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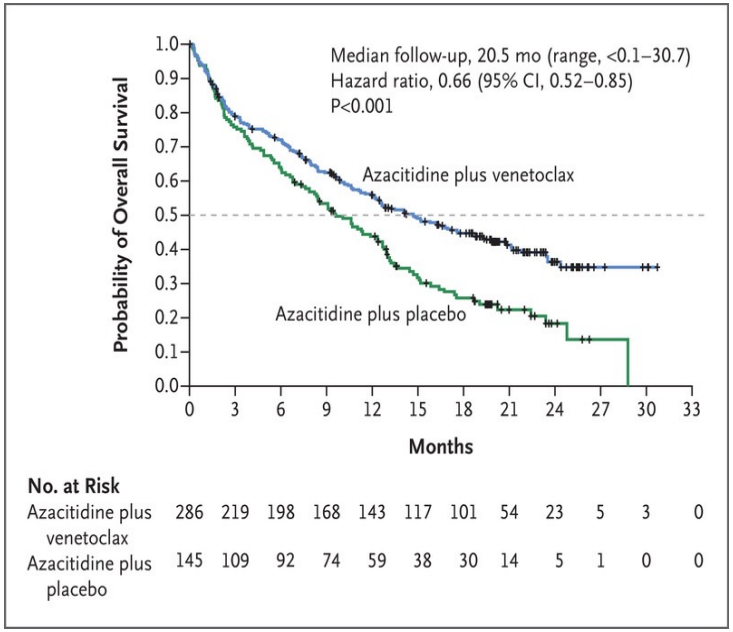
La terapia con ipometilanti-venetoclax nella AML: dalla teoria alla pratica

Key points to socialize with HMA-VEN



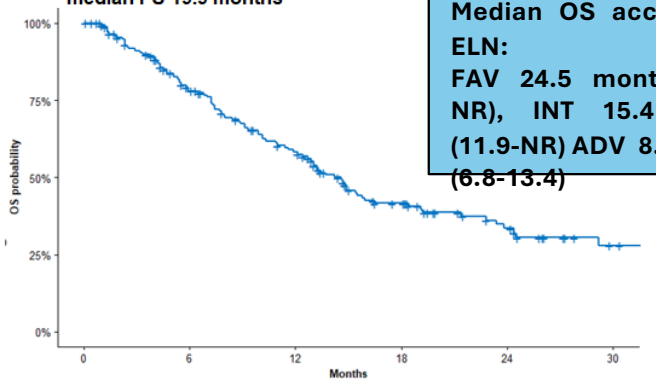
Di Nardo et al. New Engl Journ Med 2020

- Early experience with azacitidine plus venetoclax (AZA-VEN) was strikingly different to our historical experience with azacitidine alone. Response rates were markedly higher and occurred more rapidly
- We are speaking about **ACUTE MYELOID LEUKEMIA**, so you **MUST EXPECT:**
  - Prolonged neutropenia
  - Infections
- HMA-VEN is recommended for **ELDERLY** or unfit patients, so you **MUST FACE** with:
  - Comorbidity
  - Social frailty

Real World Outcome of Unfit Patients with Acute Myeloid Leukemia Treated with the Combination Venetoclax Plus Hypomethylating Agents in the GIMEMA AML2320 Observational Trial

