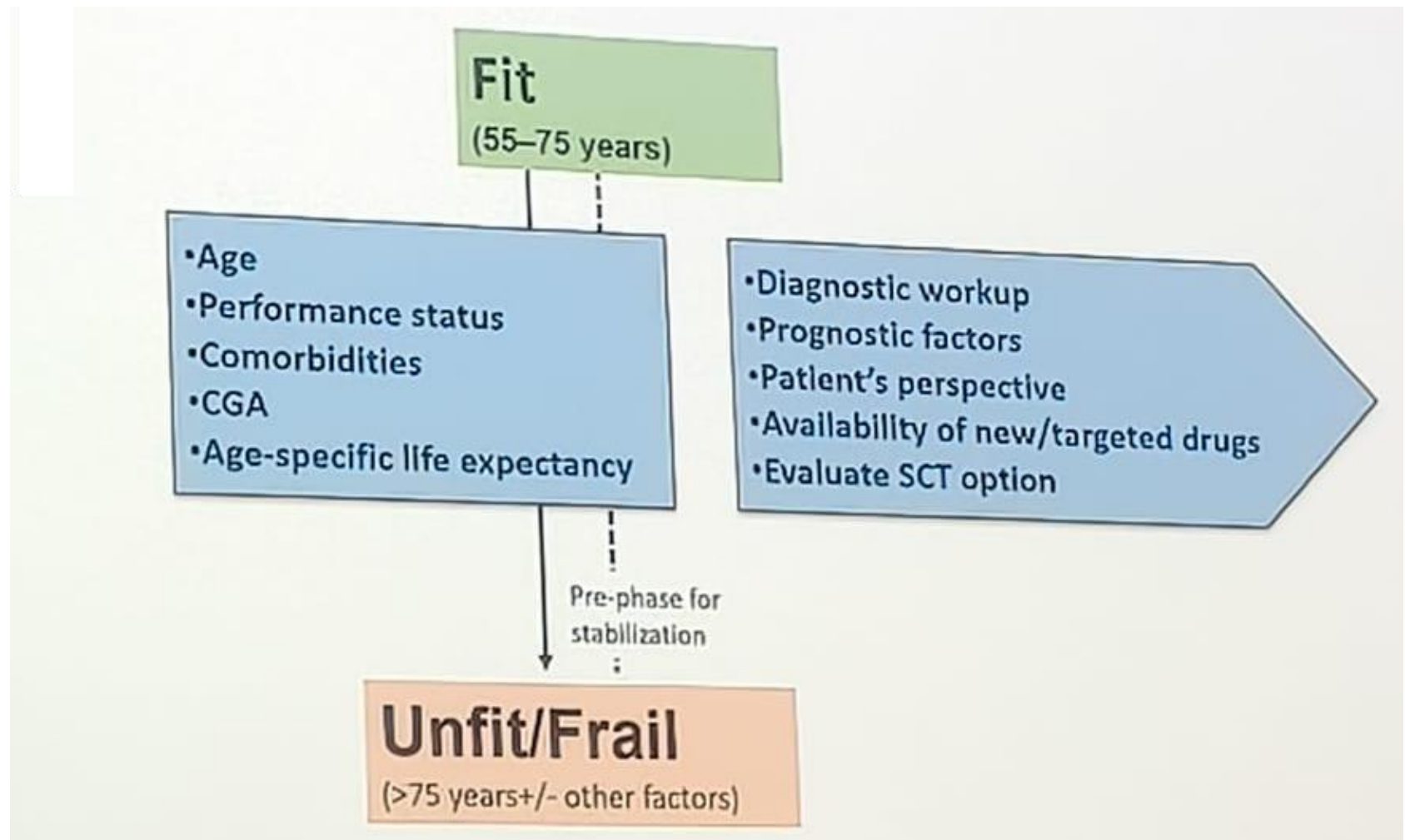


Paziente UNFIT ALL Ph negativa

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Considerations on older patients



Case 1

- **May 2024:** a 64 year old patient was diagnosed with CD20-neg, BCR-ABL neg, KMT2A neg ALL (common)
- WBC was 3.5×10^3 cells
- He had hypertension and controlled diabetes
- ECOG 1
- He was working full time
- Should we treated patient according to a protocol for younger pts? Could the immunotherapy be integrated with chemotherapy?

