


# Il paziente con LAM recidivata/refrattaria: quali prospettive?

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IRST

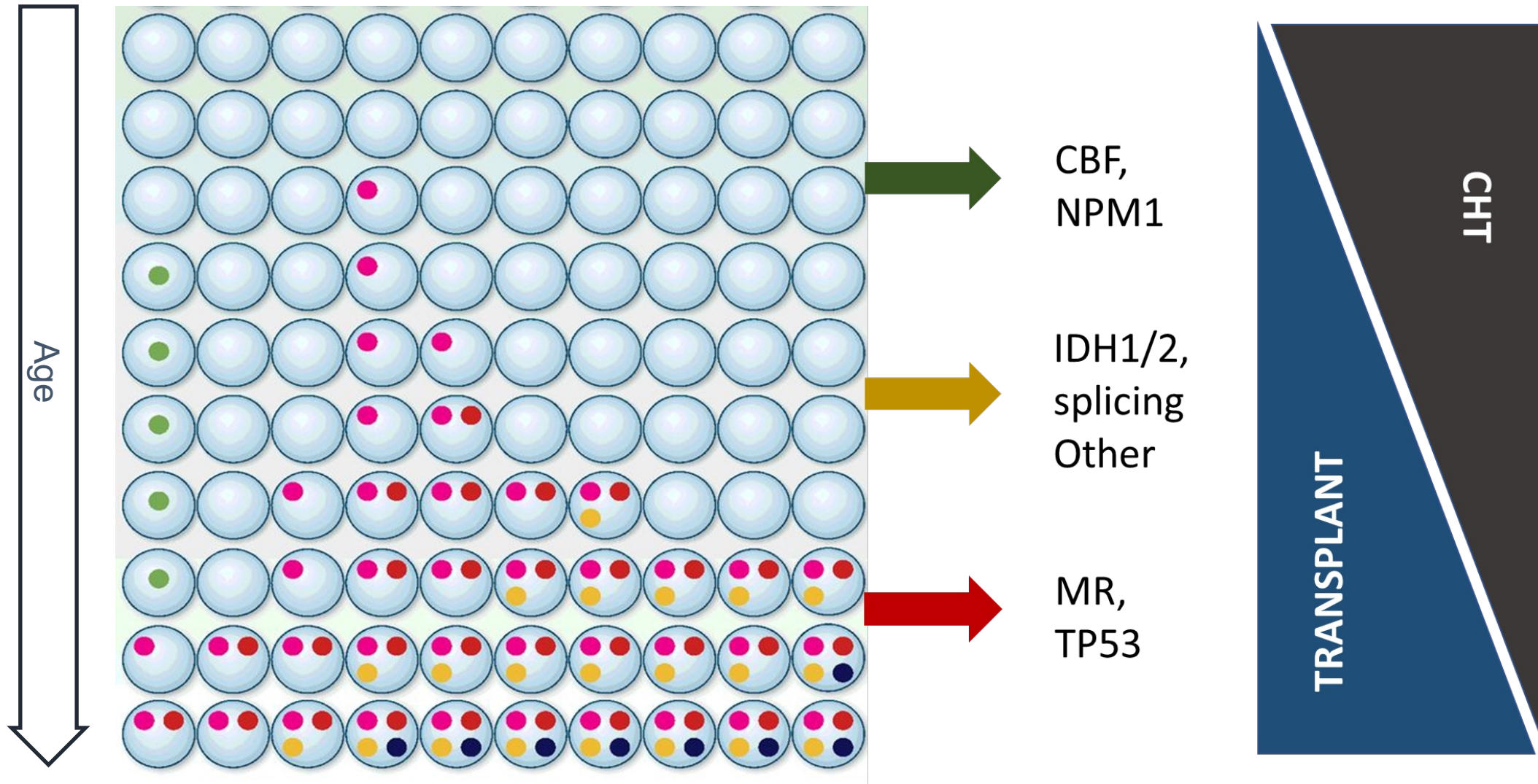
 **SERVIZIO SANITARIO REGIONALE  
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Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori"  
Istituto di Ricovero e Cura a Carattere Scientifico

ISTITUTO  
ROMAGNOLO  
PER LO STUDIO  
DEI TUMORI  
DINO AMADORI

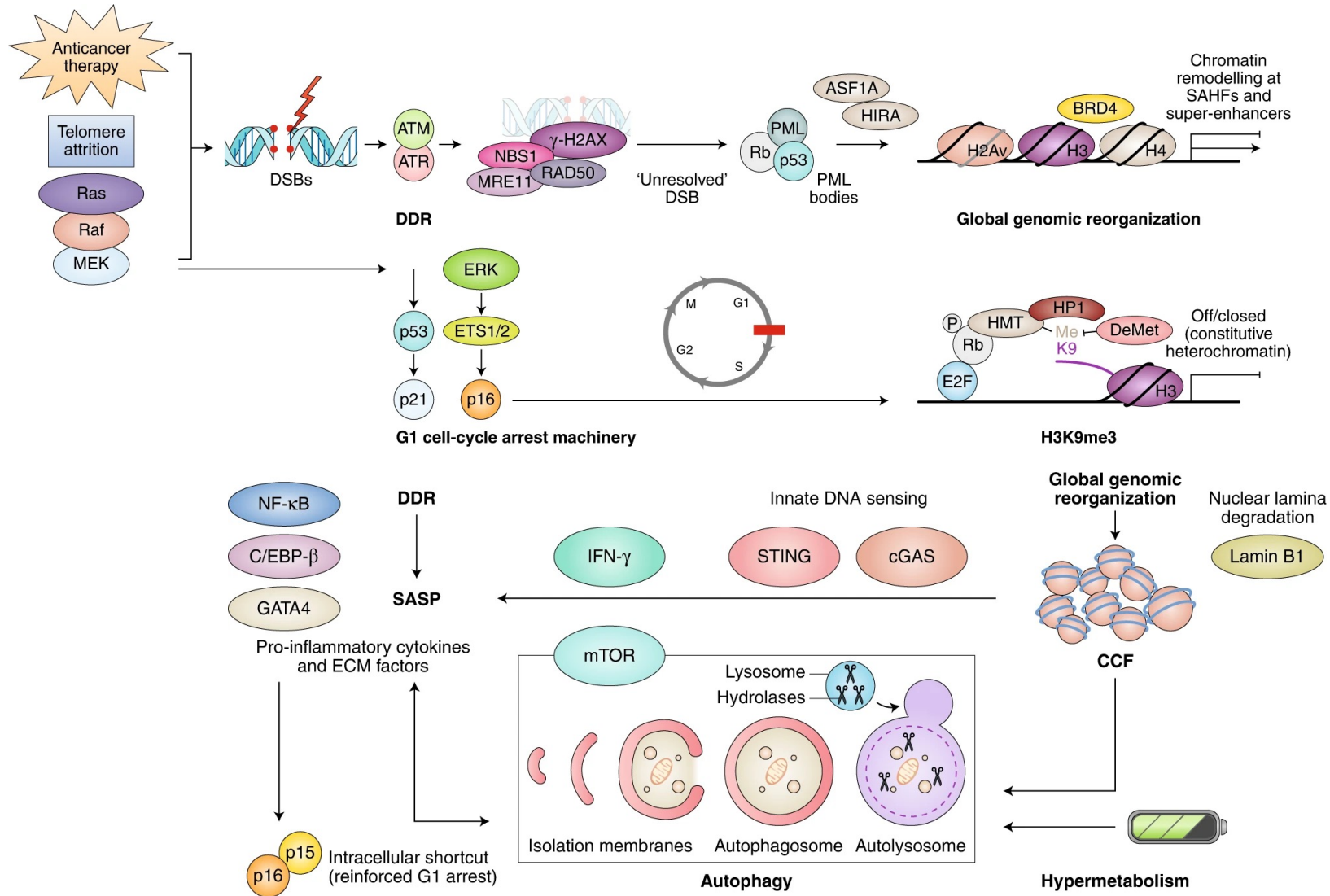
# Disclosures – Giovanni Marconi

|                   | Consultant | Speaker bureau | Research support |
|-------------------|------------|----------------|------------------|
| Abbvie            | x          | x              | x                |
| Astellas          | x          | x              | x                |
| Astrazeneca       |            | x              | x                |
| Daiichi Sankyo    |            |                | x                |
| Immunogen         | x          |                |                  |
| Jansenn           |            | x              |                  |
| Menarini/Stemline | x          | x              |                  |
| Pfizer            | x          | x              | x                |
| Ryvu              | x          |                |                  |
| Servier           |            | x              |                  |
| Syros             | x          | x              | x                |
| Takeda            |            | x              |                  |