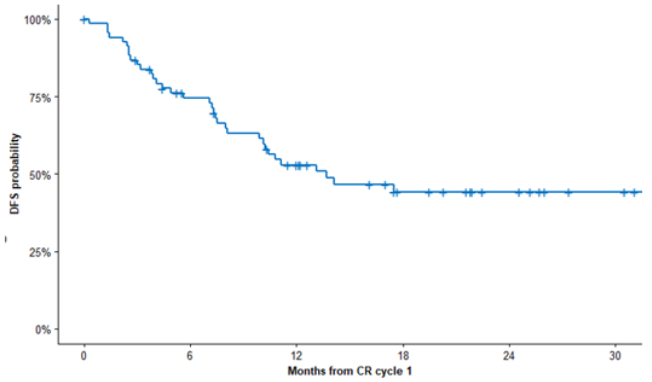
- **Prospective, observational** investigating the outcome of pts treated with the combination **Ven+HMA**, in a **real-world** setting
- **Primary endpoint OS**
- November 2020 - December 2021, **188 pts**, median age 74 years (49-85)
- **ELN 2017** (151 pts): FAV 23%, INT 46% , ADV 32%
- 75% pts received VEN+AZA , 25% VEN+DEC
- The **median** no. of delivered **courses** was **5** (1-27).
- Eleven (**6%**) underwent **HSCT** after having received 4 courses of VEN+HMA and being in CR/CRi
- After 1st course, response assessment was evaluated in 123/178 (**69%**) pts with 70 (57%) being in CR/CRi.

Figure n. 1a: Overall Survival
median FU 19.9 months



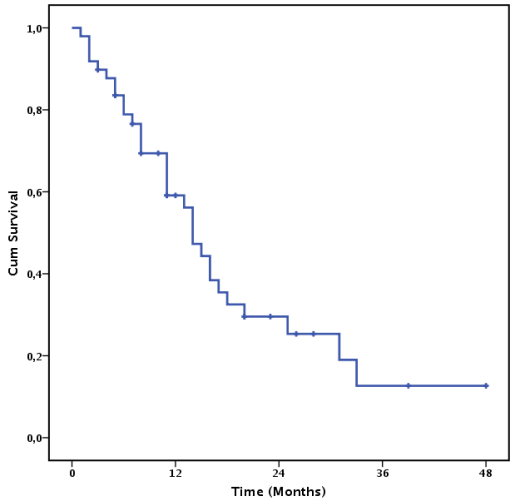
Median OS according to ELN:
FAV 24.5 months (14.2-NR), INT 15.4 months (11.9-NR) ADV 8.9 months (6.8-13.4)

Figure n. 1b: Disease Free Survival of responding pts



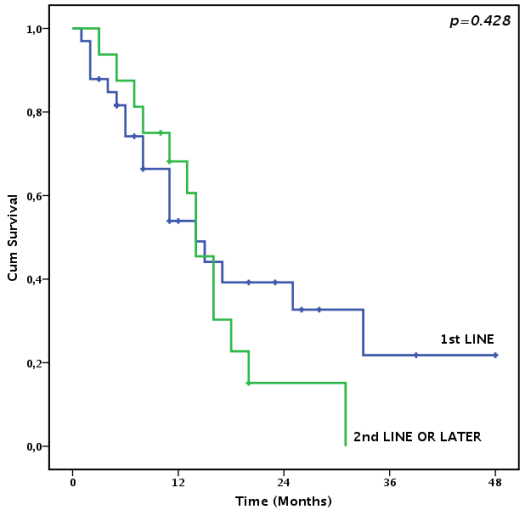
Venditti A, et al. Blood (2023) 142 (Supplement 1): 1514.

- Clinica Ematologica Unit, years 2018 – 2024
- HMA VEN as first or salvage treatment
- 48 patients, median age 74 yrs (65-84)



OS mediana globale: 14 mesi (IC 11,34-16,66) con follow-up mediano di 26 mesi (IC 95%: 16,88 – 35,12 mesi)

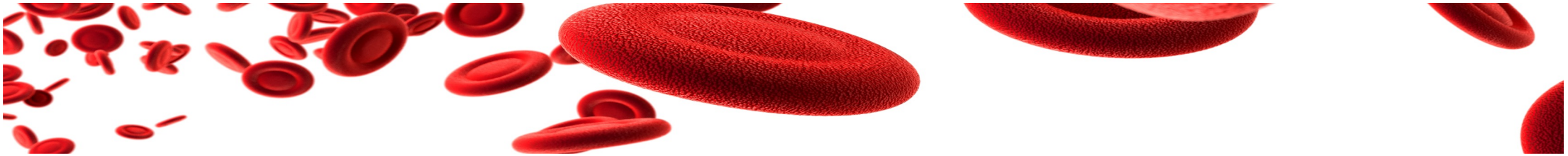
OS ad 1 anno 59,1%, a due anni 29, 6%, a tre anni 12,7%.