Case 2

- **March 2023:** A 77-yrs old patient was diagnosed with Cdneg, proB-ALL.
- Patient referred to be treated for a heart attack in 2019
- He lived alone
- Should be treated according to an age adapted pediatric –protocol? What is the role of immunotherapy?

The definition of «older patients» varies considerably

- Majority of studies identify a cut-off of 55 years, due to higher rate of death in CR in patients aged 56 to 60 years
- Patients aged above 60 years benefit from age-adapted pediatric- based protocols
- Patients having more than 70 years old cannot tolerate age –adapted pediatric porotocols

Comorbidities

Type of comorbidity	Younger patients (<55 y), %	Older patients (>55 y), %	Frail patients, %
Arrhythmias	<1	12	22
Cardiac disease	2	19	42
Pulmonary (moderate)	8	14	28
Hepatic (mild)	8	11	14
Prior malignancies	2	25	22
Diabetes	4	22	22
Obesity (BMI >35 kg/m ²)	9	11	14
Infections	15	18	22
Low HCT-CI risk score	54	25	8
High HCT-CI risk score	18	50	59

Patients > 55ys had a higher incidence of cardio-pulmonary diseases and prior malignancies

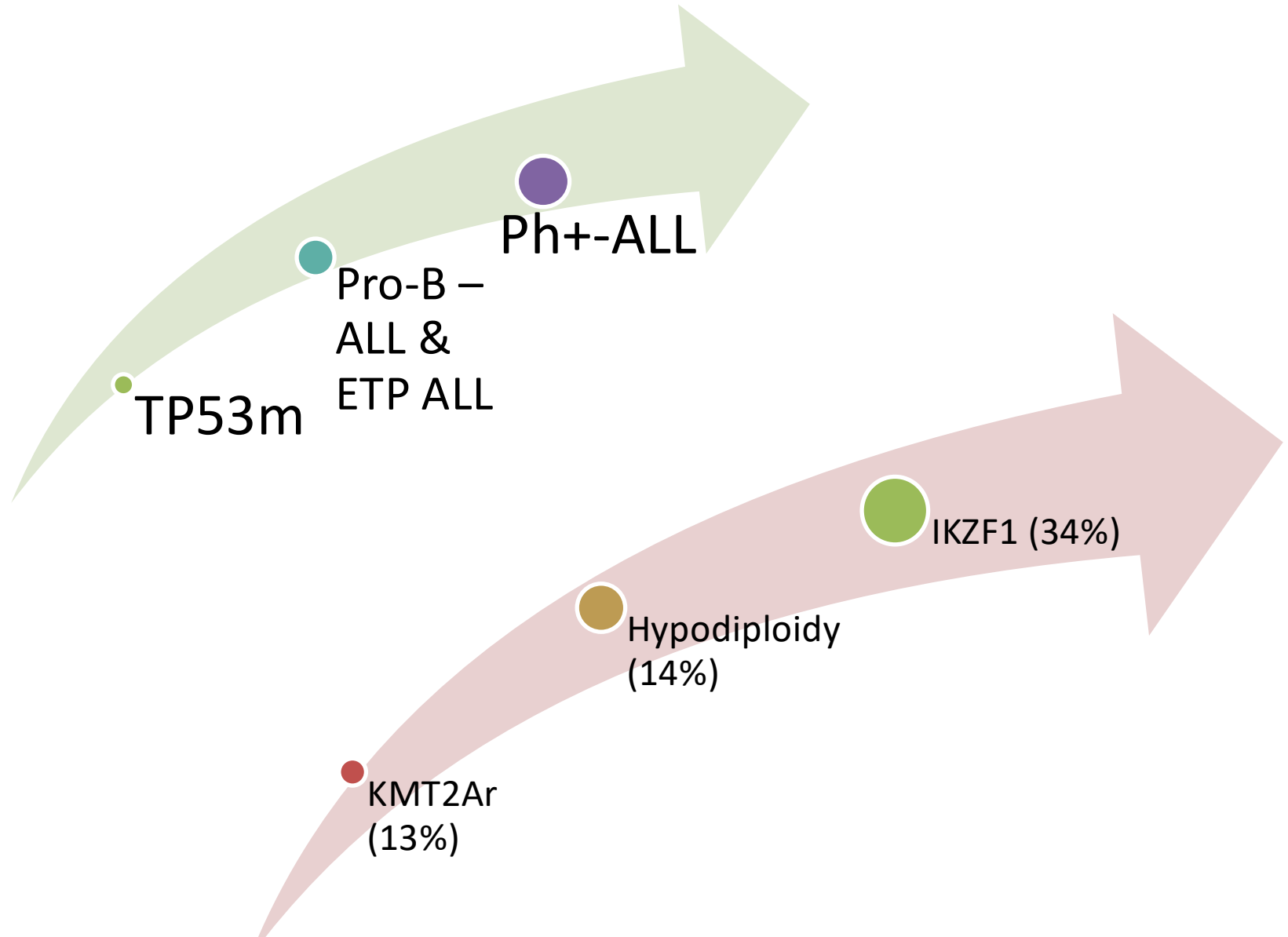
Early Death was significantly associated with comorbidity as assessed by CCI but not as assessed by the HCT-CI

