Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

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*Scientific Board:*
**Marco Ladetto** (Alessandria)
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# How I treat relapsed/refractory ALL

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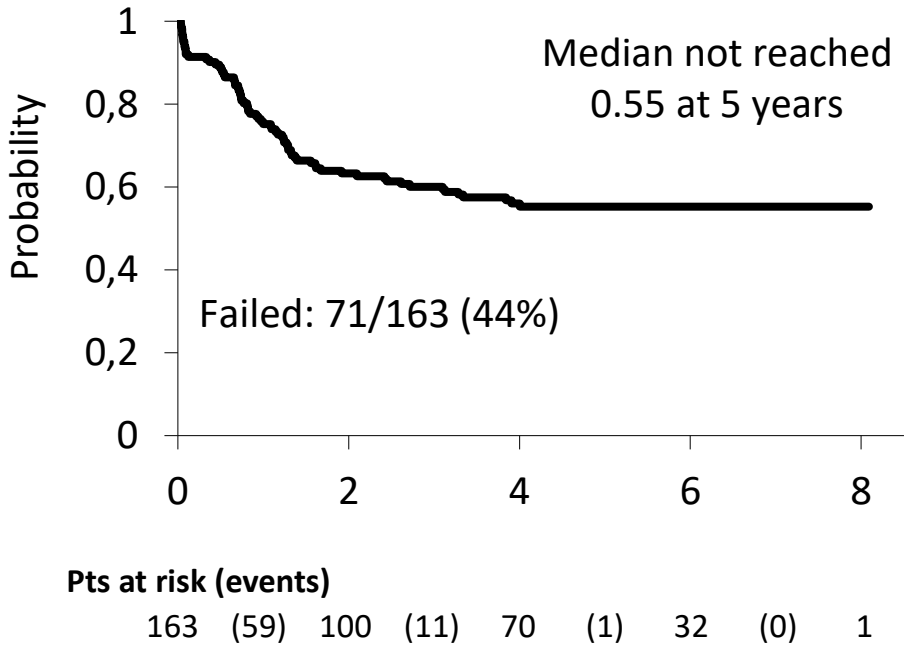
# The NILG study 10/2007 a prospective, MRD-based clinical trials in Ph-*ve* ALL

| | ALL (Ph-) n=163 |
|---|---|
| **CR** | 142 (87%) |
| **NR** | 7 (4%) |
| **ED** | 14 (9%) |

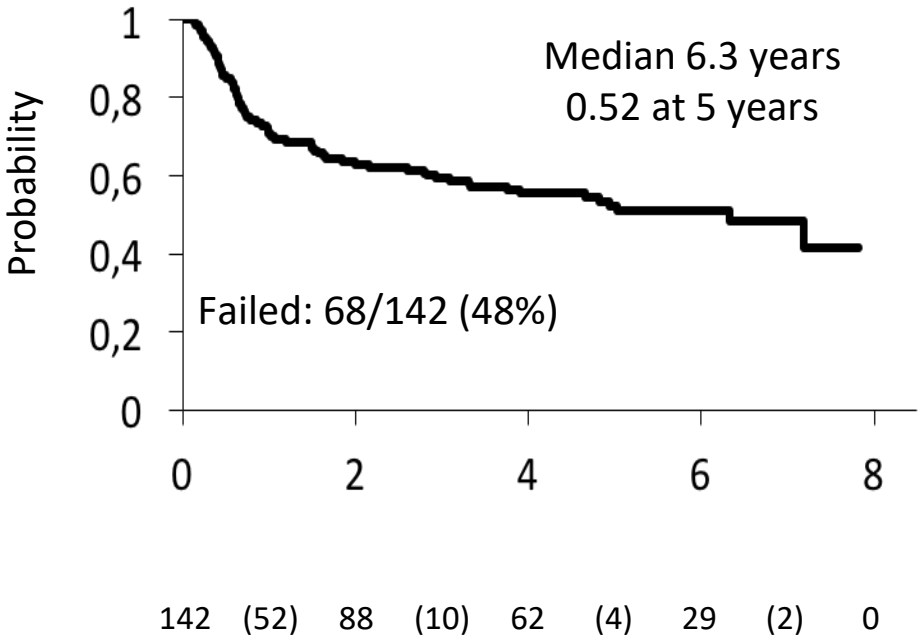
**Overall Survival**




**Pts at risk (events)**

163 (59) 100 (11) 70 (1) 32 (0) 1

**Disease-free Survival** (CR pts.)




142 (52) 88 (10) 62 (4) 29 (2) 0

# Chemotherapy for Relapsed/Refractory ALL

- **Ideal regimen is not known** and depends upon timing of relapse:
  - If relapse >2 years in CR: **induction regimen similar to newly diagnosed treatments**
  - Primary resistant disease/relapse during chemo: **reinduction with novel treatments**
  - After 2ndCR, allogeneic transplant should be performed ASAP