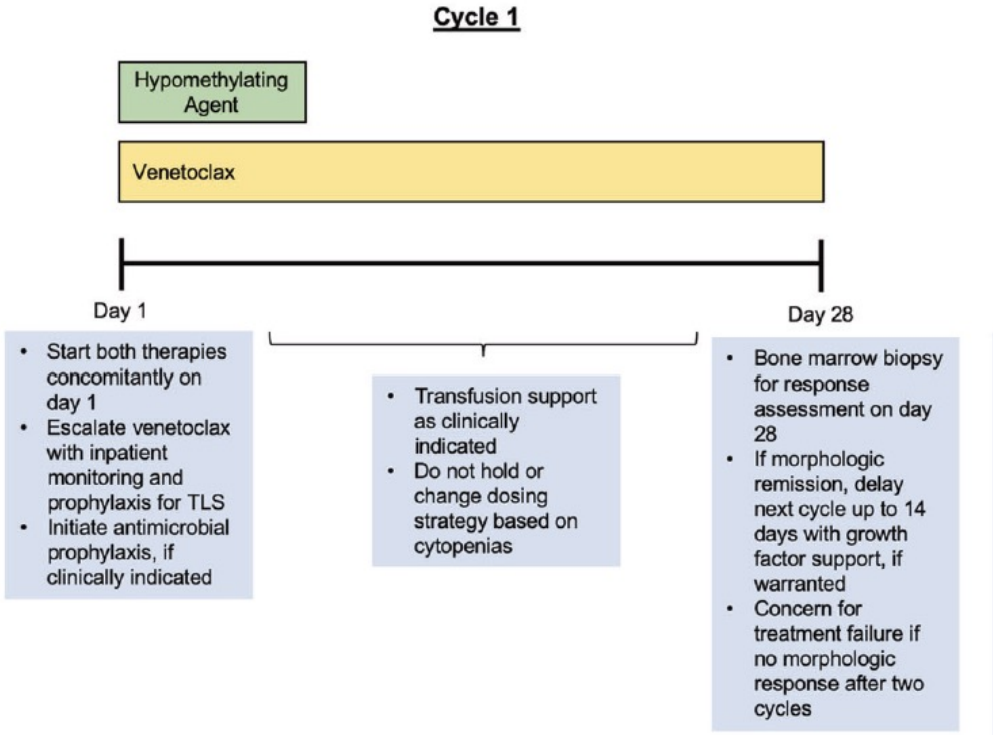


OS mediana per linea di trattamento ricevuta: 14 mesi (IC 11,42-16,58) sia in I linea che in II linea o successive (p non significativa).

- I linea OS mediana = 14 mesi (IC 7,87-20,14). OS ad un anno 53,9%, a due anni 39,2%, a tre anni 21,8%
- II linea o successive OS mediana = 14 mesi (IC 11,42-16,58). OS ad un anno 68,2%, a due anni 15,2%, a tre anni 0%.

Confidential data - unpublished





- **Post-induction marrow assessment** should be performed on **days 21-28**

- **If blast excess persists**, commence the next cycle without treatment dose interruption

