

Dalla Diagnosi alla malattia refrattaria nel paziente **borderline per la fitness**

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Bordeline Fitness per chemioterapia convenzionale

Assenza di definizione univoco in letteratura



Quale terapia migliore?

**Rischio di TRM elevata
superiore al 10%**

Età 60-75

Disfunzione d'organo
moderata

Citogenetica complessa

ELN 2022

Bordeline fitness

Presenza di variabili cliniche e biologiche che rendono incerto il risultato terapeutico della chemioterapia tradizionale a causa di un aumento del rischio di mortalità in induzione o della scarsa probabilità di risposta

Variabili cliniche
e sociali

ECOG

Età

Funzionalità
d'organo

Infezioni attive

Supporto sociale

**Elevata mortalità in
induzione**

**Basso rate di
CR e di OS**

Variabili biologiche

- TP53 biallelica
- Cariotipo complesso
- Aml secondaria
- **Mutazioni a basso rischio**
- ELN adverse
- **TP53 monoallelica**

Zona di incertezza terapeutica

Paziente Fit/unfit secondo criteri SIE/SIES/GITMO

Operational criteria defining patients not fit for intensive chemotherapy

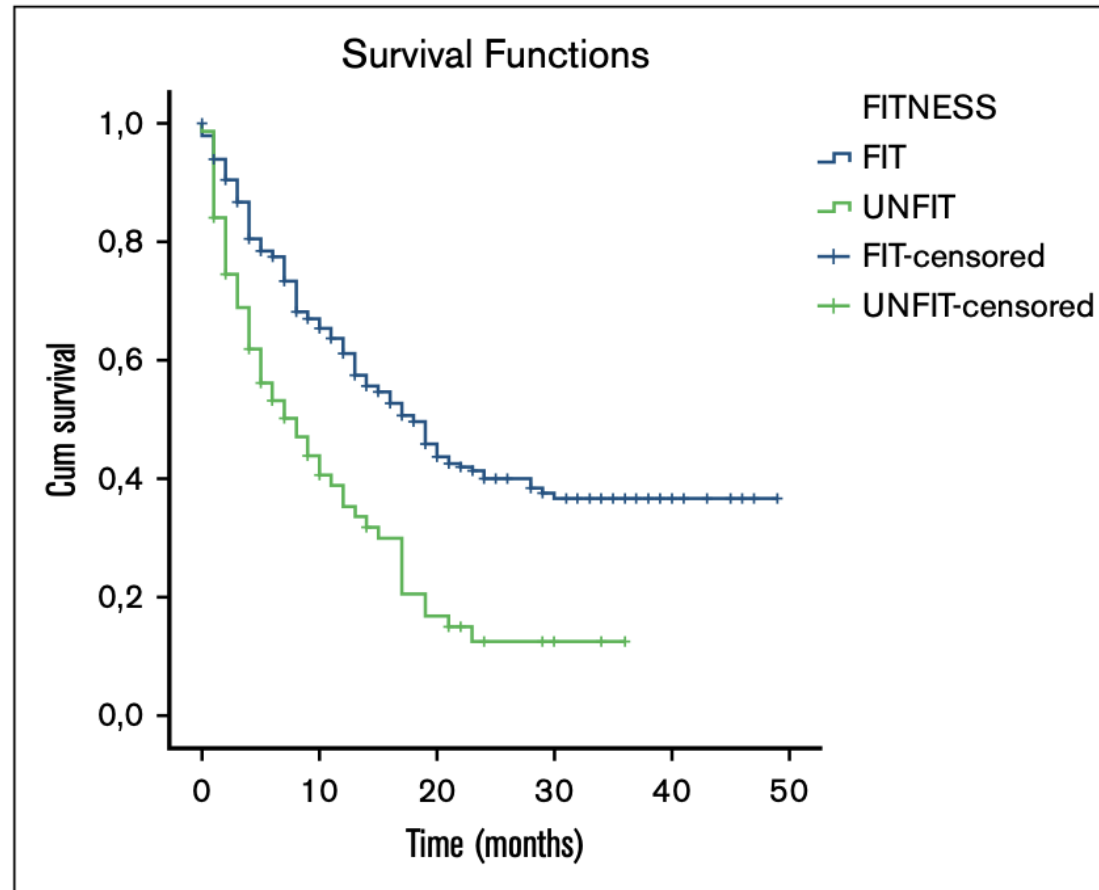
- Age >75 years
- Congestive heart failure or documented cardiomyopathy with an EF $\leq 50\%$
- Documented pulmonary disease with DLCO $\leq 65\%$ or FEV1 $\leq 65\%$, or dyspnea at rest or requiring oxygen, or any pleural neoplasm or uncontrolled lung neoplasm
- On dialysis and age >60 years or uncontrolled renal carcinoma
- Liver cirrhosis Child B or C, or documented liver disease with marked elevation of transaminases (>3 times normal values) and age >60 years, or any biliary tree carcinoma or uncontrolled liver carcinoma or acute viral hepatitis
- Active infection resistant to anti-infective therapy
- Current mental illness requiring psychiatric hospitalization, institutionalization, or intensive outpatient management, or current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver
- ECOG performance status ≥ 3 not related to leukemia
- Any other comorbidity that the physician judges to be incompatible with conventional intensive chemotherapy

Operational criteria defining patients not fit for non-intensive chemotherapy

- Refractory congestive heart failure
 - Documented pulmonary disease with DLCO $\leq 65\%$ or FEV1 $\leq 65\%$, or dyspnea at rest or requiring oxygen, or any pleural neoplasm or uncontrolled lung neoplasm
 - Liver cirrhosis Child B or C or acute viral hepatitis
 - Active infection resistant to anti-infective therapy
 - Current mental illness requiring psychiatric hospitalization, institutionalization, or intensive outpatient management, or current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver
 - Uncontrolled neoplasia
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Ferrara et al 2013
Leukemia

