Malattie mieloproliferative croniche in età pediatrica: quando interrompere le terapie?

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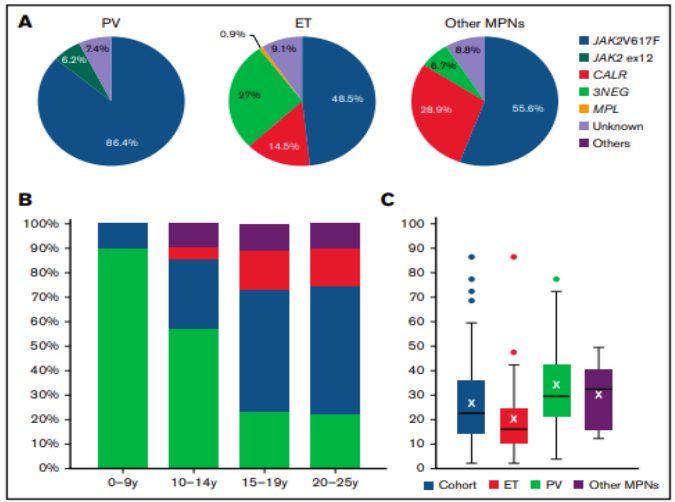
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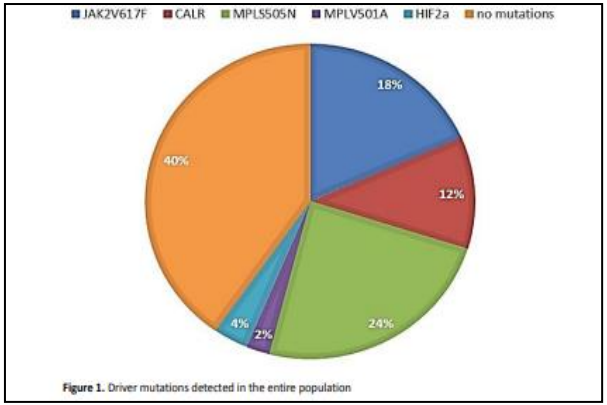
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MALATTIE MIELOPROLIFERATIVE CRONICHE IN ETA' PEDIATRICA

- Incidenza: 0.82 per 100,000 persone/anno
- Caratterizzate dalla presenza di mutazioni somatiche in specifici geni, definiti "DRIVER", nel 90% dei casi → *JAK2*, *MPL*, *CALR*
- Markers "NON-DRIVER" includono geni coinvolti in modificazioni epigenetiche (*ASXL1, EZH2, IDH1, IDH2, TET2, DNMT3A*), o geni implicati nello RNA-splicing (*SF3B1, U2AF2*)



Sobas M, Blood Adv 2022



Bianchi S, EHA 2022, poster session

WHO 2022 Myeloproliferative Neoplasms
Chronic myeloid leukemia
Polycythemia vera
Essential thrombocythemia
Primary myelofibrosis
Chronic neutrophilic leukemia
Chronic eosinophilic leukemia
Juvenile myelomonocytic leukemia
Myeloproliferative neoplasm, not otherwise specified

International Consensus Classification of Myeloid Neoplasms 2022
Chronic myeloid leukemia
Polycythemia vera
Essential thrombocythemia
Primary myelofibrosis
Early/prefibrotic primary myelofibrosis
Overt primary myelofibrosis
Chronic neutrophilic leukemia
Chronic eosinophilic leukemia, not otherwise specified
Pediatric and/or germline mutation-associated disorders
Juvenile myelomonocytic leukemia
Juvenile myelomonocytic leukemia-like neoplasms
Noonan syndrome-associated myeloproliferative disorder
Refractory cytopenia of childhood

Policitemia vera e Trombocitemia Essenziale

- patologie Ph neg che, contrariamente all'adulto, sembrano essere legate a mutazioni somatiche **non driver**

- incidenza 0,82 per 100.000/anno

- scale, criteri e standard diagnostici sono calibrati sull'adulto, pertanto difficili da utilizzare nella popolazione pediatrica

- più della metà dei pazienti sono **asintomatici** all'esordio (sintomi più comuni cefalea, eritromelalgia, stanchezza)
TUTTI presentano **SPLENOMEGALIA**