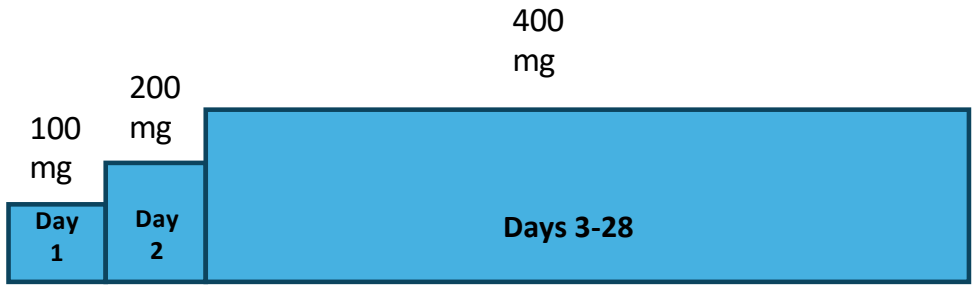
- **If marrow blasts <5%, hold venetoclax** and start next cycle when there has been **at least partial hematologic recovery:**
  - Neutrophils > 500/mmc
  - Platelets > 50.000/mmc
  - G-CSF may be used to accelerate neutrophil recovery

Di Nardo CD, Wei AH. Blood. 2020;135:85-96
Wei A.H., et al. Blood 2024; blood.2024024009

TLS prevention

RAMP UP VENETOCLAX
NO CYP3A4 inhibitors

VENETOCLAX



If
POSACONAZOLE is administerred

VENETOCLAX — **100 MG/DIE Days 1-28**

POSACONAZOLE — **300 MG/DIE Days 3- > ANC 500**

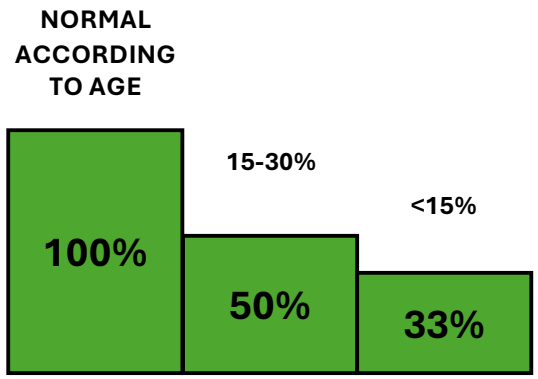
Managing myelosuppression once CR is achieved

- Once disease remission is confirmed consider reducing venetoclax duration if prolonged severe myelosuppression (**stepwise reductions recommended: 28 days --> 21 days --> 14 days**) and HMA dose reduction if marrow cellularity is reduced).

VENETOCLAX

- DAYS 1-28
- DAYS 1-21
- DAYS 1-14

HMA DOSE



Di Nardo CD, Wei AH. Blood. 2020;135:85-96
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Anti Infectious Prophylaxis

ANC < 500

For about
28 days

Antifungal prophylaxis

- Low frequency of fungal infections reported (**8% grade 3/4**) by Di Nardo et al, despite exclusion of CYP3A inhibitor azole antifungals.
- Explanation given is prophylactic use of alternative antifungals such as echinocandins in 46% of patients and/or the relatively low rate of invasive fungal infection found in patients given HMA-based therapies

- **In our institution: posaconazole prophylaxis administered. Venetoclax dosing adjustment is required**

Antibacterial prophylaxis

- In our institution we do not recommend prophylaxis with fluorochinolone which can be used for outpatient treatment of febrile neutropenia

Caso clinico

S.G. 19.10.1943

Maggio 2021: Leucemia Acuta Mieloide. NPM1-mut, FLT3-ITD mut HIGH, citogenetica: 46 XY normali. Intermediate risk sec. ELN 2022.

WBC 3340 Hb 5.4 MCV 90.3 PLT 7000.
BM infiltrato midollare pari al 70% della cellularità

31.05.2021 START I ciclo AZA/VEN – venetoclax 21 gg totali

START C1

STOP Ven (21 gg)

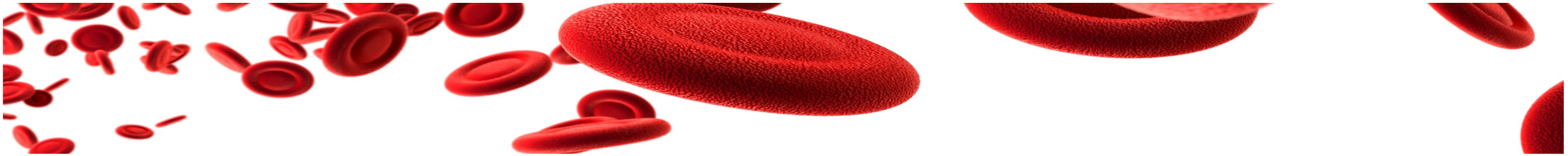
+ 3 g-csf

Aspirato con difficoltà, midollo ipocellulato, non eccesso di elementi mieloidi immaturi

