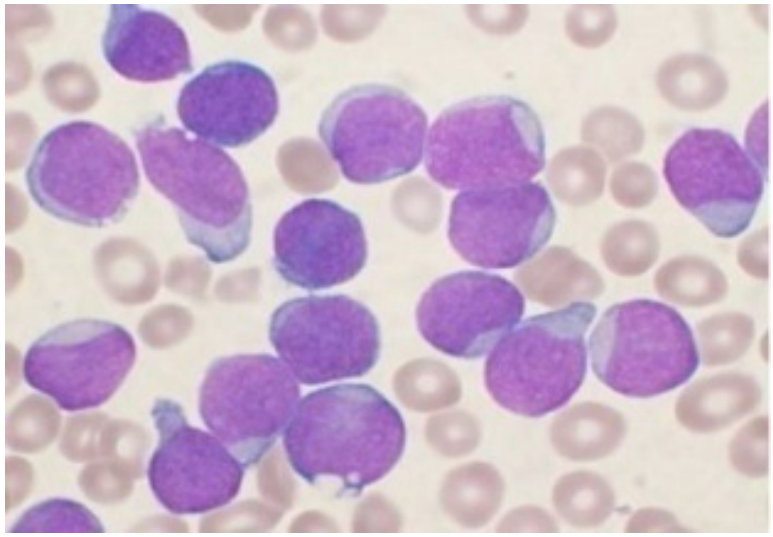

# CD22: Inotuzumab ozogamicin

Sabina Chiaretti, MD PhD

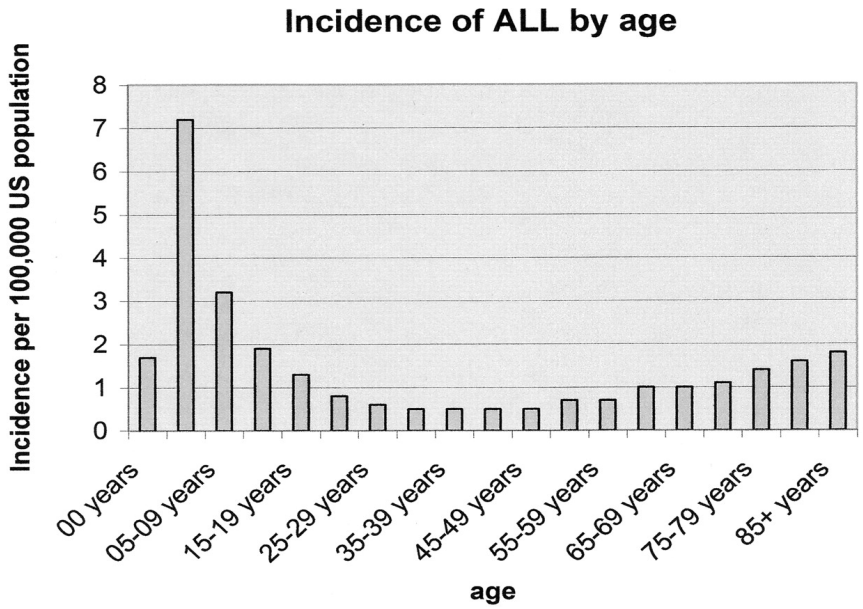
May 17th, 2018

Sapienza,University of Rome

# Acute lymphoblastic leukemia (ALL)



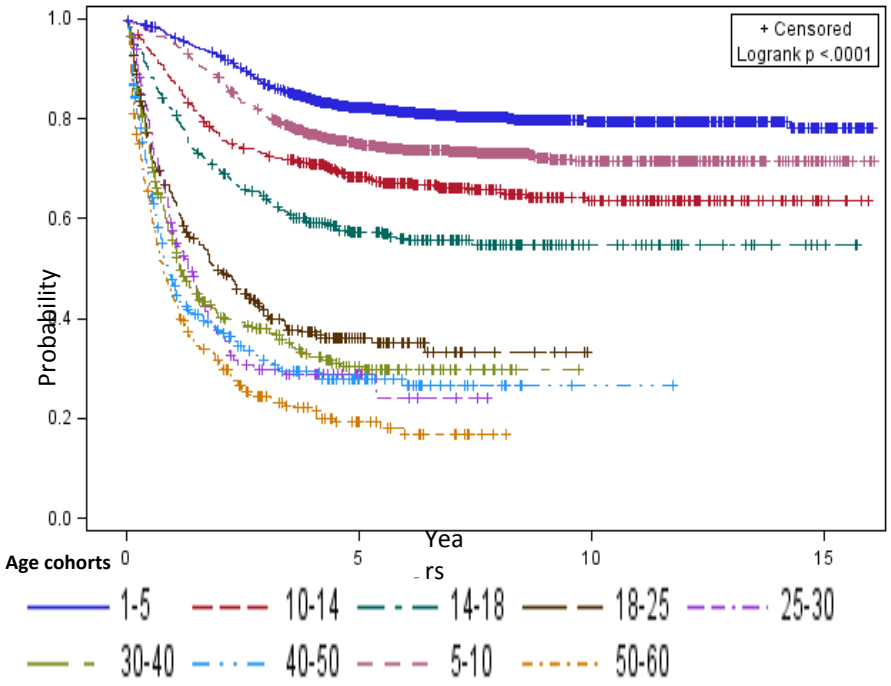
ALL is a malignant disorder characterized by the uncontrolled proliferation and accumulation of immature cells




ALL affects both children -being the most common neoplasm in childhood- and adults: highest incidence in children aged 2-5

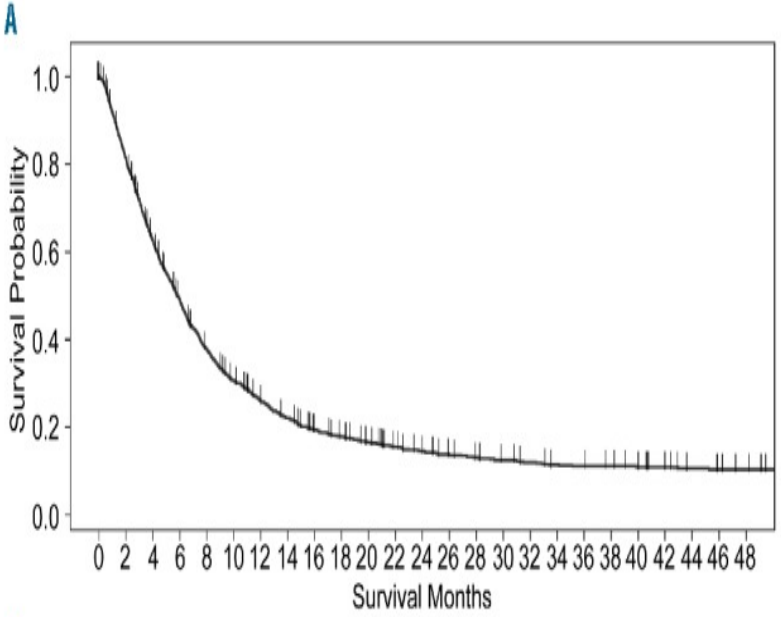
# Premises. Outcome of ALL

At diagnosis (5202 cases)




Chiaretti S et al. *Haematologica* 2013

At relapse (1618 cases)




Gökbuget N et al. *Haematologica* 2016.