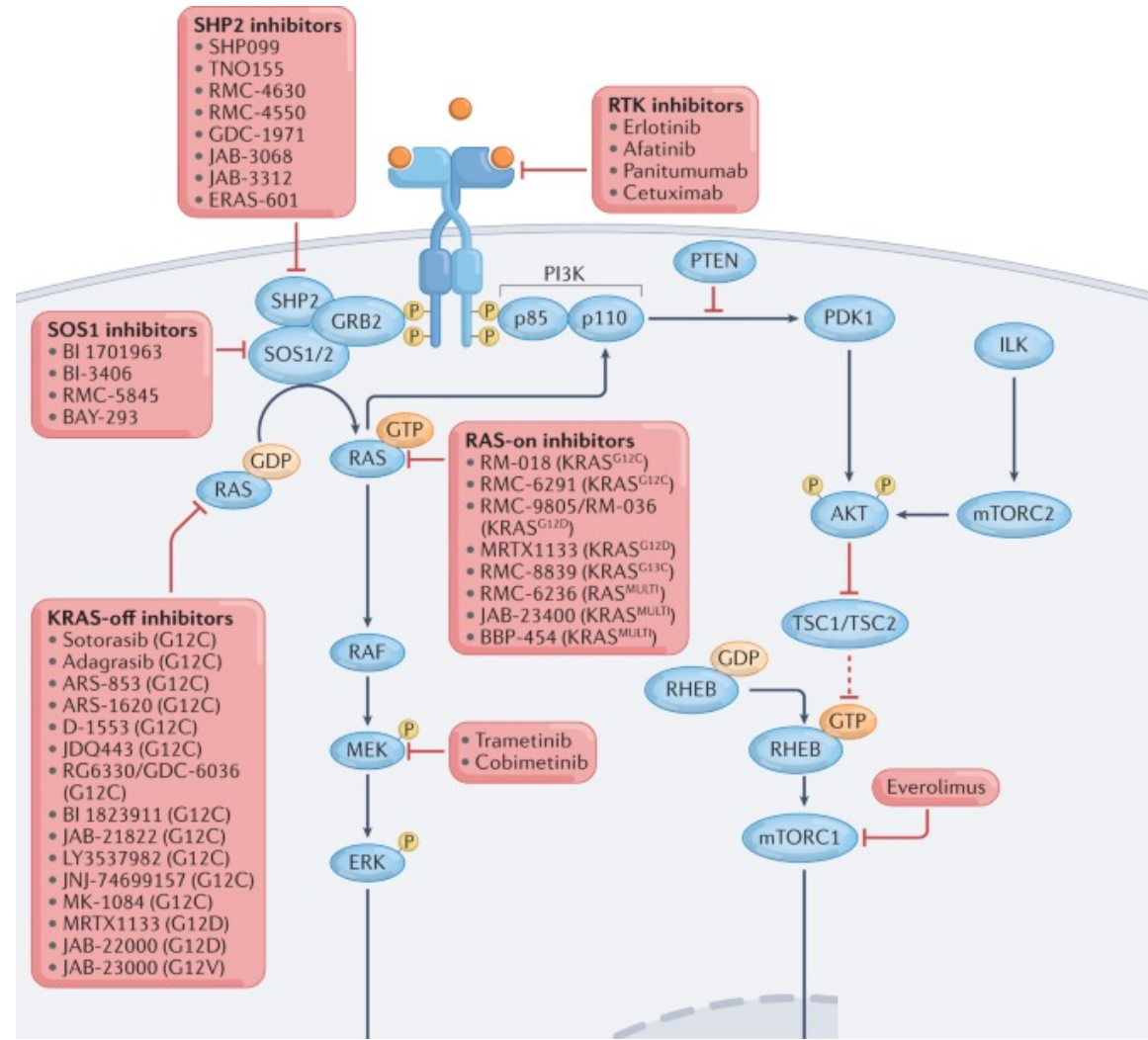
# AML heterogeneity



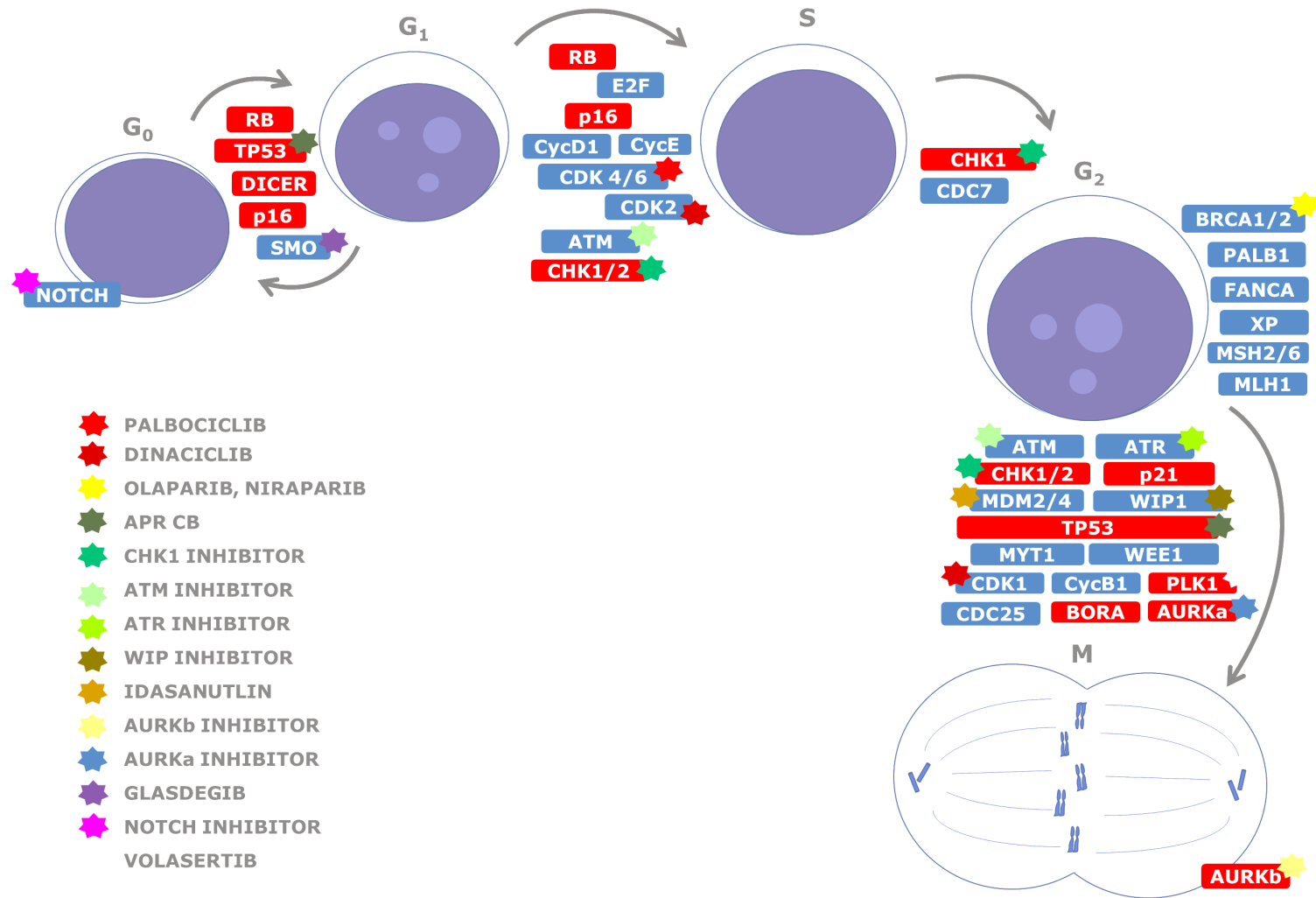
# Senescence and autophagy



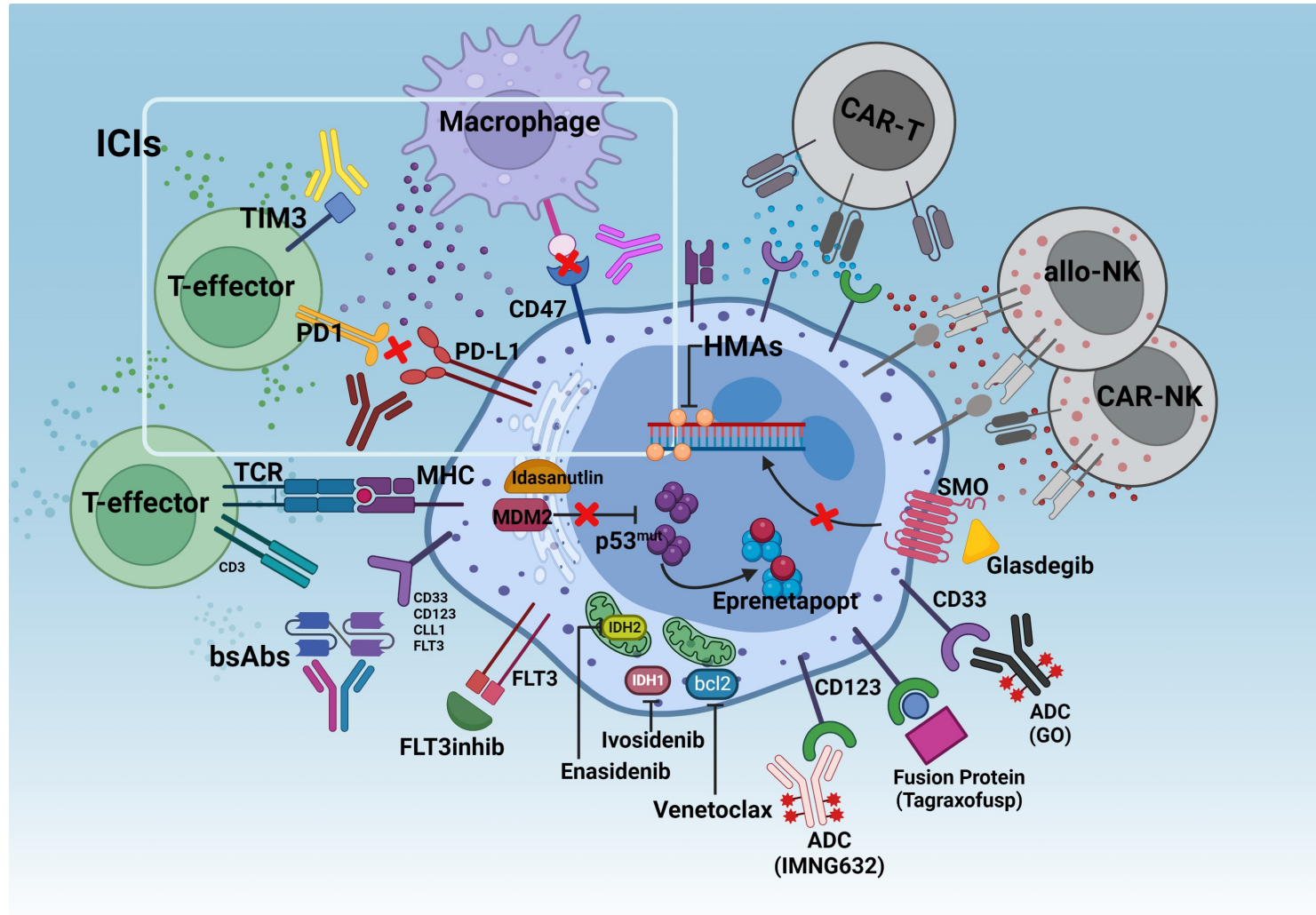
# Inhibit mechanisms of clonal excape



# Act on cell cycle

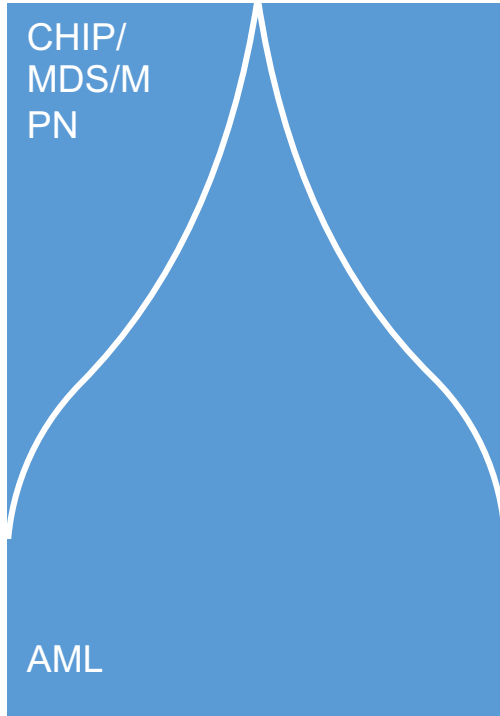


# Biological therapies



# Track subclonal disease

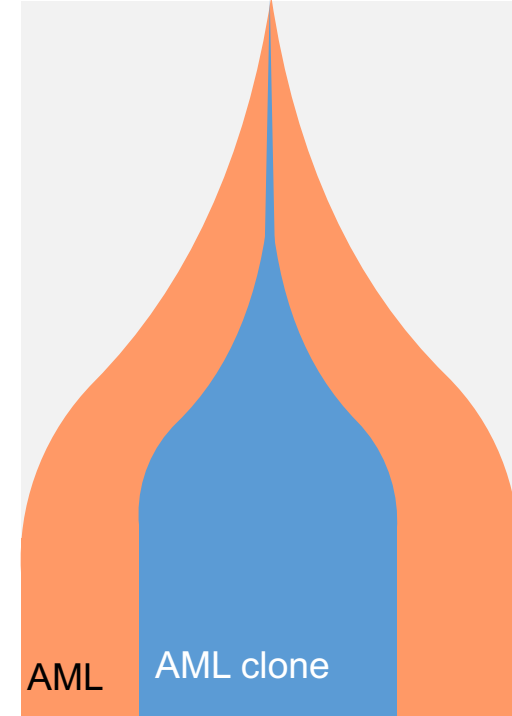
AML arise from mutated  
CHIP/MDS/MPN



de novo AML



AML Policlonal



R/R

Similar  
CLONE

Divergent  
CLONE

Similar CLON

Divergent  
CLONE

Dominant  
Sub  
CLONE

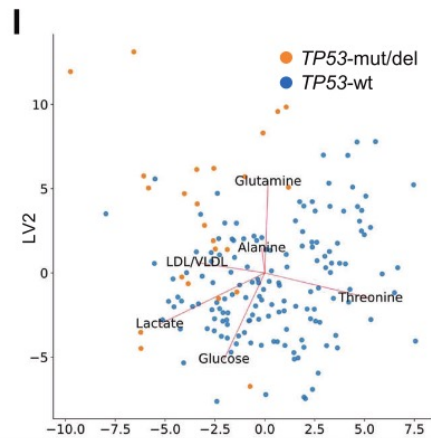
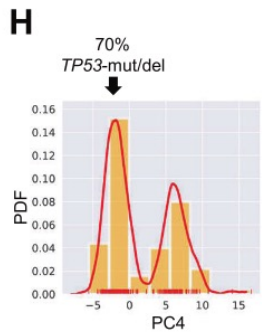
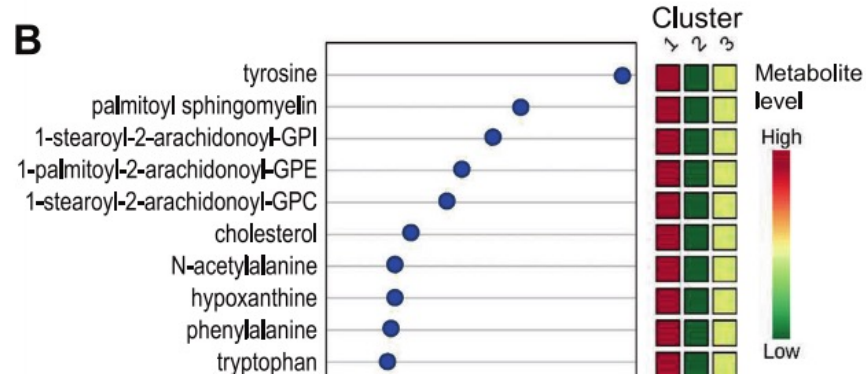
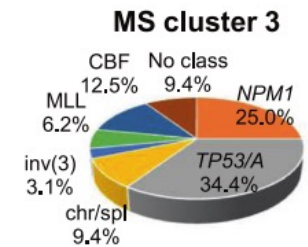
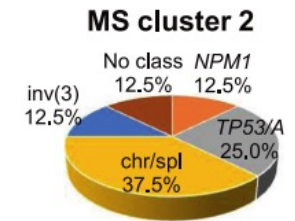
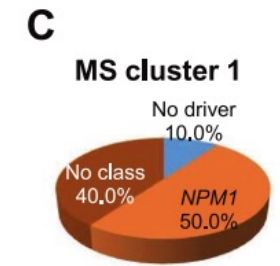
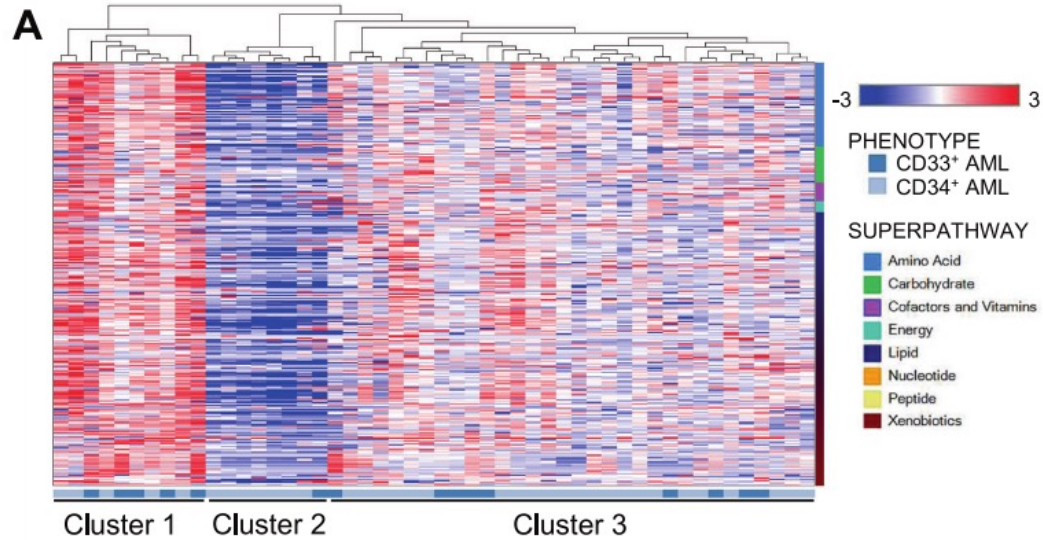
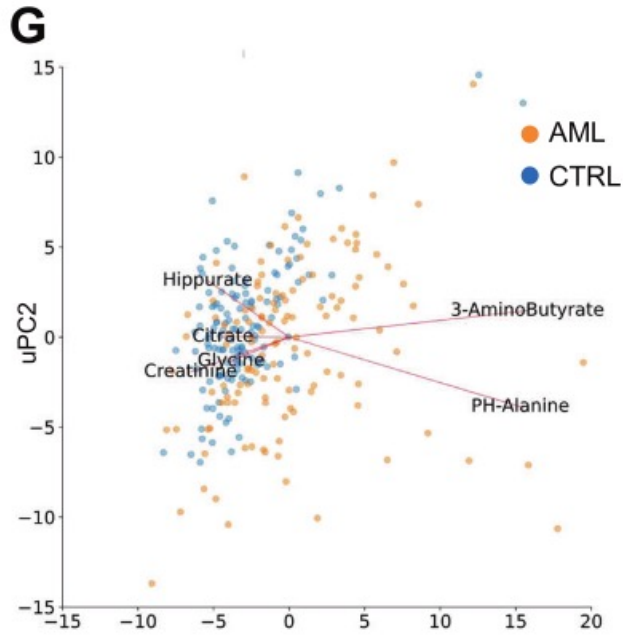
Main  
CLONE

New  
CLONE

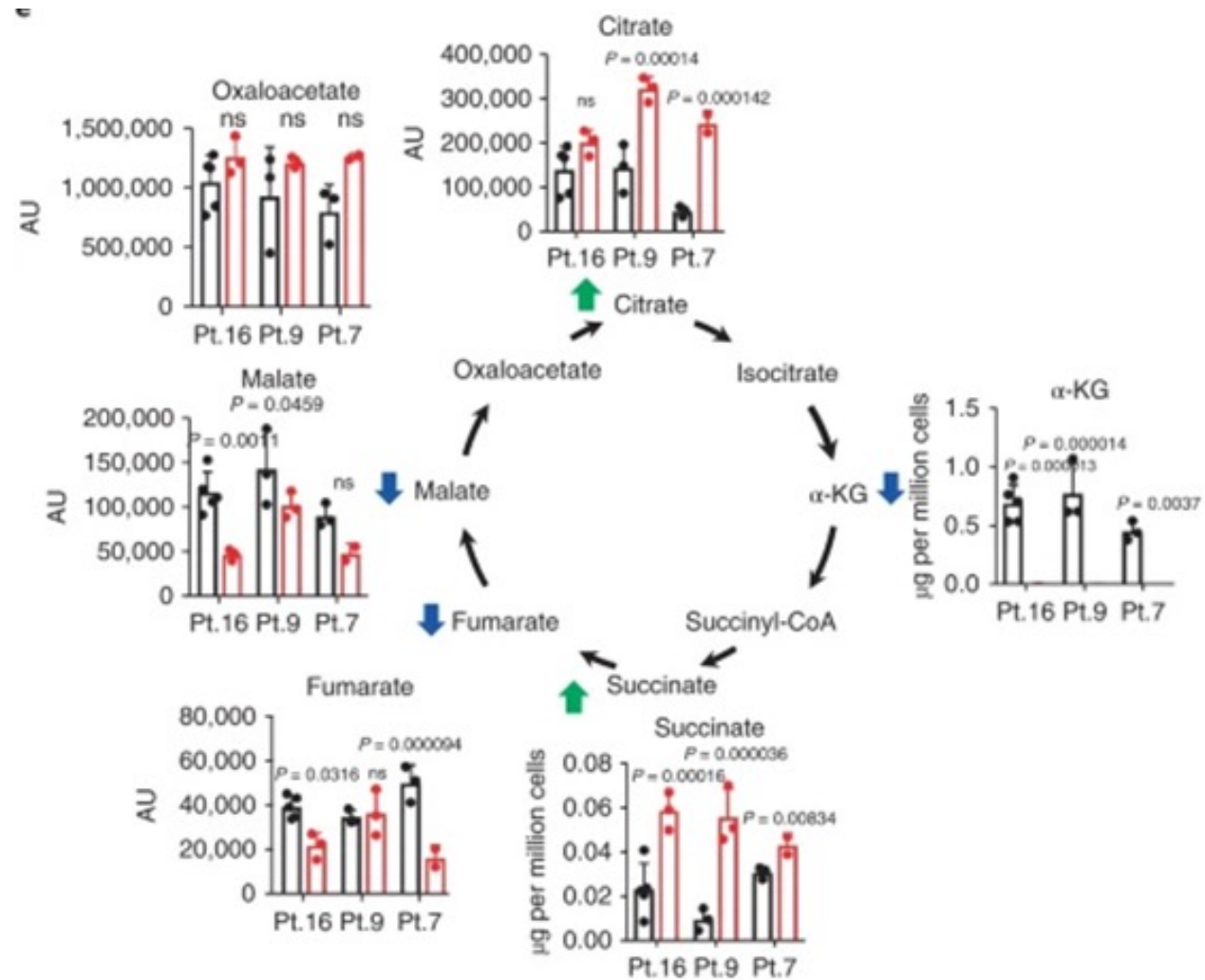
*personal*



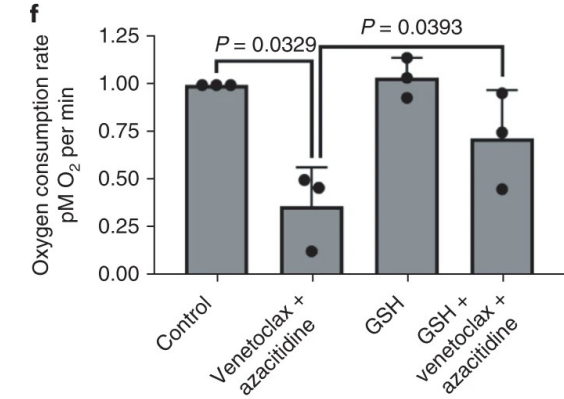
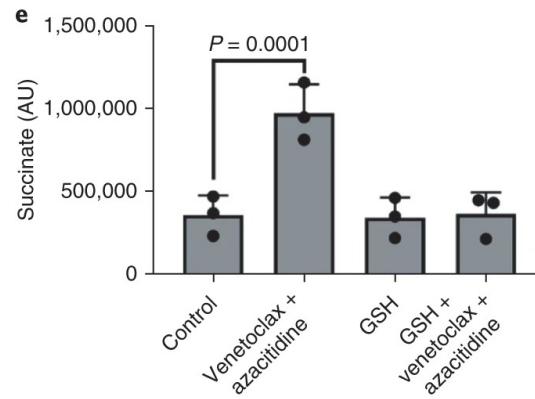
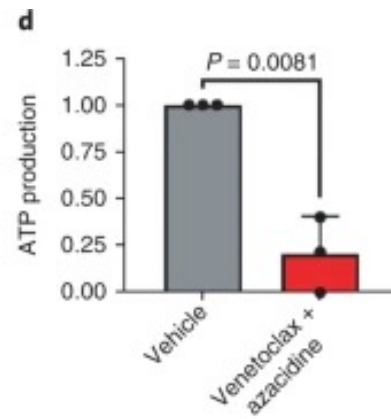
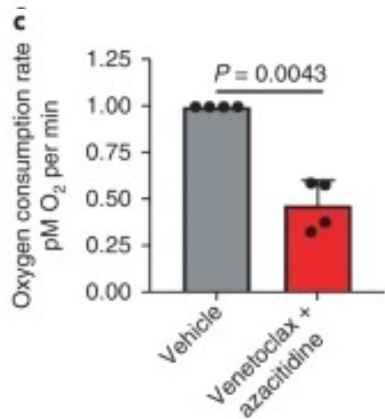
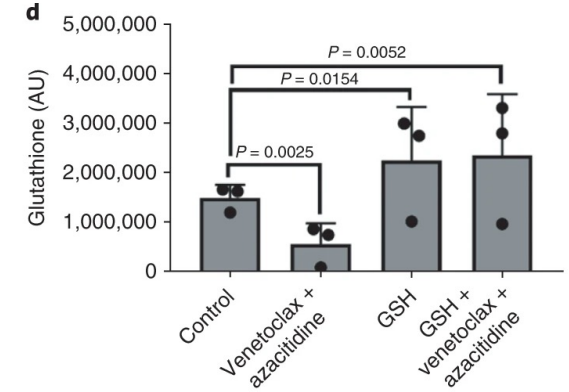
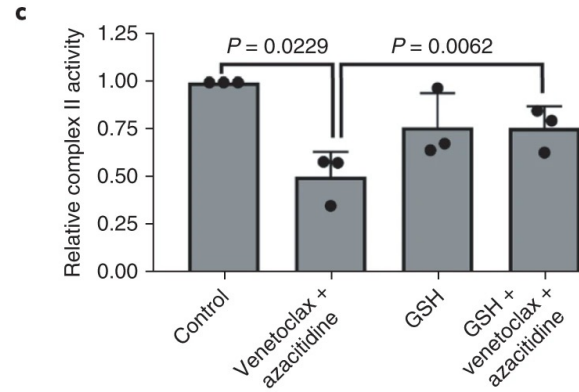
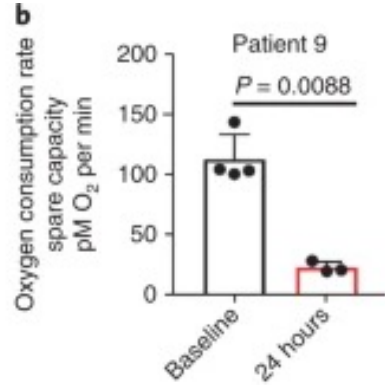
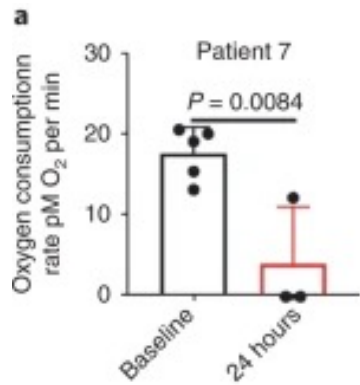
# AML have different metabolism