- **Single-agent therapy**
  - Liposomal vincristine (*Ph-neg ALL that has failed 2 prior treatments)*
  - Clofarabine (*ages 1-21 years that has failed 2 prior treatments*)
  - Nelarabine (*relapsed T-ALL that has failed 2 prior treatments*)

- **Multiple-agent chemotherapy regimens:**
  - MOpAD, Hyper-CVAD, BFM, etc

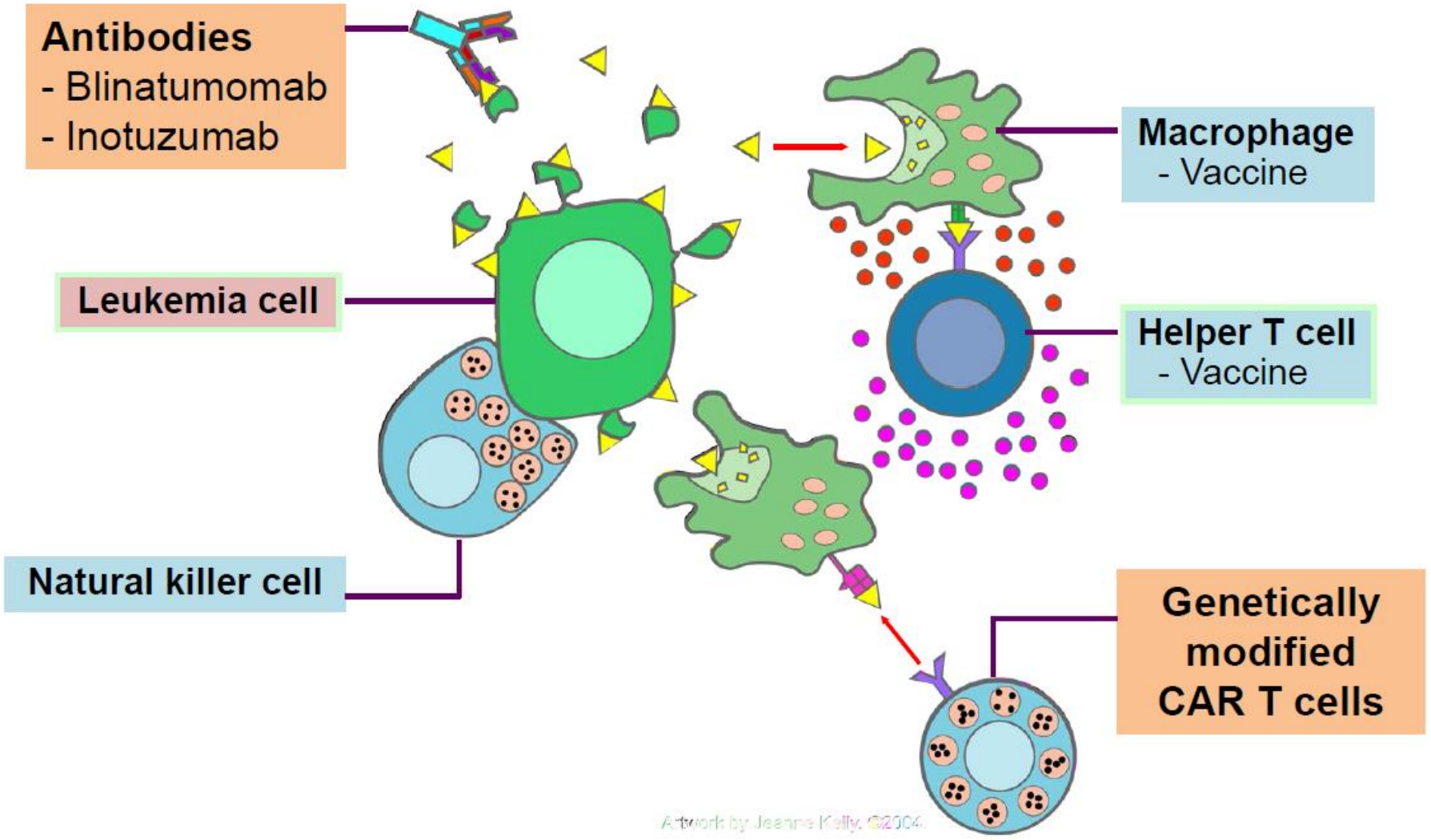
# Chemotherapeutic Efficacy in Relapsed/Refractory Adult ALL

| Setting | CR Rates, % | Median OS, Mos |
|---|---|---|
| First relapse[1-5] | 30-45 | 5 - 9 |
| Primary refractory disease, short CR,* or relapse after HCT[2,3] | 20-30 | 3 - 6 |
| Second relapse[6-7] | 18-20† | 3 - 4.6 |