Progressive worsening with age

Improvement in survival obtained with:
-Pediatric-inspired regimens
-MRD-driven intensification

Survival after relapse does not outreach 20-30%

After II CR achievement, allo-SCT is a must

Novel strategies required

# Monoclonal antibodies

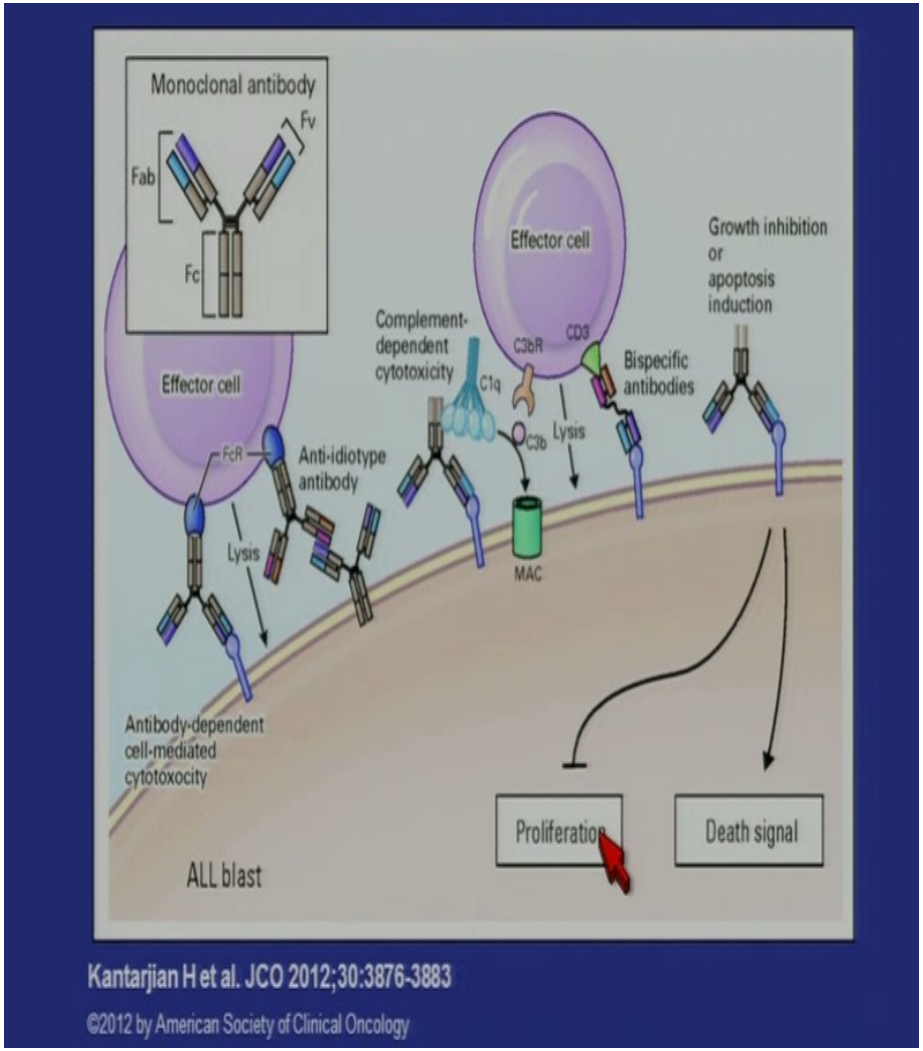
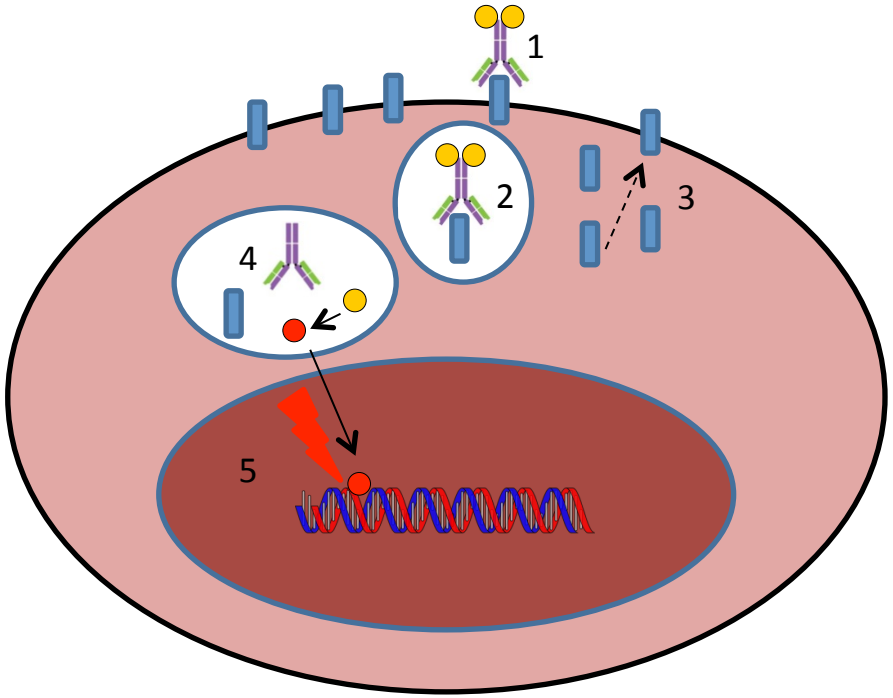



**Table 2** Monoclonal Antibodies for ALL

| Drug | Target | Comment |
|---|---|---|
| Rituximab (Rituxan) | CD20 | Improves overall survival in younger adults with de novo Ph– ALL |
| Ofatumumab (Arzerra) | CD20 | Binding site distinct from that of rituximab, may be beneficial |
| Epratuzumab | CD22 | Studied as part of combination chemotherapy in relapsed pediatric ALL |
| Inotuzumab | CD22 | Antibody-drug conjugate linked to the cytotoxin calicheamicin |
| Blinatumomab | CD19 | Bispecific antibody that engages CD3+ T cells and directs them to CD19+ B cells |
| SAR3419 | CD19 | Antibody-drug conjugate linked to the tubulin toxin maytansine |
| Alemtuzumab (Campath) | CD52 | Limited activity as a single agent in adults with refractory disease |

