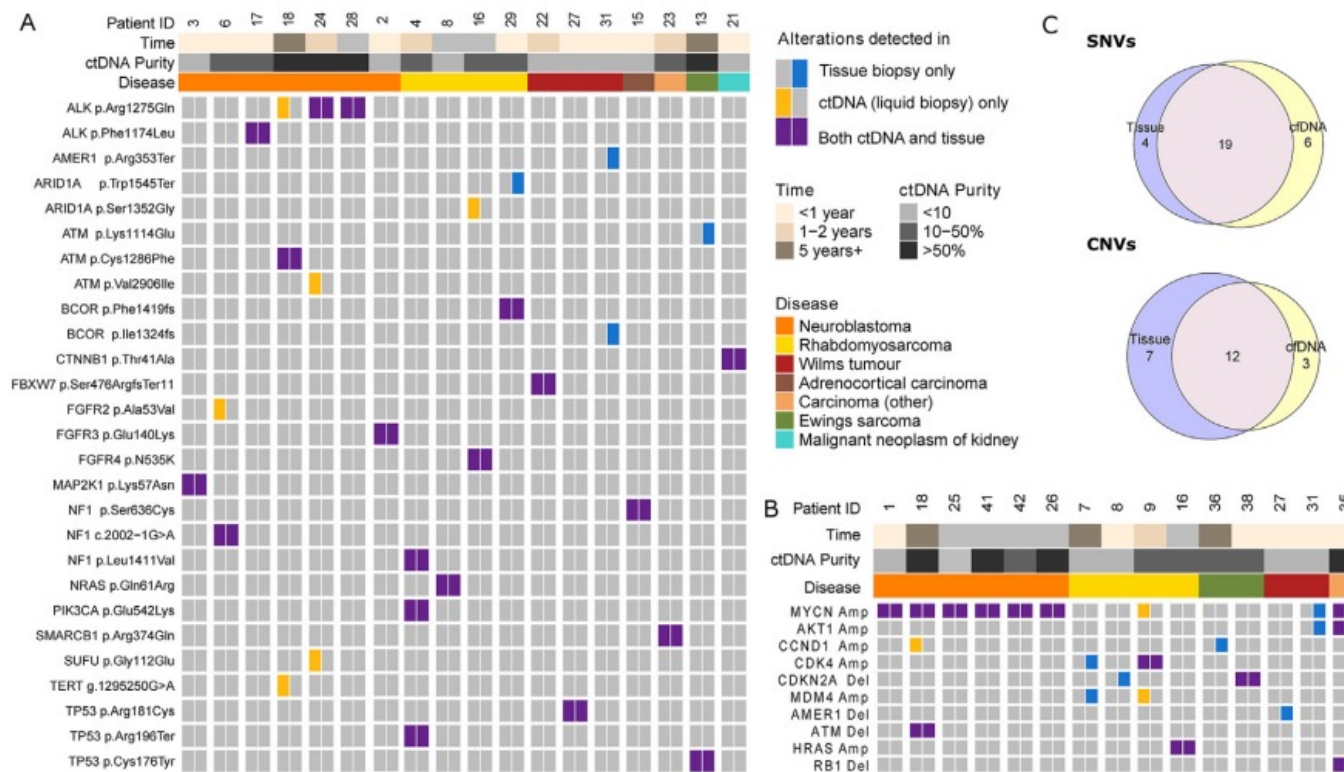


Fig. 3. Comparison of findings between paediatric cfDNA and tissue samples in extracranial tumours. A. Comparison of SNVs detected in plasma versus tissue sequencing B. Comparison of CNVs detected in plasma versus tissue sequencing. Each column represents a single patient, colour coded for disease type at the top and ctDNA purity and time between tissue and liquid biopsy indicated at the scale on top for each patient. C Venn diagram comparing numbers of alterations detected in tissue versus cfDNA. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)



Terapia molecolari mirate:
spera nel peggio, preparati per il meglio.

Terapia molecolare mirata: IL PARADIGMA

ACUTE PROMYELOCYTIC LEUKEMIA

Hypergranular or typical APL (M3)

- 60% to 70% of cases.
- Low white blood cell count.
- Abnormal promyelocytes with numerous red to purple cytoplasmic granules that are typically darker and larger than normal neutrophil granules.
- Identifiable faggot/matchstick cells with numerous Auer rods.

Hypogranular or microgranular APL (M3v)

- Leukocytosis.
- Numerous abnormal promyelocytes readily identified on a peripheral blood smear.
- Irregular nucleus and granulations sparser and finer compared with the hypergranular form.
- Faggot cells with multiple Auer rods less commonly seen.

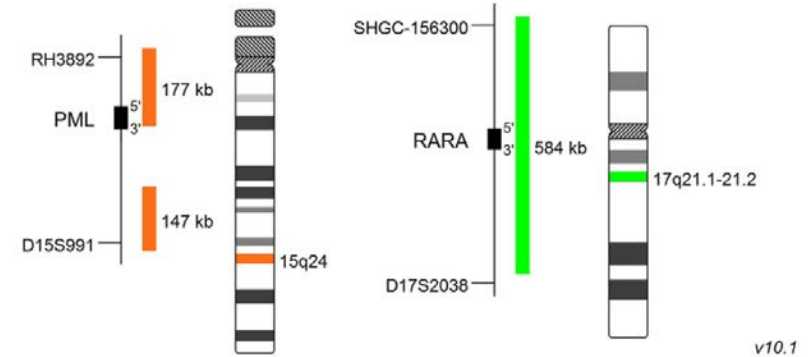
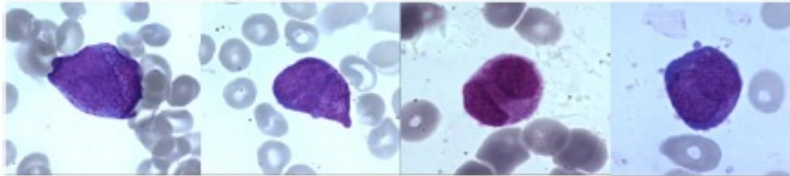
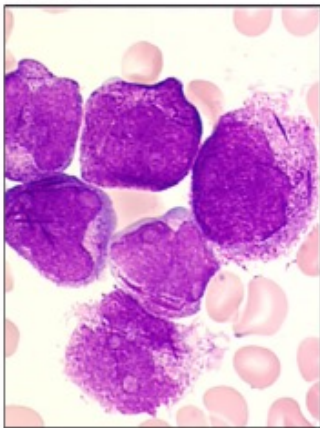
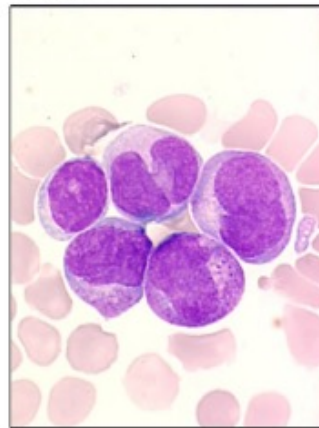