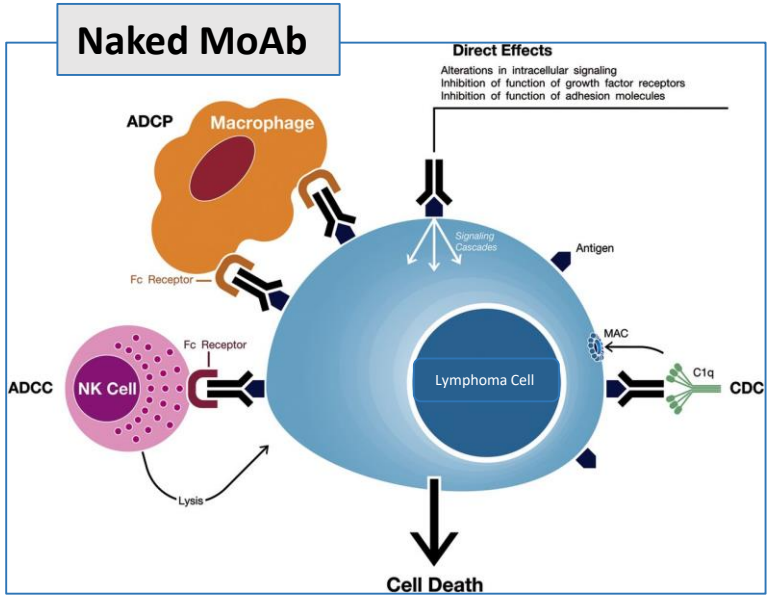
*CR < 12 mos.
†CR + CRi.

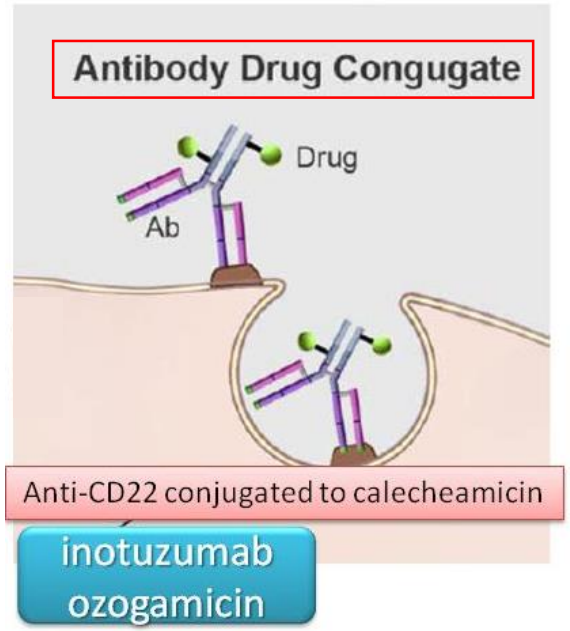

1. Fielding AK, et al. Blood 2007;109:944-950.
2. Gökbuget N, et al. Blood. 2012;120:2032-2041.
3. Kantarjian HM, et al. Blood. 2010;116:5568-5574.
4. Oriol A, et al. Haematological. 2010;95:589-596.
5. Tavernier E, et al. Leukemia. 2007;21:1907-1914.
6. O'Brien S, et al. Cancer. 2008; 113:3186-2191.
7. O'Brien et al. J Clin Oncol. 2013;31:676-683.