# Inotuzumab ozogamicin: not an immunotherapy!



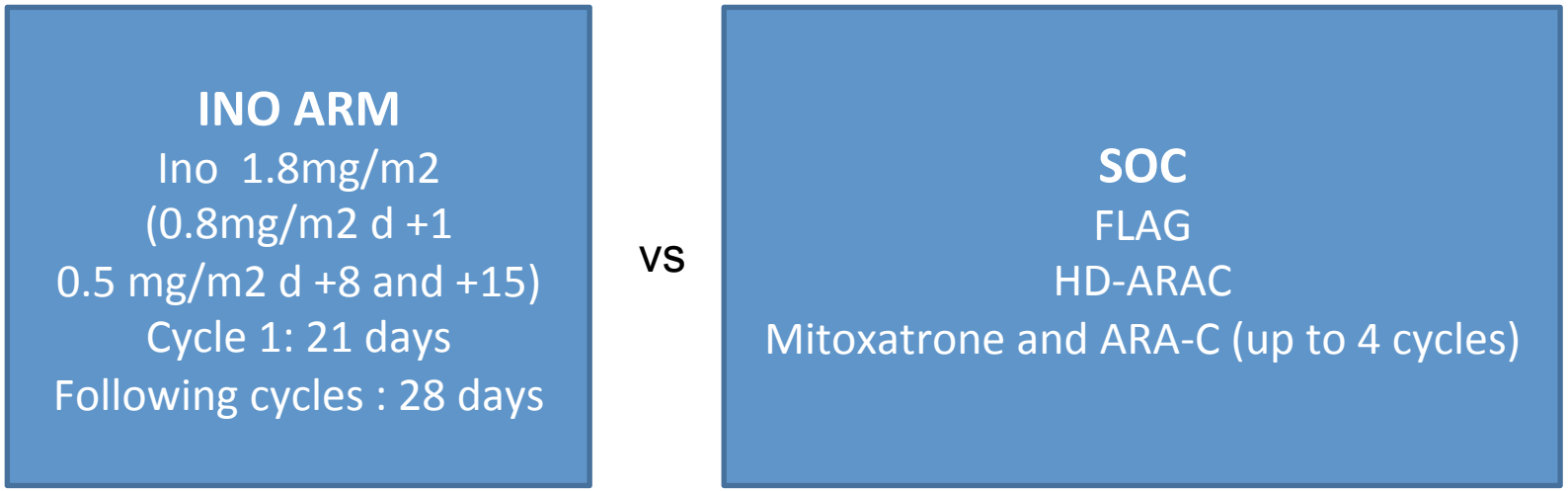

1) Inotuzumab binds to CD22; 2) the complex inotuzumab ozogamicin-CD22 is internalized; 3) CD22 is later re-expressed on lymphoblast surface; 4) calicheamicin is activated by the enzymatic action; 5) calicheamicin is transported in the nucleus, leading to DNA break and apoptosis

# Topics

- As salvage monotherapy
- As salvage therapy in combination
- In the front-line setting

# INO-VATE ALL

Phase III multi-center randomized studyfor R/R ALL




Median cycles received: 3

Median cycles received: 1

*Primary end points*: CR and OS

*Secondary end points*: safety measures, duration of remission, PFS, rate of SCT feasibility, and MRD negativity

Kantarjian et al, NEJM 2016

# INO-VATE ALL: patients

**Table 1. Baseline Patient Characteristics in the Remission-Analysis Population.***

| Characteristic | Inotuzumab Ozogamicin Group (N = 109) | Standard-Therapy Group (N = 109) |
|---|---|---|
| Age | | |
| Median (range) — yr | 47 (18–78) | 47 (18–79) |
| Distribution — no. (%) | | |
| <55 yr | 66 (61) | 69 (63) |
| ≥55 yr | 43 (39) | 40 (37) |
| Male sex — no. (%) | 61 (56) | 73 (67) |
| Race — no. (%)† | | |
| White | 76 (70) | 79 (72) |
| Asian | 17 (16) | 17 (16) |
| Black | 1 (1) | 2 (2) |
| Other | 15 (14) | 11 (10) |
| ECOG performance-status score — no. (%)‡ | | |
| 0 | 43 (39) | 45 (41) |
| 1 | 50 (46) | 53 (49) |
| 2 | 15 (14) | 10 (9) |
| Missing data | 1 (1) | 1 (1) |
| Salvage-treatment phase — no. (%) | | |
| First | 73 (67) | 69 (63) |
| Second | 35 (32) | 39 (36) |
| Missing data | 1 (1) | 1 (1) |
| Duration of first remission — no. (%) | | |
| <12 mo | 62 (57) | 71 (65) |
| ≥12 mo | 47 (43) | 38 (35) |
| Previous stem-cell transplantation — no. (%) | 17 (16) | 22 (20) |
| No. of previous induction therapies — no. (%) | | |
| 1 | 75 (69) | 69 (63) |
| 2 | 33 (30) | 39 (36) |
| 3 | 1 (1) | 1 (1) |
| Response to most recent previous induction therapy — no. (%) | | |
| Complete response | 78 (72) | 74 (68) |
| Partial response | 9 (8) | 7 (6) |
| Treatment-resistant disease | 17 (16) | 18 (17) |
| Progressive or stable disease | 4 (4) | 10 (9) |
| White-cell count — per $mm^3$ | | |
| Median | 3500 | 3800 |
| Range | 0–47,400 | 100–51,000 |
| Peripheral-blast count§ | | |
| Median — per $mm^3$ | 175.4 | 39.3 |
| Range — per $mm^3$ | 0–42,660 | 0–31,500 |
| Missing data — no. (%) | 1 (1) | 1 (1) |
| No circulating peripheral blasts — no. (%) | 42 (39) | 48 (44) |
| Bone marrow blasts — no. (%) | | |
| <50% | 30 (28) | 29 (27) |
| ≥50% | 77 (71) | 78 (72) |