BM day 30

START C2

	31.05.21	03.06.21	07.06.21	14.06.21	17.06.21	21.06.21	25.06.21	29.06.21	05.07.21
WBC (ANC) [*10^3/mmc]	1,25 (0.38)	0,99 (0,33)	0,77 (0,22)	0,75 (0,27)	0,79 (0,28)	0,69 (0,17)	0,61 (0,12)	1,0 (960)	3, 19 (2,25)
Hb [g/dL]	8.9	8.4	8.1	8,2	8.7	8.2	9.5	9.9	9.5
Plt [*10^3/mmc]	29	31	29	18	20	34	78	94	60



Caso clinico

→ **05.07.21: II ciclo -** WBC 3190 (ANC 2250), Hb 9.5, PLT 60.000 - **VENETOCLAX 21 gg** + 2 giorni G-CSF ⚠
BM post II ciclo - MRD **NPM-1: 3**
→ **02.08.2021: III ciclo** - WBC 1860 (ANC 1000), Hb 8.9, PLT 102.000 - **VENETOCLAX 14 gg** + 2 giorni di G-CSF
→ **30.08.21: IV ciclo -** WBC 1110 (ANC 470), Hb 10.7, PLT 168.000 - **VENETOCLAX 14 gg** + 3 gg di G-CSF
BM post IV ciclo - MRD **NPM-1: non valutabile per mancata amplificazione**
→ **30.09.21: V ciclo -** WBC 1610 (ANC 740), Hb 11.1, PLT 151.000 -**VENETOCLAX 14 gg** + 3 gg di G-CSF
→ **04.11.21: VI ciclo - WBC** 1140/mmc (ANC) 210/mmc, Hb 11.1 gr/dL, PLT 130000/mmc - **VENETOCLAX 14 gg**

Caso clinico

Singolo episodio di febbricola con TA 37.2°C, EO negativo, PCR 106 mg/L, PCT negativa, emocolture in corso. 10.12.2021 C7d36 visita ORL per riferita sensazione di ovattamento auricolare destro da qualche giorno. Lieve otite esterna destra. Avviata antibioticoterapia gtt auricolari. Hb 10.6 g/dL, plt 102.000/mmc, WBC 1540/mmc, N 320/mmc, creatinina e ionogramma nella norma, PCR in netto calo (14.7 mg/L), PCT negativa. + 3 gg G-CSF

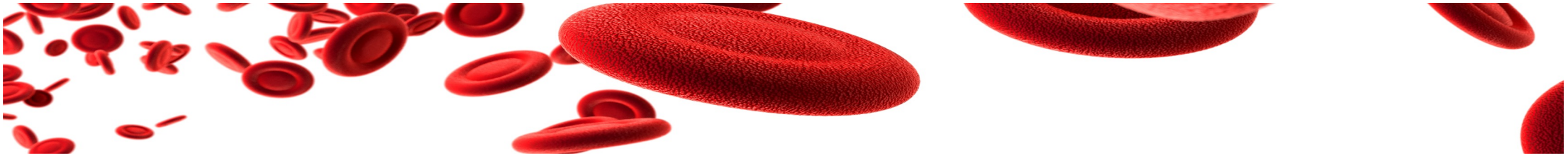
→ **16.12.21: VII ciclo -** WBC 1850/mmc ANC 720, Hb 10.2 g/dl; **Plt 57.000/mmc**

20.12.21: WBC 1400 (ANC 770/mmc), Hb 9.3, PLT 40.000/mmc. - EE completi con screening infettivologico.