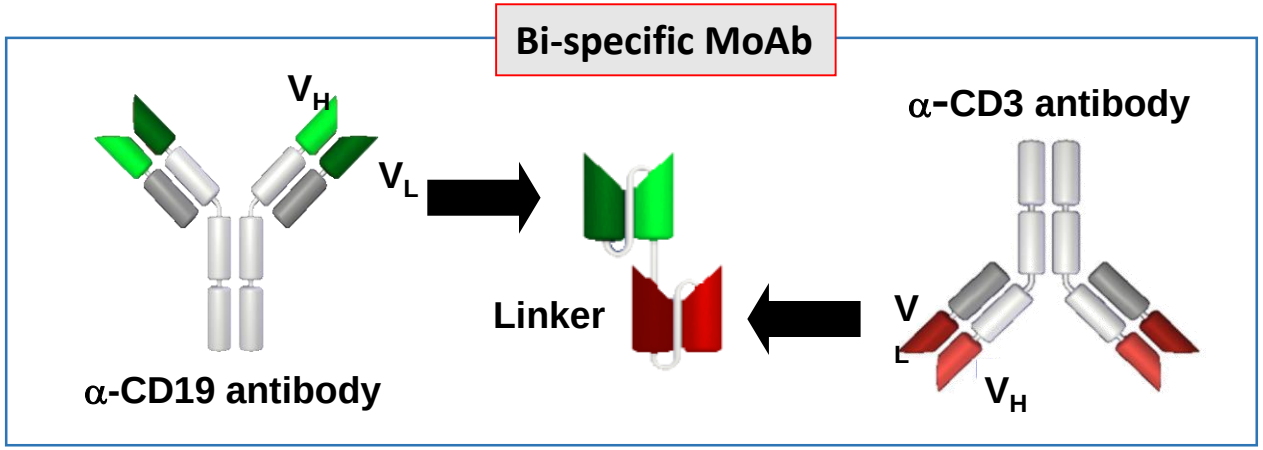
# Harnessing the Immune System for ALL Therapy