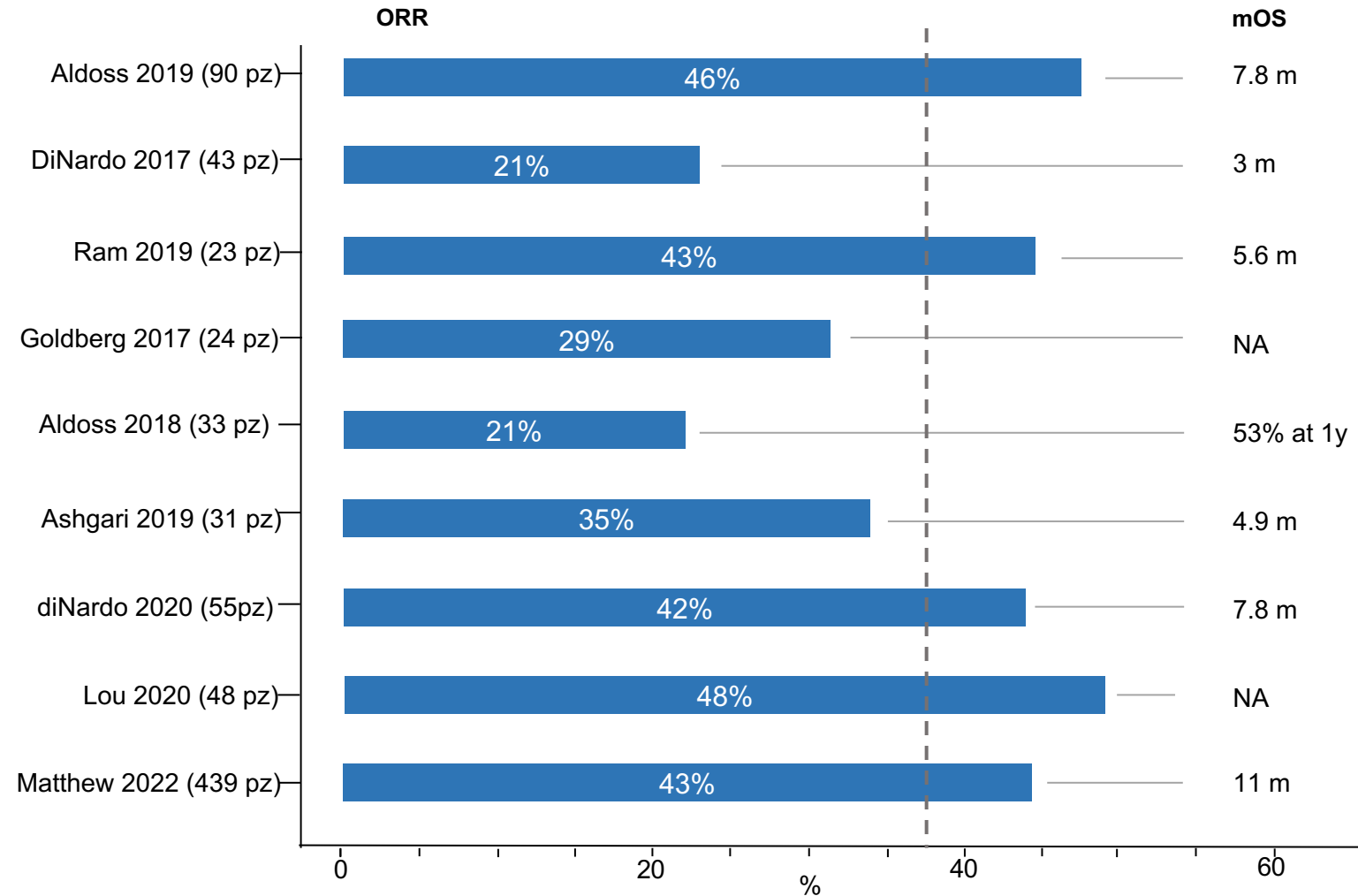
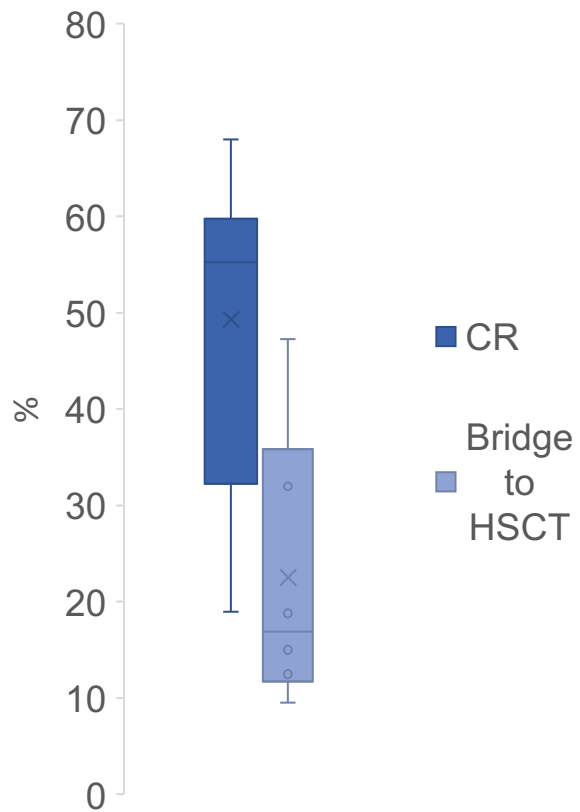
# Senolytic drugs arrest cell cycle



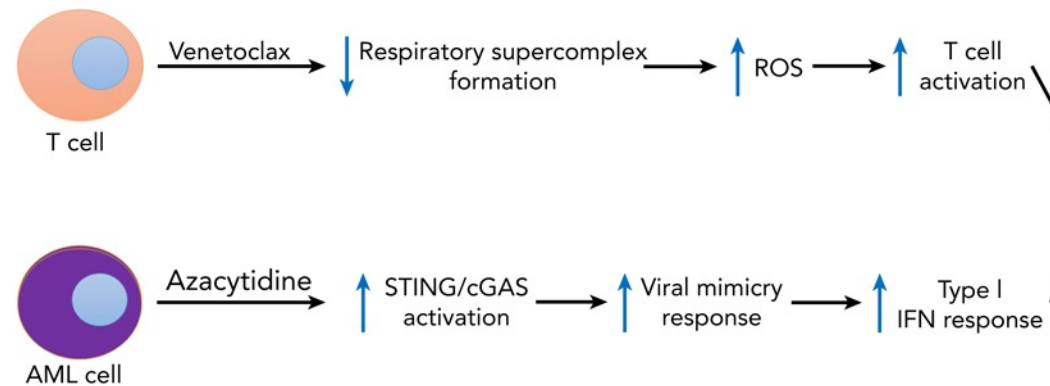
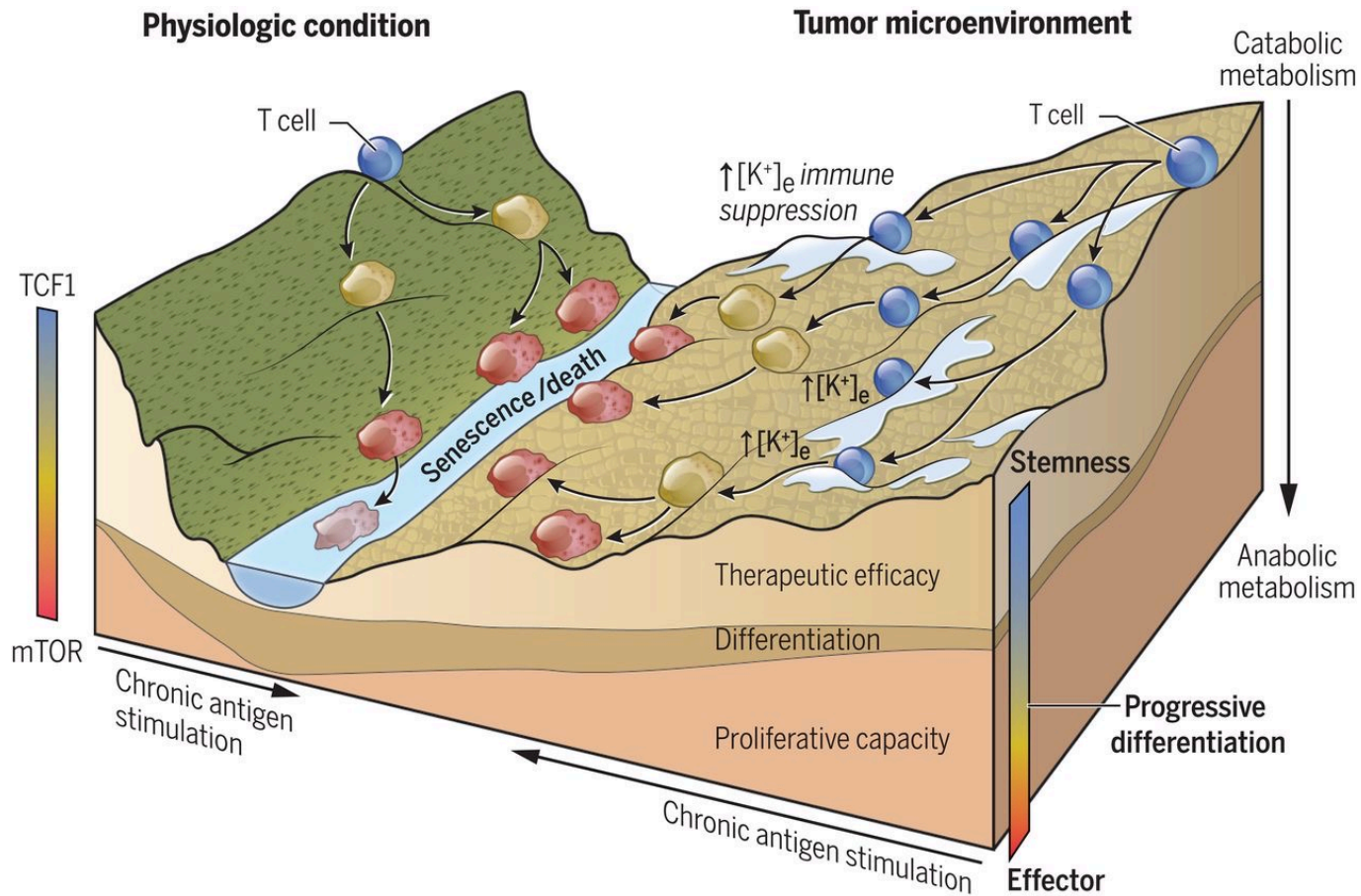
# Senolytic drugs cause metabolic cell crisis



# Venetoclax in addition to HMA, R/R AML



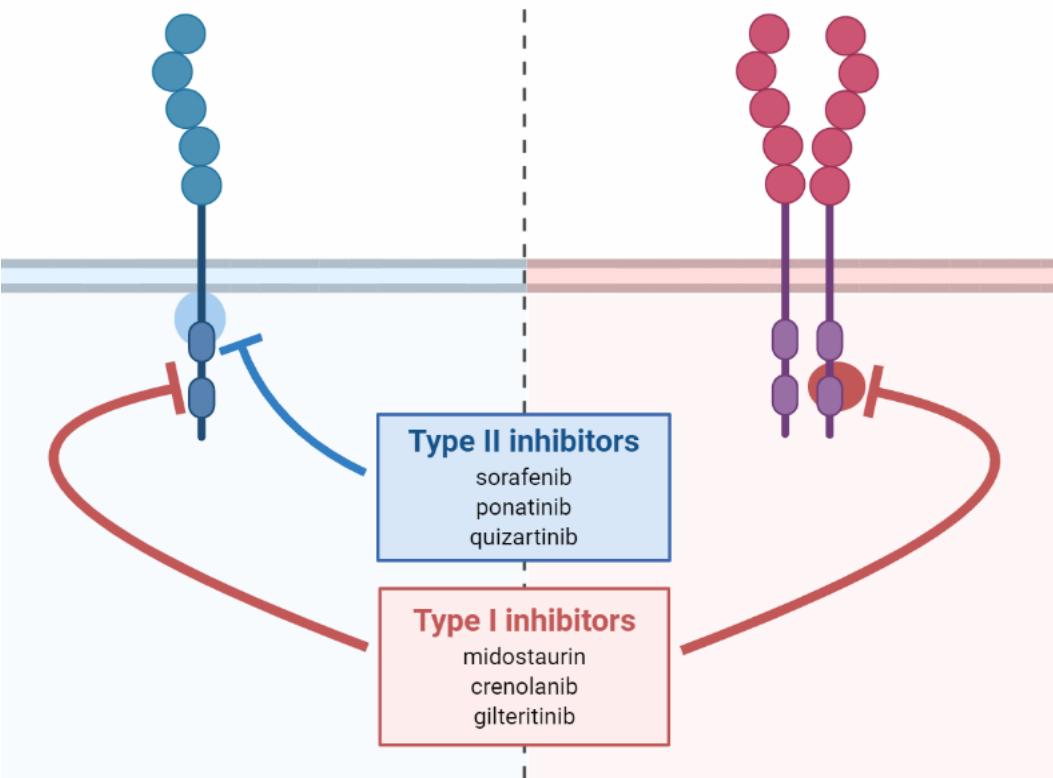
# Immunological effect of bcl2 inhibitors