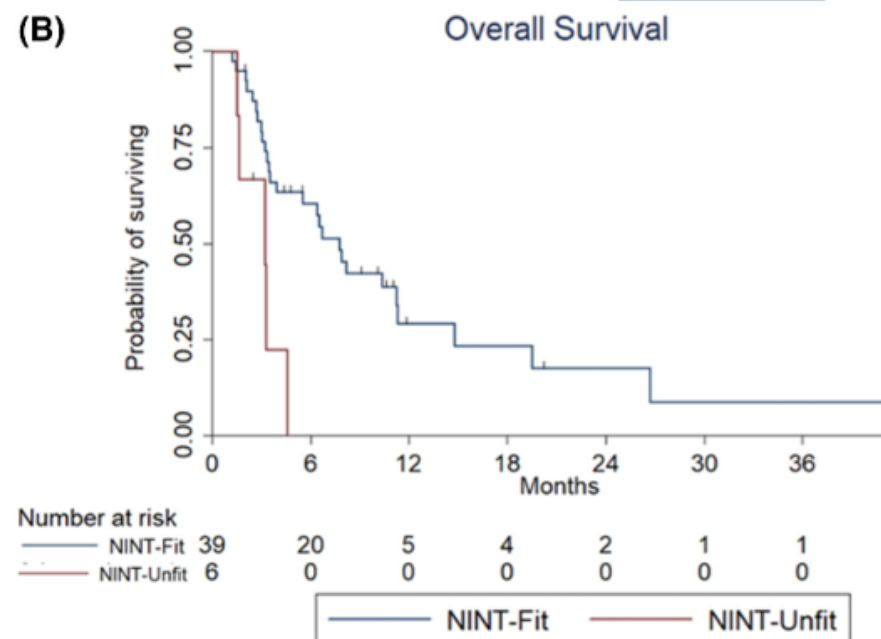
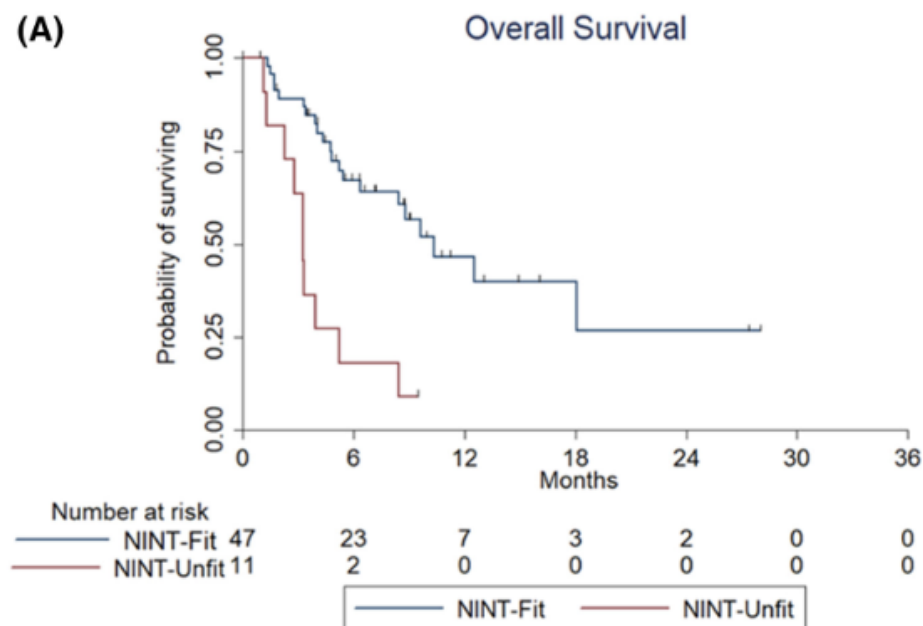
Impact of fitness categorization according to SIE/SIES/GITMO criteria in therapy-related and AML-MRC receiving CPX-351



TRM fit vs unfit 14 vs 32%

Figure 1. OS of the whole study population when stratified according to fitness level. Cum, cumulative.

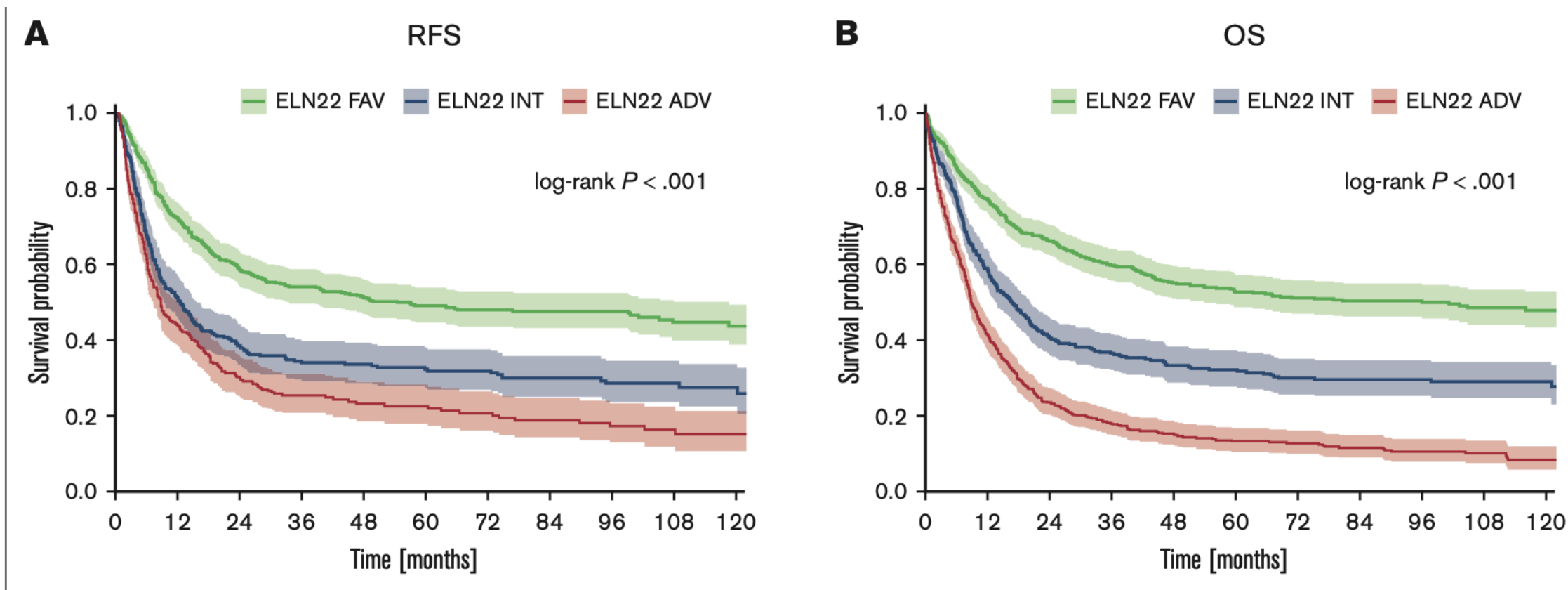
Validation of SIE/SIES/GITMO consensus criteria for unfitness to predict early mortality and survival in acute myeloid leukaemia patients treated with hypomethylating agents and venetoclax