# Types of MoAbs already used for the treatment of ALL



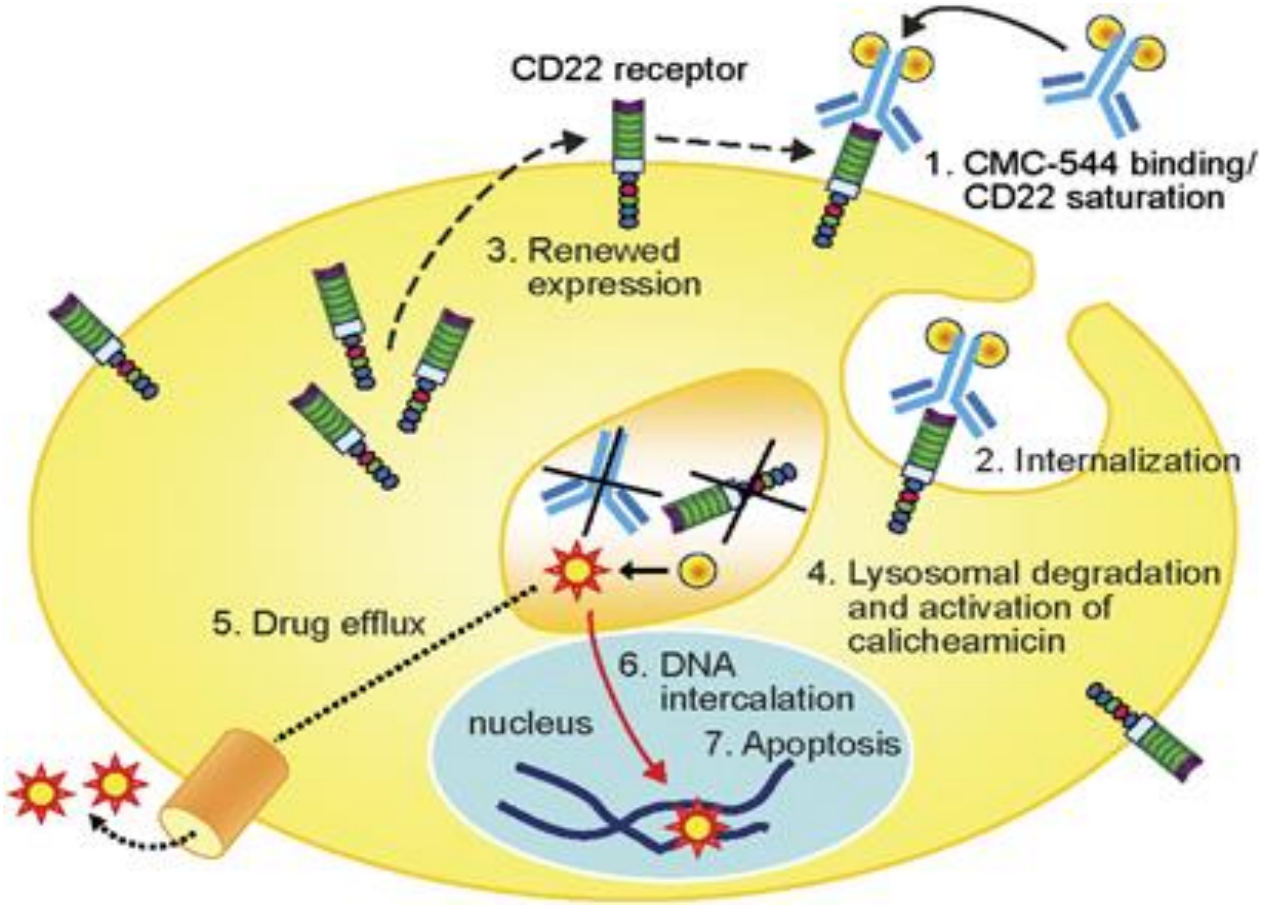



# MoAb in ALL
## *Summary of known data (2018)*

| Agent | R/R | MRD+ | Untreated |
|---|---|---|---|
| Rituximab (CD20) | - | - | + |
| Ofatumumab (CD20) | - | - | + |
| Inotuzumab ozogamicin (CD22) | + (incl. Phase III) | planned | + |
| Blinatumomab (CD19/CD3) | + (incl. Phase III) | + | (+) ongoing |

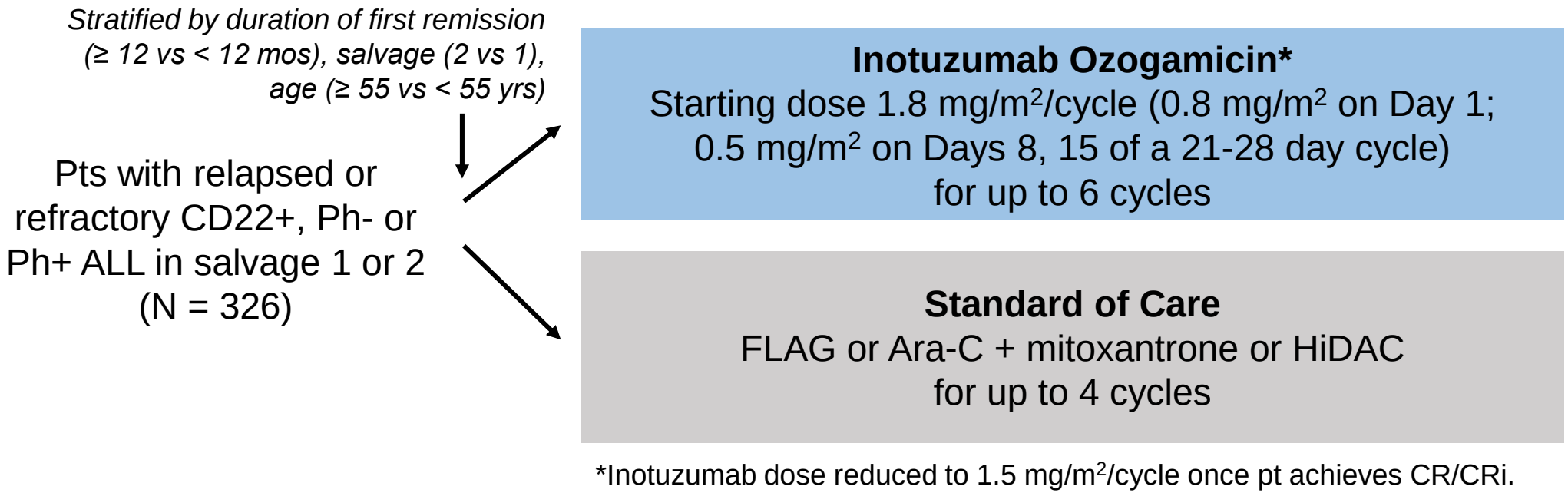
# The anti-CD22 Drug Conjugate Inotuzumab Ozogamicin MoAbs




JF de Vries, Leukemia 2012

# Phase III INO-VATE: Inotuzumab vs SoC in Relapsed/Refractory CD22+ ALL

- Multicenter, randomized, open-label phase III study




*Inotuzumab dose reduced to 1.5 mg/m$^2$/cycle once pt achieves CR/CRi.