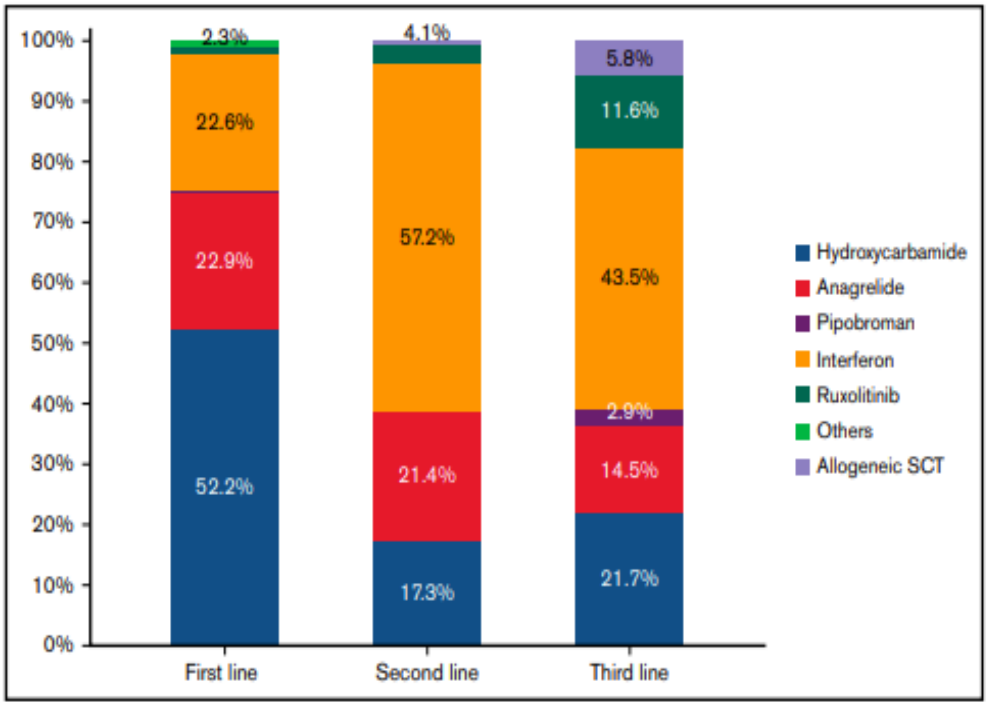
- progressione possibile in MDS/LMA e raramente in mielofibrosi

Trattamento

PV
Flebotomia
Terapie citoriduttive
IDROSSIUREA
IFN-ɣ

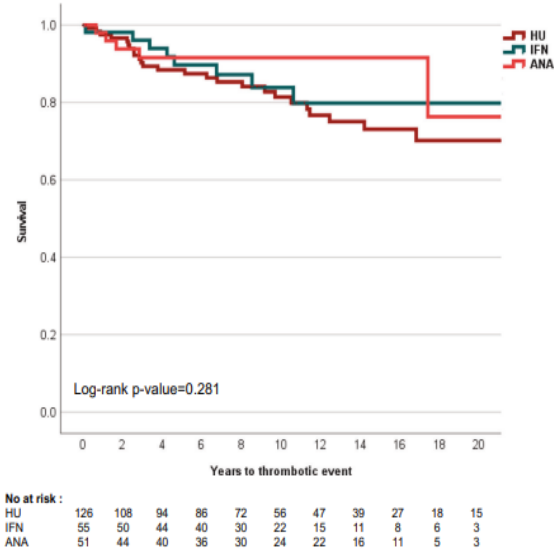
TE
Bambini asintomatici: WATCH&WAIT
Bambini sintomatici/casi selezionati→

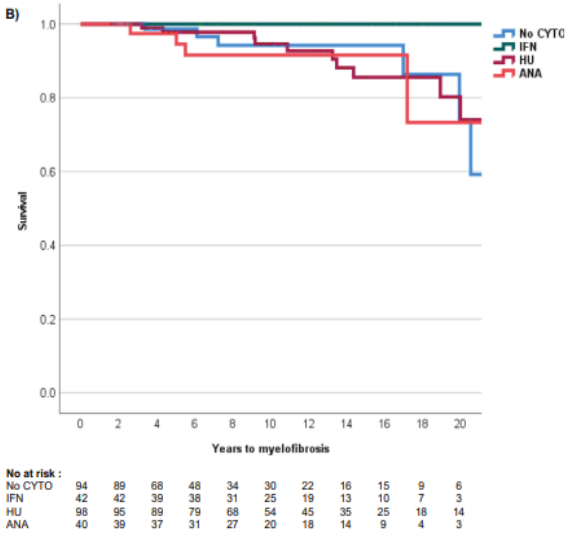
terapie citoriduttive
IDROSSIUREA
ANAGRELIDE
IFN-ɣ
RUXOLITINIB



Sobas M, Blood Adv 2022

Quando sospendere in PV e TE?





Beauverd Y, Leukemia 2025

IL TRATTAMENTO NON SI SOSPENDE A MENO DI EVOLUZIONE IN MFI

Leucemia Mieloide Cronica

Ph + con gene di fusione BCR/ABL

Online calculator
for the EUTOS long-term survival score

Age in completed years: years
Spleen size in cm below costal margin: cm
Blasts in peripheral blood: %
Platelet count in 10^9/L: 10^9/L