**Table 1. (Continued.)**

| Characteristic | Inotuzumab Ozogamicin Group (N = 109) | Standard-Therapy Group (N = 109) |
|---|---|---|
| CD22 expression — no. (%)¶ | | |
| <90% | 24 (22) | 24 (22) |
| ≥90% | 74 (68) | 63 (58) |
| Missing data | 11 (10) | 22 (20) |
| Karyotype — no. (%)‖ | | |
| Normal** | 27 (25) | 23 (21) |
| Ph-positive | 14 (13) | 18 (17) |
| t(4;11)-positive | 3 (3) | 6 (6) |
| Other abnormalities | 49 (45) | 46 (42) |
| Unknown or missing data | 16 (15) | 16 (15) |

Based on ITT: 109 pts in each arm
Majority of patients in 1° or 2° salvage treatment

Ph+ ALL and t(4;11)+ representing about 20% of population for each arm

Kantarjian et al, NEJM 2016

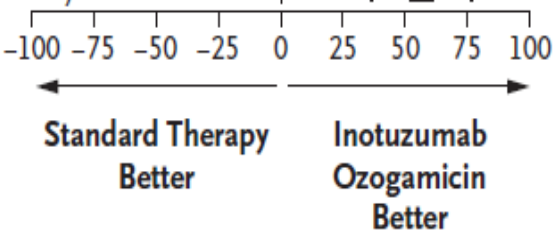
# INO-VATE ALL: Results

| Inotuzumab | SOC |
| --- | --- |
| Dose reduction: 12% | Dose reduction: 3% |
| Dose interruption for CR:35% | Dose interruption for CR: 15% |
| CR: 80.7% | CR:29.4% (33%) |
| MRD negativity in CR: 78.4% | MRD negativity in CR: 28.1% |
| SCT feasibility: 41% | SCT feasibility: 11% |

Kantarjian et al, NEJM 2016

# INO-VATE ALL: Results according to subgroups

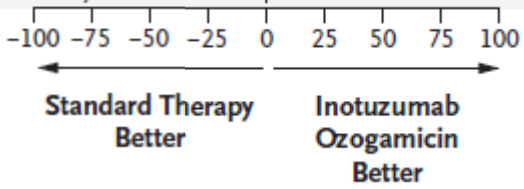
| | Inotuzumab Ozogamicin Group | Standard-Therapy Group | Complete Remission: Inotuzumab Ozogamicin Group | Complete Remission: Standard-Therapy Group | Between-Group Difference (97.5% CI) | P Value |
|---|---|---|---|---|---|---|
| | | | % (95% CI) | | percentage points | |
| All patients | 109 | 109 | 80.7 (72.1 to 87.7) | 29.4 (21.0 to 38.8) | 51.4 (38.4 to 64.3) | <0.001 |
| Duration of first remission | | | | | | |
| <12 mo | 71 | 71 | 77.5 (66.0 to 86.5) | 23.9 (14.6 to 35.5) | 53.5 (37.6 to 69.4) | <0.001 |
| ≥12 mo | 38 | 38 | 86.8 (71.9 to 95.6) | 39.5 (24.0 to 56.6) | 47.7 (25.8 to 69.0) | <0.001 |
| Salvage-treatment phase | | | | | | |
| First | 73 | 73 | 87.7 (77.9 to 94.2) | 28.8 (18.8 to 40.6) | 58.9 (44.2 to 73.6) | <0.001 |
| Second | 36 | 36 | 66.7 (49.0 to 81.4) | 30.6 (16.3 to 48.1) | 36.1 (11.5 to 60.7) | 0.002 |
| Age | | | | | | |
| <55 yr | 66 | 69 | 80.3 (68.7 to 89.1) | 31.9 (21.2 to 44.2) | 48.4 (31.7 to 65.1) | <0.001 |
| ≥55 yr | 43 | 40 | 81.4 (66.6 to 91.6) | 25.0 (12.7 to 41.2) | 56.4 (36.1 to 76.7) | <0.001 |




Kantarjian et al, NEJM 2016

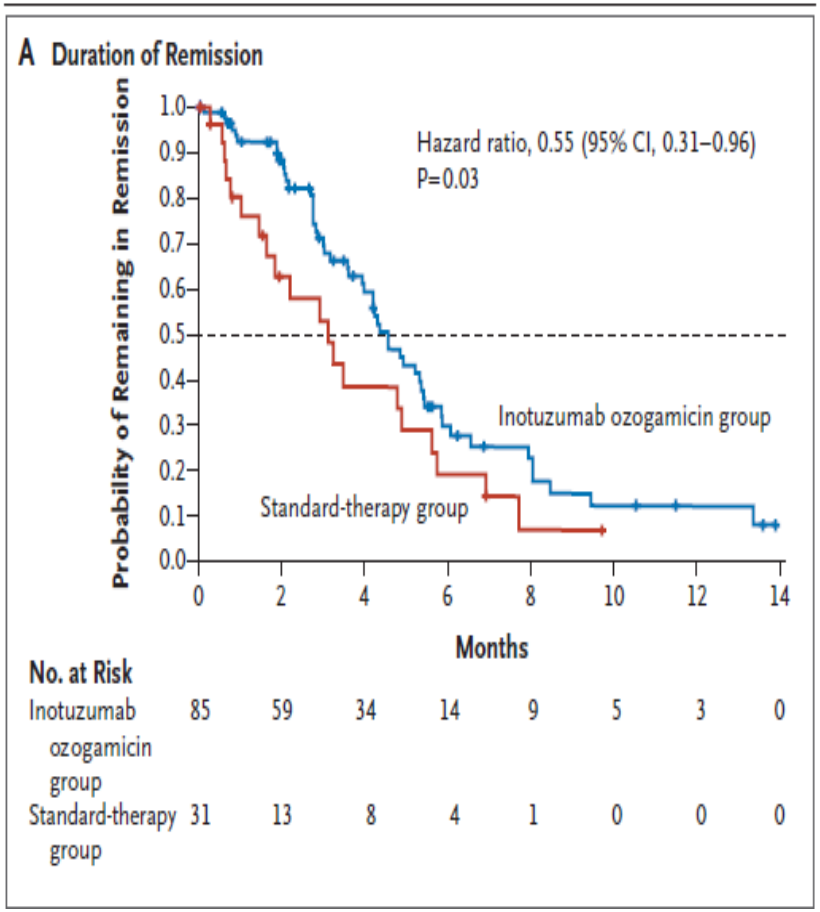
# INO-VATE ALL: Results according to subgroups