- Primary endpoints: CR/CRi and OS
- Secondary endpoints: MRD negativity, DoR, PFS, HSCT rate, safety

# INO-VATE: Pt Characteristics

| Characteristic | InO (n = 164) | SoC (n = 162) |
|---|---|---|
| **Median age, yrs (range)** | **47 (18-78)** | **48 (18-79)** |
| Salvage status, n (%) | | |
| ▪ **1** | **111 (68)** | **104 (64)** |
| ▪ 2 | 51 (31) | 57 (35) |
| Duration of CR1, n (%) | | |
| ▪ < 12 mos | 98 (60) | 108 (67) |
| ▪ **≥ 12 mos** | **66 (40)** | **54 (33)** |
| **Prior HSCT, n (%)** | **28 (17)** | **29 (18)** |
| Median WBC, $10^3$ cells/$mm^3$ (range) | 4.1 (0-47.4) | 4.0 (0.1-68.8) |

| Characteristic | InO (n = 164) | SoC (n = 162) |
|---|---|---|
| Bone marrow blasts, n (%) | | |
| ▪ < 50% | 53 (32) | 48 (30) |
| ▪ ≥ 50% | 109 (67) | 113 (70) |
| ▪ Missing | 2 (1) | 1 (1) |
| Karyotype, n (%) | | |
| ▪ Normal | 46 (28) | 42 (26) |
| ▪ **Ph+** | **22 (13)** | **28 (17)** |
| ▪ t(4;11) | 6 (4) | 7 (4) |
| ▪ Complex | 27 (16) | 22 (14) |
| ▪ Other/unknown/missing | 63 (38) | 63 (39) |

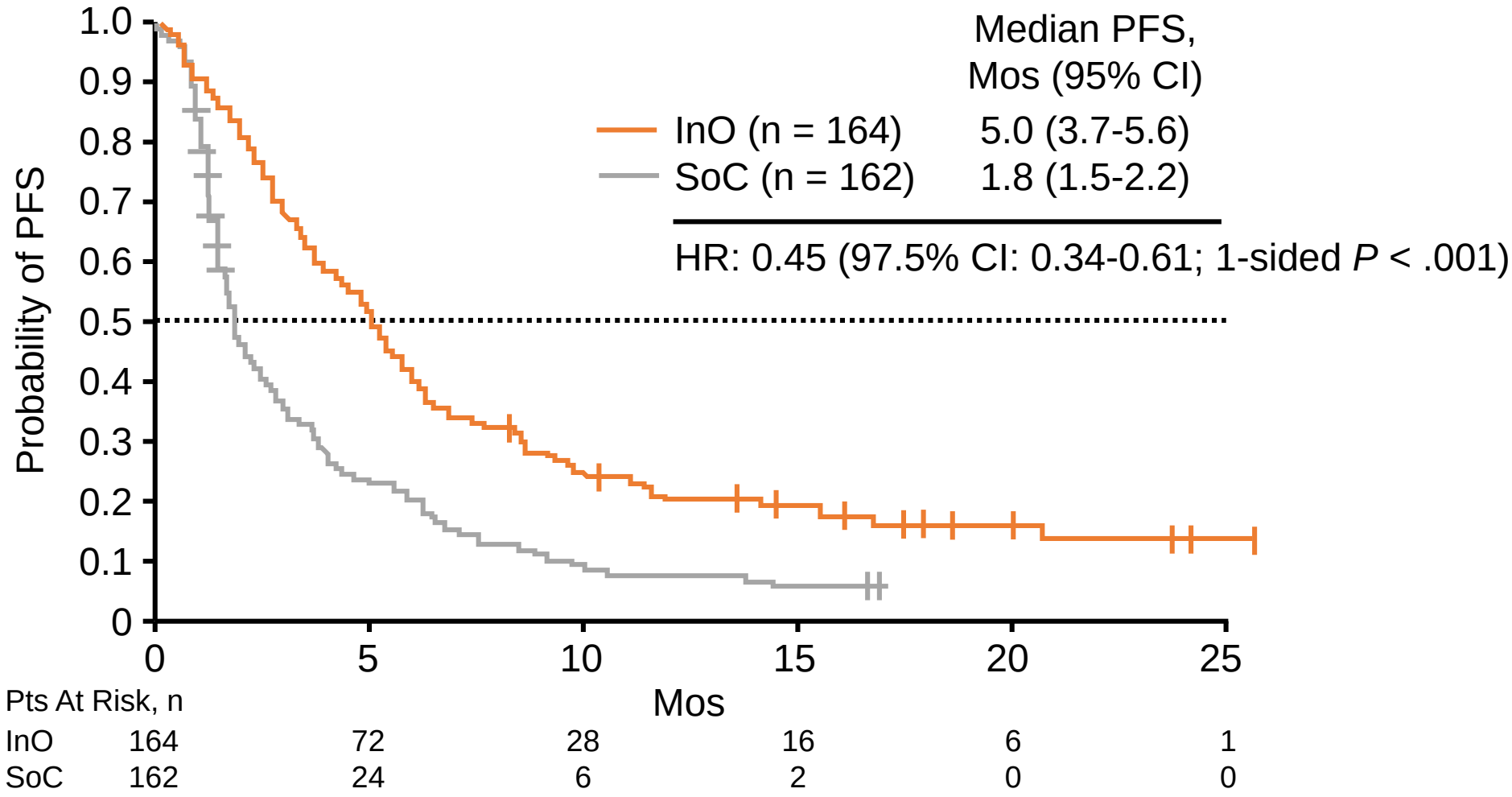
# INO-VATE: CR/CRi of Remission-Analysis Population