Fig. 4 APL is characterized by a specific balanced reciprocal translocation $t(15;17)$ that fuses the *PML* gene on chromosome 15 to the *RAR α* gene on chromosome 17

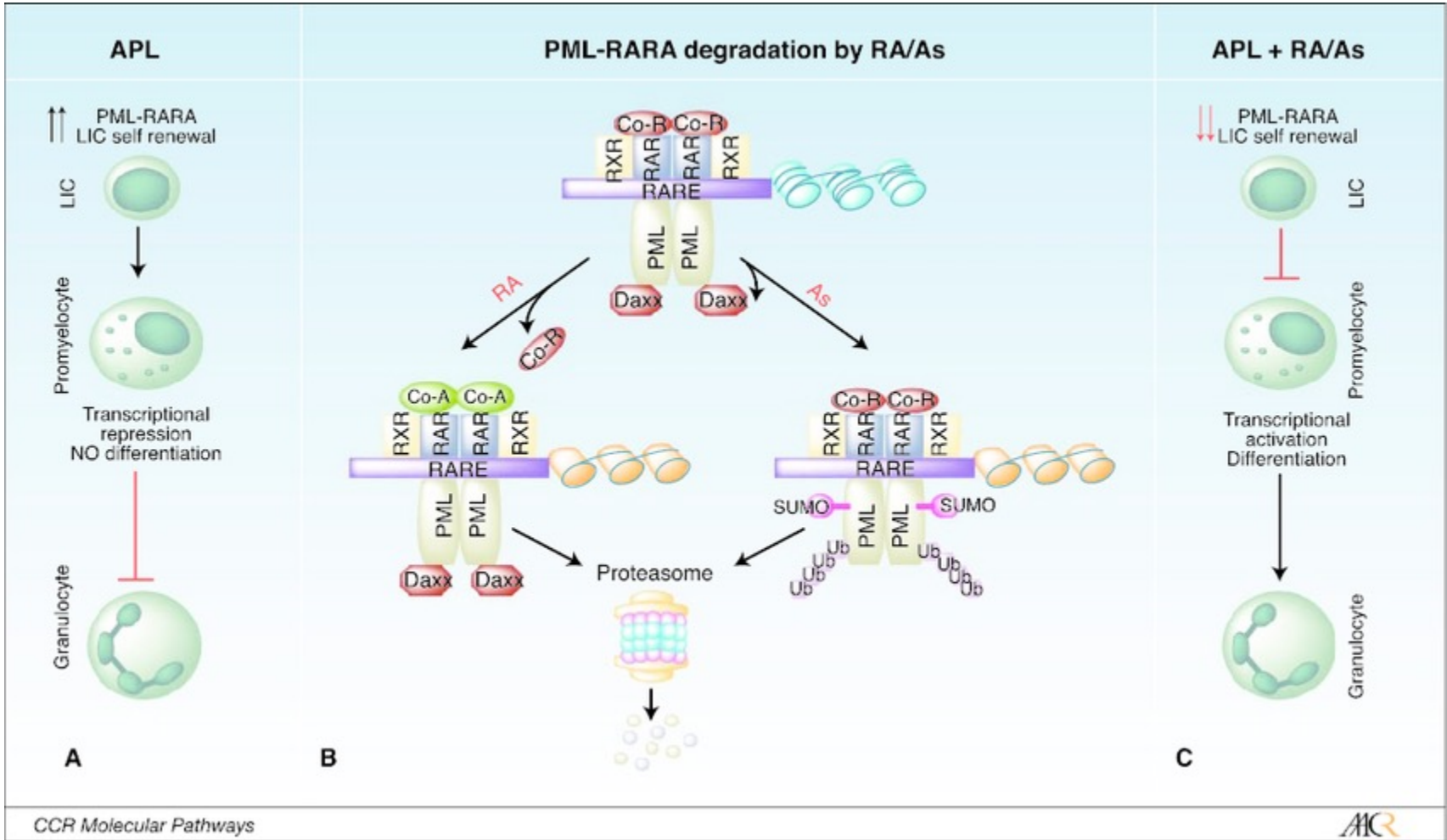
AML-3



AML-3v

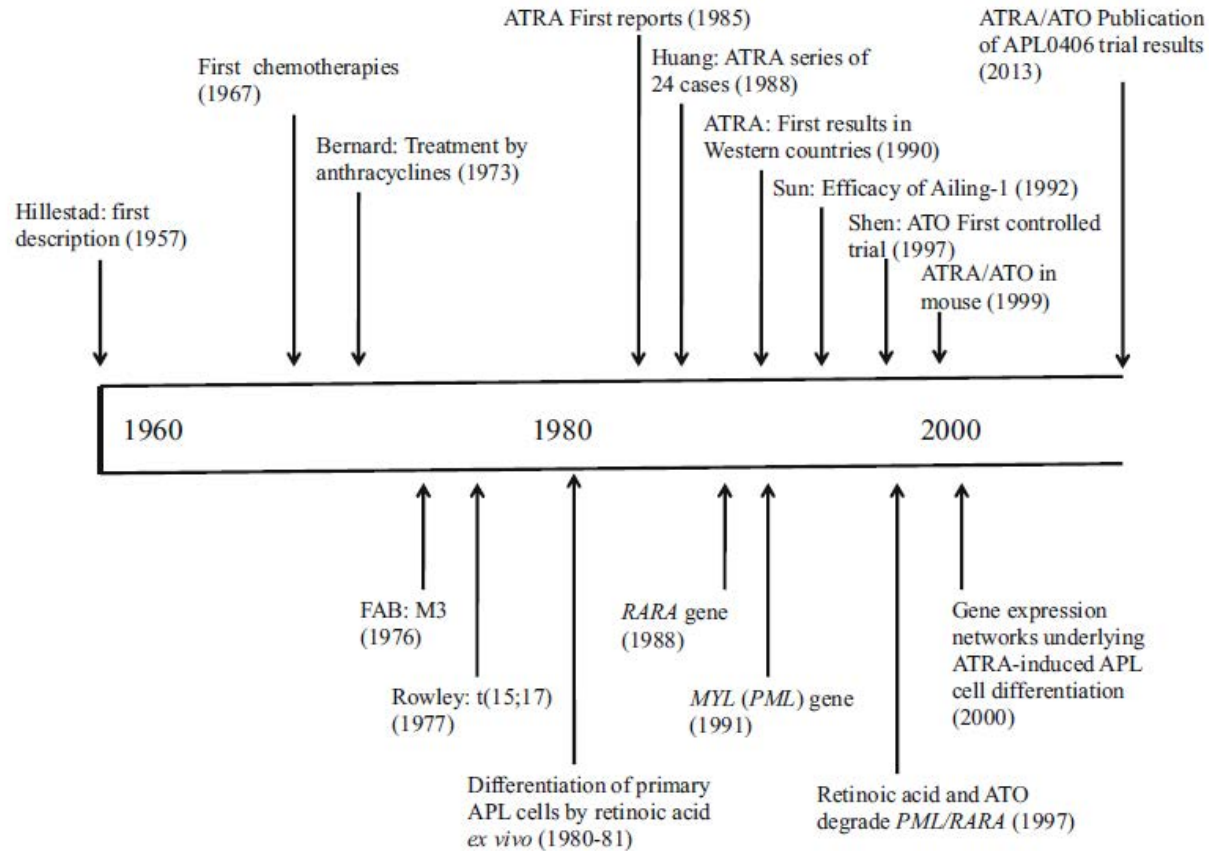


Terapia molecolare mirata: IL PARADIGMA