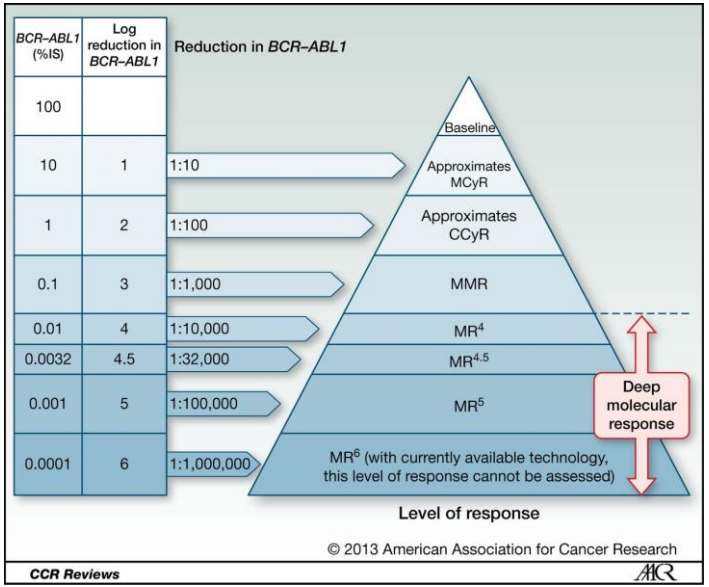
Risk Score:
Risk Score Group:
Run Reset

The ELTS score is rounded to four decimal places.

- An ELTS score value ≤ 1.5680 defines the low-risk group.
- An ELTS score value > 1.5680 but ≤ 2.2185 defines the intermediate-risk group.
- An ELTS score value > 2.2185 defines the high-risk group.

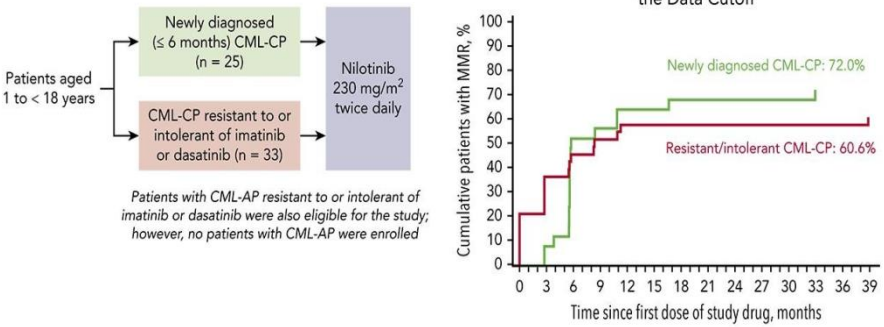
- Acknowledgement: The help of Kirsi Manz in programming the online calculator is gratefully appreciated.

- Pfirrmann M, Baccarani M, Saussele S, Guilhot J, Cervantes F, Ossenkoppele G, Hoffmann V S, Castagnetti F, Hasford J, Hehlmann R, Simonsson B. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. Leukemia 2015. Article in press.



TKIs approvati
IMATINIB
DASATINIB
NILOTINIB

Indicazioni I linea Imatinib se non HR
Dasatinib o Nilotinib se HR



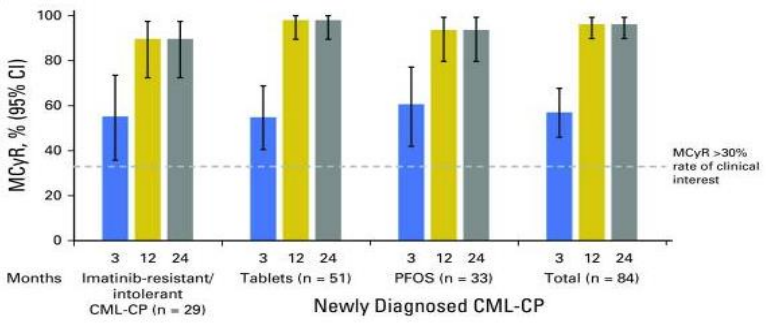
Primary Endpoint Results

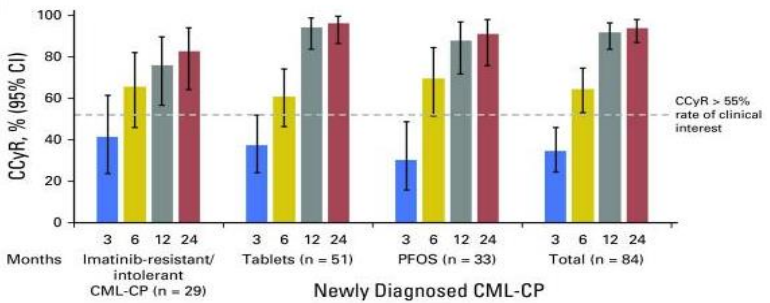
Newly diagnosed CML-CP
- Cumulative MMR rate by 12 cycles: 64.0%
- CCyR rate at 12 cycles: 64.0%

CML-CP resistant to or intolerant of imatinib or dasatinib
- MMR rate at 6 cycles: 39.4%