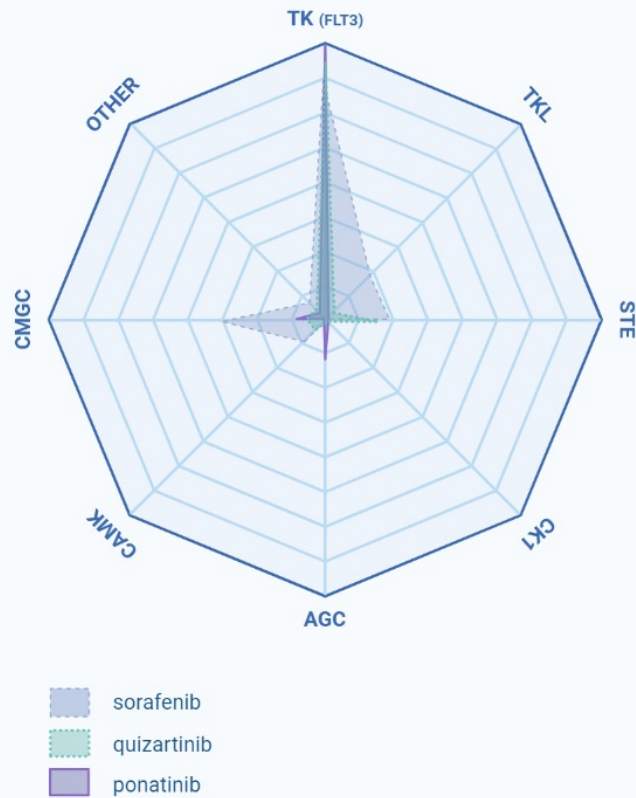
# Inhibit FLT3

## FLT3 ITD mutation

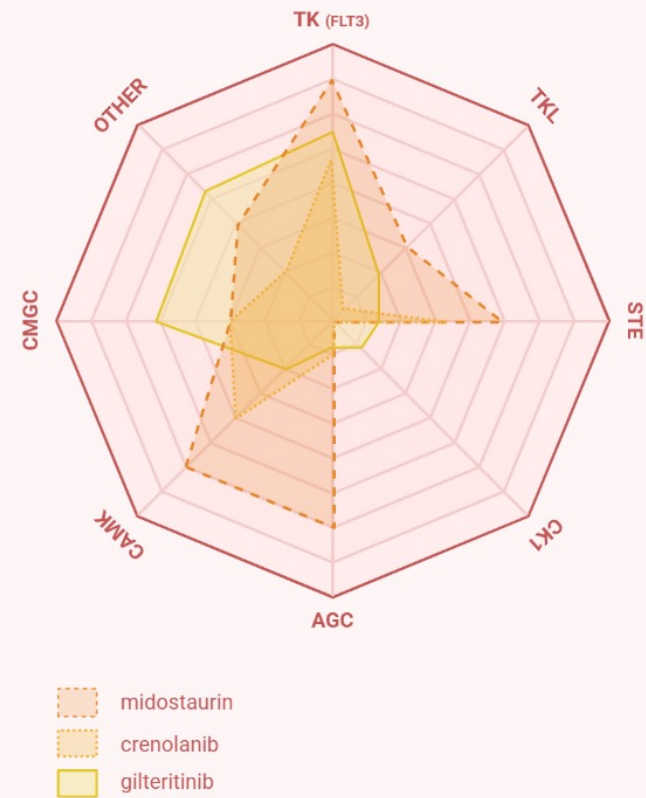
## FLT3 TKD ± ITD mutation



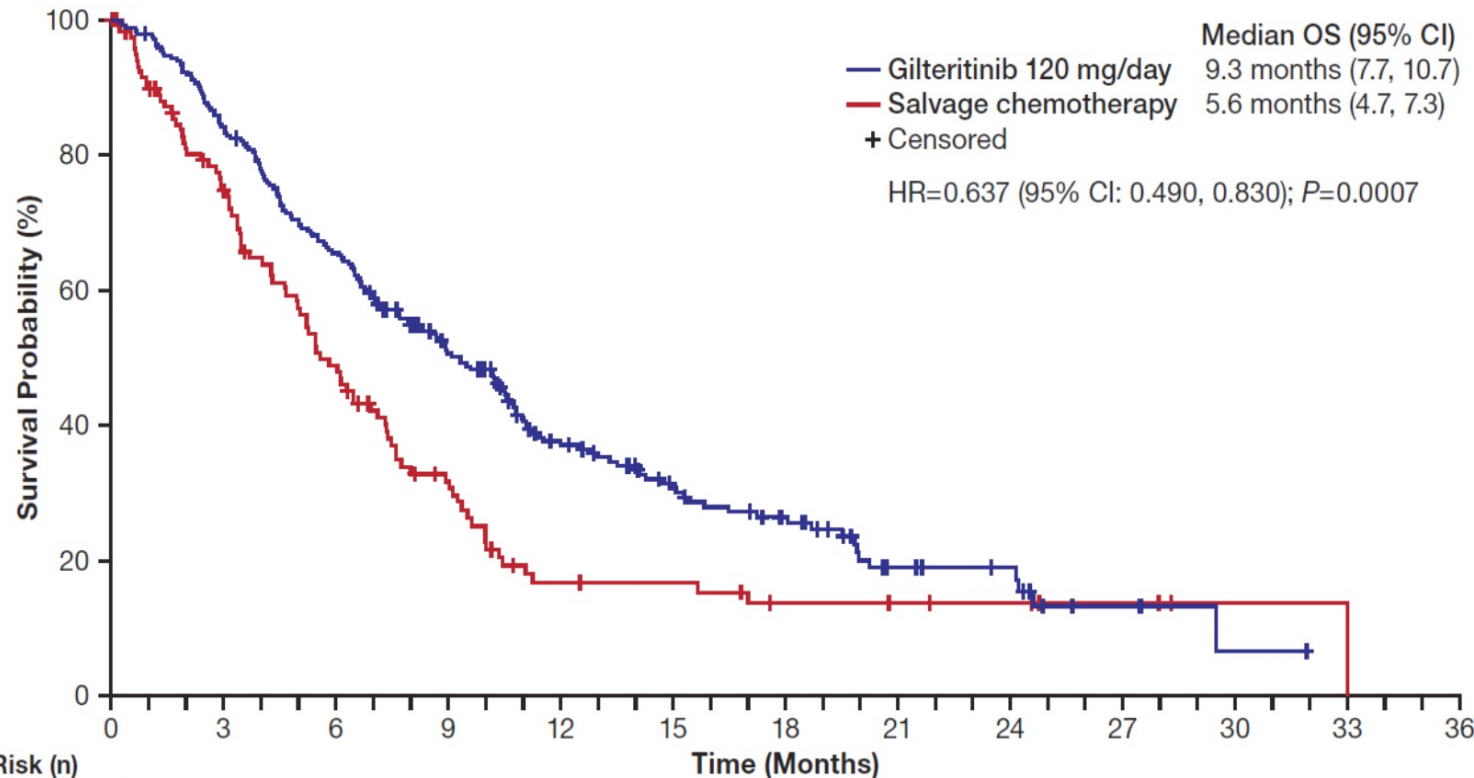
## Type II inhibitors



## Type I inhibitors

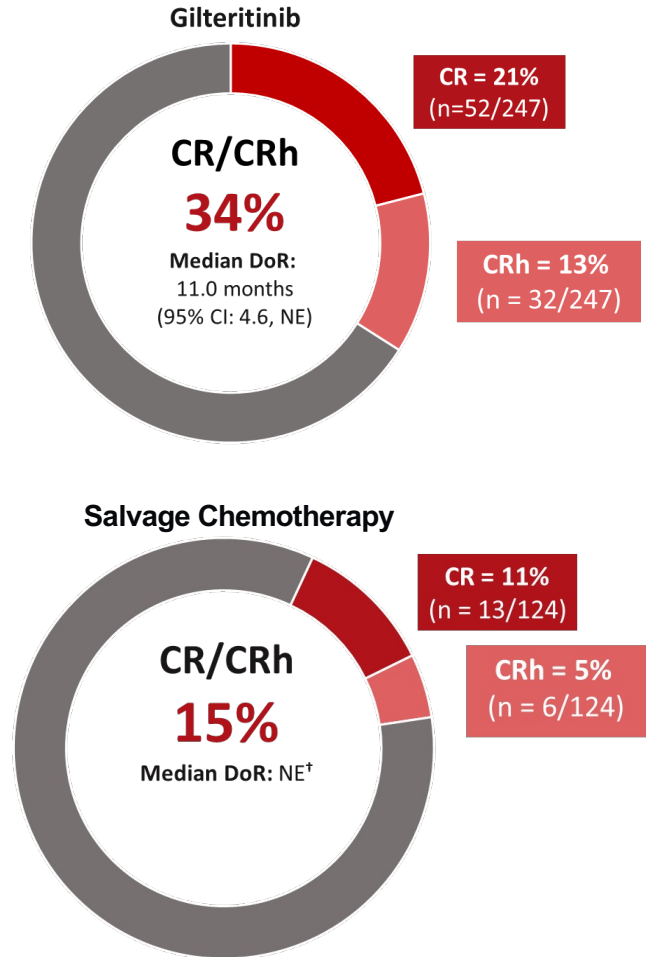


# Gilteritinib for R/R FLT3+ AML



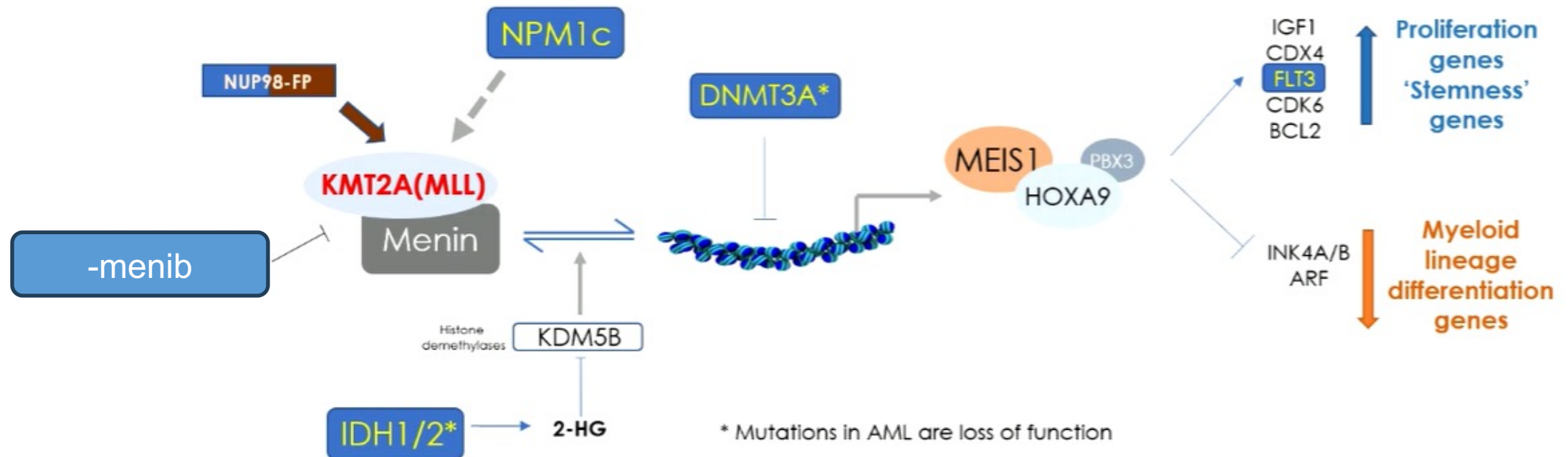
|                             | 0   | 3   | 6   | 9   | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 |
|-----------------------------|-----|-----|-----|-----|----|----|----|----|----|----|----|----|----|
| <b>Patients at Risk (n)</b> |     |     |     |     |    |    |    |    |    |    |    |    |    |
| Gilteritinib 120 mg/day     | 247 | 206 | 157 | 106 | 64 | 44 | 31 | 14 | 11 | 4  | 1  | 0  | 0  |
| Salvage chemotherapy        | 124 | 84  | 52  | 29  | 13 | 12 | 8  | 7  | 5  | 3  | 1  | 0  | 0  |

**Gilteritinib (n=247)** 37% (95% CI: 31, 43)  
**Salvage Chemotherapy** 17% (95% CI: 10, 25)



# Menin inhibitors are a new promising target therapy

- *NPM1*-m and *KMT2A*-r drive overexpression of *HOXA9/MEIS1* genes, critical for transformation to AML
- *KMT2A*(*MLL*) sits upstream from major AML targets (*i.e.*, *FLT3*, *IDH1/2*, *DNMT3A*)
- *KMT2A*(*MLL*)-dependent genes contribute to therapeutic resistance and relapse to current therapies
- Menin inhibition downregulates *HOXA9/MEIS1*, leading to differentiation of leukemic blasts



KMT2A = lysine[K]-specific methyltransferase 2; MEIS1 = meis homeobox 1; MLL-mixed lineage leukemia; NPM1-c = cytoplasmic localization of nucleophosmin-1

1. Lu et al. *Cancer Cell* 2016;30(1):92–107; 2. Ferrelra et al. *Oncogene* 2016;35(23):3079–82; 3. Jeong et al. *Nat. Genet* 2014;46(1):17–23; 4. Wang et al. *Blood* 2005;106(1):254–64; 5. Chowdhury et al. *EMBO Rep* 2011;12(5):463–9; 6. Schmidt et al. *Leukemia* 2019;33(7):1608–19; 7. Xu et al. *Cancer Cell* 2016;30(6):863–78; 8. Collins & Hess. *Curr Opin Hematol* 2016;23(4):354–61; 9. Brunetti et al. *Cancer Cell* 2018; 34(3):499–512.

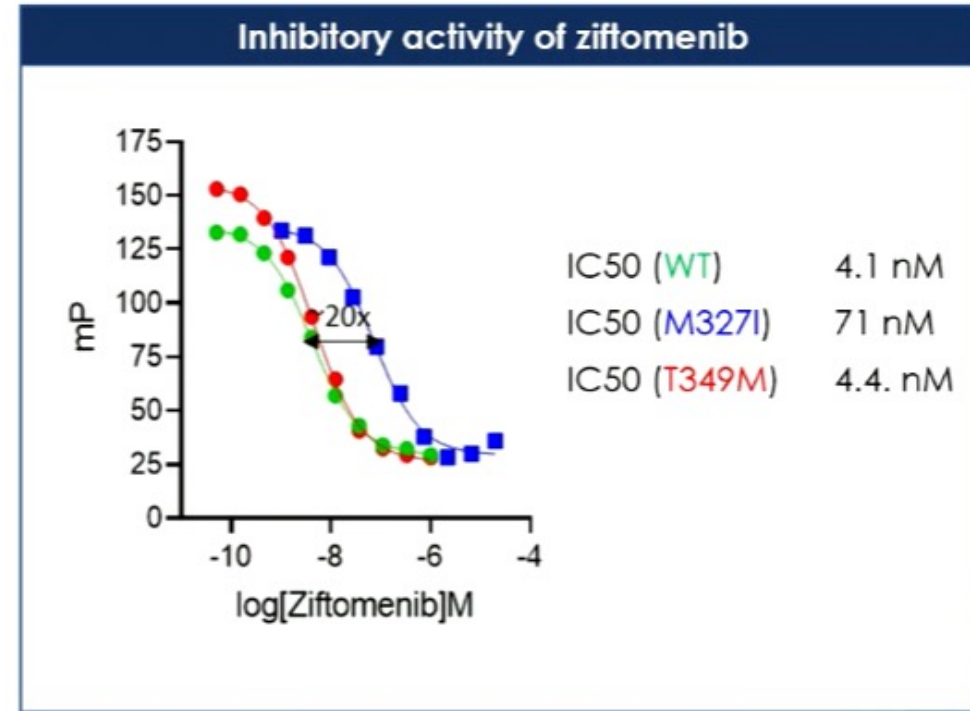
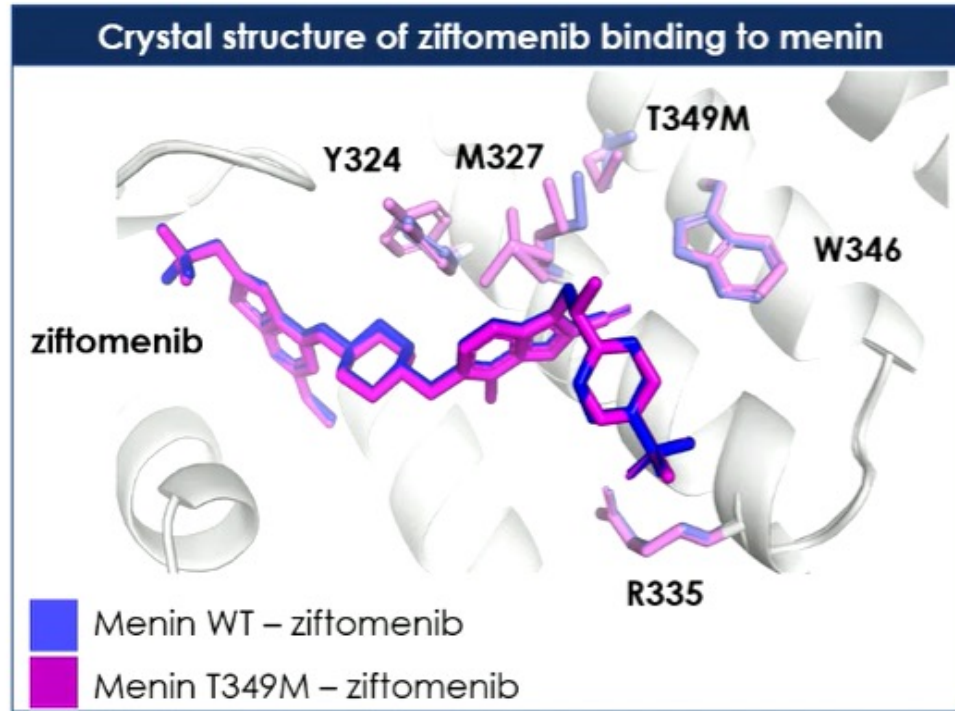


# Response to -menib



# Ziftomenib Active Against Known Menin Gatekeeper Mutations

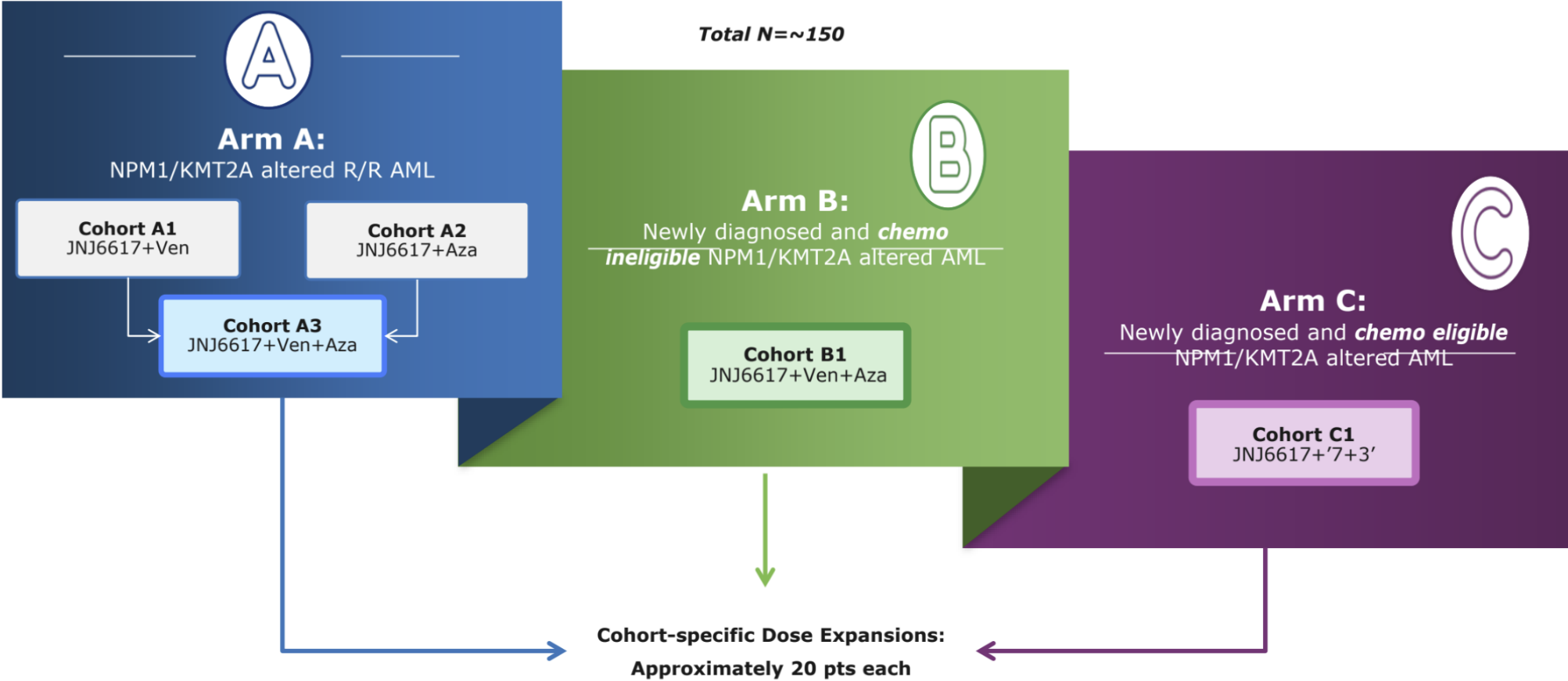
- No major conformational changes observed in Menin<sup>T349M</sup> vs. wild-type (WT) protein
- M327 and Y324 side chains adopt new conformations in Menin<sup>T349M</sup> but do not affect ziftomenib binding
- Binding affinity of ziftomenib is reduced for Menin<sup>M327I</sup> but unaffected for Menin<sup>T349M</sup>
  - Per Armstrong lab<sup>1</sup>, ziftomenib also retains activity against Menin<sup>G331R</sup>
- Ziftomenib retains activity against 2 of 3 known *MEN1* mutant loci



<sup>1</sup>Perner et al. Abstract #3457 presented at AACR April 14-19, 2023, Orlando, FL

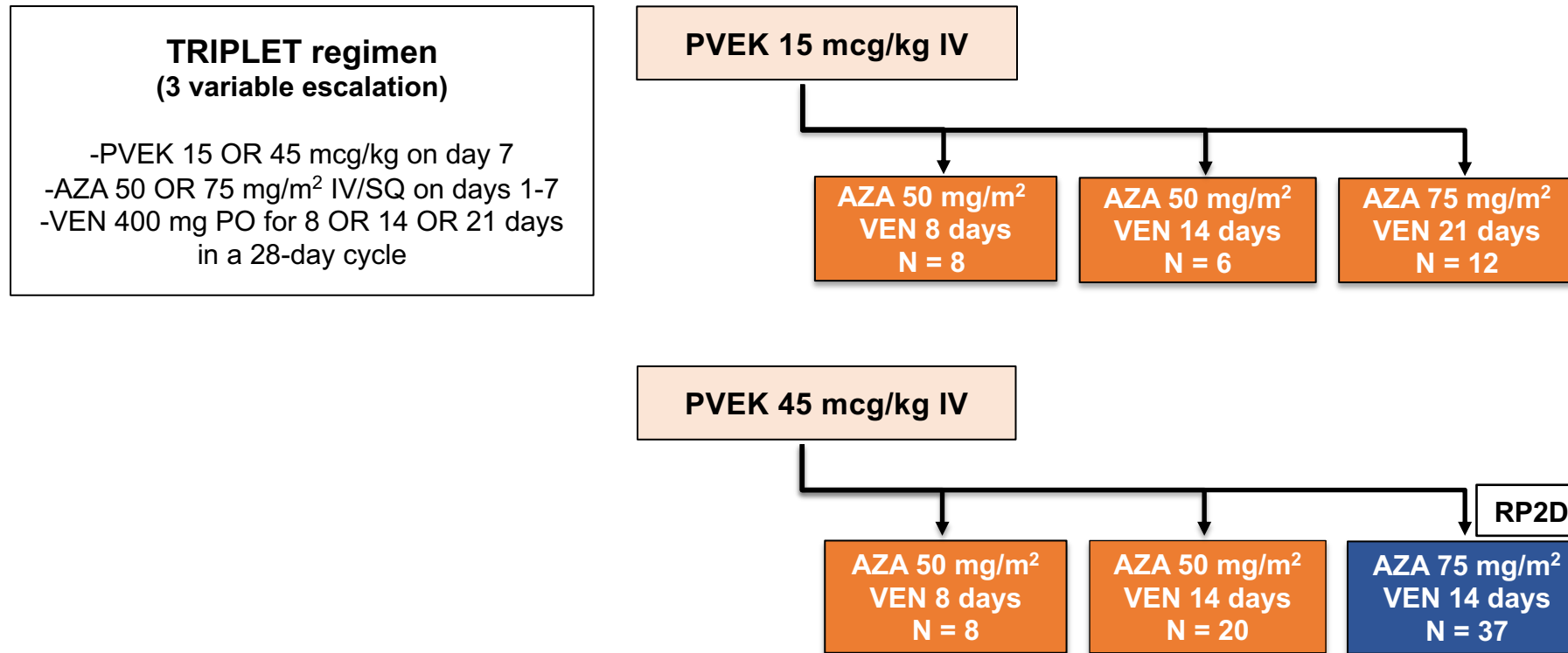
# ALE1002

## Ph1b Exploratory Study: JNJ75276617 as Backbone Therapy in KMT2A/NPM1 altered AML



Aza = azacitidine; Ven = venetoclax;  
7+3= cytarabine + anthracycline (daunorubicin or idarubicin)