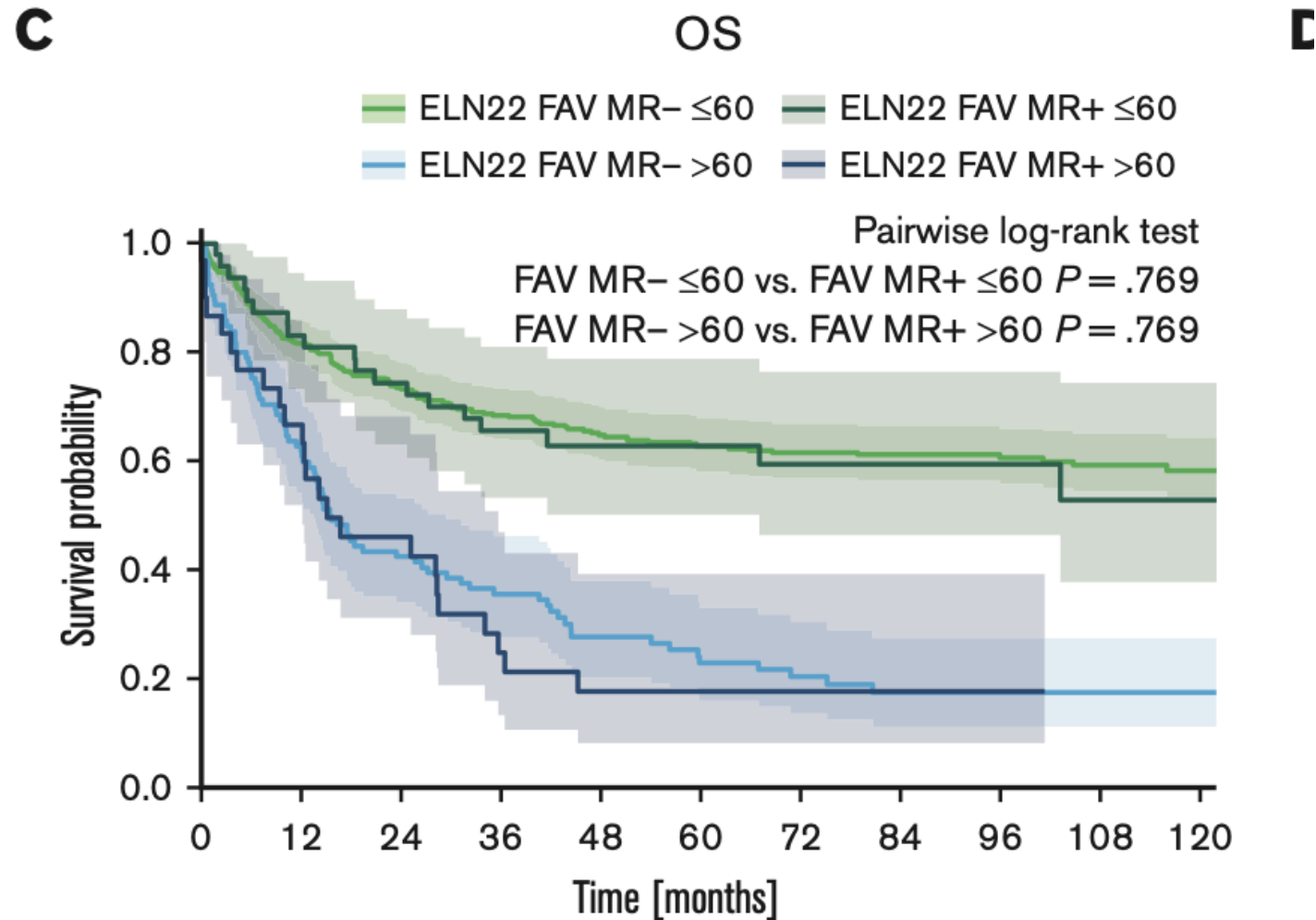
Studio molecolare in NGS e citogenetico

- Informazioni essenziali per stimare la probabilità di risposta alla chemioterapia
- Attendere fino a tre settimane i dati molecolare per la scelta terapeutica non sembra influire sulla sopravvivenza
- Permette di identificare i sottotipi di aml con bassa probabilità di risposta alla chemioterapia
- Permette di identificare i sottotipi di aml con bassa probabilità di risposta alla terapia ipometilante associata a anti bcl-2