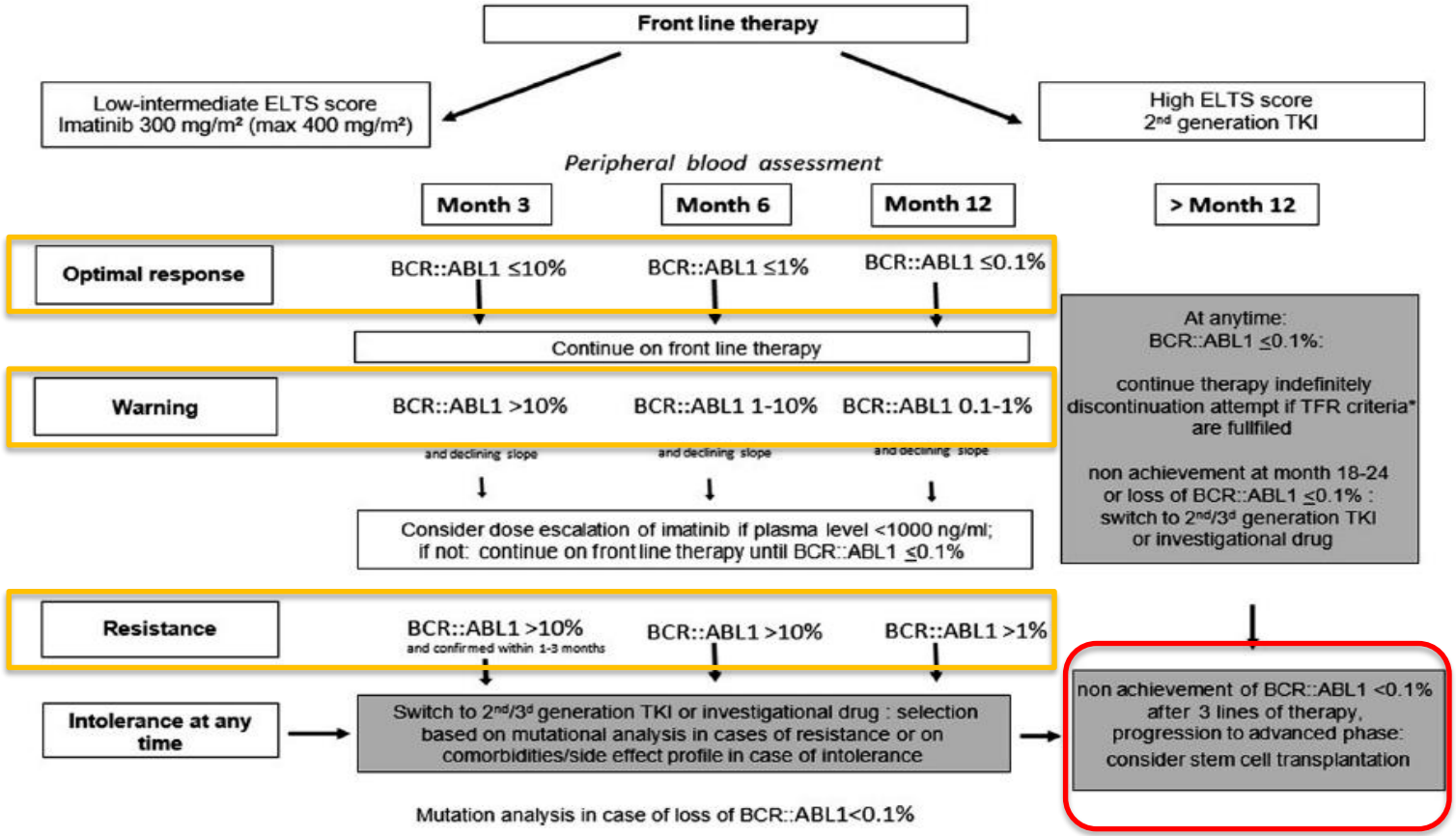
AP, accelerated phase; CCyR, complete cytogenetic response; CML, chronic myeloid leukemia; CP, chronic phase; MMR, major molecular response.

Hijiya N. Blood 2019.