# Broad activity for the pivekimab sunirine (PVEK, IMGN632), azacitidine, and venetoclax triplet in high-risk patients with relapsed/refractory and frontline acute myeloid leukemia (AML)

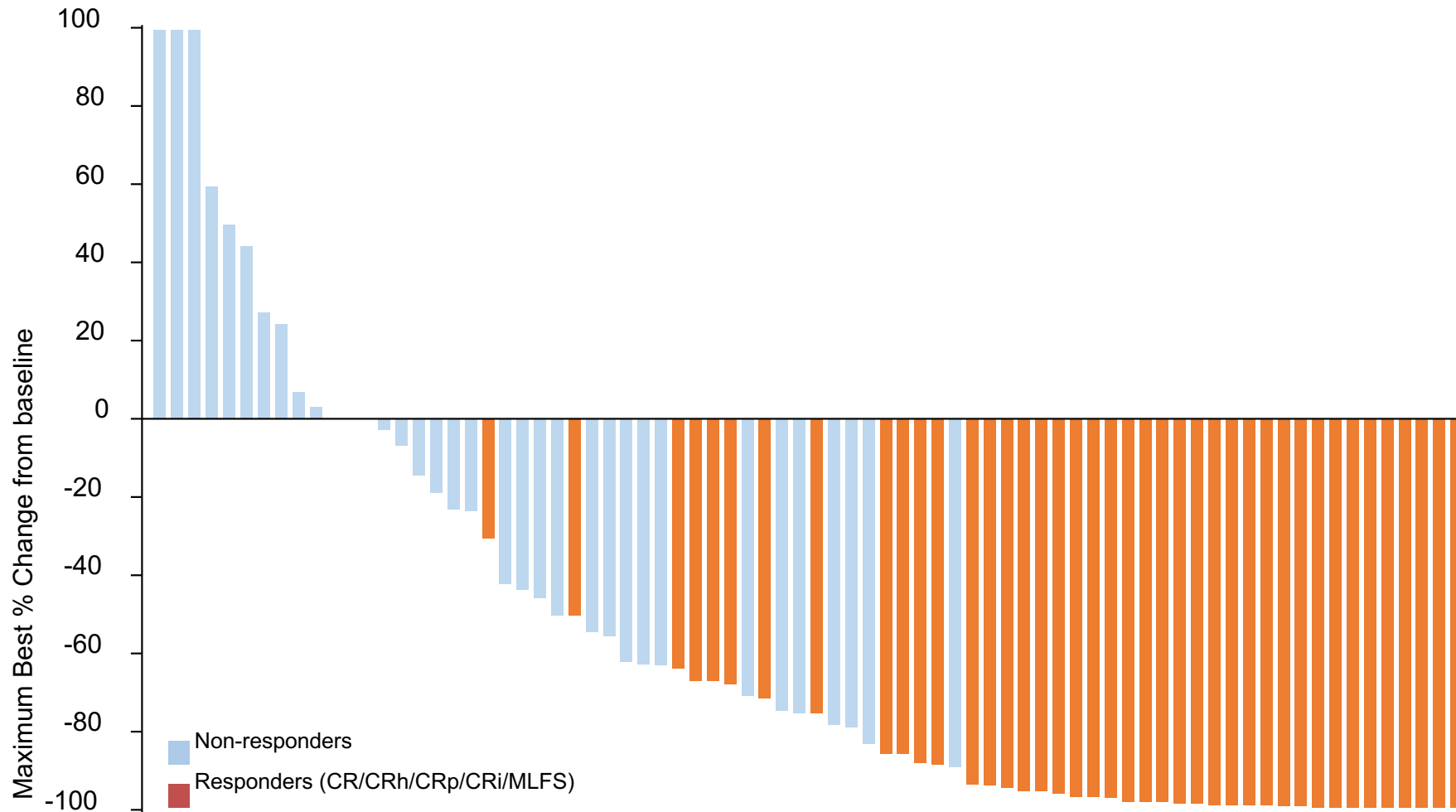


# R/R AML Patient Characteristics (N=91)

| Demographics                               |   |  |
|--|---|--|
| Age  | Median (range), years<br>≥ 65y                                | 67 (25-83)<br>57% (52)                       |
| Gender                                     | Male:Female   | 1.8:1  |
| AML Disease Characteristics                |   |  |
| History/Type of AML                        | De Novo<br>Secondary  | 74% (67)<br>26% (24)                         |
| ELN 2017 risk                              | Intermediate<br>Adverse<br>Not Determined/Missing             | 24% (22)<br>53% (48)<br>22% (20)             |
| Key Molecular Features                     |   |  |
| FLT3 Mutant<br>TP53 Mutant<br>RUNX1 Mutant |   | 14% (13)<br>18% (16)<br>20% (18)             |
| Prior Therapies                            |   |  |
| Prior Lines of Treatment                   | 2 +   | 53% (48)                                     |
| Previous Treatment                         | First Relapse<br>Primary Refractory<br>Prior SCT<br>Prior VEN | 35% (32)<br>35% (32)<br>25% (23)<br>48% (44) |

All values are % (N), unless noted otherwise

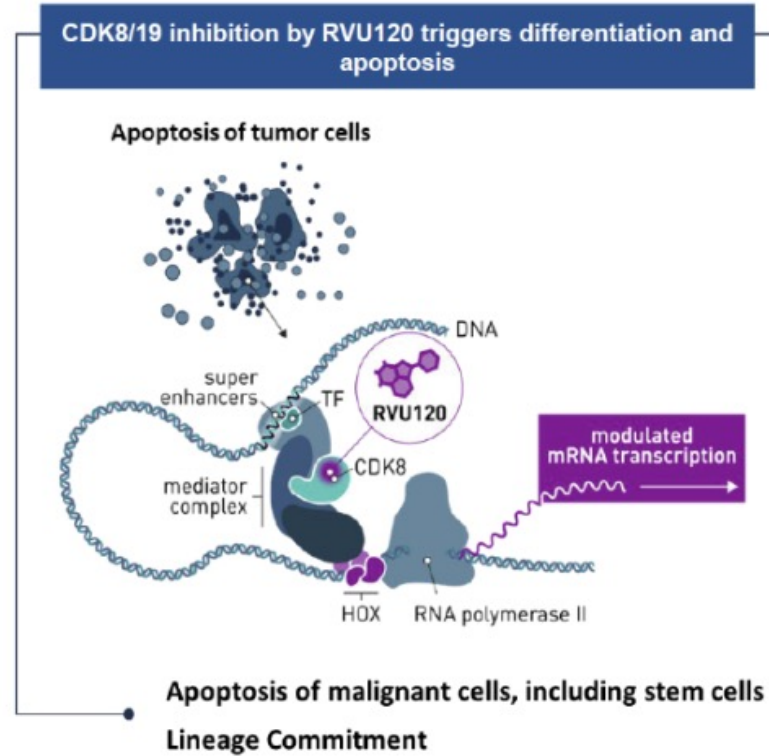
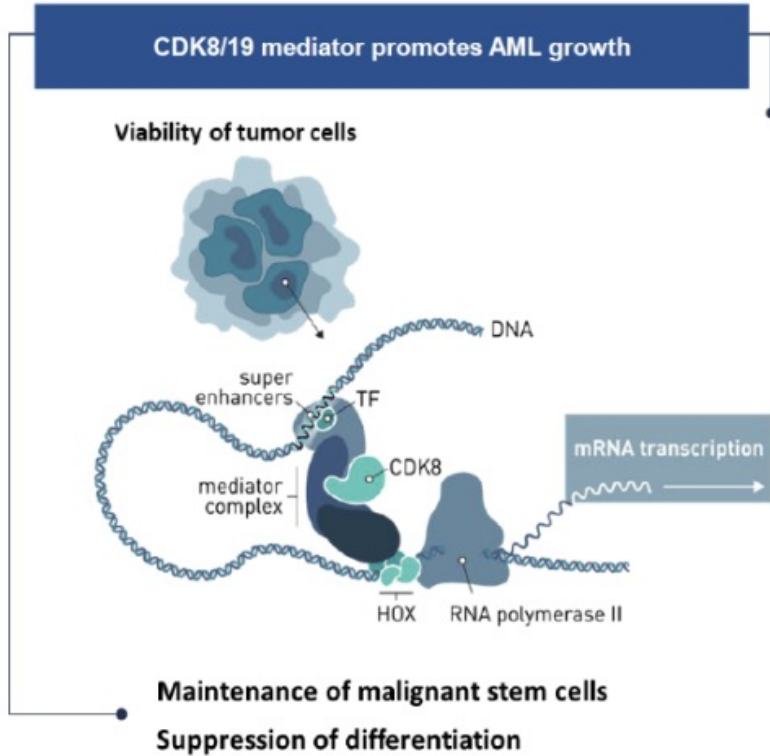
# Anti-Leukemic Activity in R/R AML ITT Population



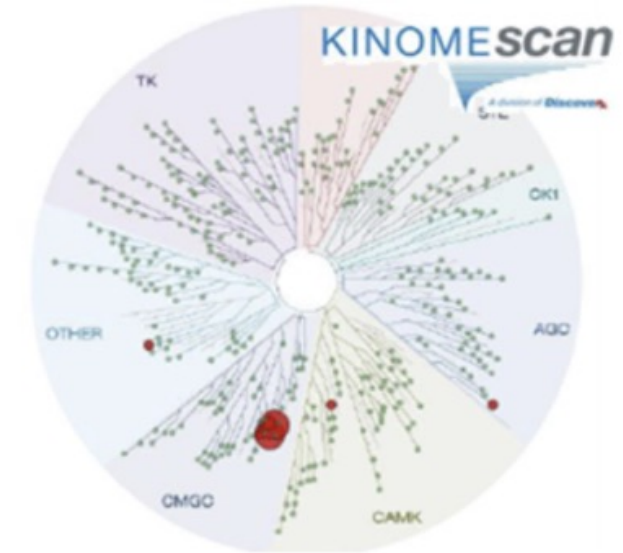
- Median time to CCR was 1.1 months (range 0.5-6.5)
- Median duration of CCR was 7.7 months (range 0.3-15.6 months)
- Of MRD-evaluable responders, 8 (32%) achieved MRD-negativity\*
- 24% of responders (10/41) proceeded to SCT

Note: 15 patients are not represented on the plot due to missing bone marrow data: 10 had clinical disease progression; 3 died without an assessment; 2 were otherwise unevaluable

# RVU120 is a first-in-class CDK8/19 inhibitor currently in clinical development.



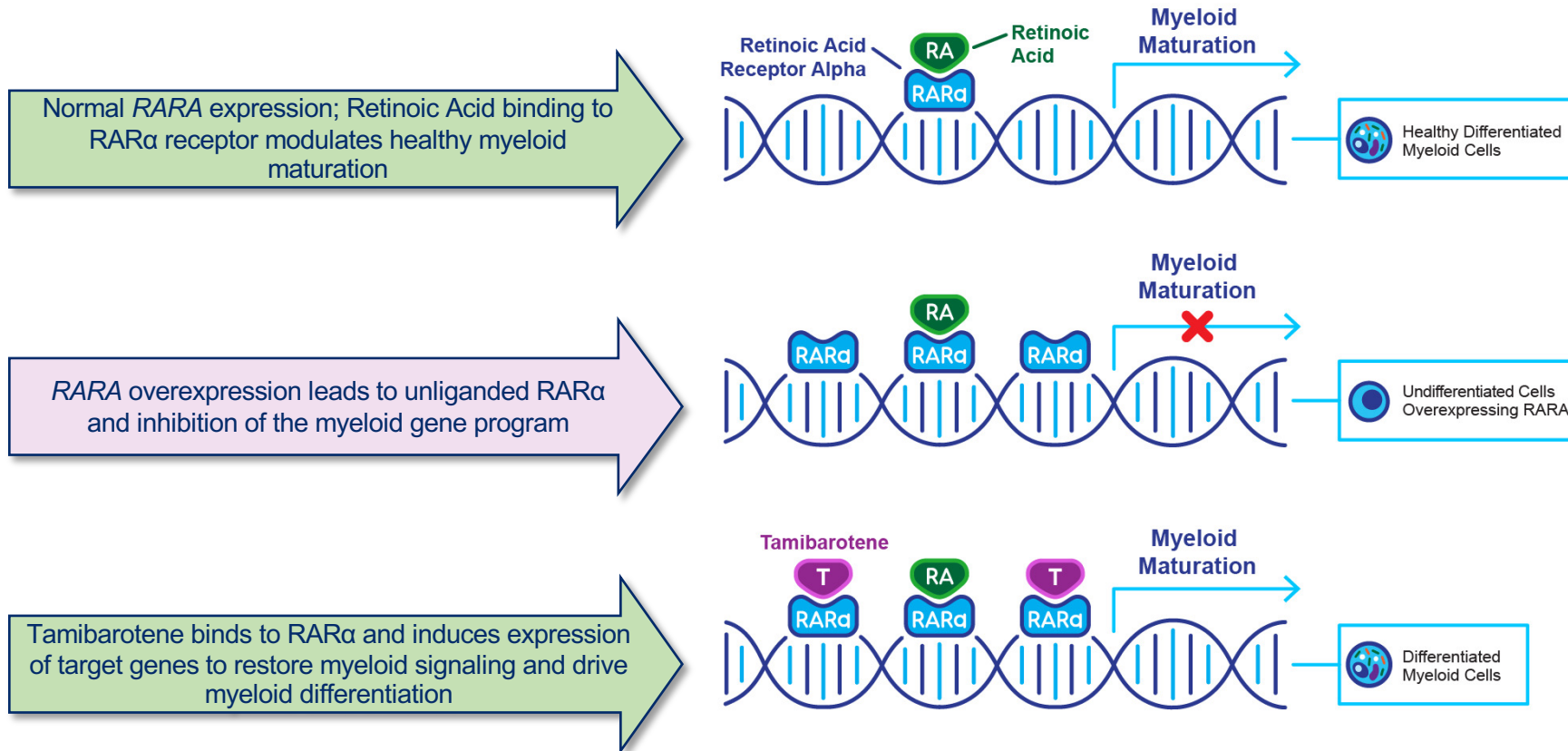
RVU120 is highly selective for CDK8/19



**There is potential to use RVU120 in patients with AML/ MDS**

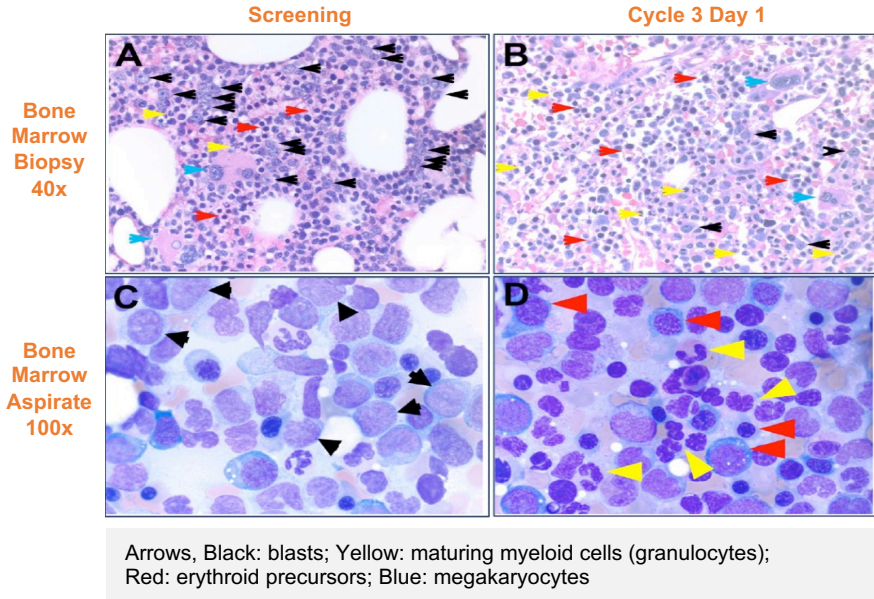
# Transcriptional reprogramming with tamibarotene

In cells that overexpress *RARA*, tamibarotene induces transcription of *RARα* target genes and restores myeloid differentiation





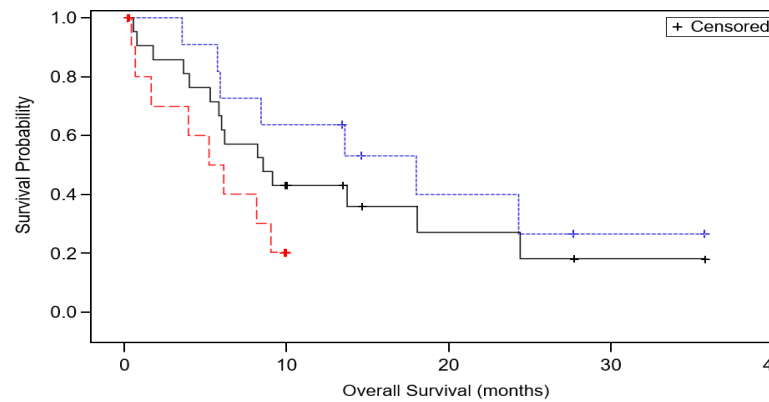
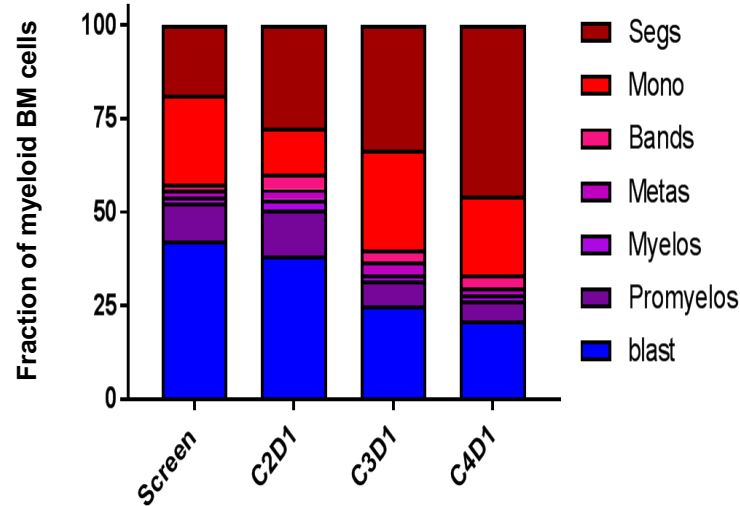
# Tamibarotene in AML