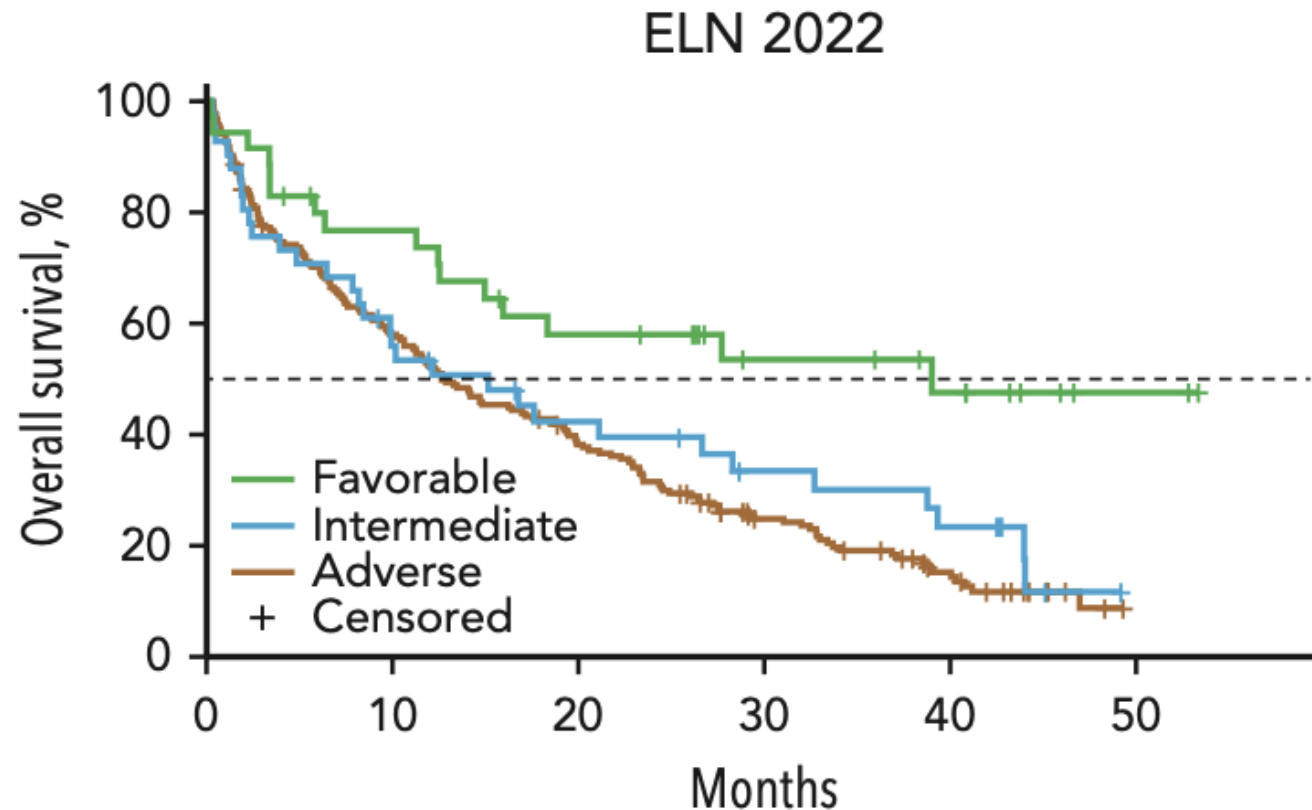
Validation of the revised 2022 European LeukemiaNet risk stratification in adult patients with acute myeloid leukemia



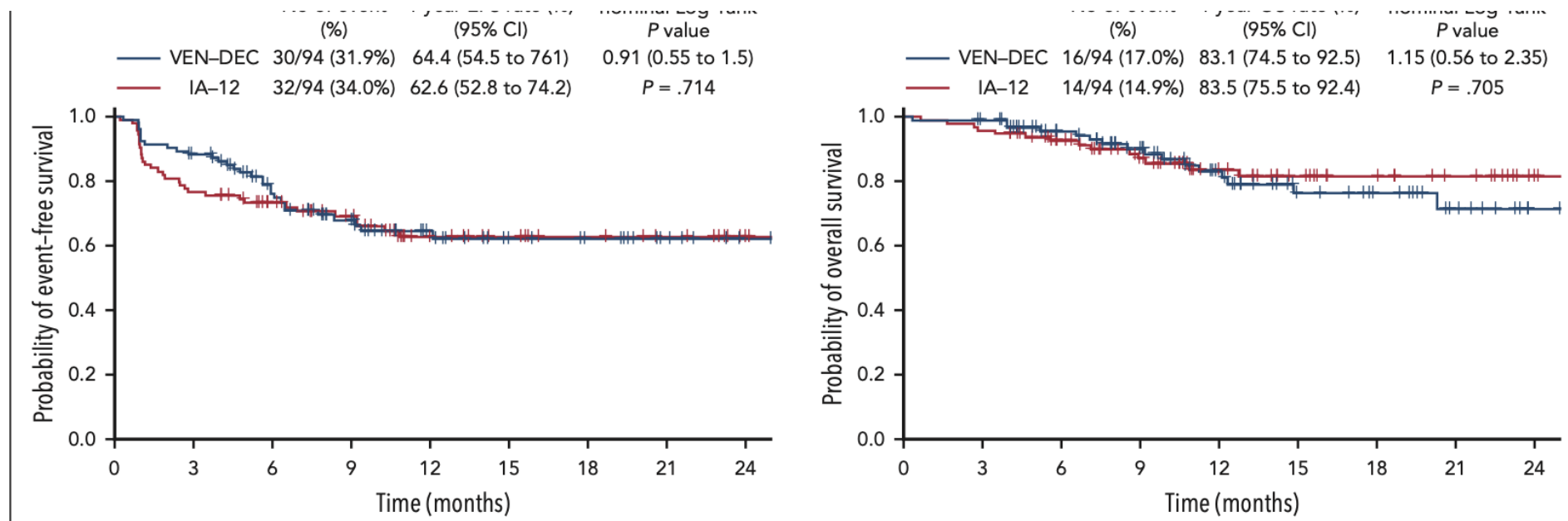
Rischio favorevole → borderline ??