Terapia molecolare mirata: IL PARADIGMA



Highlights in the history of APL treatment

CT-free therapy for APL is the best example of how targeted therapies can trigger definitive cures.



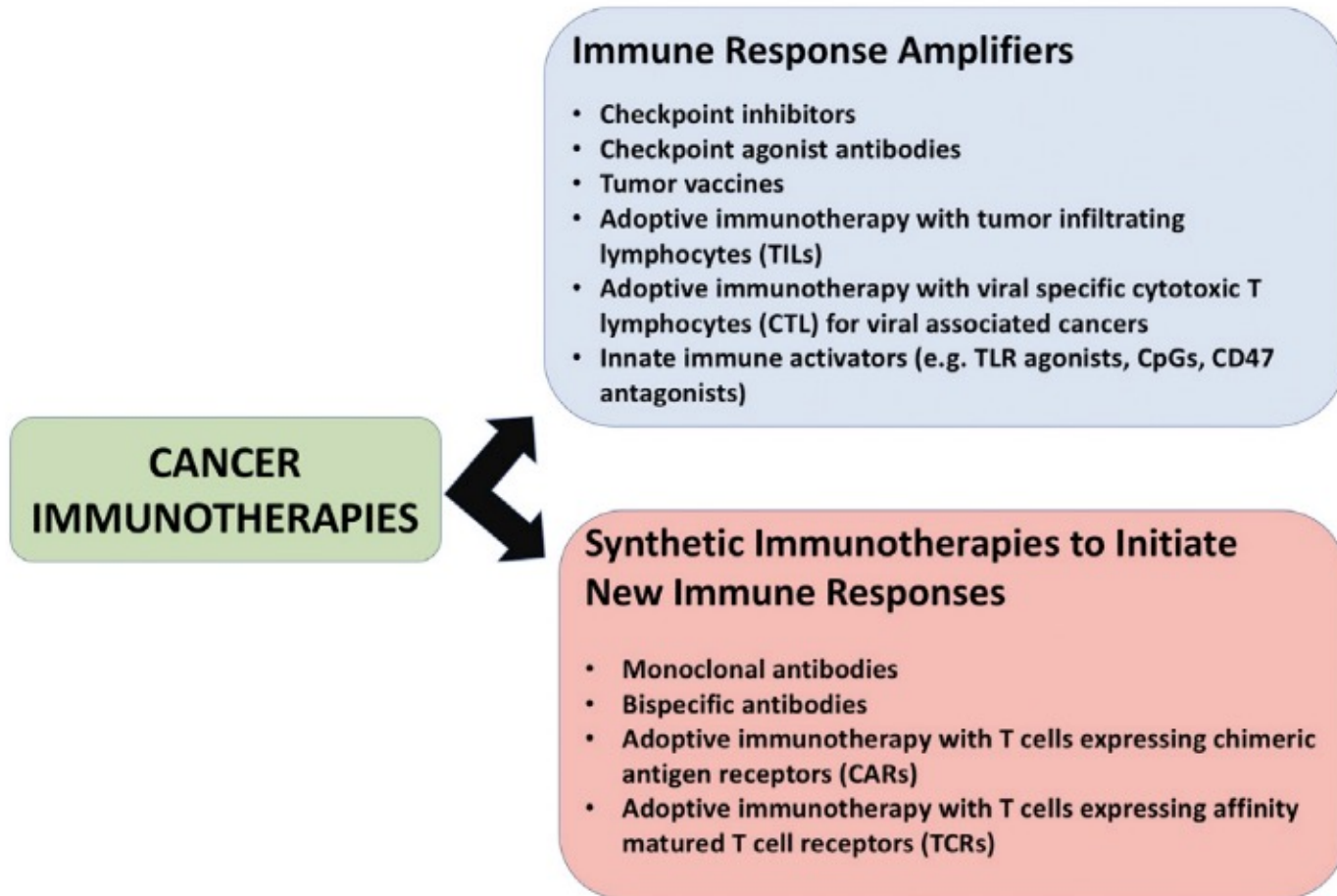
Terapia multimodale integrata: *lenti ma inesorabili.*