Patients aged > 70 years and GA

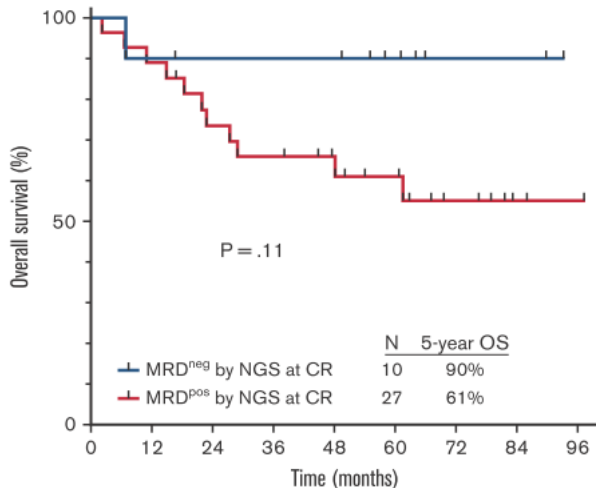
Geriatric Assessment:

- Predict chemotherapy toxicity
- Estimate noncancer life expectancy
- Potential interactions with antileukemic medications
- Screening for depression, cognitive impairment and malnutrition

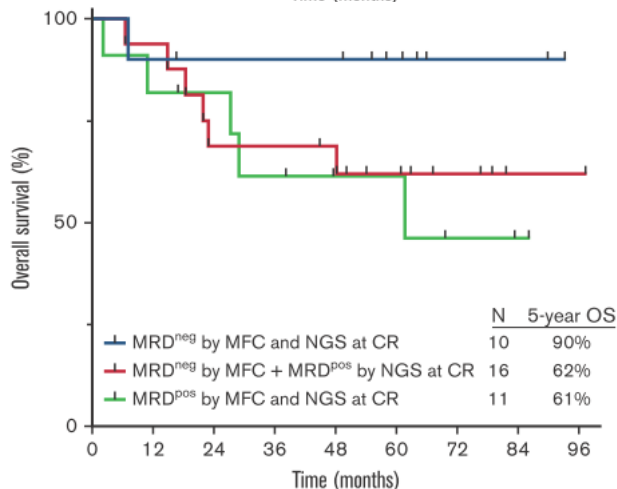
Biologic Features of older ALL



Measurable Residual Disease



- The most crucial prognostic factor regardless of age
- Older tends to have higher rates of MRD persistence which is linked to 90% of risk of relapse
- Using a cutoff of 10⁻⁶ identifies a subgroup of patients with extremely low risk of relapse