Stratificazione genetica e outcome nei pazienti trattati con aza ven

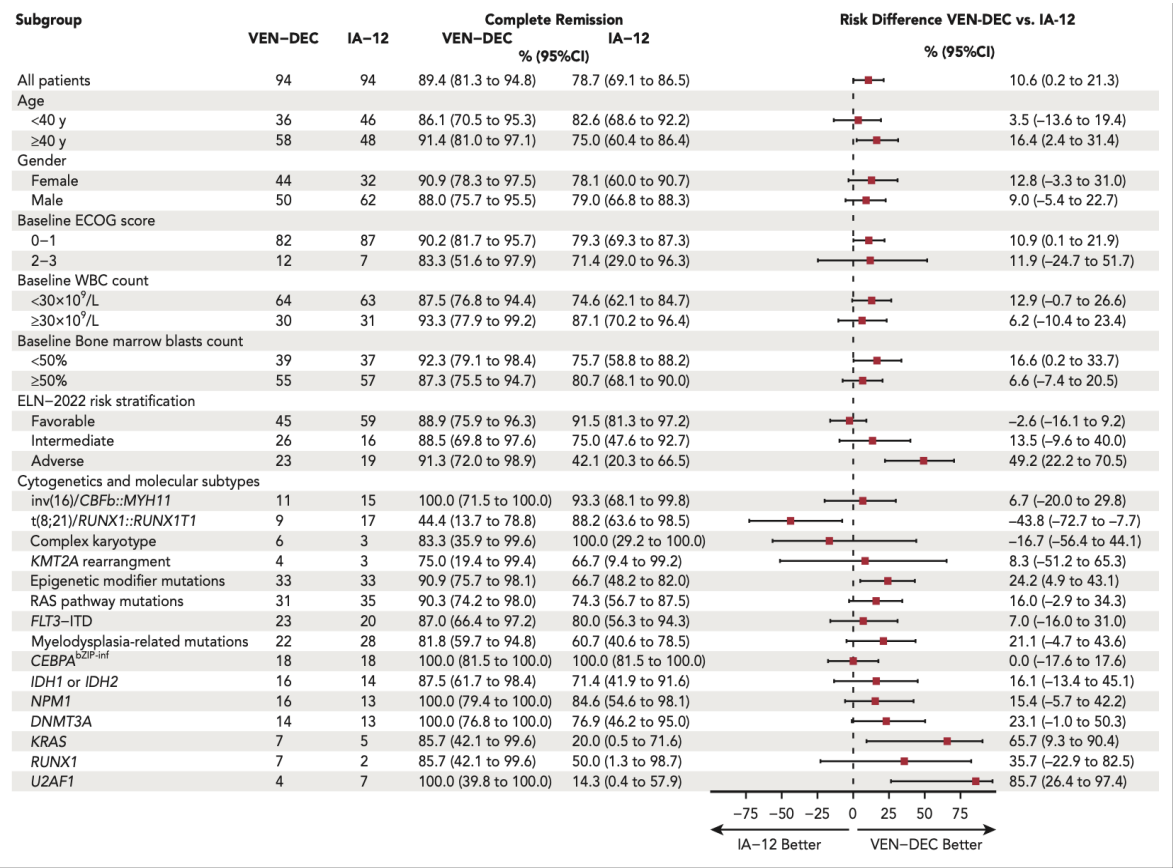


Dilemma dell'approccio terapeutico: chemioterapia versus terapia bassa intensità



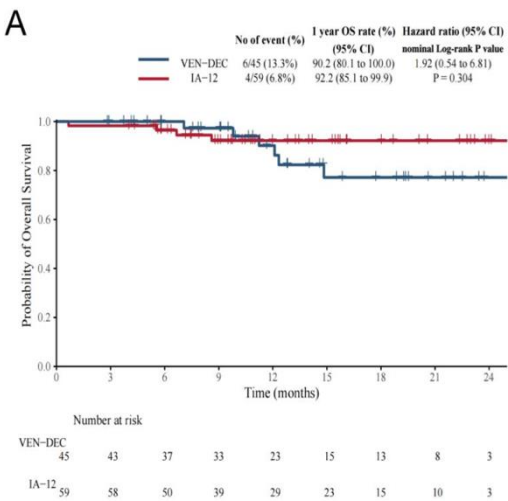
Ven-dec vs 7+3 phase IIb EFS e OS non differenze significative

Differenze di CR nei diversi sottogruppi a favore di VEN DEC o della chemioterapia



CR ELN 2022 rischio
avverso HR a favore di ven
dec

CR Runx1-RUNXt a
favore di 7+3



OS nel rischio favorevole a favore della
chemioterapia

Paradigm trial rischio intermedio/avverso aza ven versus chemioterapia 3+7/CPX 351 phase IIb nel paziente fit

No differenze in termini di OS

Endpoint primario di EFS a favore del braccio ven aza raggiunto

tasso di trapianto maggiore nel braccio aza ven

Pazienti FLT3 esclusi

Alcuni profili molecolare potrebbero giovare della terapia a bassa intensità indipendentemente dalla fitness?

- Evidenze non solide
- Dati da studi di fase II nel paziente FIT
- Conferma negli studi di fase III e nei diversi sottogruppi
- **Quale terapia nel braccio controllo???**
- Endpoint primario? OS o EFS
- Il basso rischio potrebbe avere un outcomes peggiori coi regimi a bassa intensità

American Society of Hematology 2025 guidelines for treating newly diagnosed acute myeloid leukemia in older adults

Mikkael A. Sekeres, Ryan Mattison, Andrew Artz, Maria R. Baer, Chong Chyn Chua, Roberta Demichelis-Gómez, Pamela C. Egan, Luke Fletcher, Charles Foucar, Jacqueline S. Garcia, Linda Gilberto, Andres Gómez de León, Jeffrey Lancet, Kah Poh Loh, Luca Malcovati, Bernard Marini, Uwe Platzbecker, Mohamed L. Sorrow, Sara Tinsley-Vance, John Treitz, Maria Jose Oliveros, Sara Ibrahim, Yetiani Roldan, Gordon Guyatt, Romina Brignardello-Petersen



Check for updates

Blood Adv (2026) 10 (6): 1897–1928.