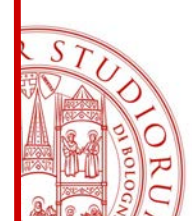
Immunoterapia: *la quinta strada verso la guarigione.*



Immunoterapia: STRATEGIE



Majzner, Robbie G., Sabine Heitzeneder, and Crystal L. Mackall. "Harnessing the Immunotherapy Revolution for the Treatment of Childhood Cancers." *Cancer Cell* 31, no. 4 (2017): 476–85. 2017.



Immunoterapia: STRATEGIE

Table 1 | **Monoclonal antibody-based therapeutics**

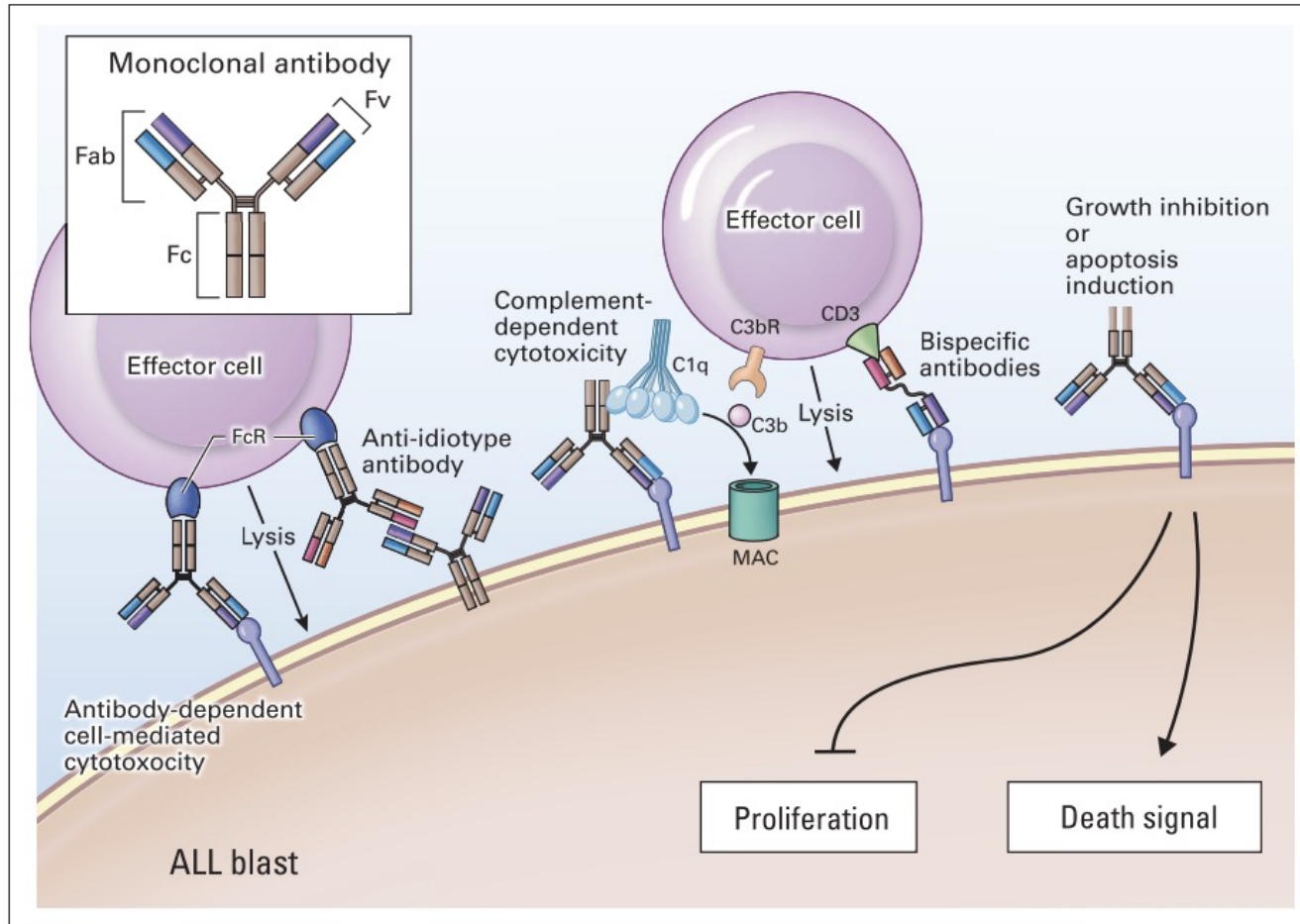
mAb-based therapeutic	Structure	Characteristics of target antigen	Example of major ongoing research questions
Antitumour mAbs	Unmodified IgG or IgG modified to mediate enhanced ADCC	Tumour-associated surface antigen	Are IgGs with enhanced affinity for Fc receptors more clinically effective than unaltered IgG?
Angiogenesis inhibition	Unmodified IgG	Host molecules that control angiogenesis	What is the best way to evaluate clinical response in patients treated with angiogenesis inhibitors?
T cell checkpoint blockade	IgG1 (blocks checkpoint and mediates ADCC) or IgG4 (blocks checkpoint without mediating extensive ADCC)	Molecules that limit the anticancer T cell response	How should we combine checkpoint blockade mAbs with each other, with other immunotherapeutics and with other anticancer agents?
Radioimmunotherapy	Unmodified IgG or mAb fragment	Tumour-associated antigen that is not shed or present in the circulation	How can the logistics of administering successful radioimmunotherapeutic agents be simplified to enhance their clinical utility?
Antibody–drug conjugate	IgG modified with cleavable linker and drug	Highly specific tumour-associated antigen that can internalize when bound by a mAb	What is the best combination of linkers and drugs with each mAb and target antigen?
Bispecific antibody	Variable regions from cancer-specific mAbs linked to variable regions specific for activating receptors on T cells	Tumour-associated antigen that is not commonly absent in antigen-loss-resistant cancer variants	Can effective bispecific constructs that have modified kinetics (thereby avoiding the logistic complexities of continuous infusion) be developed?
Chimeric antigen receptor T cell	Gene therapy approach to modifying T cells by inserting DNA coding for the mAb variable region fused to DNA coding for signalling peptides	Highly tumour-specific antigen that is not commonly absent in antigen-loss-resistant cancer variants	Can very promising preliminary results be extended to solid tumours, or will toxicity be associated even with low levels of target antigen expression by benign cells?