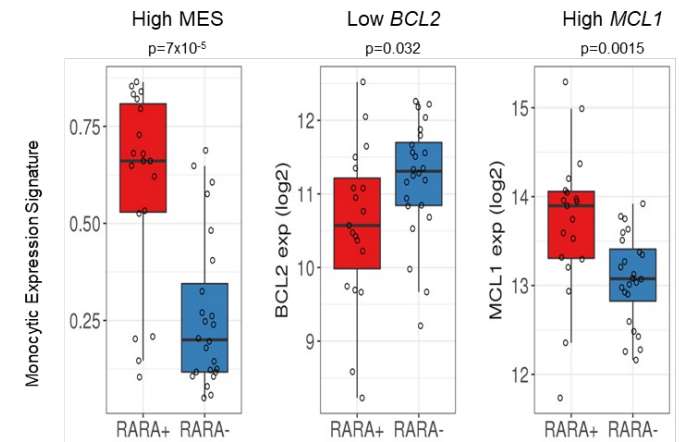
|                               | Patients with IWG response |   |   |   |   |   |   |   |   |    |    |    | Patients without IWG response |    |    |    |    |    |
|-------------------------------|----------------------------|---|---|---|---|---|---|---|---|----|----|----|-------------------------------|----|----|----|----|----|
|                               | 1                          | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13                            | 14 | 15 | 16 | 17 | 18 |
| TP53                          |                            |   |   |   |   |   |   |   |   |    |    |    |                               |    |    |    |    |    |
| ASXL1                         |                            |   |   |   |   |   |   |   |   |    |    |    |                               |    |    |    |    |    |
| RUNX1                         |                            |   |   |   |   |   |   |   |   |    |    |    |                               |    |    |    |    |    |
| NPM1                          |                            |   |   |   |   |   |   |   |   |    |    |    |                               |    |    |    |    |    |
| FLT3                          |                            |   |   |   |   |   |   |   |   |    |    |    |                               |    |    |    |    |    |
| CEBPA                         |                            |   |   |   |   |   |   |   |   |    |    |    |                               |    |    |    |    |    |
| IDH1                          |                            |   |   |   |   |   |   |   |   |    |    |    |                               |    |    |    |    |    |
| IDH2                          |                            |   |   |   |   |   |   |   |   |    |    |    |                               |    |    |    |    |    |
| DNMT3A                        |                            |   |   |   |   |   |   |   |   |    |    |    |                               |    |    |    |    |    |
| TET2                          |                            |   |   |   |   |   |   |   |   |    |    |    |                               |    |    |    |    |    |
| BCORL1                        |                            |   |   |   |   |   |   |   |   |    |    |    |                               |    |    |    |    |    |
| BCOR                          |                            |   |   |   |   |   |   |   |   |    |    |    |                               |    |    |    |    |    |
| EZH2                          |                            |   |   |   |   |   |   |   |   |    |    |    |                               |    |    |    |    |    |
| KRAS                          |                            |   |   |   |   |   |   |   |   |    |    |    |                               |    |    |    |    |    |
| CBL                           |                            |   |   |   |   |   |   |   |   |    |    |    |                               |    |    |    |    |    |
| PHF6                          |                            |   |   |   |   |   |   |   |   |    |    |    |                               |    |    |    |    |    |
| Cytogenetic Risk <sup>a</sup> |                            |   |   |   |   |   |   |   |   |    |    |    |                               |    |    |    |    |    |

Data shown for the 18 response evaluable patients <sup>a</sup>Cytogenetic risk per NCCN AML guidelines 2018

Key: ■ Achieved IWG response ■ Presence of the indicated molecular mutation ■ Intermediate cytogenetic risk ■ Poor cytogenetic risk

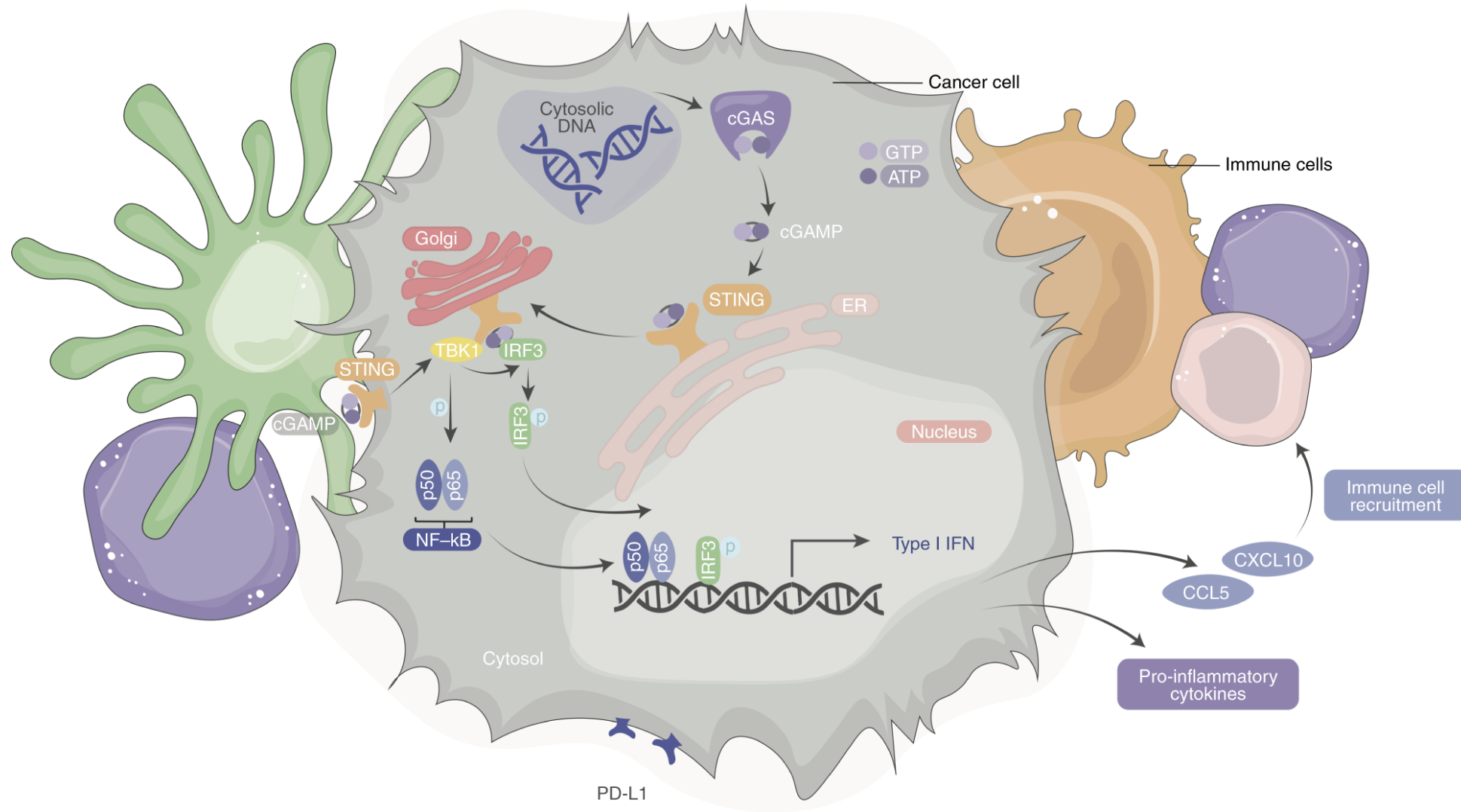


| Patients at risk: | 0  | 10 | 20 | 30 | 40 |
|-------------------|----|----|----|----|----|
| All patients      | 22 | 7  | 3  | 1  | 0  |
| Responders        | 11 | 7  | 3  | 1  | 0  |
| Non-responders    | 11 | 0  |    |    |    |

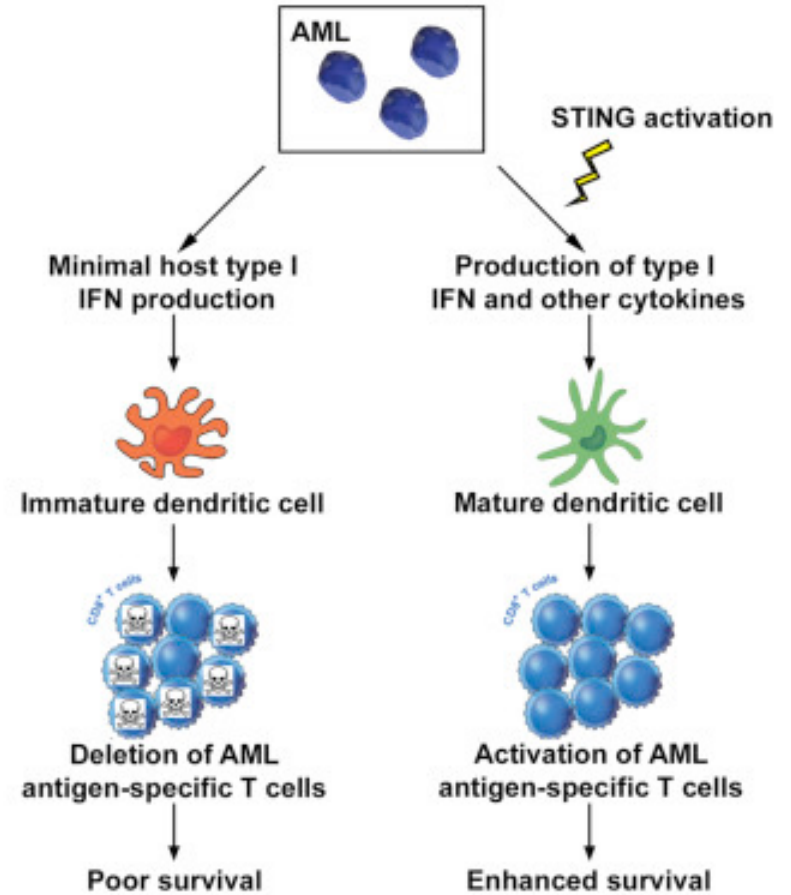
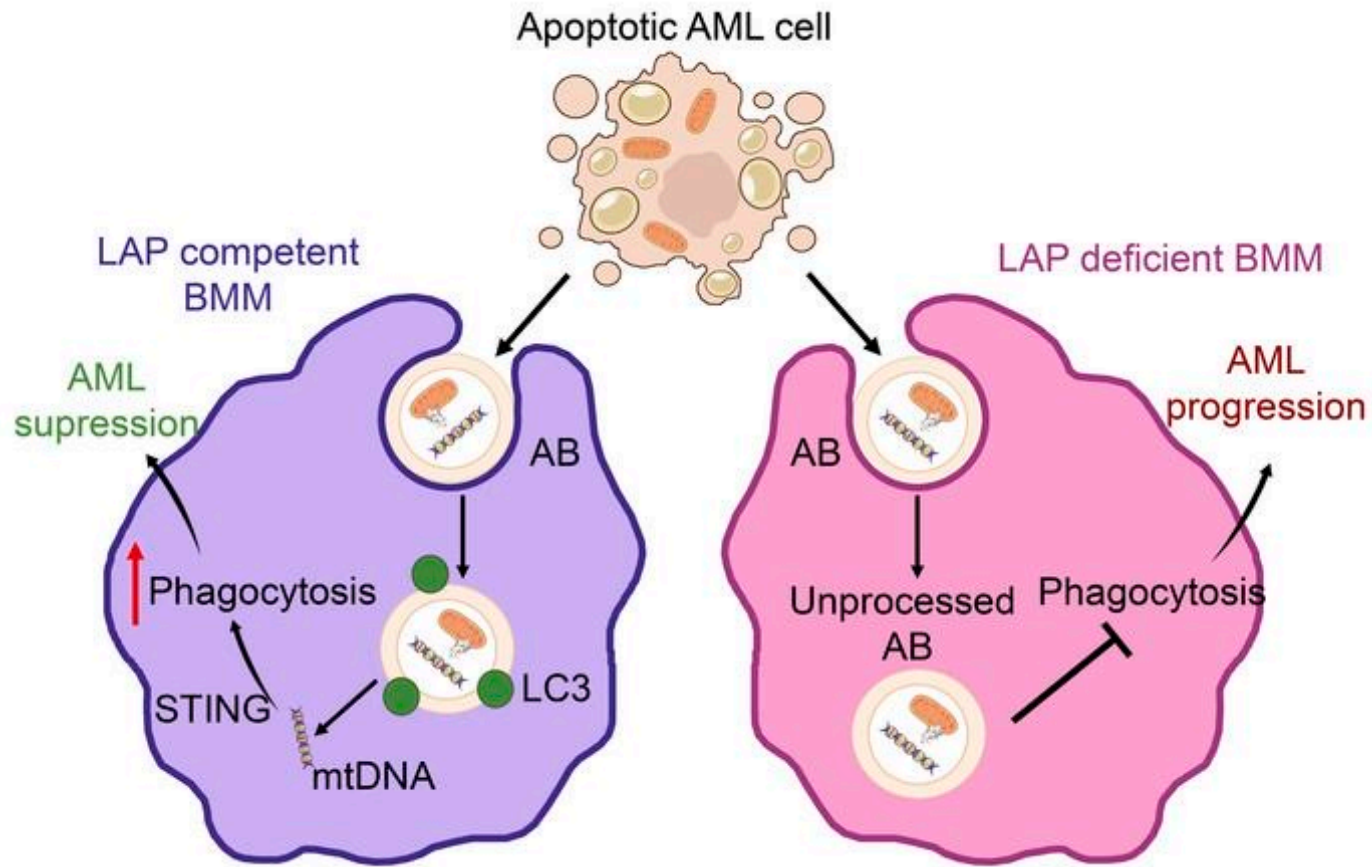


Yuric ASH 2017; de button Blood Adv 2023

# STING agonist



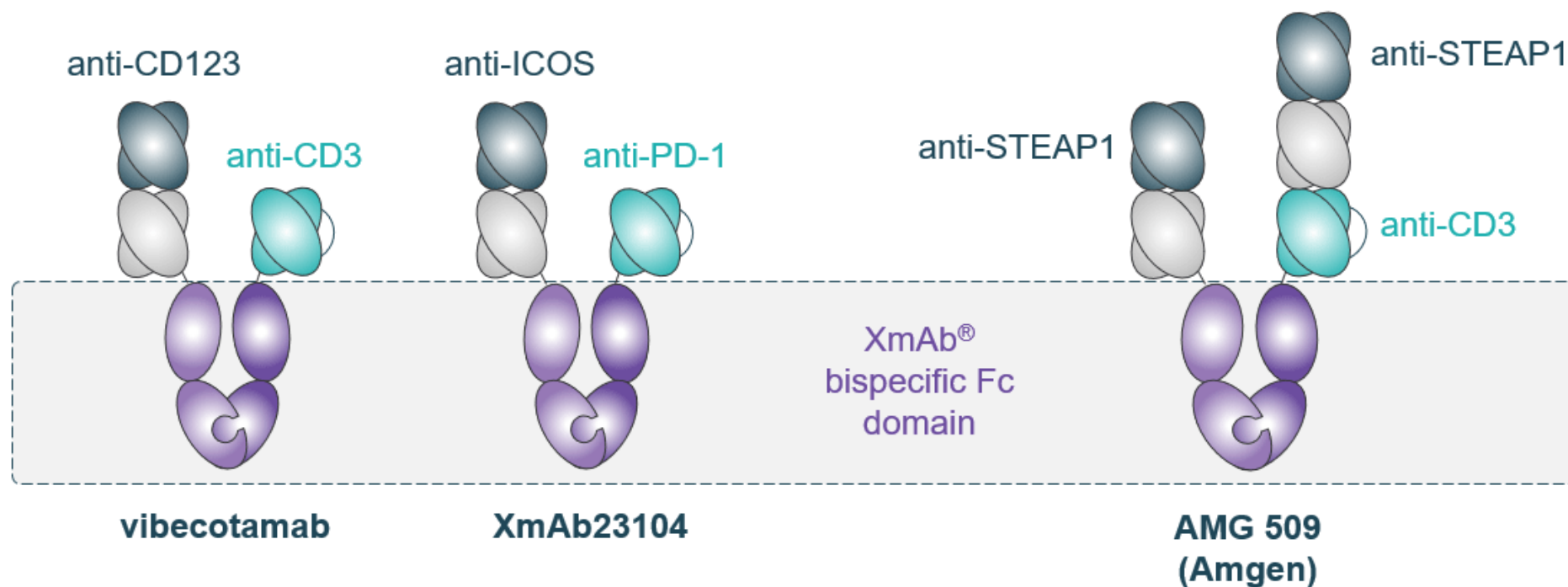
# STING agonist



A phase II study of vibecotamab, a CD3-CD123 bispecific T-cell engaging antibody, for MRD-positive AML and MDS after hypomethylating agent failure.