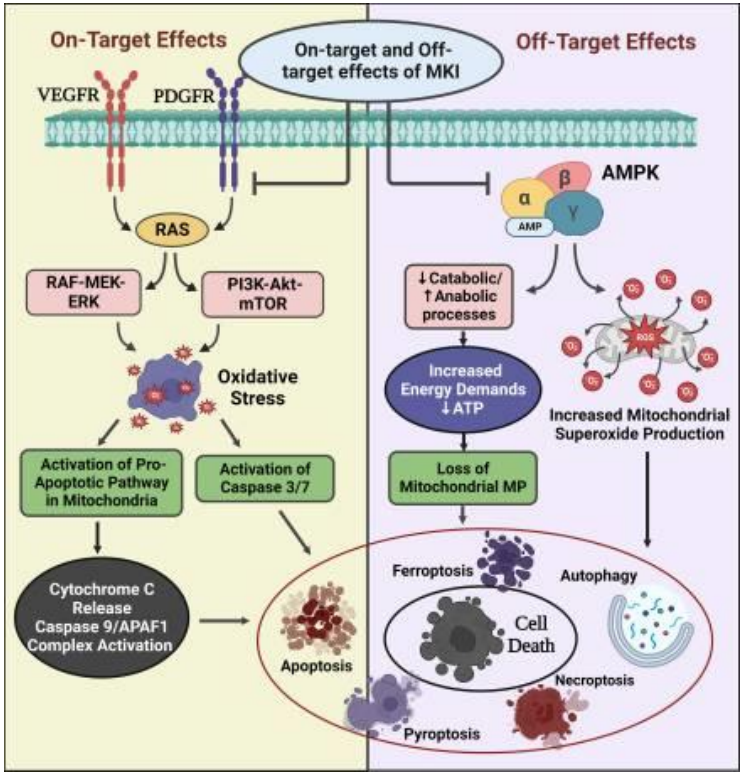




Gore L. J Clin Oncol. 2018


Front line therapy
Low-intermediate ELTS score
Imatinib 300 mg/m² (max 400 mg/m²)
High ELTS score
2nd generation TKI
Peripheral blood assessment
Month 3
Month 6
Month 12
> Month 12
Optimal response
BCR::ABL1 ≤10%
BCR::ABL1 ≤1%
BCR::ABL1 ≤0.1%
Continue on front line therapy
Warning
BCR::ABL1 >10%
BCR::ABL1 1-10%
BCR::ABL1 0.1-1%
and declining slope
and declining slope
and declining slope
Consider dose escalation of imatinib if plasma level <1000 ng/ml;
if not: continue on front line therapy until BCR::ABL1 ≤0.1%
At anytime:
BCR::ABL1 ≤0.1%:
continue therapy indefinitely
discontinuation attempt if TFR criteria* are fullfiled
non achievement at month 18-24
or loss of BCR::ABL1 ≤0.1% :
switch to 2nd/3d generation TKI
or investigational drug
Resistance
BCR::ABL1 >10%
and confirmed within 1-3 months
BCR::ABL1 >10%
BCR::ABL1 >1%
Intolerance at any time
Switch to 2nd/3d generation TKI or investigational drug : selection based on mutational analysis in cases of resistance or on comorbidities/side effect profile in case of intolerance
non achievement of BCR::ABL1 <0.1% after 3 lines of therapy, progression to advanced phase:
consider stem cell transplantation
Mutation analysis in case of loss of BCR::ABL1<0.1%

Sospendere: perché?



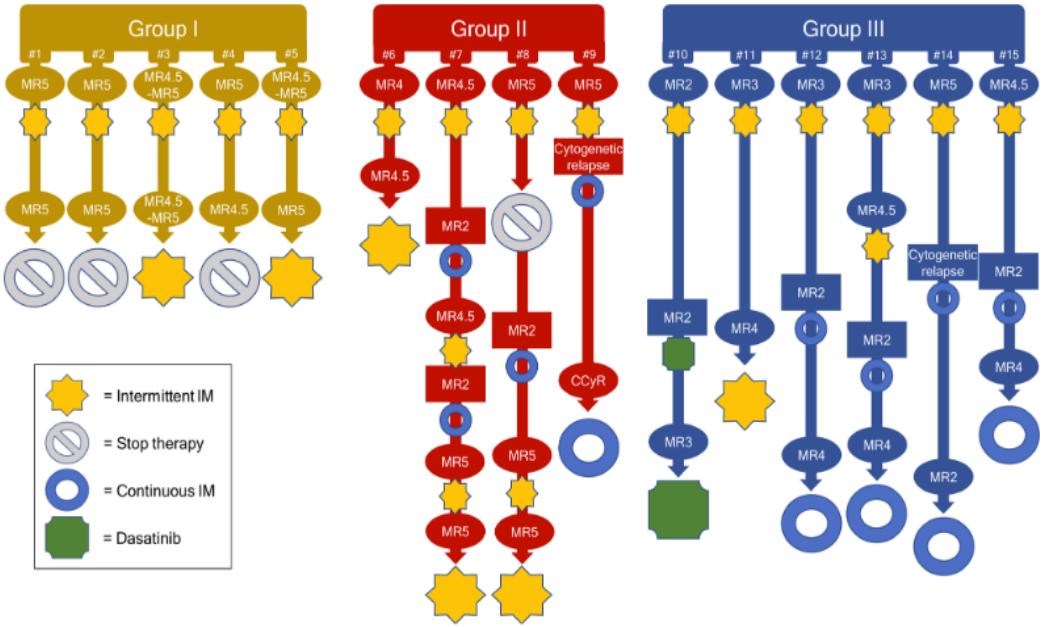
Ritardo crescita	Peso, altezza, stadio puberale ogni visita	Valutazione specialistica endocrinologica
Alterazione densità minerale ossea	MOC, calcemia, fosforemia, ALP, PTH, vitamina D annualmente	Calcio e vitamina D
Alterazioni endocrinologiche	Assetto tiroideo, FSH, LH, cortisolo, HbA1c annualmente	Valutazione specialistica endocrinologica e terapie se necessario
Alterazioni cardiologiche (allungamento QT, disfunzione miocardica, versamento pericardico, ipertensione polmonare)	ECG e Ecocardiogramma annualmente	
Alterazioni di natura Neuropsichiatrica/Comportamentale	Valutazione ad ogni visita	Valutazione specialistica NPI se necessario