Remission analysis population: first 218 pts randomized in the ITT population

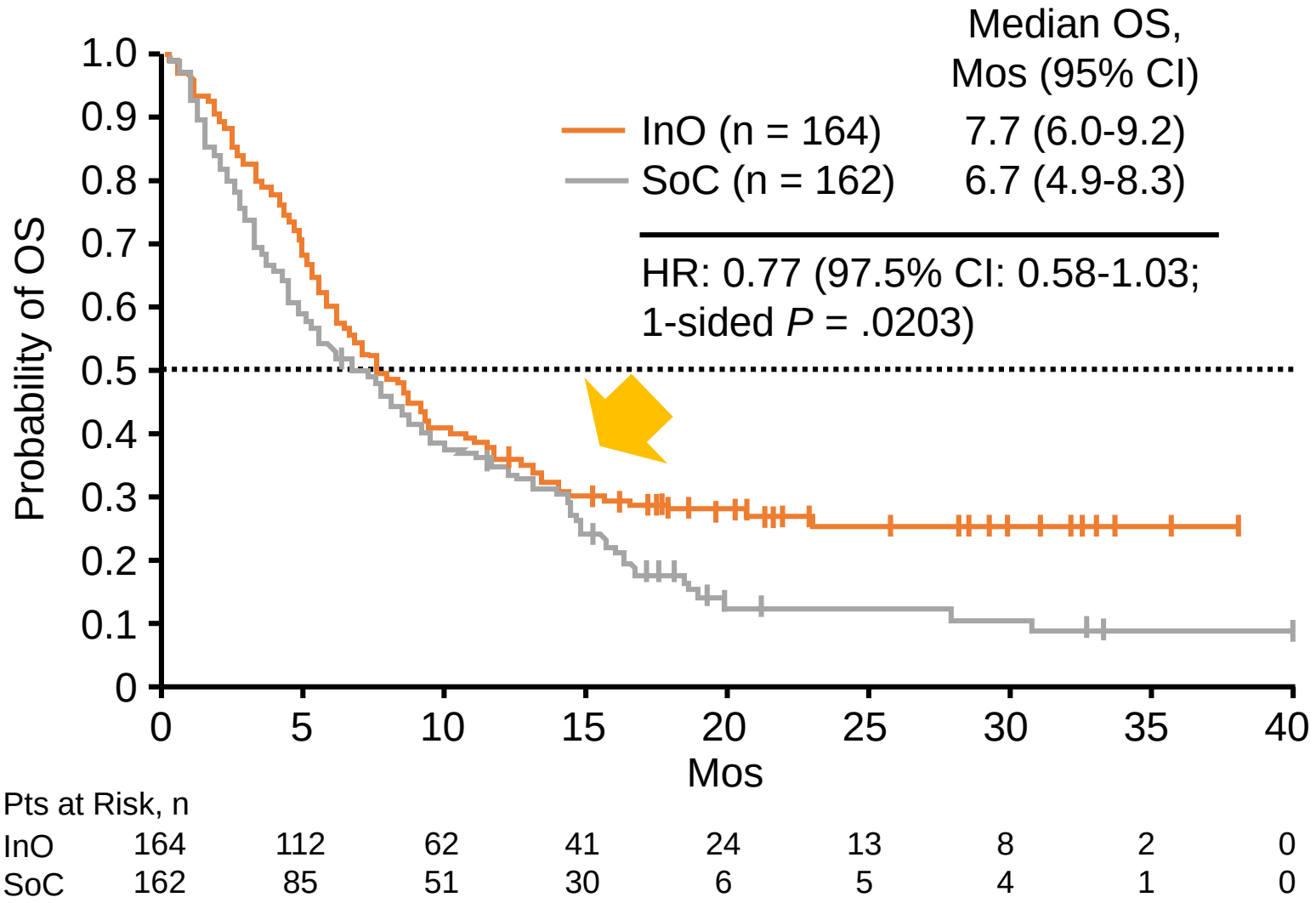
| Response, % (95% CI) | InO (n = 109) | SoC (n = 109) | 1-Sided *P* Value |
|---|---|---|---|
| CR/CRi | 80.7 (72.1-87.7) | 29.4 (21.0-38.8) | < .0001 |
| MRD negative | 78.4 (68.4-86.5) | 28.1 (13.7-46.7) | < .0001 |