ADCC, antibody-dependent cellular cytotoxicity; IgG, immunoglobulin G; mAb, monoclonal antibody.

Weiner, George J. "Building Better Monoclonal Antibody-Based Therapeutics." *Nature Reviews Cancer* 15, no. 6 (2015): 361–70.



Immunoterapia: STRATEGIE



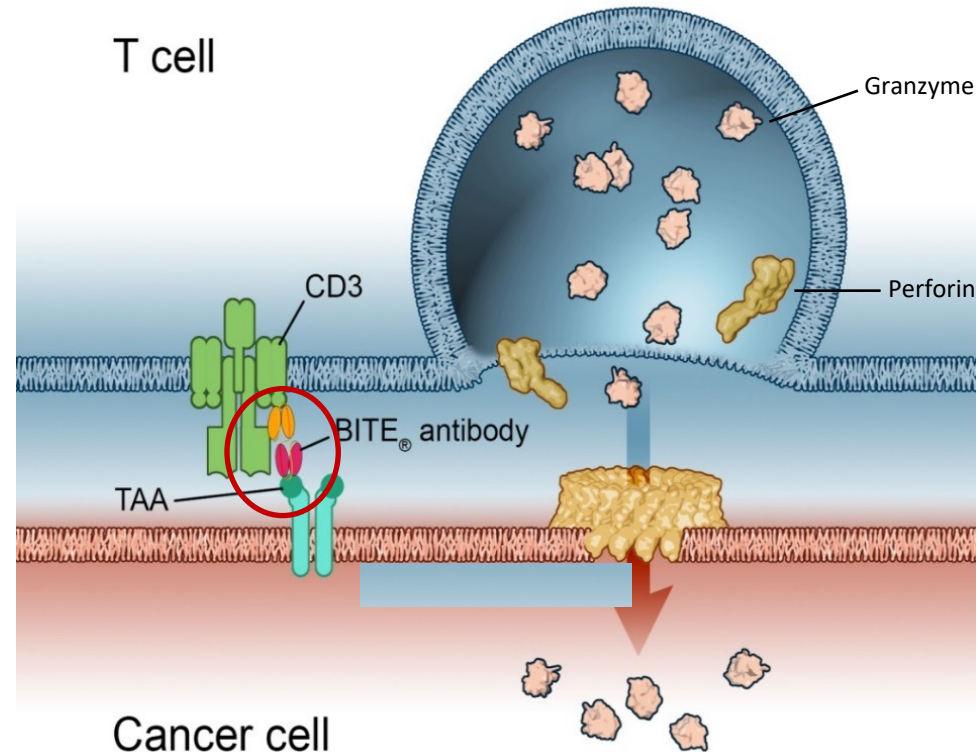
Kantarjian, Hagop, Deborah Thomas, Alan S. Wayne, and Susan O'Brien. "Monoclonal Antibody-Based Therapies: A New Dawn in the Treatment of Acute Lymphoblastic Leukemia." *Journal of Clinical Oncology* 30, no. 31 (2012): 3876–83. 2012

Immunoterapia: Blinatumomab

L'anticorpo è disegnato per attivare le cellule T contro le cellule tumorali.

Gli anticorpi monoclonali presentano domini che collegano i recettori CD3 nelle cellule T e gli antigeni associate al tumore.

Quando si instaura la sinapsi immunologica si verifica l'attivazione dell'immunità specifica **indipendentemente dalla specificità del TCR, dalla co-stimolazione e dalla presentazione antigenica.**