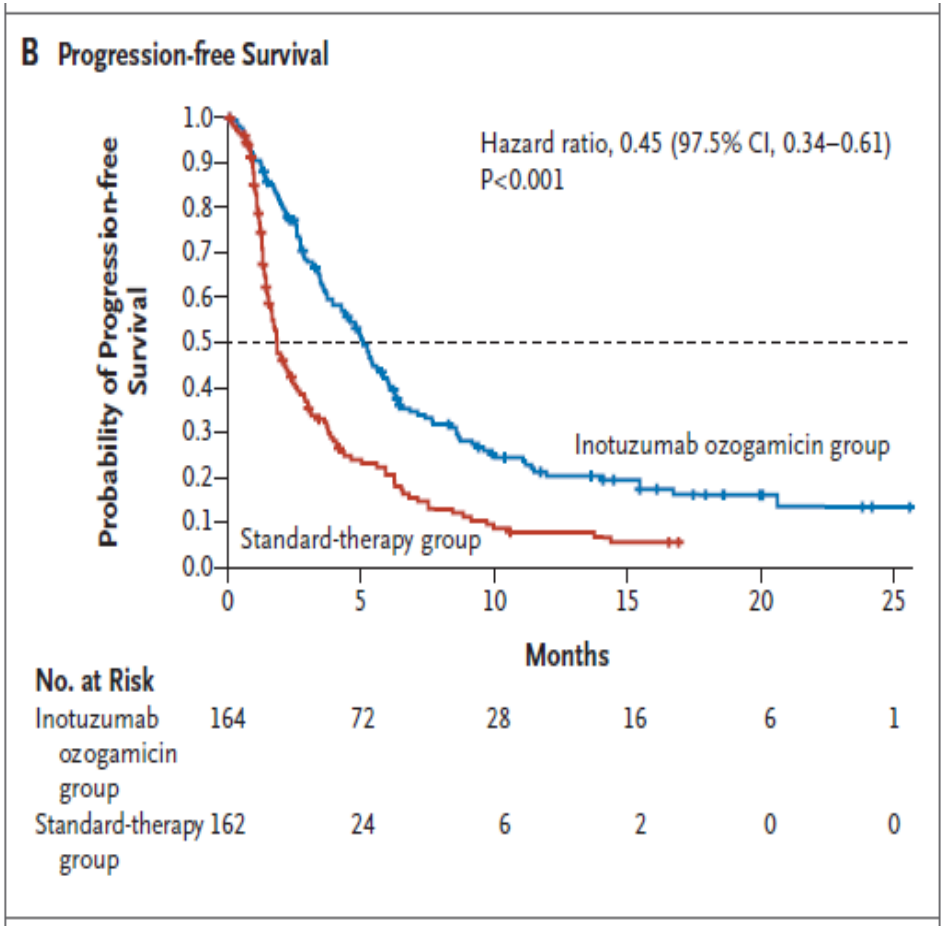
| Subgroup | No. of Patients | | Complete Remission | | Between-Group Difference (97.5% CI) | P Value |
|---|---|---|---|---|---|---|
| | Inotuzumab Ozogamicin Group | Standard-Therapy Group | Inotuzumab Ozogamicin Group | Standard-Therapy Group | | |
| | | | % (95% CI) | | percentage points | |
| All patients | 109 | 109 | 80.7 (72.1 to 87.7) | 29.4 (21.0 to 38.8) | 51.4 (38.4 to 64.3) | <0.001 |
| Peripheral blasts | | | | | | |
| 0 | 42 | 48 | 90.5 (77.4 to 97.3) | 41.7 (27.6 to 56.8) | 48.8 (29.9 to 67.7) | <0.001 |
| >0 to 1000 | 32 | 35 | 71.9 (53.3 to 86.3) | 20.0 (8.4 to 36.9) | 51.9 (28.5 to 75.3) | <0.001 |
| >1000 | 34 | 25 | 76.5 (58.8 to 89.3) | 20.0 (6.8 to 40.7) | 56.5 (32.2 to 80.7) | <0.001 |
| Bone marrow blasts | | | | | | |
| <50% | 30 | 29 | 86.7 (69.3 to 96.2) | 41.4 (23.5 to 61.1) | 45.3 (20.5 to 70.1) | <0.001 |
| ≥50% | 77 | 78 | 77.9 (67.0 to 86.6) | 24.4 (15.3 to 35.4) | 53.6 (38.4 to 68.8) | <0.001 |
| CD22 expression | | | | | | |
| <90% | 24 | 24 | 79.2 (57.8 to 92.9) | 25.0 (9.8 to 46.7) | 54.2 (27.0 to 81.3) | <0.001 |
| ≥90% | 74 | 63 | 82.4 (71.8 to 90.3) | 36.5 (24.7 to 49.6) | 45.9 (29.1 to 62.8) | <0.001 |
| Karyotype | | | | | | |
| Normal | 20 | 20 | 95.0 (75.1 to 99.9) | 30.0 (11.9 to 54.3) | 65.0 (39.6 to 90.4) | <0.001 |
| Ph-positive | 14 | 18 | 78.6 (49.2 to 95.3) | 44.4 (21.5 to 69.2) | 34.1 (−1.8 to 70.1) | 0.08 |
| t(4;11)-positive | 3 | 6 | 33.3 (0.8 to 90.6) | 33.3 (4.3 to 77.7) | 0.0 (−74.7 to 74.7) | 1.00 |
| Other abnormalities | 49 | 46 | 85.7 (72.8 to 94.1) | 26.1 (14.3 to 41.1) | 59.6 (41.3 to 78.0) | <0.001 |
| Previous stem-cell transplantation | | | | | | |
| Yes | 17 | 22 | 76.5 (50.1 to 93.2) | 27.3 (10.7 to 50.2) | 49.2 (17.8 to 80.6) | 0.004 |
| No | 92 | 87 | 81.5 (72.1 to 88.9) | 29.9 (20.5 to 40.6) | 51.6 (37.4 to 65.9) | <0.001 |