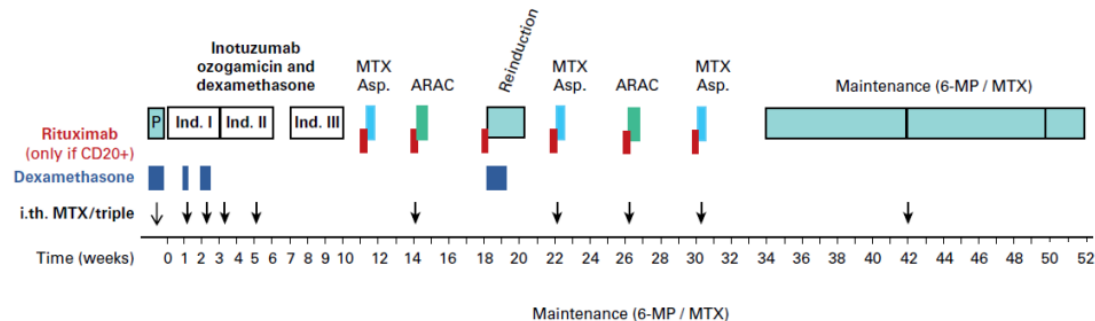


Chemotherapy

Author	Year	Feature	Age, y	Patients (N)	CR/CRi	Early death	Failure	Death in CR	CCR ⁺	DFS/EFS ⁺	OS ⁺
Chemotherapy (selected recent trials)											
Hunault-Berger et al ⁴⁴	2011	CI-Dox	68 (55-77)	31	90%	7%	3%	32% (2 y)	32% (2 y)	n.r.	35% (2 y)
	Arm 1	PEG-Dox	66 (60-80)	29	72%	10%	17%	19% (2 y)	52% (2 y)		24% (2 y)
	Arm 2										
Ribera et al ⁴⁵	2016	Ped based	66 (56-79)	54	74%	14%	14%	3%	30%	9% (5 y)	12% (5 y)
Gökbuget et al ⁴	2022	Ped based (total)	68 (56-86)	841	73%	14%	13%		37% (3 y)	n.r.	28% (5 y)
	Group 1	Original		593	72%	15%	13%				32%
	Group 2	Int.Cons. + MRD-based Blina		248	75%	9%	16%				50%
Jabbour et al ⁴⁶	2023	HCVAD ± rituximab	n.r.	60	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	27% (5 y)