Recommendation 2b

For older adults with newly diagnosed AML considered candidates for intensive ALT, the ASH guideline panel *suggests* using either conventional induction and postremission therapy or HMA- or LDAC-based induction and postremission therapy in combination with venetoclax (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Remarks:

- Conventional induction and postremission therapy may be preferred for patients who have favorable-risk cytogenetics or molecular mutations and for those for whom a long

hospital stay would not be a deterrent. Furthermore, “younger” older adults (eg, sexagenarians) may better tolerate conventional induction and postremission chemotherapy.

- HMA- or LDAC-based induction and postremission therapy in combination with venetoclax may be preferred for patients who are older (eg, aged ≥ 70 years) or with certain poor-risk cytogenetics or molecular mutations that may compromise response to conventional therapy. Furthermore, those patients who wish to avoid admission to the hospital may prefer this treatment approach.

Leucemia mieloide acuta relapse refractory retesting for target therapy o terapia olistica

Diagnostic work up for R/R AML pts: BM assessment, mutational analysis

1. Question: Possibility of enrollment into clinical trial?

If yes, 1st priority

2. Question: Is the patient a candidate for allogeneic HCT?

Yes

No

Mutation agnostic therapies

Targeted therapies

Mutation agnostic therapies

Step1 *

Salvage therapies: e.g. FLAG-IDA, MEC, HAM
(possibly with the addition of Venetoclax)

Step 1

FLT3 mutated: Gilteritinib[#]
IDH1 mutated: Ivosidenib[#]
Olutasidenib[#]
IDH2 mutated: Enasidenib[#]

Step 1

No standard therapy
• --> clinical trials best choice
• Change agents
(e.g. HMA/VEN if no prior VEN)
• BSC

rapid

Step 2: Allogeneic HCT[¶]

If no allogeneic HCT
continue treatment

Step 3: Consider maintenance therapy

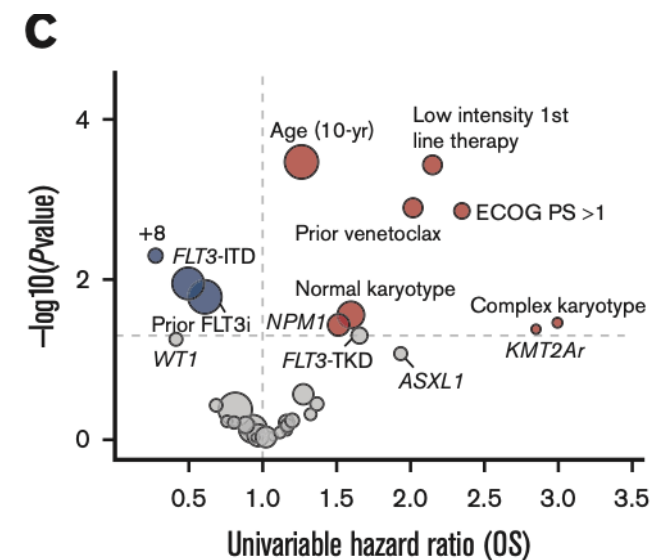
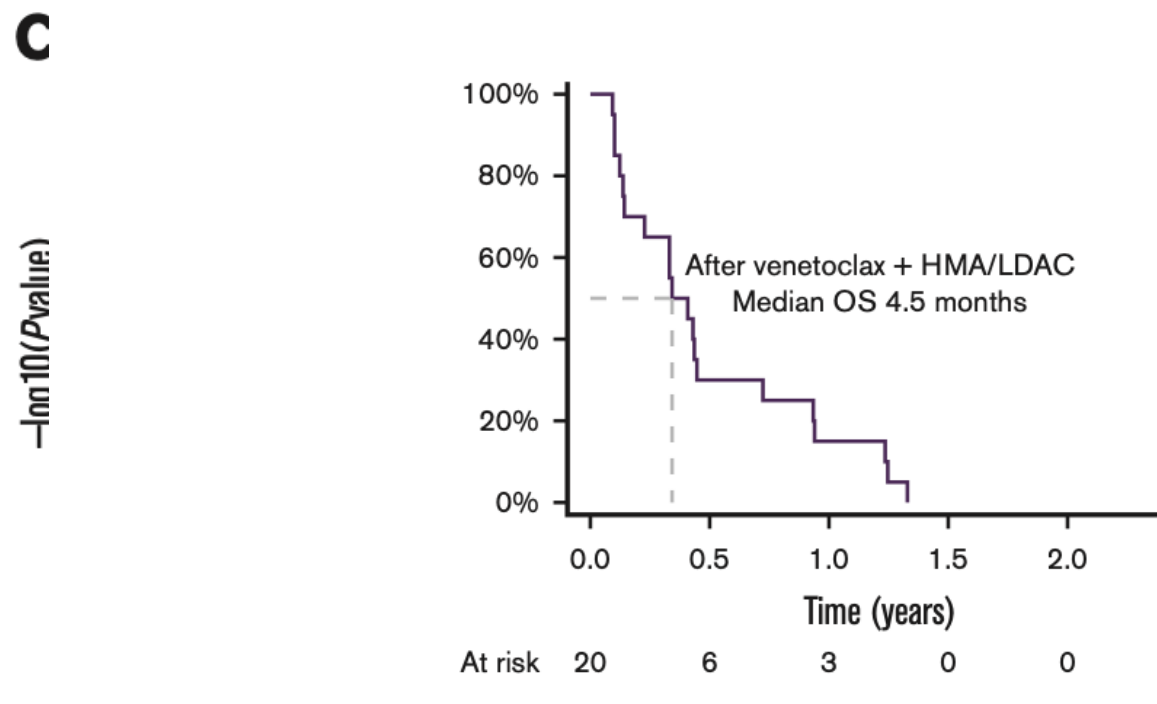
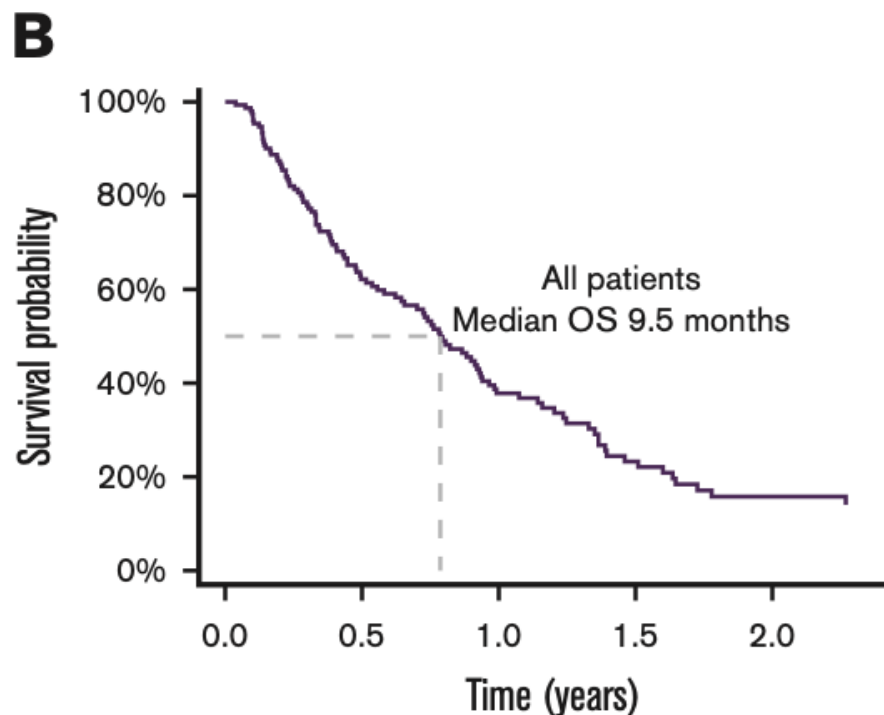
* Some patients might go directly to allogeneic HCT or
receive lower intensity regimens