Kantarjian et al, NEJM 2016

# INO-VATE ALL: duration of remission and PFS



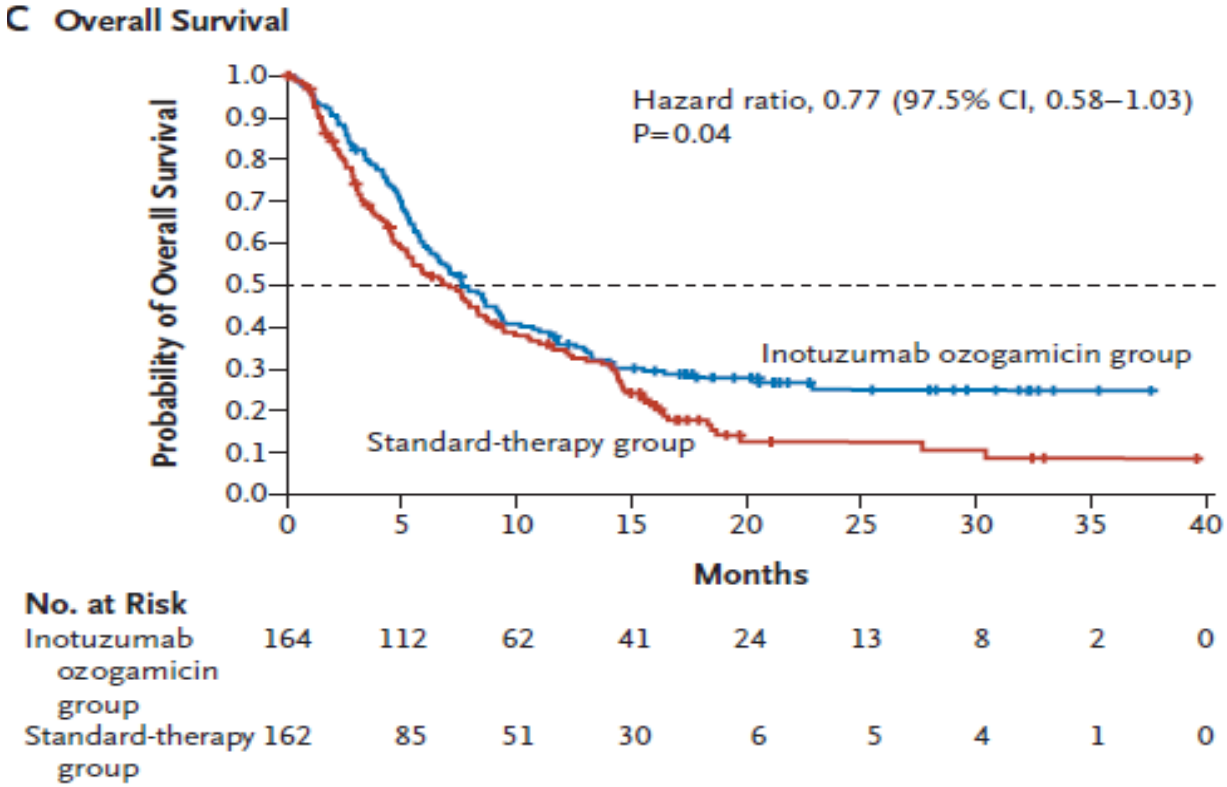




Median duration of remission: 4.6 months *vs* 3.1 months

Median PFS: 5.5 months *vs* 1.8 months

Kantarjian et al, NEJM 2016

# INO-VATE ALL: OS




Exploratory post-hoc analysis of restricted mean surival time applied

Median OS: 7.7 months *vs* 6.7 months

“ it was noted that the data for OS appeared to depart from the proportional-hazards assumption, as reflected by an apparent heterogeneity in the curve for standard therapy. Because of this, an exploratory post hoc analysis of restricted mean survival time was performed, which showed longer mean OS with inotuzumab ozogamicin than with standard therapy (P=0.005). On the basis of the apparent separation of the overall survival curves after approximately 14 months, it may be speculated that the survival benefit occurs at later time points”.

# Hepatic toxicity after inotuzumb: a concern

| | Ino arm (n=109) | | SOC arm (n=120) | |
|---|---|---|---|---|
| | Any grade (%) | Grade ≥ 3 (%) | Any grade (%) | Grade ≥ 3 (%) |
| Febrile neutropenia | 16 (12) | 15 (11) | 22 (18) | 21 (18) |
| VOD | 15 (11) | 13 (9) | 1 (1) | 1 (1) |
| Sepsis | 3 (2) | 3 (2) | 6 (5) | 6 (5) |

Liver-related adverse events of any grade:
Increased aspartate aminotransferase level: 20% of Ino and 10% of SOC patients
Hyperbilirubinemia: 15% of Ino and 10% of SOC patients
Increased alanine aminotransferase level: 14% of Ino and 11% of SOC patients
VOD: 15 patients (11%) up to 2 years after randomization, 10 had veno-occlusive disease after transplantation.

Kantarjian et al, NEJM 2016

# Inotuzumab and allo-SCT (I)

**Aim**: to identify factors associated with outcomes after allo-SCT in prev treated R/R ALL pt with InO.

**Background and population**: Phase 3 INO-VATE trial; InO n=77; SOC n=31

**Results:**

-More InO pts achieved $MRD^{neg}$ (71%) vs control group(26%)

-Less InO group received add therapy before HSCT(14% vs 55%)

-NRM rates were higher in InO group at 1yr (36% vs 20%) and at 2yrs (39% vs 31%) but relapse rate were lower both at 1yr (23% vs 29%) and 2yrs (33% vs 46%)

-No significant difference in post allo-SCT survival observed among groups.

**VOD** observed in 5 pts (all during the first 100 days after allo-SCT) InO and 0 in SOC group.

**Conclusions**:

- Compared with the SOC, InO permitted more pts with R/R ALL to proceed to allo-SCT in CR/Cri with MRDneg
- In order to reduce NRM and improve OS avoid dual alkylator conditionings regimens, especially those containing Thiotepa.

Stellijesn et al, EHA 2017 abs#P525

# Inotuzumab and allo-SCT (II)

- **Aim**: to investigate transplant outcomes for pts with or without InO exposure.
- **Method**: Nested control comparison of pts transplanted during the year in which they recived InO.
- **Population**: 251 pts with B-ALL (median age 35yr; range 4-70) who received allo-SCT
- **Results**:
  - VOD: 21 pts (8%); median onset 19 days following allo-SCT;
  - Fatal VOD: in 5 overall pts (2%),

***Factors contributing to VOD***

- Prior exposure to InO (HR 3.05, 95% C.I. 1.3-7.2, p=0.01)
- Receiving a busulfan-based transplant preparative regimen (HR 3.4, 95% C.I. 1.02-12, p=0.05).

***Protective factors to VOD***

- Not receving a prior SCT (HR 0.3, 95% C.I. 0.1-0.8, p=0.02).

Classification and regression tree analysis show that the combination of InO and a double alkylator preparative regimen was significantly associated with VOD(HR 5.9, 95% C.I. 1.9-18, p=0.002).