Adattata da Millot F, 2025

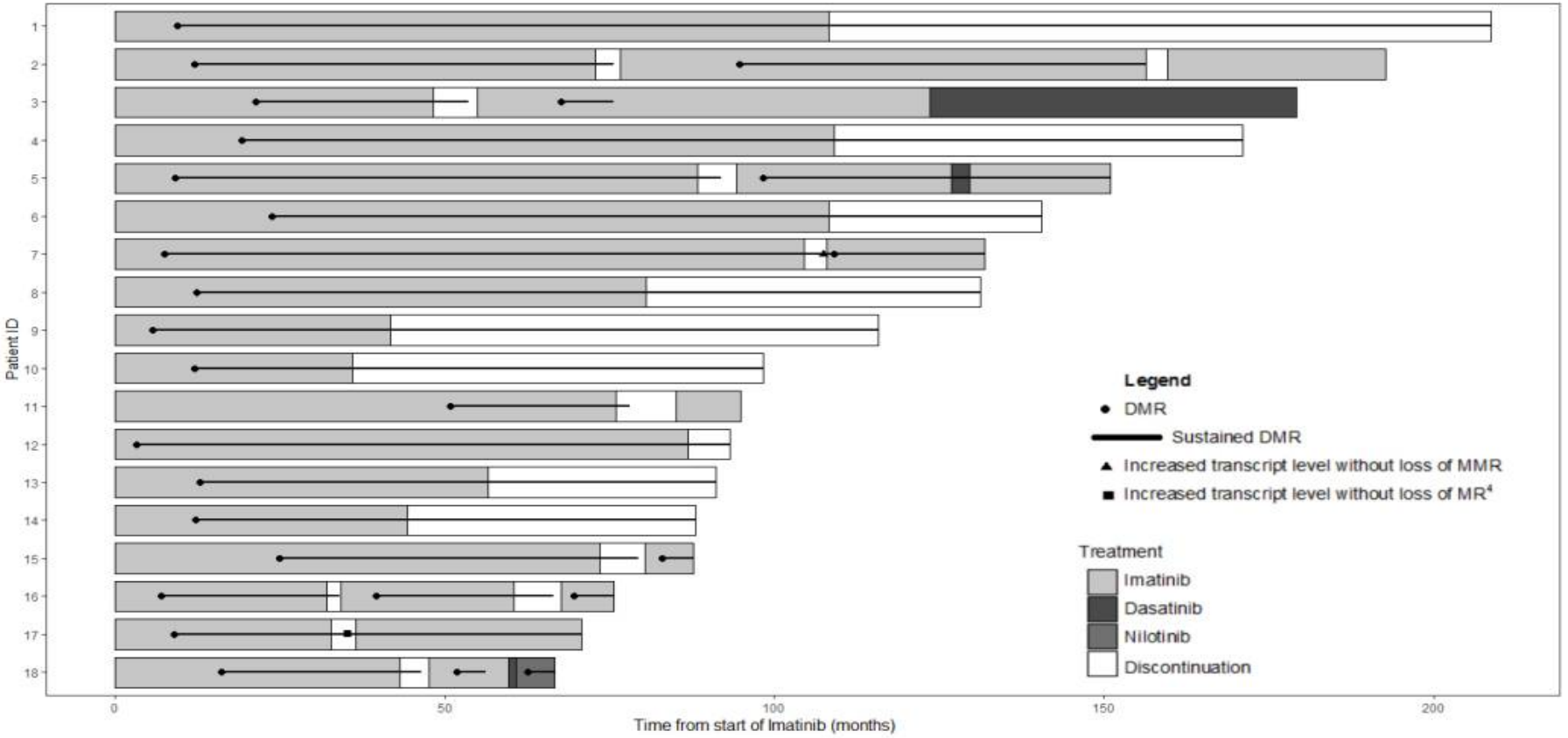
Sospendere: quando?

- Almeno 3 anni di trattamento
- Con una stabile risposta molecolare profonda DMR (almeno MR4.0) per almeno 2 anni consecutivi
- In anamnesi → non progressione
  non fallimenti terapeutici
  non segni di «warning»