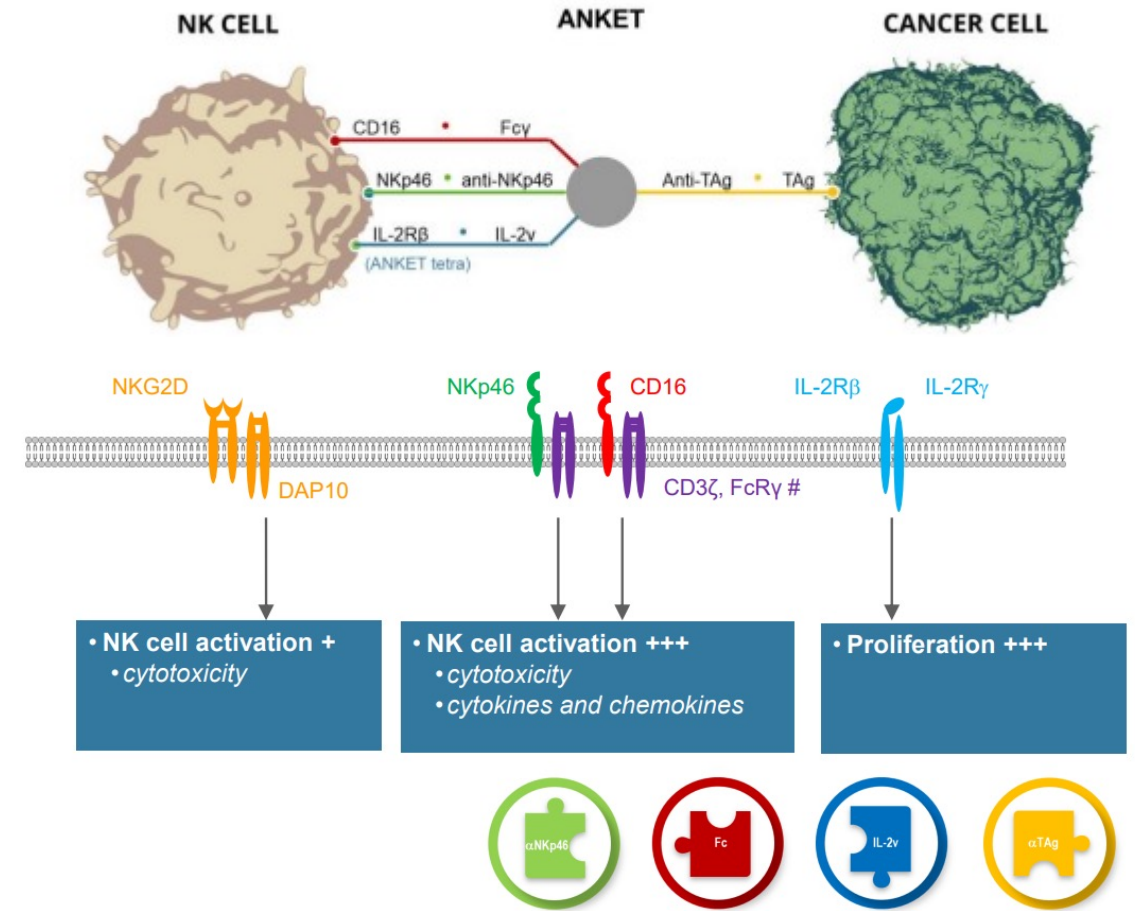
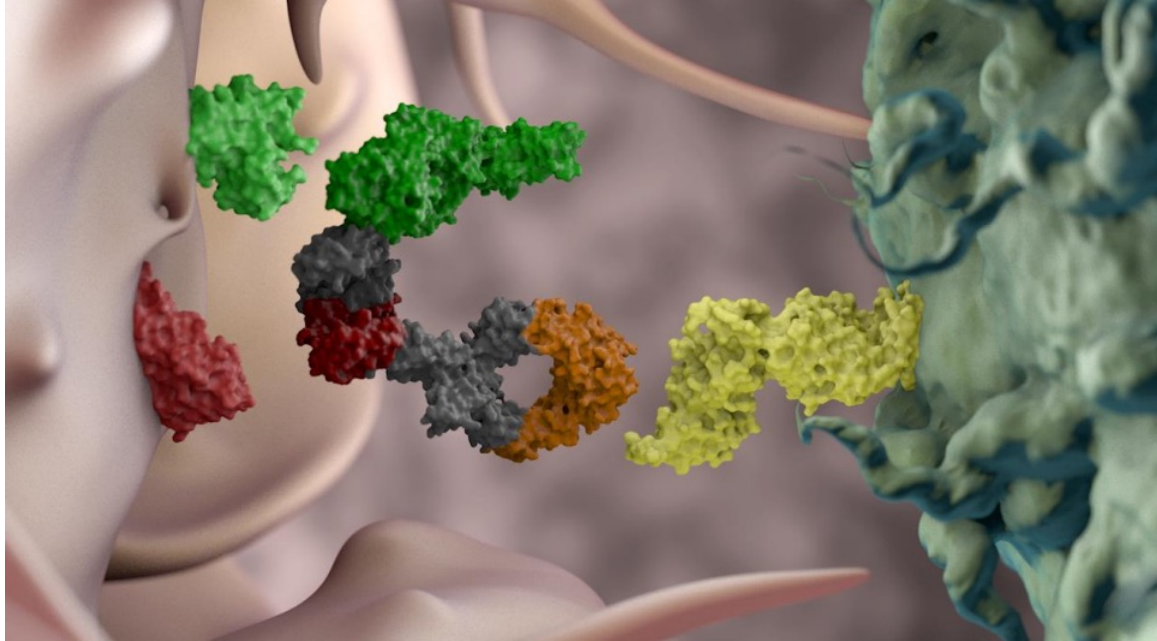
### XmAb<sup>®</sup> bispecific antibodies

### XmAb<sup>®</sup> 2+1 bispecific antibody



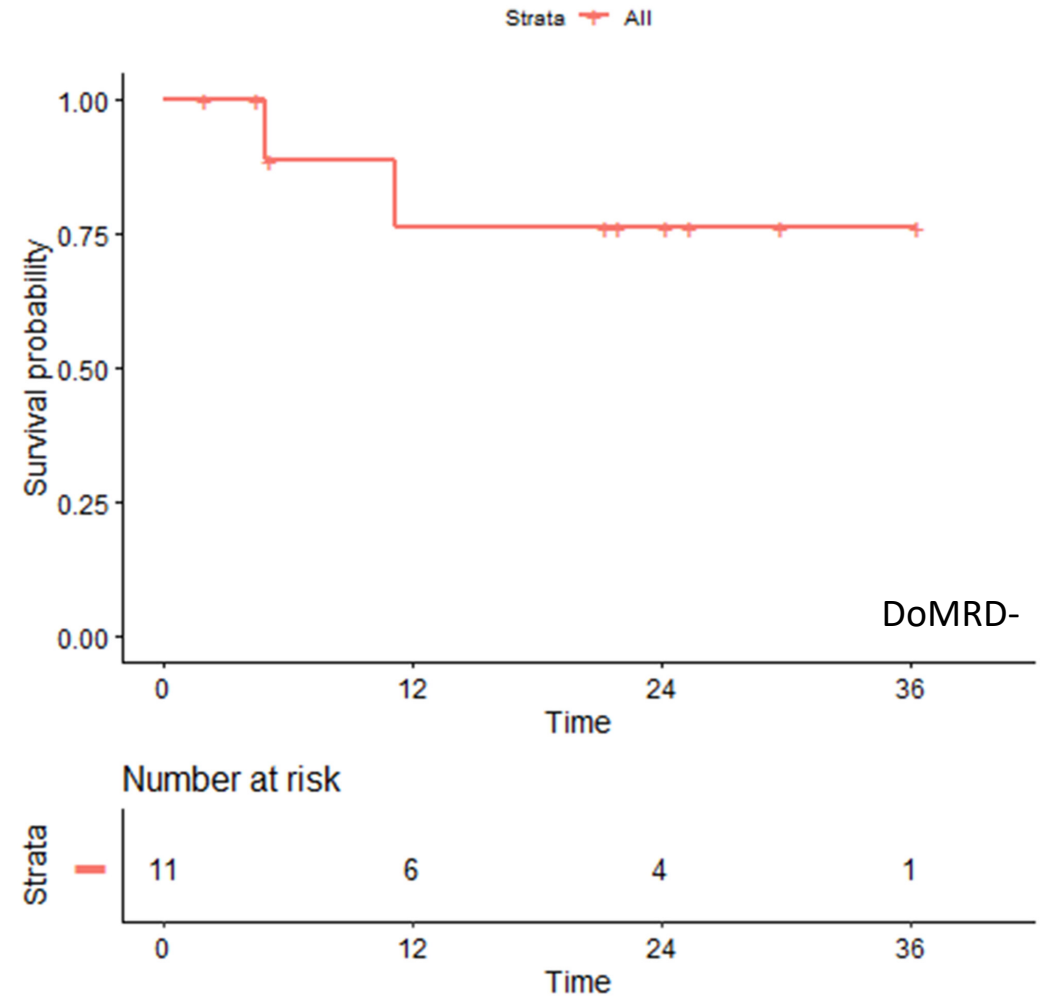
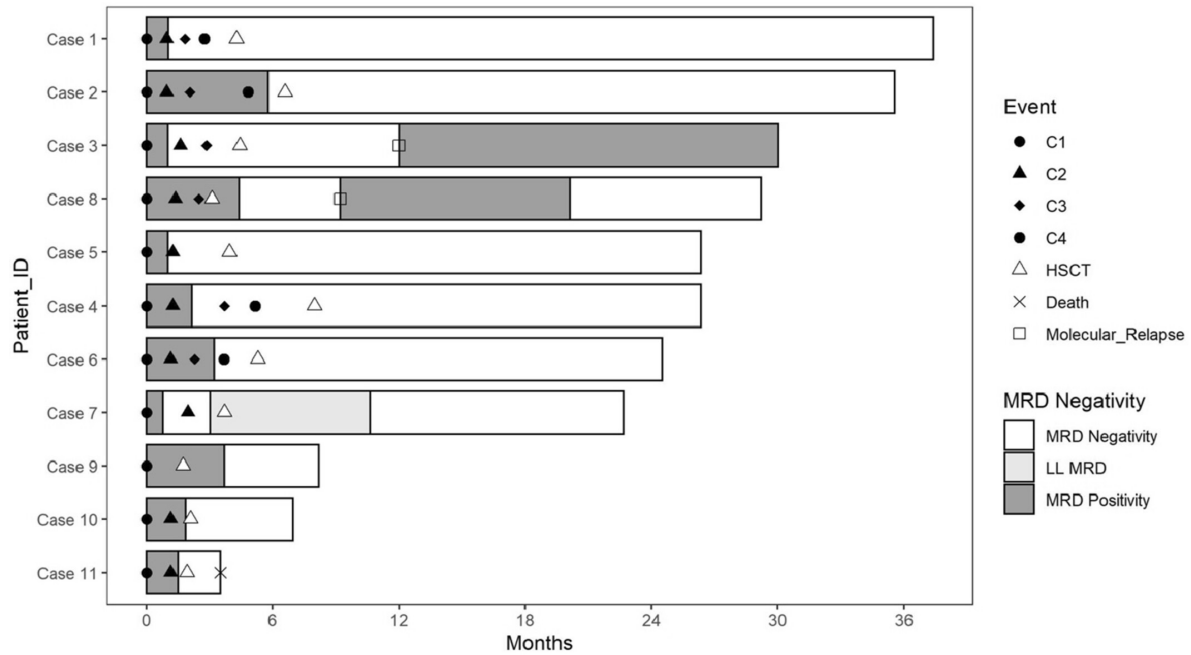
To date, 13 patients have been enrolled (7 in the AML MRD cohort and 6 in the MDS/CMML cohort)

# A first-in-human study of CD123 NK cell engager SAR443579 in relapsed or refractory acute myeloid leukemia, B-cell acute lymphoblastic leukemia, or high-risk myelodysplasia.

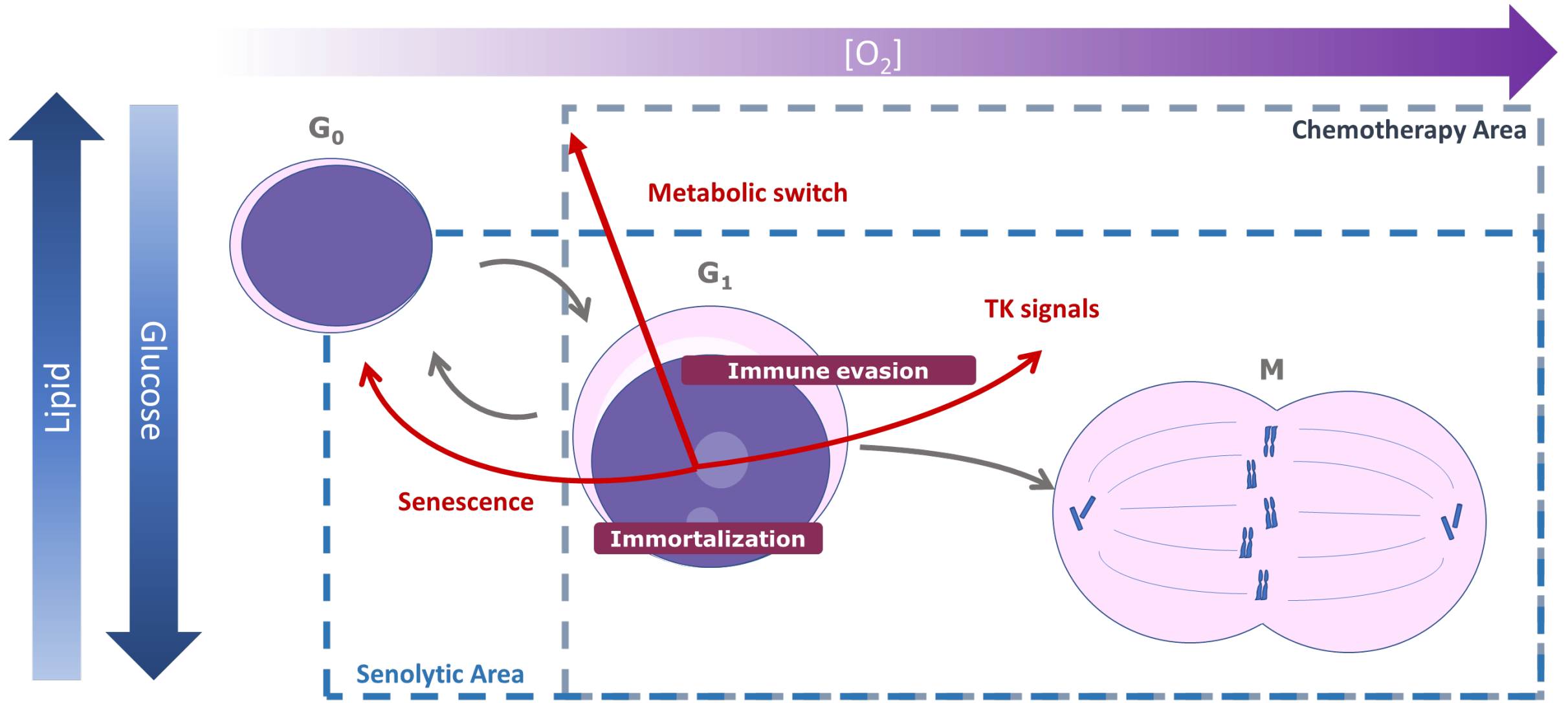


In DLs with a highest dose of 1000  $\mu\text{g}/\text{kg}$  QW, 3/8 (37.5%) patients achieved a CR (2 CR/1 CRi).

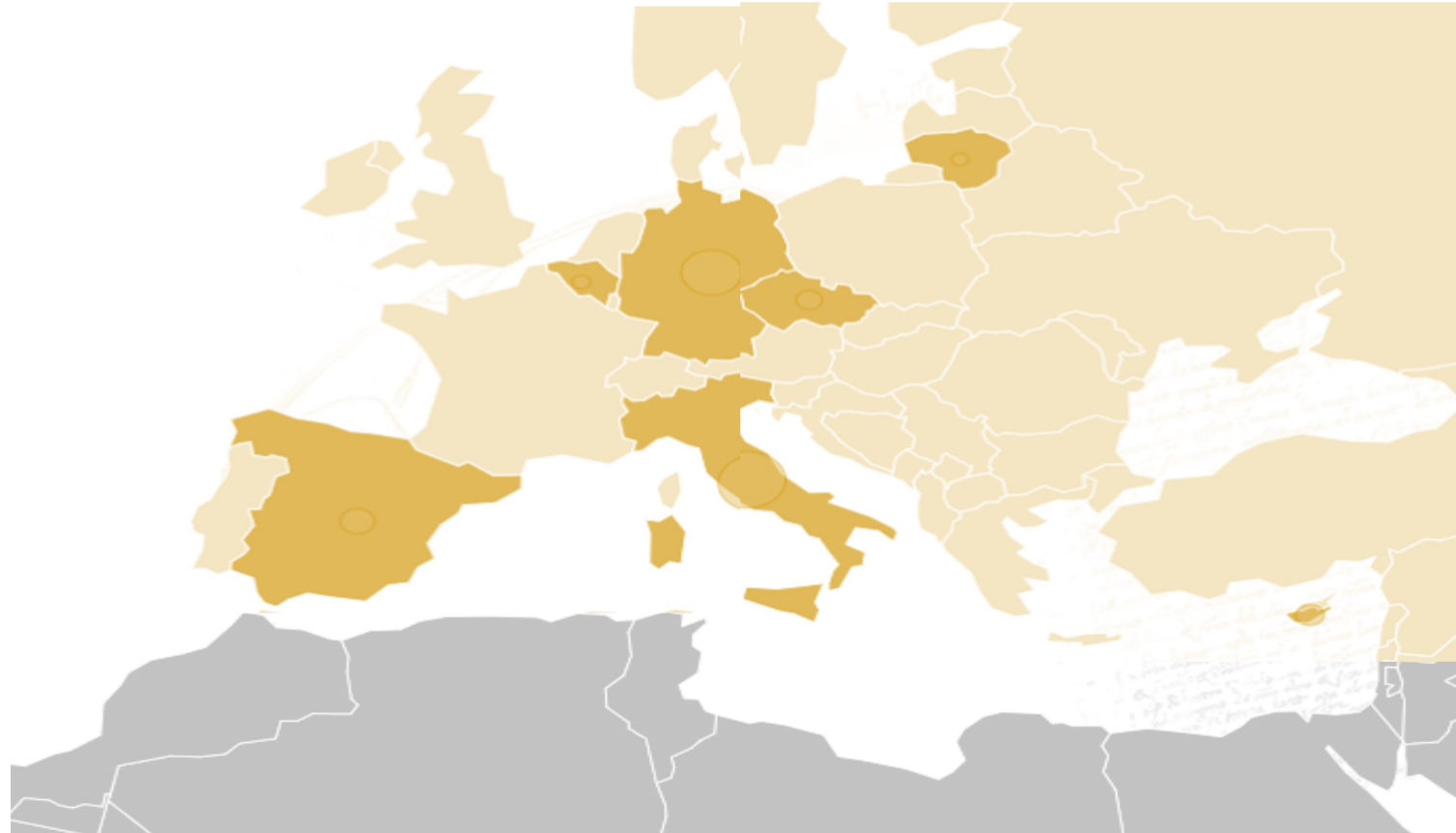
# Tackling MRD+ (NPM1)