Kebriaei et al, EHA 2017 abs #P739

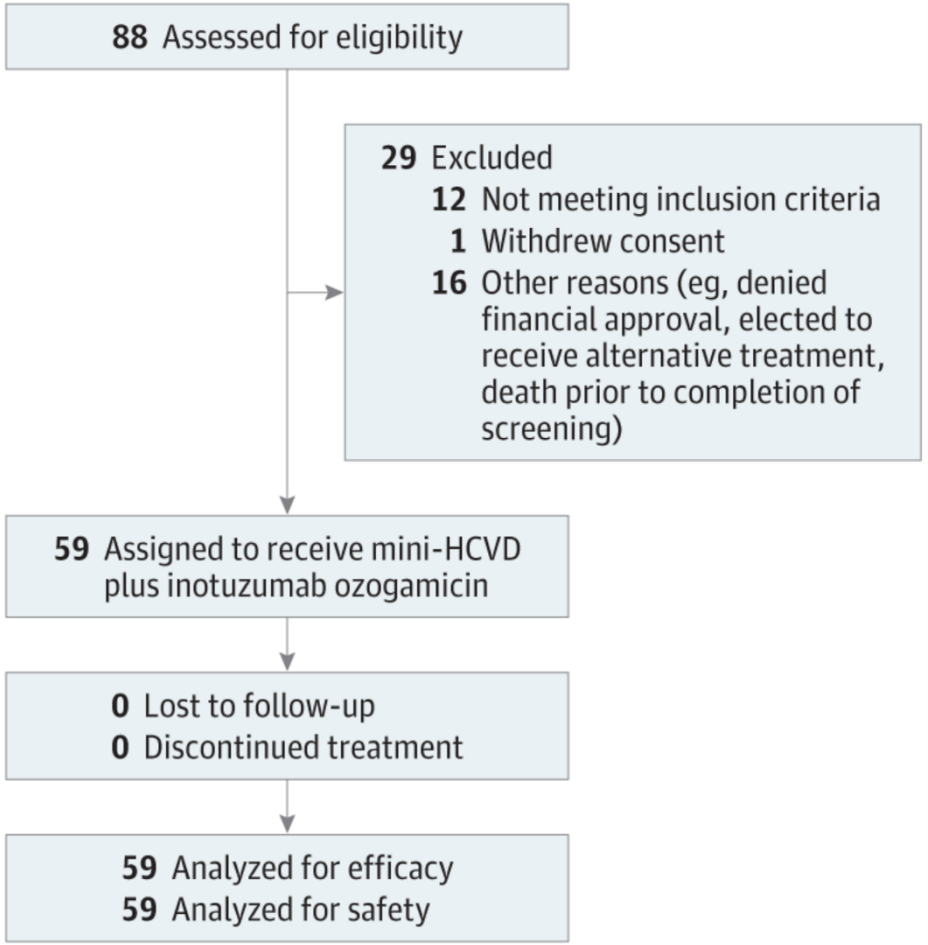
# Topics

- As salvage therapy in combination

# Mini-HCVD + inotuzumab

**Treatment scheme:**
Mini-HCV+ inotuzumab (and rituximab)

Amended dose:
(1.3 mg/m$^2$ for cycle 1; 1 mg/m$^2$ for cycles 2-4)




| Characteristic | Category | N (%)/ Median [range] |
|---|---|---|
| Age (years) | | 35 [18-87] |
| Gender | Male | 29 (49) |
| ECOG performance status | ≥2 | 7 (12) |
| WBC (x $10^9$/L) | Median | 3.7 [0.1-194.7] |
| | ≥50 | 1 (2) |
| PB blasts percentage | | 4 [0-93] |
| BM blasts ≥50% | | 42 (71) |
| Karyotype | Diploid | 12 (20) |
| | MLL | 10 (17) |
| | Miscellaneous | 28 (47) |
| | ND/IM | 9 (15) |
| CD22 expression | Median | 95 [20-100] |
| CD20 expression | ≥20% | 12 (20) |
| Prior ASCT | | 15 (25) |
| Salvage status | Salvage 1 | 33 (56) |
| | Salvage 1, primary refractory | 5 (8) |
| | Salvage 1, CRD1 <12 months | 15 (25) |
| | Salvage 1, CRD1 ≥12 months | 13 (22) |
| | Salvage 2 | 13 (22) |
| | ≥Salvage 3 | 13 (22) |

ECOG= Eastern Cooperative Oncology Group; BM=bone marrow; WBC=White blood

Jabbour et al, *JAMA Oncology*, 2018

# Mini-HCVD + inotuzumab

CR: 35 patients (59%)

ORR: 46 patients (78%)

Toxicity:

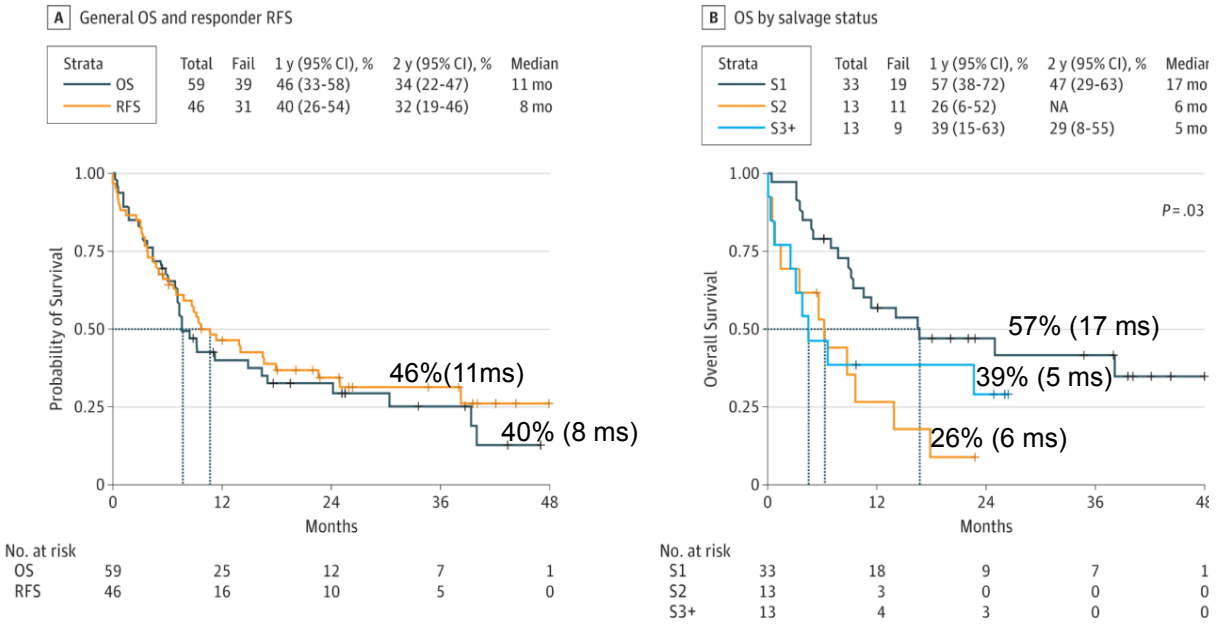
Thrombocytopenia: 81%

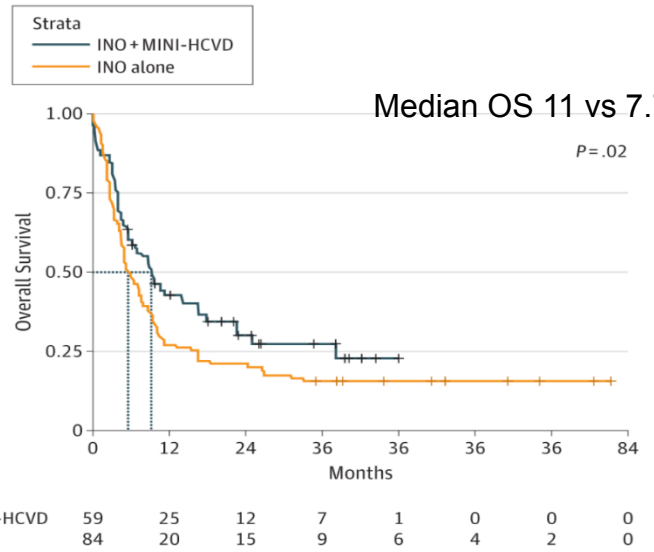
Liver toxicity: 95%

VOD: 15% (median of 3 cycles)

Toxicity higher than Ino alone

Median follow-up: 1 year




Jabbour et al, JAMA Oncology, 2018

# Topics

- In the front-line setting

# Inotuzumab in the front-line setting: elderly

- 52 patients (median age: 68 years) treated with mini-hyper-CVD; 48 “treatment-naive”
- 47 (98%) achieved a response; MRD (flow-cytometry) negativity: 78% upon induction and 96% within 3 cycles
- Median follow-up: 29 months
- Grade 3–4 AEs: thrombocytopenia: 81%

  infections during induction: 52% and consolidation: 69%, VOD: 8%.
- 12 deaths in CR

Kantarjian et al, *Lancet Oncology* 2018

# Inotuzumab in the front-line setting: elderly

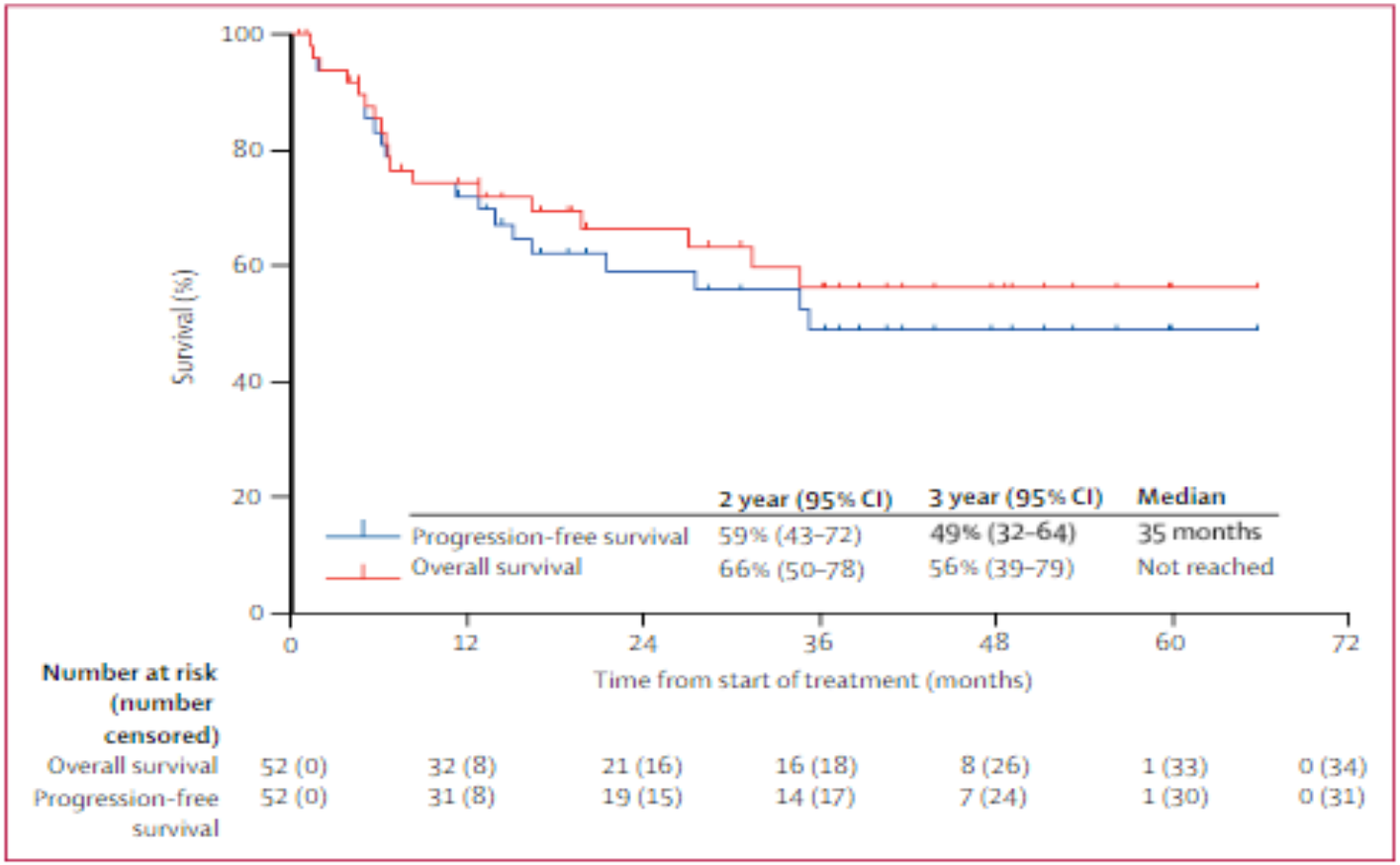



*Figure 2*: Progression-free and overall survival

Kantarjian et al, Lancet Oncology 2018

# Concluding remarks and open points

- Monoclonal antibodies are changing the natural history of ALL; in the R/R setting better survival and higher HSCT feasibility.
- Toxicity, different from historical ones, must be considered
- Earlier use (MRD, front-line) ➡ Less CHT needed? Less HSCT?? cure???
- The solution for elderly/unfit patients?
- Should we start thinking combining Moabs??
- While there an impressive development in B-ALL, in T-ALL few molecules.