- 2-yrs OS was less than 30%
- ED was near to 15%
- CR rate was near to 75%

INITIAL-1 Trial

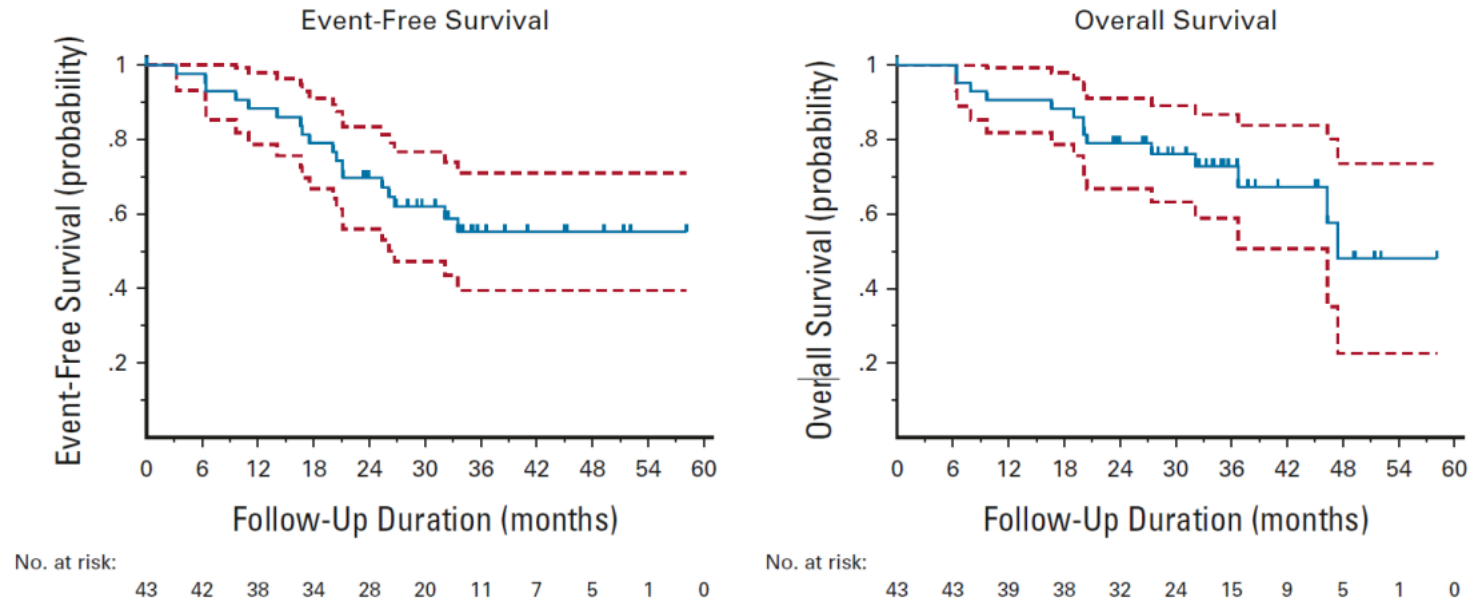


Patients Evaluable for Response

N = 43

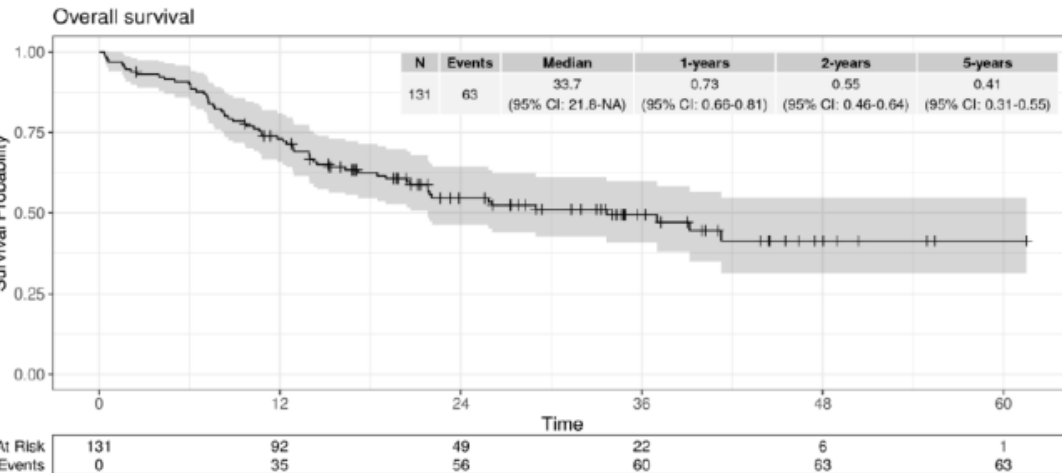
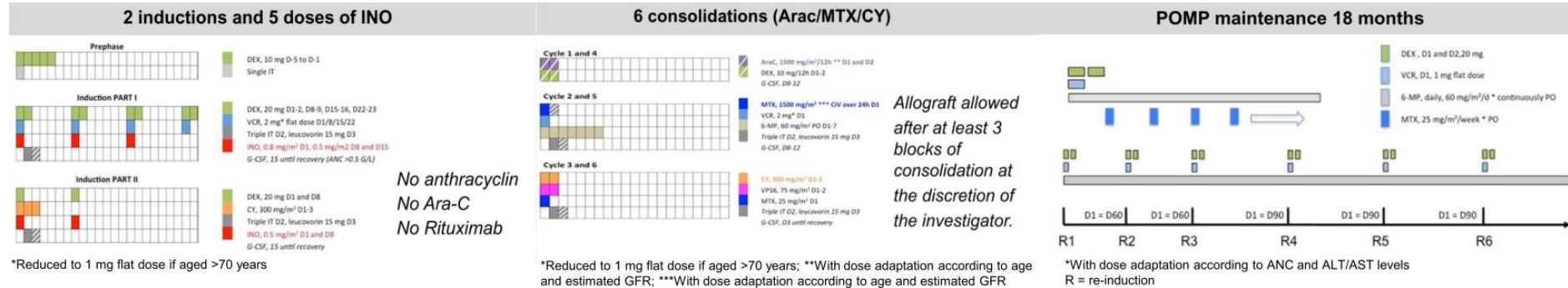
CR/CRi after induction I, No. (%)	38 (88)
MRD negative (MoICR), No. (%)	11 (29)
MRD positive $>10^{-4}$ (MoIFail), No. (%)	13 (34)
MRD intermediate (MoIMR) ^a , No. (%)	14 (37)
CR/CRi after induction II, No. (%)	43 (100)
MRD negative (MoICR), No. (%)	23 (53)
MRD positive $>10^{-4}$ (MoIFail), No. (%)	6 (14)
MRD intermediate (MoIMR) ^a , No. (%)	14 (33)
CR/CRi after induction III, No. (%)	42 (100) ^b
MRD negative (MoICR), No. (%)	30 (71)
MRD positive $>10^{-4}$ (MoIFail), No. (%)	4 (10)
MRD intermediate (MoIMR) ^a , No. (%)	8 (19)
Deaths during first 6 months, No. (%)	0 (0)
Events (relapse, death) during first 12 months, No. (%)	5 (12)