[¶] Consider DLIs for relapse post alloHCT, second alloHCT
only indicated in selected pts

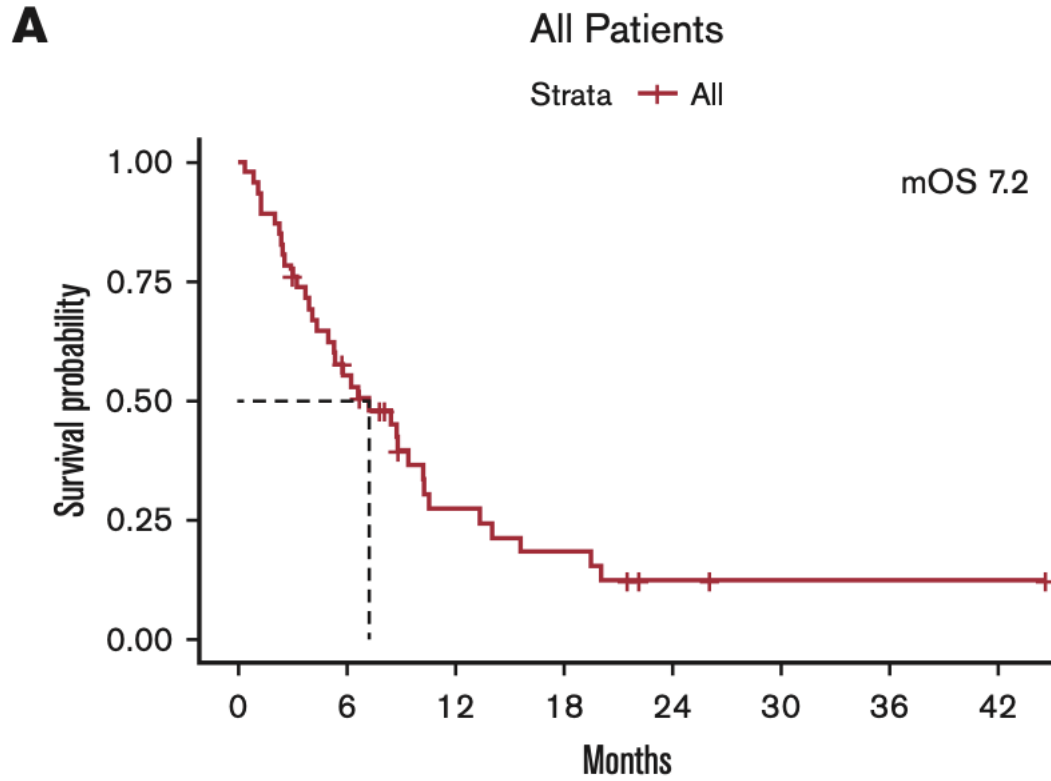
[#] approved by FDA but not EMA for R/R AML pts