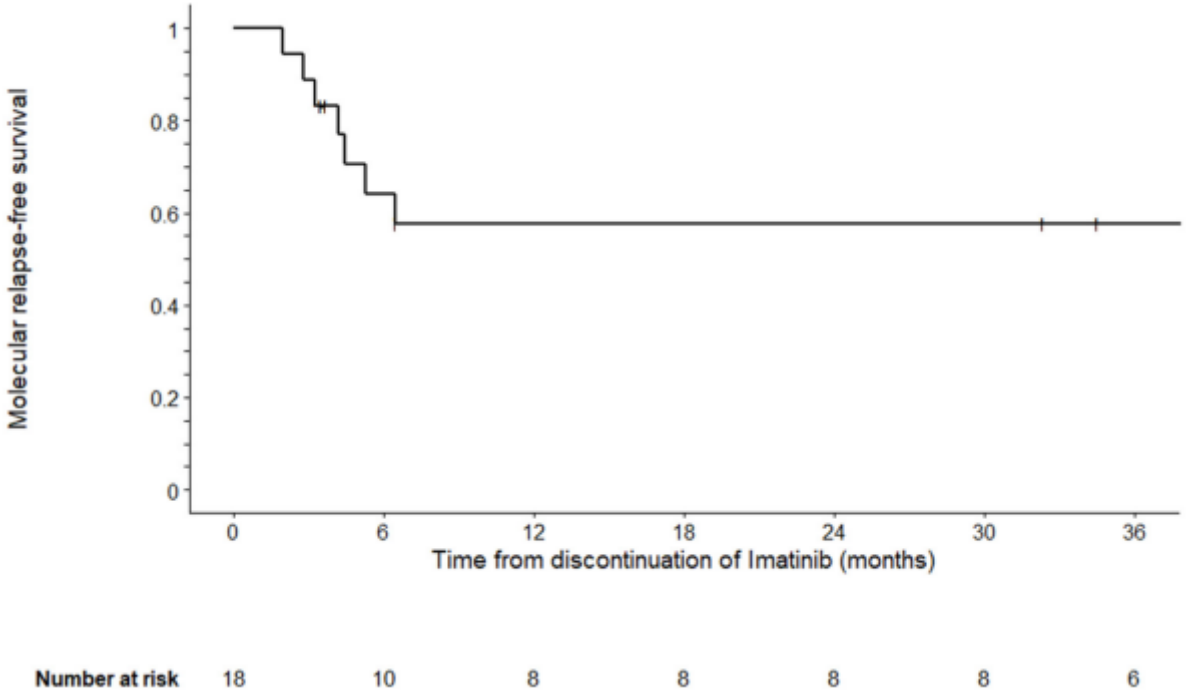
Sospendere: come?