Survival



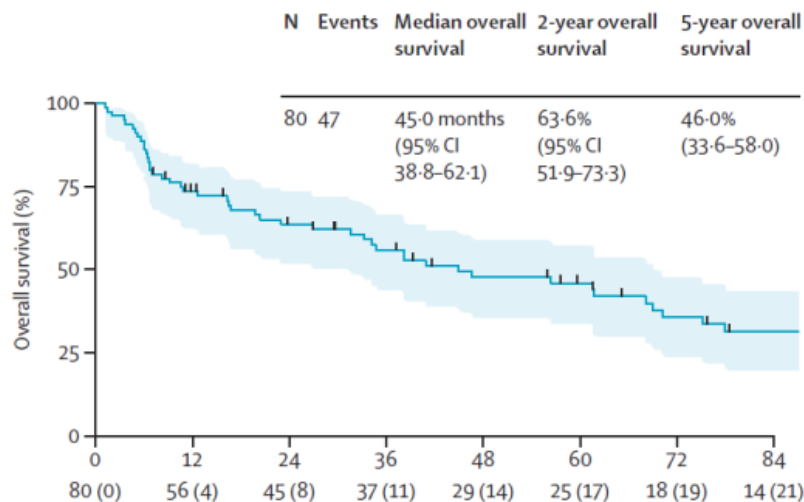
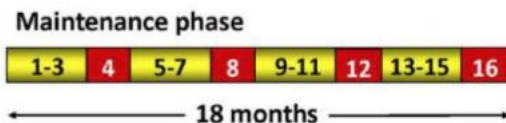
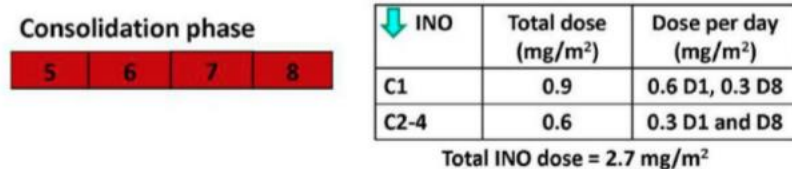
- OS rates were 91% and 73% at year 1 and year 3, respectively
- Cumulative incidence non-relapse mortality were 7% and 17% at 1 and 3 years, respectively
- **Median age 64 (56-80)**