23.12.21 PLT 28.000/mmc **START PDN 75 mg/die con successivo decalage** per mancato beneficio. → **Nadir plt 13.000/mmc al 31.12.**

BOM del 21.01.22: Cellularità disomogenea in media pari a circa il **30%** (normocellulato per fascia d'età) costituita da elementi delle tre serie emopoietiche. **Granulopoiesi ridotta**, ricca in precursori e **scarsamente maturante**. Eritropoiesi presente, con **diseritropoiesi** e scarsamente maturante. **Megacariopoiesi** normorappresentata, caratterizzata da elementi anisodimensionali e a varia lobulazione nucleare, anche con presenza di forme distrofiche e forme di dimensione ridotta con alterato rapporto nucleo/citoplasma e nucleo ipolobulato o binucleate, di aspetto displastico, molti dei quali con le caratteristiche morfologiche dei micromegacariociti; non si osserva formazione di cluster e/o aggregati. Presenza di elementi ad habitus blastico (in percentuale inferiore al 5% (pari a circa il 3-4% per quanto valutabile immunomorfologicamente). **Lieve incremento della trama reticolinica (MF-1).**

NPM1: 0



Caso clinico

3.02.2022 (solo AZA) ciclo VIII WBC 2730/mmc, ANC 1720/mmc.Hb 99 g/L, PLT 46000/mmc,

28.03.22 (solo AZA) ciclo IX (solo 5 giorni), WBC 3600/mmc, ANC 2480/mmc, Hb 118 g/l, plt 37000/mmc

09.05.22 X (solo AZA) - WBC 1380/mmc, ANC 580/mmc, Hb 12 g/l, **plt 78000**/mmc

Venetoclax and hypomethylating agents in octogenarians and nonagenarians with acute myeloid leukemia

- Multicenter retrospective analysis of VEN-HMA treatment in octogenarians and nonagenarians to further understand the tolerability, feasibility, dosing considerations, and clinical efficacy
- More than half (53%) of patients had European Leukemia Net 2017 adverse-risk AML; another third had intermediate-risk disease (notably, 35% of patients in the study had AML with a TP53 mutation and/or complex karyotype)
- With a median follow-up of 7.7 months, 36 patients (23%) remained in remission, with 31 (20%) still on VEN-HMA.
- The 30-day and 60-day mortality rates were 8.5% and 17%, respectively, with most **early deaths** due to **sepsis** or **disease progression**.
- Median overall survival (OS) was 8.1 months, and in patients who achieved a response (CRc), median OS was 13.2 months (4.1 months in non-responders)
- A VEN duration of 28 days during cycle 1 was associated with response when compared with <28 days (CRc rate, 61% vs 48%; *P* = .003). However, the number of patients receiving <28 days in cycle 1 was small (n = 25), and this association was driven by patients receiving ≤7 days (*P* < .001).
- **Patients receiving 14 to 21 days had similar response outcomes compared with those receiving 28 days**.
- Landmark analysis from the time CRc was first achieved showed that patients receiving VEN for ≤14 days had improved OS; median, 24.0 months.
- About 25% of the 154 patients on study had prolonged survival of two years or more

Madarang E, et al. Blood Neoplasia 2024; 1 (2): 100016.

Take home messages

- Increased exposure to venetoclax (dose and duration) enhances anti-leukemic efficacy, but also the risk of damage to hematopoietic stem and progenitor cells (HSPCs).
- The aim of therapy is to deliver an **optimal, rather than excessive dose** of venetoclax to maximize the safety and clinical benefit of therapy. **Haematologist =Taylor**
- BM evaluation after first cycle(s) is fundamental for evaluation of the response. Also bone marrow cellularity and dysplasia are useful information to modulate the dose intensity on subsequent cycles
- Elderly age is not a parameter for not to treat decision – but you must modulate your intervention
- The decision to treat in inpatient or outpatient setting should be performed after a careful analysis of pros and cons (Italian guidelines do not help hematologist)

OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria

Thank you for your attention!

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