# Room for improvement



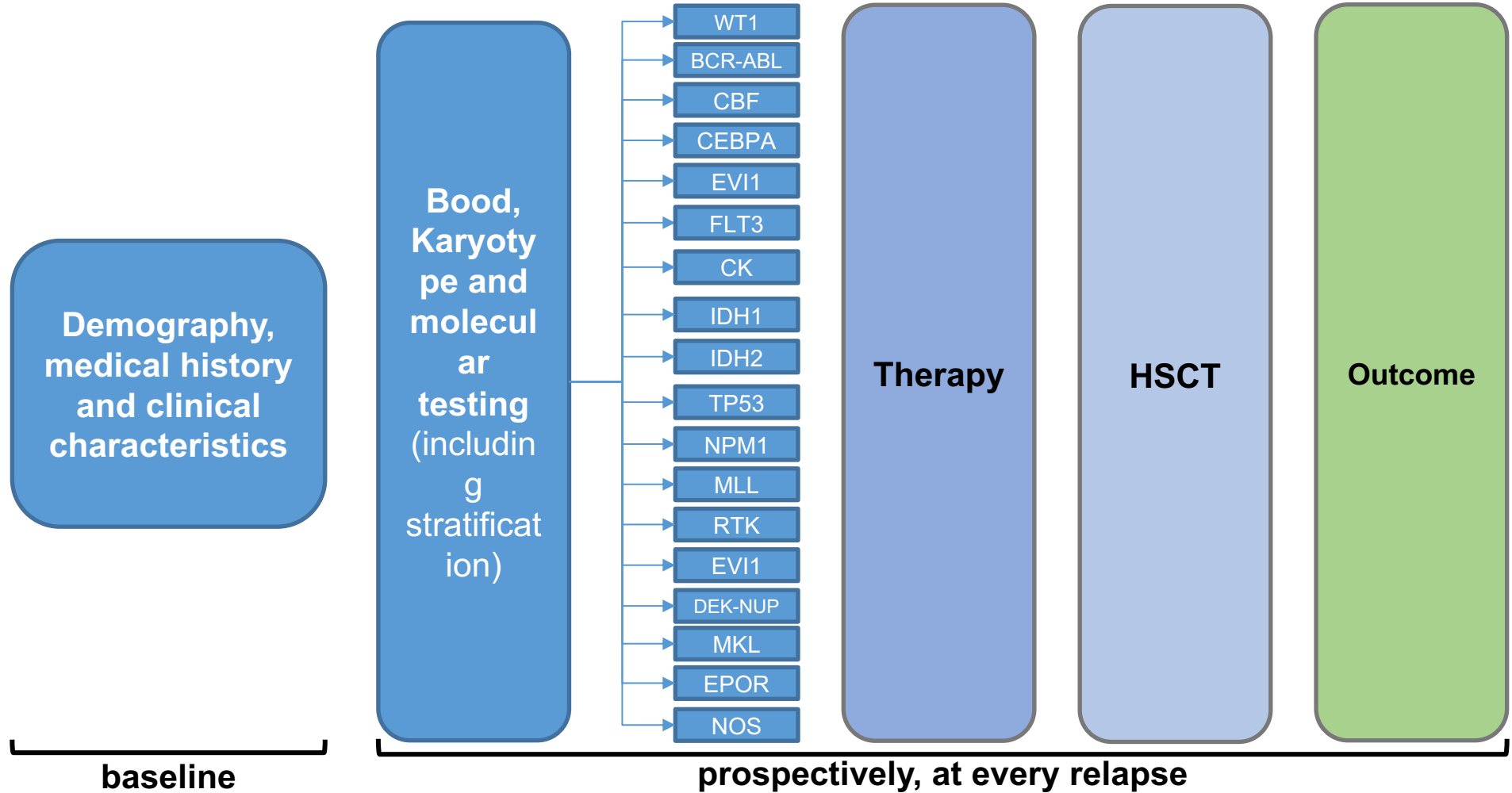
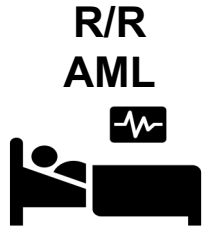
# IMPACT-AML cohoperative network





# STREAM

Up to 22.000px/y in Europe  
Registration of all R/R Patients



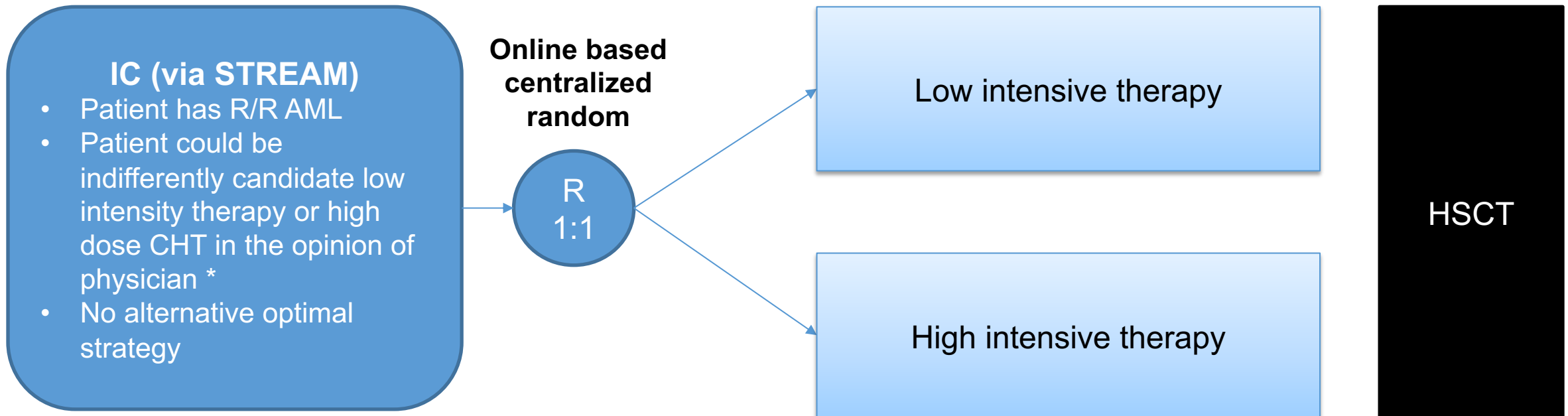
*personal*

# RPCT

Randomized Pragmatic Clinical Trial:  
Low intensity therapy vs High intensity standard Chemotherapy

**OBJ: Is it beneficial to use low intensity therapy as a rescue?**

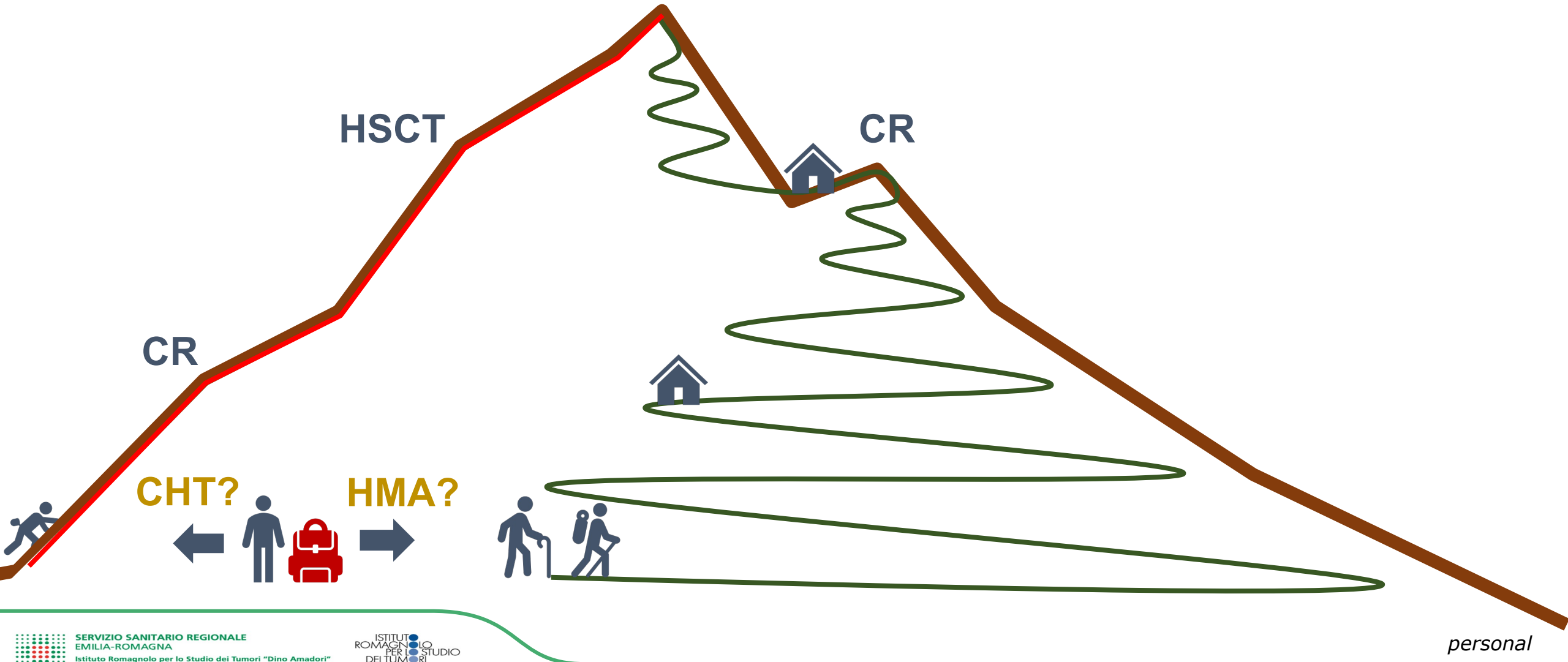
1<sup>st</sup>/2<sup>nd</sup> relapse/refractory, no previous HSCT will be the primary cohort

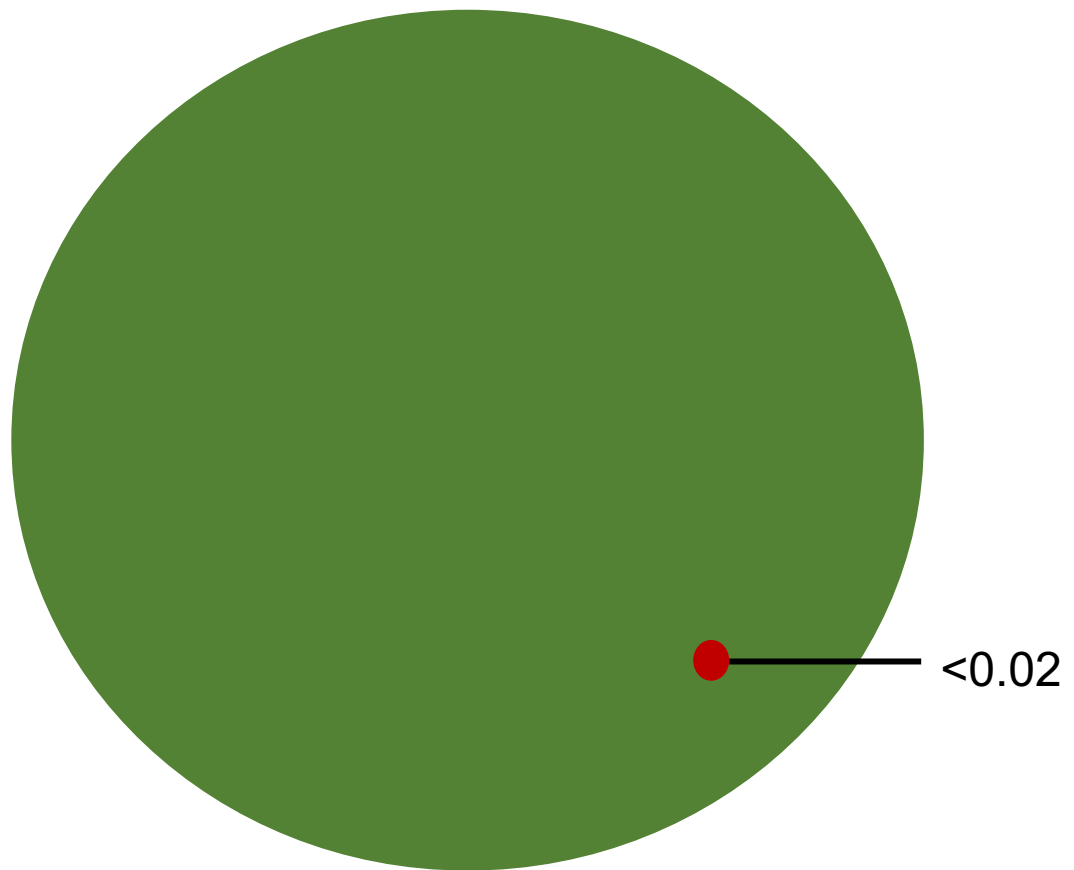


*personal*

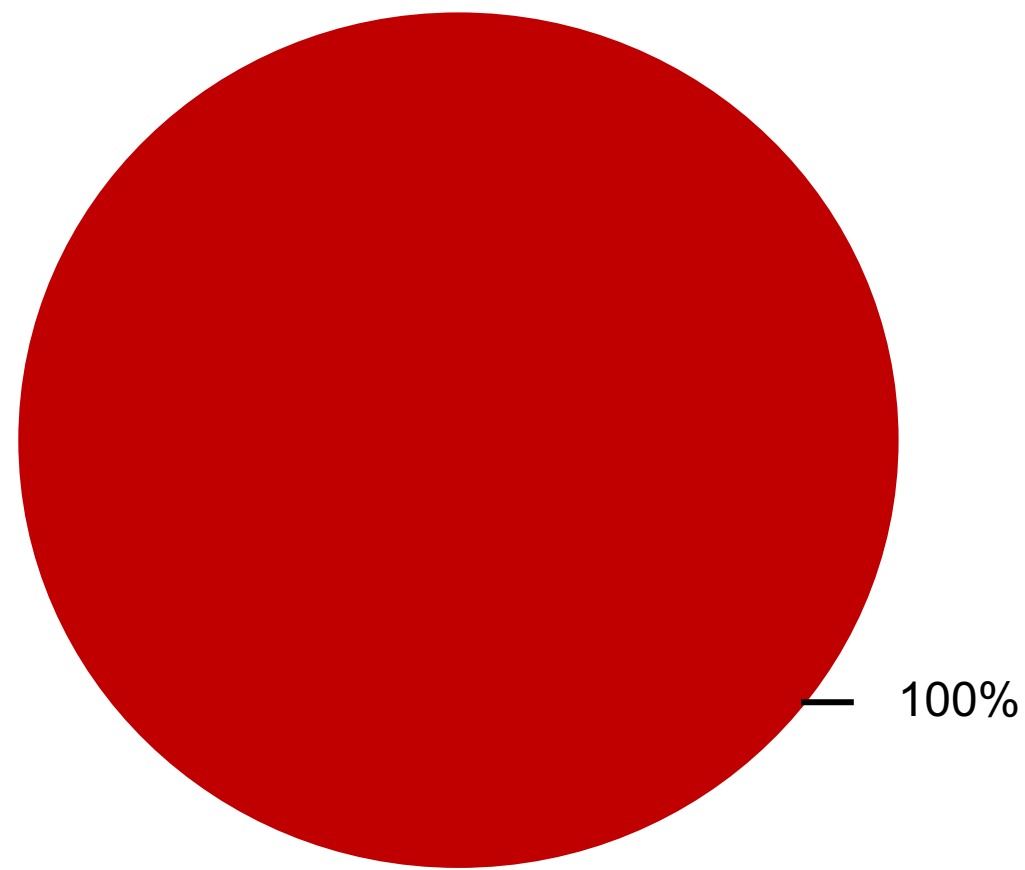
# The best path

long term survival



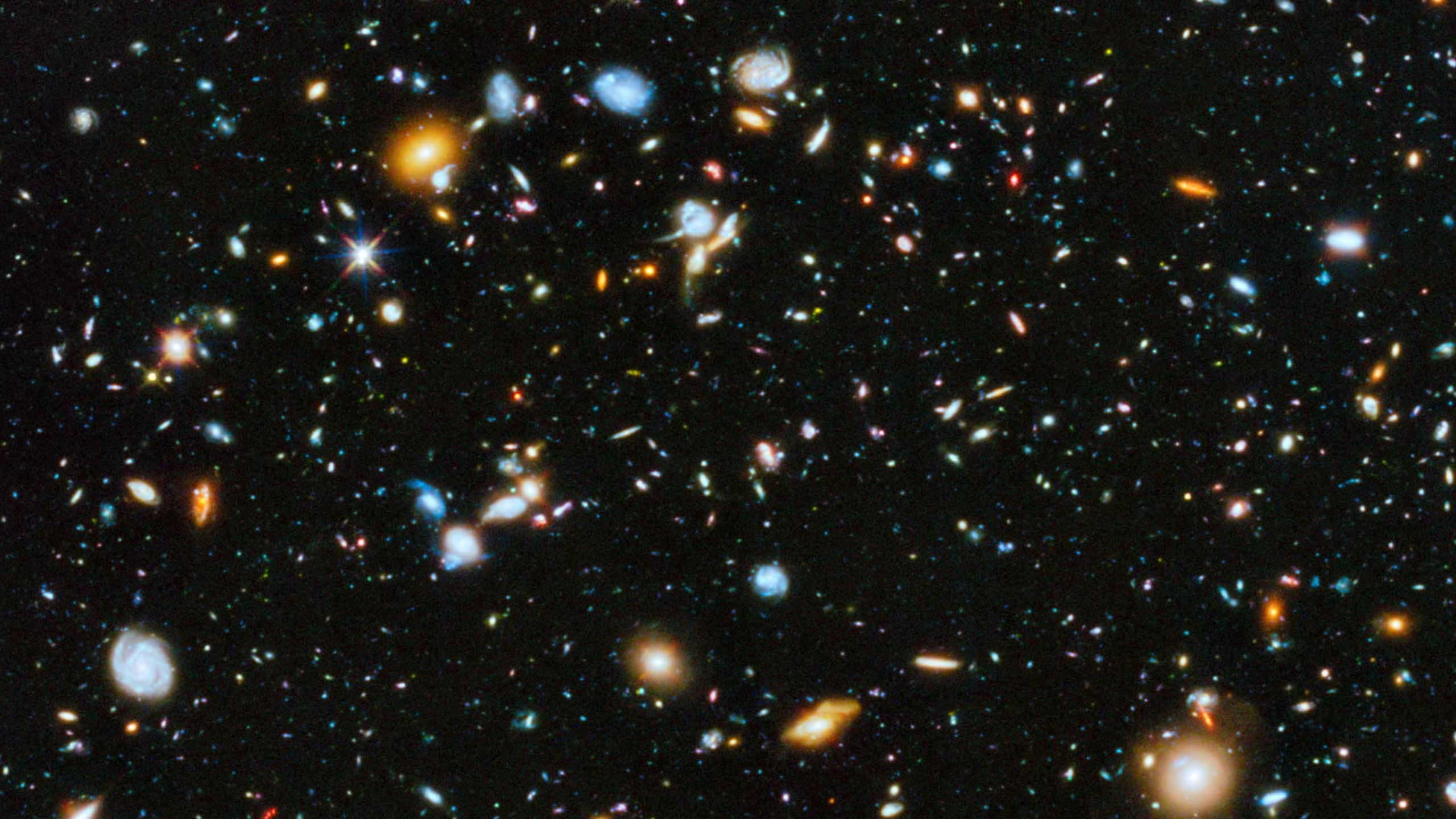


General population



Your patient

*personal*



# Grazie per l'attenzione



**GIOVANNI M.**  
Medico



**CINZIA C.**  
Infermiera



**GIORGIO V.**  
Volontario



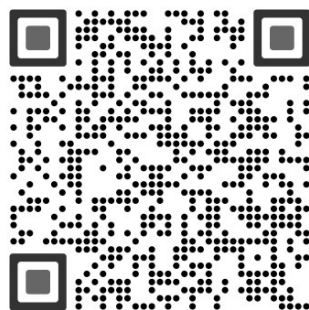
**CLAUDIA B.**  
Guarita



**ALESSIA A.**  
Familiare



**CHIARA S.**  
Ricercatrice



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PER LO STUDIO  
DEI TUMORI  
DINO AMADORI