EWALL-InO



- 1-years OS rate was 73% while 2-years OS rate was 55%
- Median age 68 (55-84)

Mini HCVD +Ino with/without Blina in older Ph-negative ALL



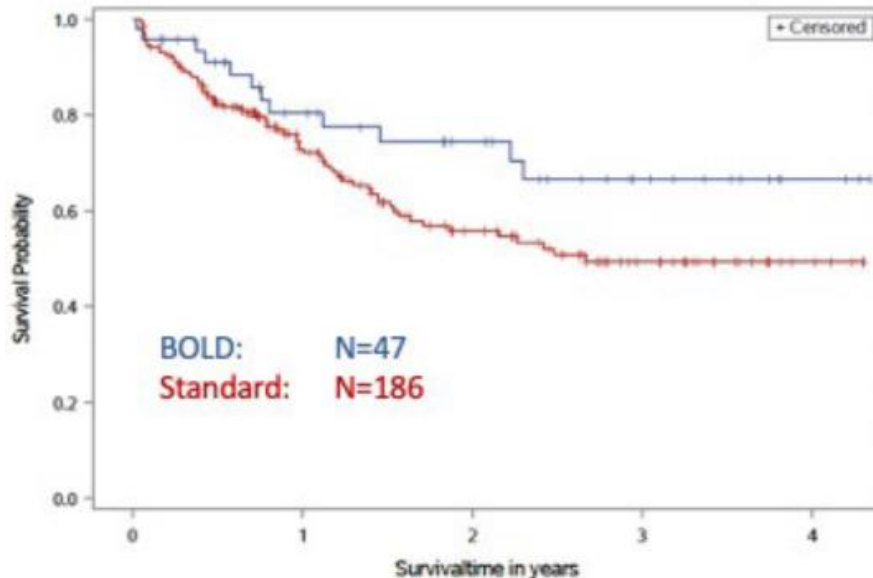
After a median FU of 92.8 mhs:

- 89% of patients achieved a CR while MRD negativity rate (94%)
- 2 years and 5 years OS were 63.6% and 46%, respectively
- **Median Age 68 (60-81)**

Dose reduced chemotherapy in sequence with Blinatumumab in older Ph-negative –ALL: results from GMALL-BOLD



Volume 142, Supplement 1, 2 November 2023, Page 964



	Induction I	Blina I
N Hematologic Response*	50	47
Hematologic CR	38 (76%)	40 (85%)
Early death	2 (4%)	2 (4%)
Failure/PR/Relapse	10 (20%)	5 (11%)
N Molecular Response**	34	37
Molecular CR	6 (18%)	28 (82%)
Molecular IMR	5 (15%)	2 (6%)
Molecular Failure	23 (68%)	4 (12%)

- Os after 1 and 3 – yrs was 80% and 67%, respectively
- Importantly, 3-yr OS was 81% for patients aged 55-65 and 55% for patients older than 65 yrs.
- From a comparison with GMALL SOC a longer 3-yr OS was showed (67% vs 49%)

Case 1 (continued)

- Patients was treated by GIMEMA LAL1913-like protocol
- He achieved a CR (MRD negativity)
- MRD was monitored by flow (sensitivity 10^{-5})
- At march 2026 maintenance interruption occurred due to a pancytopenia (secondary MDS?)

Case 2 (continued)

- The patient received treatment according to GIMEMA LAL 1104 protoco (PDN+VCR)
- He achieved a CR (MRD neg, $< 10^{-4}$) after induction
- He died after 6 months (MRD negative one month before)
- **If No CR, InO could be administered in order to achieve a CR**
- **If MRD persistence Blina could be administered subsequently**

Conclusions