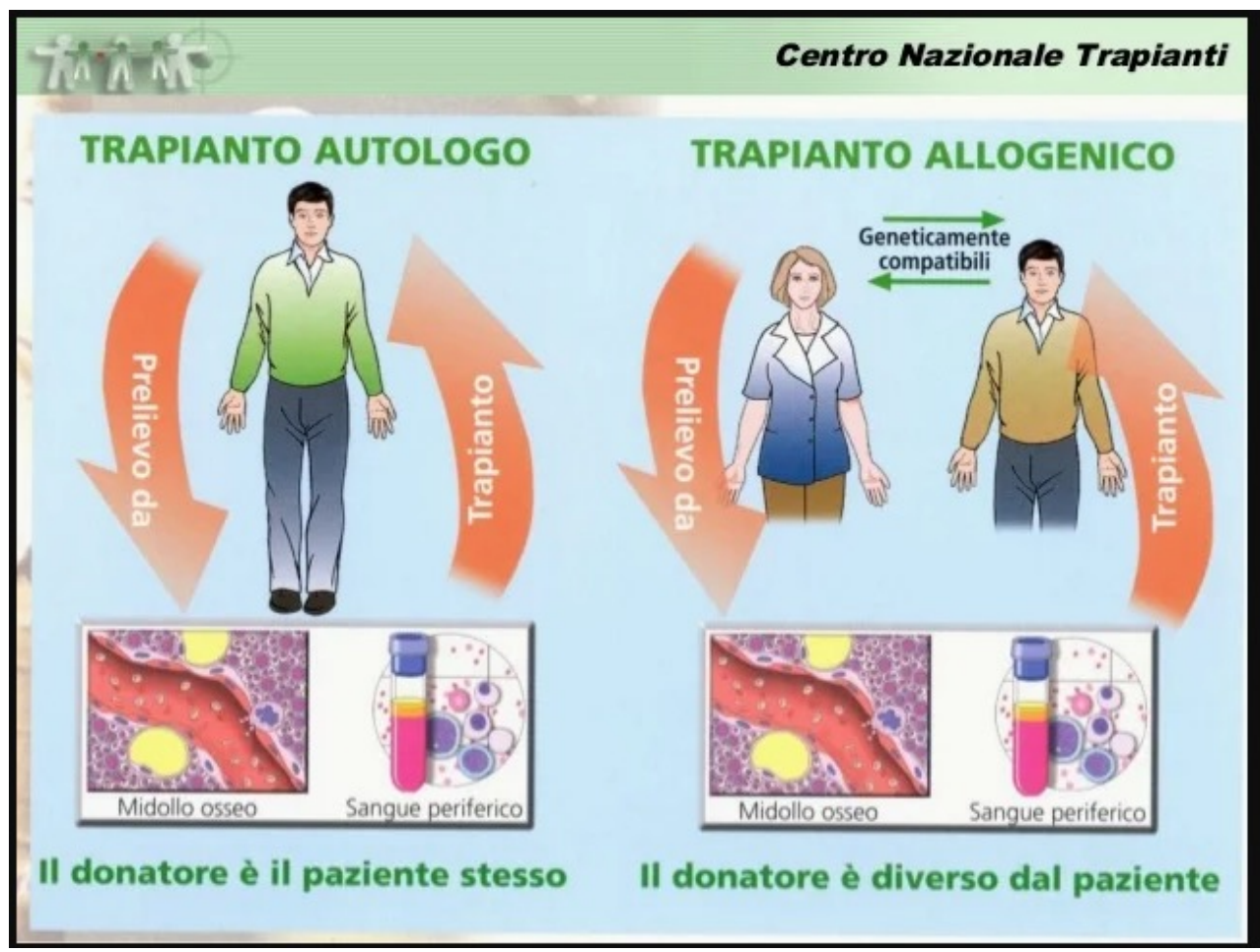
1. Baeuerle PA, Reinhardt C. Cancer Res 2009;69:4941-4;
2. Hoffman P, et al. Int J Cancer 2005;115:98-104;
3. Frankel SR, Baeuerle PA. Curr Opin Chem Biol 2013;17:385-92;
4. Dreier T, et al. Int J Cancer 2002;100:690-7;
5. Offner S, et al. Mol Immunol 2006;43:763-71.



Terapie cellulari:

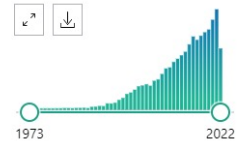
mai dare nulla per scontato.