Gilteritinib in aml FLT3+

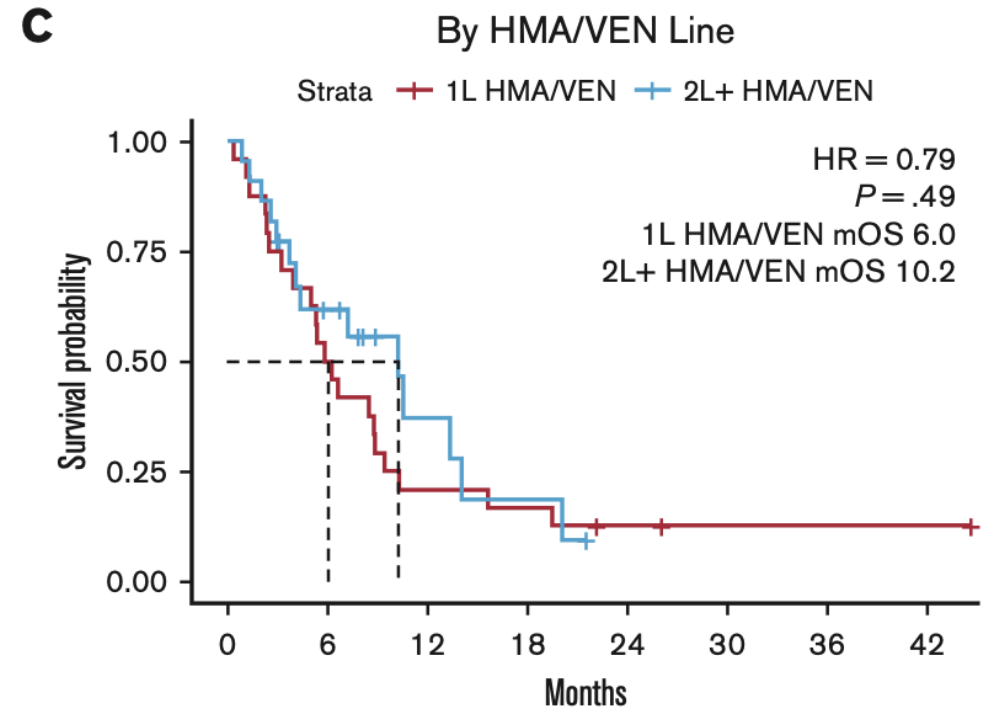
Nei dati di RW i paziente precedentemente trattati con venetoclax presentano una OS peggiore rispetto ai pazienti trattati con chemio



Intensive chemotherapy after hypomethylating agent and venetoclax in adult acute myeloid leukemia



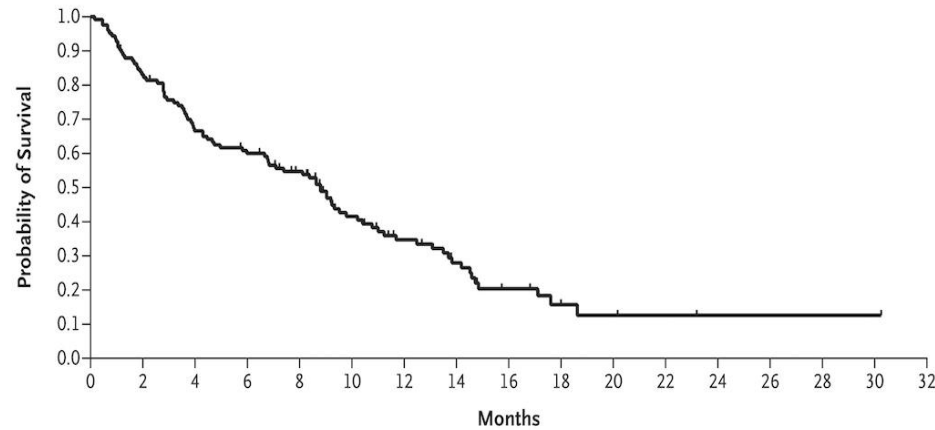
Number at risk



OS dopo terapia con aza ven 4 mesi

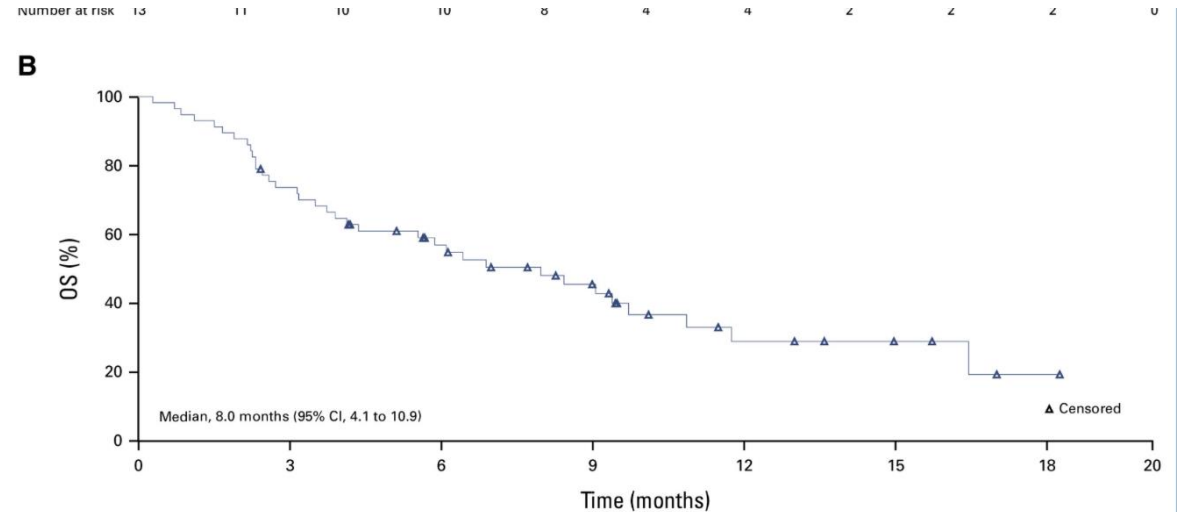
Ricerca di mutazioni target per inibitori di IDHs o per inibitori della menina per NPM1/KMT2A

Overall Survival



No. at Risk

OS aml IDH1 mutati
trattati con ivosidenib



OS aml R/R KMT2A mutati
trattati con revumenib

Grazie per l'attenzione