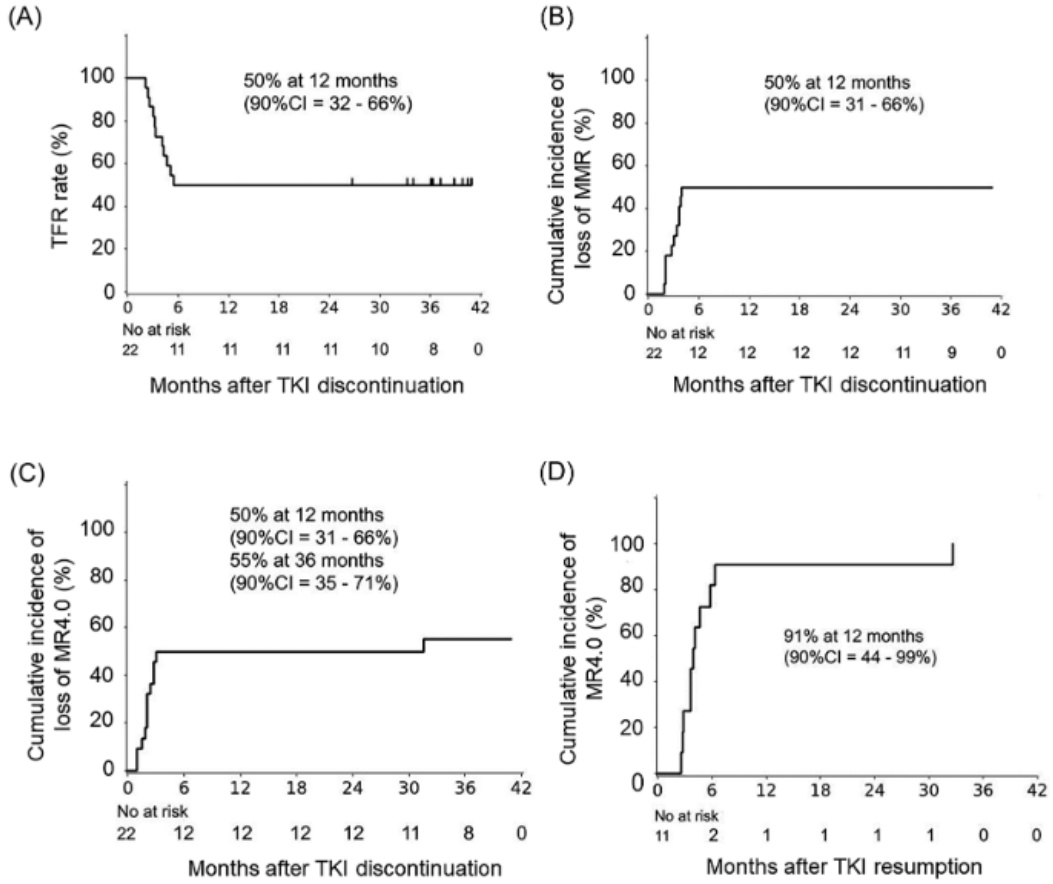
Giona F, BJH 2020



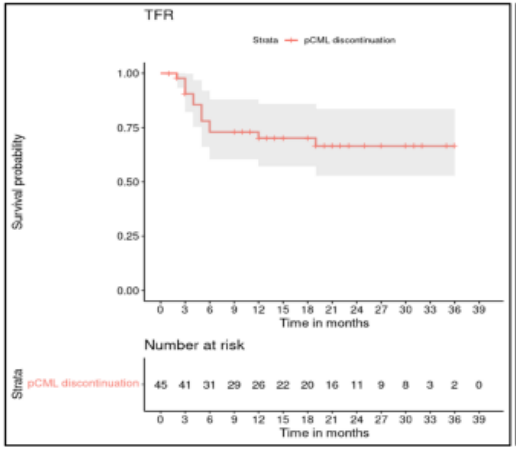
Millot F, et al. Discontinuation of imatinib in children with chronic myeloid leukemia: a study from the International Registry of Childhood CML. Cancers. 2021;13:4102–9

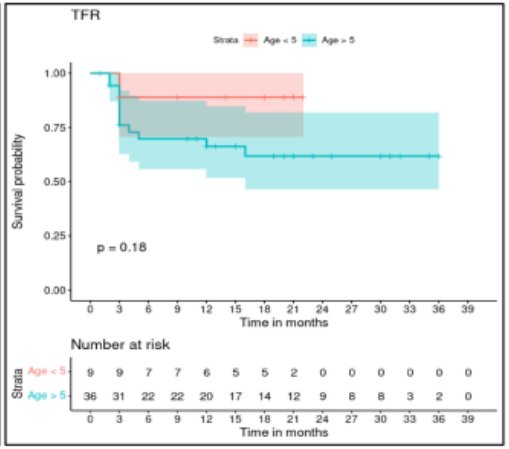


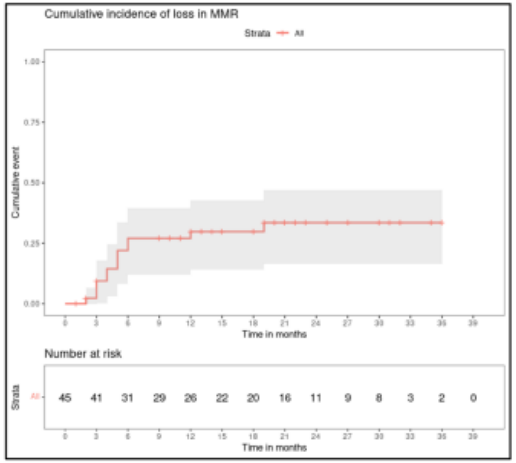
Millot F, et al. Discontinuation of imatinib in children with chronic myeloid leukemia: a study from the International Registry of Childhood CML. Cancers. 2021;13:4102–9

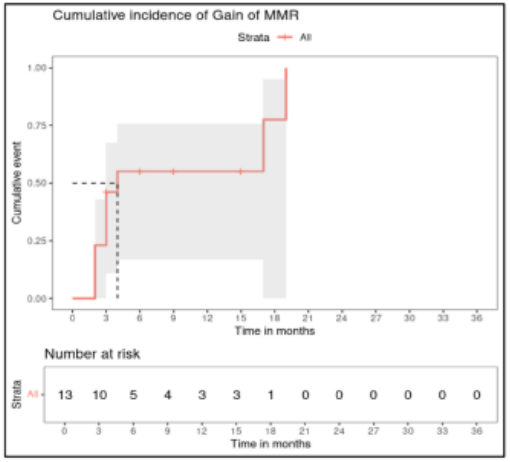


Shima, ped Blood Cancer 2022









Roy Moulik N, et al. Treatment-free remissions in children with chronic myeloid leukemia (CML): a prospective study from the Tata Memorial Hospital (TMH) pediatric CML (pCML) cohort. Am J Hematol. 2024;100:210–7.

Experience with 2G-TKI discontinuation or a second discontinuation after successful retreatment is currently limited in children

Millot F, Suttorp M, Ragot S, Leverger G, Dalle JH, Thomas C, et al. Discontinuation of imatinib in children with chronic myeloid leukemia: a study from the International Registry of Childhood CML. Cancers. 2021;13:4102–9.

In conclusione

- **È possibile interrompere il trattamento con TKI DOPO** Almeno **3 anni** di trattamento e con una **stabile risposta molecolare** profonda DMR (almeno MR4.0) per almeno 2 anni consecutivi

Monitoraggio strettissimo

In caso di recidiva molecol **ento di MMR entro 3 mesi dalla ripresa del trattament**
- **Citogenetica su sangue**
- **Test per mutazione BCR**

Studi cooperativi

Registro

Ad oggi non ci sono studi in età pediatrica che attestano il beneficio di una de-escalation del TKI rispetto ad una interruzione, nè esperienze su seconda interruzione

Siamo certi che le mutazioni non driver non impattino sulle scelte terapeutiche e sulla discontinuation..