Terapie cellulari: TRAPIANTO DI CSE

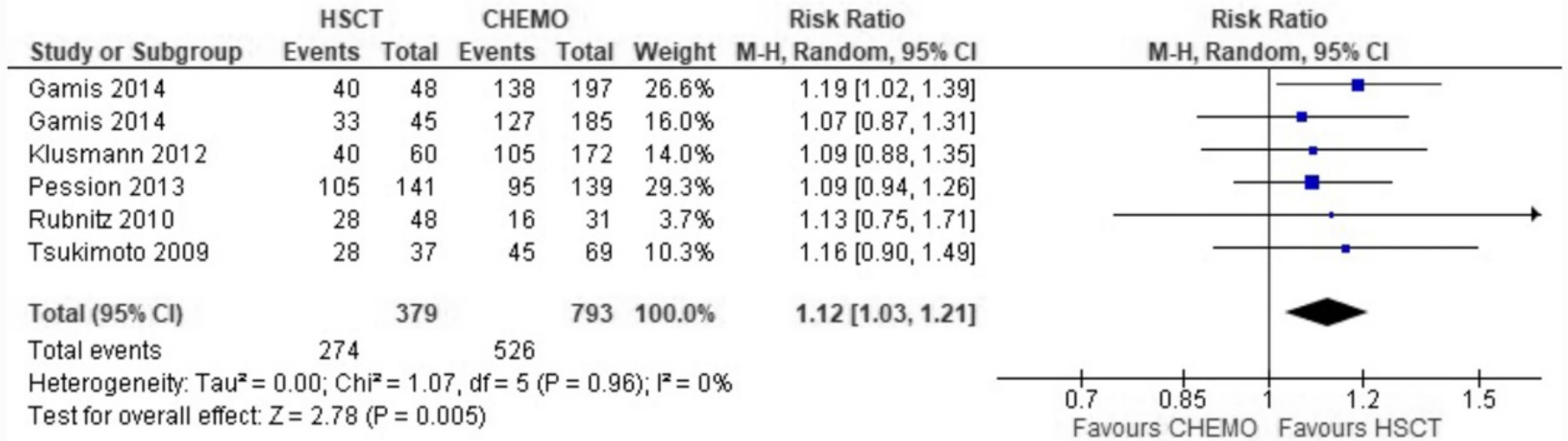


Terapie cellulari: TRAPIANTO DI CSE

RESULTS BY YEAR



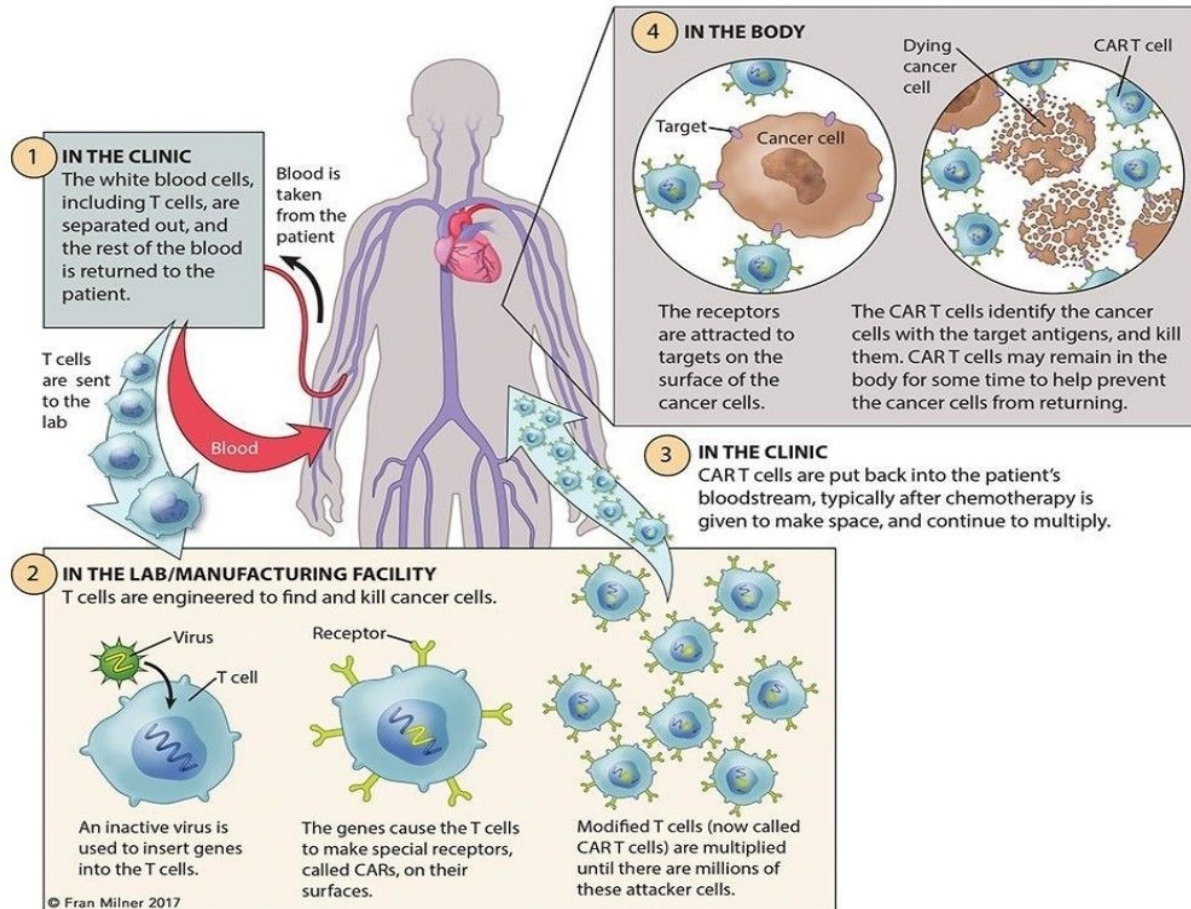
B



Masetti R et Al. Allogeneic hematopoietic stem cell transplantation for pediatric acute myeloid leukemia in first complete remission: a meta-analysis. Ann Hematol. 2022 Aug 30. doi: 10.1007/s00277-022-04965-x. Epub ahead of print. PMID: 36038660.

Terapie cellulari: CAR-T

Chimeric Antigen Receptor T-Cell Therapy: How it Works

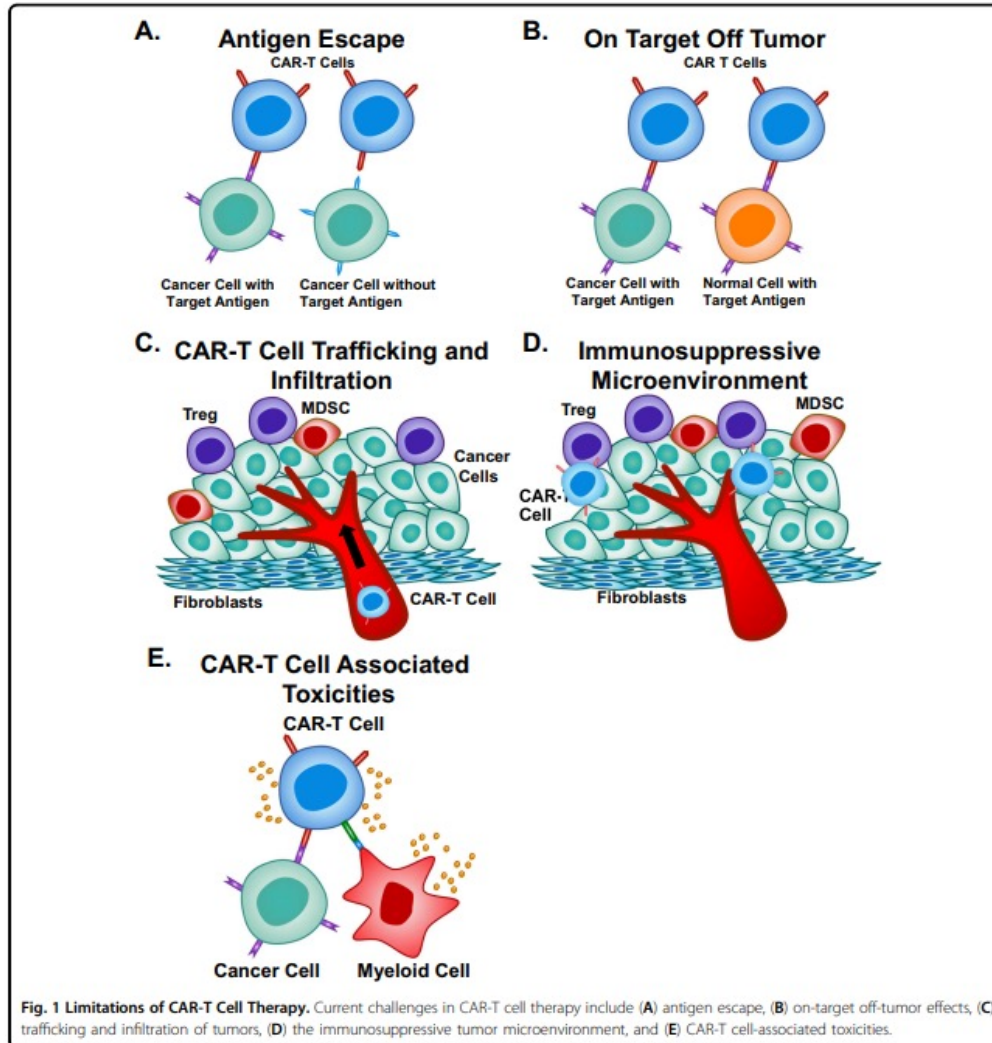


Terapie cellulari: CAR-T

Results of selected clinical trials testing CD19-directed CAR T-cell therapies in B-ALL

Product	Tisa-cel pediatric (multicenter)	JCAR017 pediatric (SC)	CD28-CART19 pediatric (NCI)	CD28-CART19 pediatric (MSKCC)	CD28-CART19 adults (MSKCC)	JCAR015 adults (ROCKET)
Age, y (range)	11 (3 to 24)	12 (1 to 25)	13 (5 to 27)*	13.5 (1 to 22.5)	44 (23 to 74)	39 (19 to 69)
Centers	25	1	1	2	1	n.a.
Costimulation	4-1BB	4-1BB	CD28	CD28	CD28	CD28
Patients, no.	79	43	53	24	53	38
Prior allo-SCT, %	61	62	38*	20	36	37
High tumor burden, %	68 (≥ 50)†	48.9 (>25)	38* (≥ 50)	40 (>5)	51 (>5)	84 (>5)
Lymphodepletion	Flu/Cy†	Flu/Cy; Cy	LD or HD Flu/Cy	HD and LD Cy; Flu/Cy	Flu/Cy; Cy	Flu/Cy; Cy
Severe CRS, %	48 (gr3 to 4)‡	23	13.5 (gr3 to 4)	16 (gr3 to 5)	26 (gr3 to 5)	21 (gr3 to 4)
Severe neurotoxicity, %	13 (gr3 to 4)	21 (gr3 to 4)	5 (gr3)	28 (gr3 to 4)	42 (gr3 to 4)	52 (gr3 to 5)
CR%	82	93	61	75	83	52
Post-allo-SCT, %	10	26	40	83	39	n.a.
EFS/LFS/RFS	Median EFS not reached†	Median EFS 12 mo	Median LFS 18.5 mo§	n.a.	Median EFS 6.1 mo	Median RFS 4.4 mo
Reference	8 11†	12	6* 13	1	7	9
NCT	02435849	02028455	01593696	01860937	01044069	02535364

Terapie cellulari: CAR-T



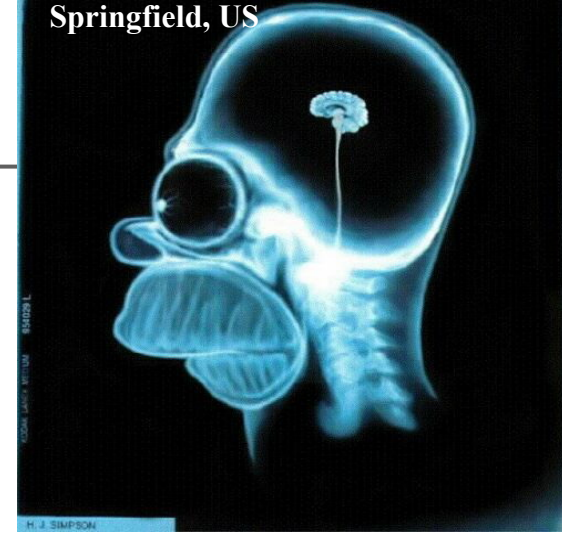


Approccio olistico centrato sul paziente e la sua famiglia: *la chiave di volta.*



Corpo e Mente

Mr. HOMER SIMPSON
Director - Nuclear Power Station
Springfield, US



L'abissale differenza tra
CORPO VISSUTO,
specialmente dal bambino/adolescente, e
CORPO/I OGGETTIVATO/I dalla scienza.

II BUON MEDICO assiste
secondo scienza e coscienza
il **VISSUTO** del proprio paziente.



La ricetta della responsabilità



No alla legge di Hume: uno dei nodi dell'etica normativa contemporanea che vieta di fondare il dover essere sull'essere.

La frattura tra essere e dover essere ha per conseguenza il carattere puramente soggettivo dei valori e dunque il **relativismo etico**.



La ricetta della responsabilità



Fondare il “bene” o il “valore” nell’essere significa colmare il presunto divario fra essere e dover essere.

Hans Jonas.

Il principio responsabilità. Un’etica per la civiltà tecnologica.

1979 – Biblioteca Einaudi



un manifesto della cultura sperimentale

oncologia pediatrica



Incredulità di S. Tommaso, Caravaggio.
(1601-1602) olio su tela; 107x149 cm. Potsdam-Sanssouci, Bildergalerie, Berlin.



*Grazie a tutti
ed in particolare ...*

*ai Maestri che ci ispirano
e*

agli Allievi che ci motivano

XXXIV Congresso Nazionale SIPP
**Dagli albori della vita ...
un cammino insieme**