Among this population, more than 4x the number of pts achieved CR/CRi and proceeded directly to HSCT with inotuzumab vs SoC (n = 41/109 [38%] vs n = 10/109 [9%]; *P* < .0001)

# INO-VATE: PFS


Median PFS, Mos (95% CI)
InO (n = 164) 5.0 (3.7-5.6)
SoC (n = 162) 1.8 (1.5-2.2)
HR: 0.45 (97.5% CI: 0.34-0.61; 1-sided P < .001)
Probability of PFS
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
Mos
Pts At Risk, n
InO 164 72 28 16 6 1
SoC 162 24 6 2 0 0

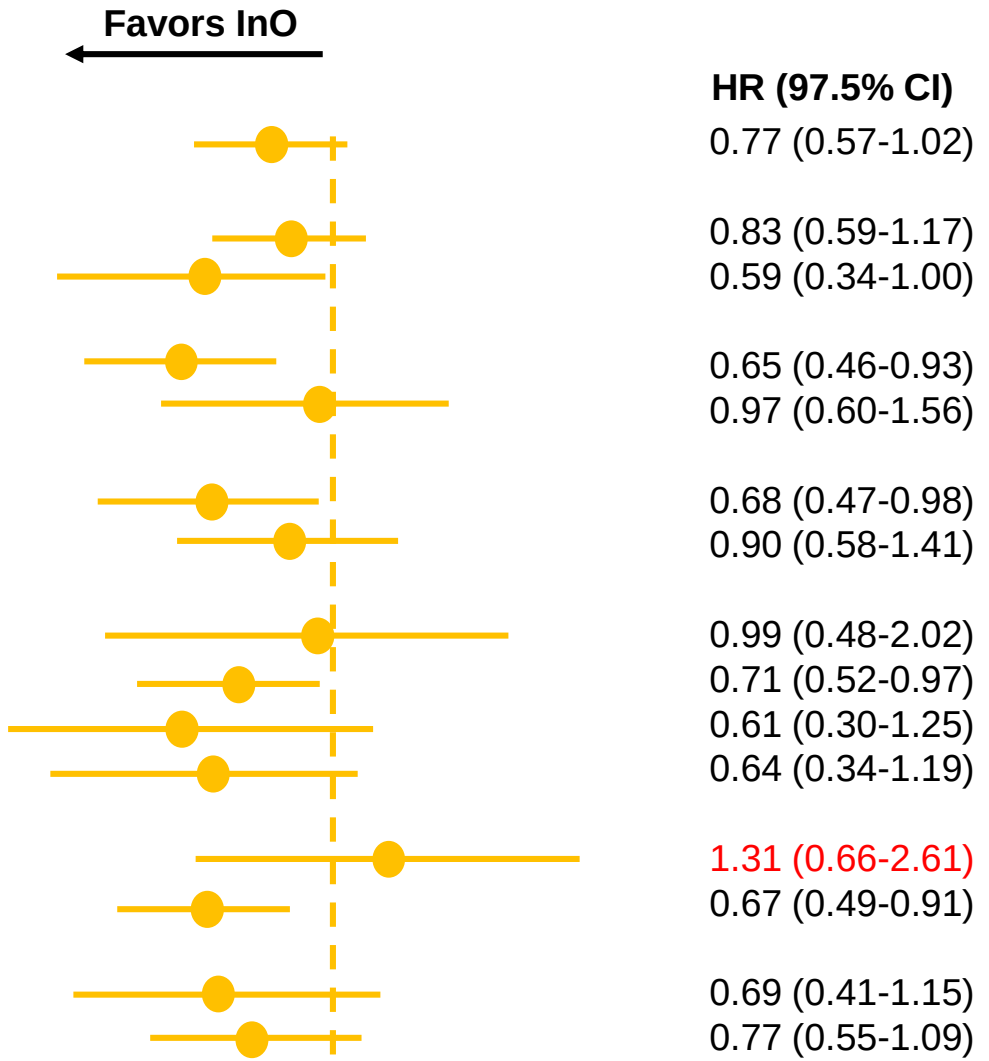
# INO-VATE: OS




- 2-yr OS probability higher with InO vs SoC
  - 23% (95% CI: 16-30) vs 10% (95% CI: 5-16)

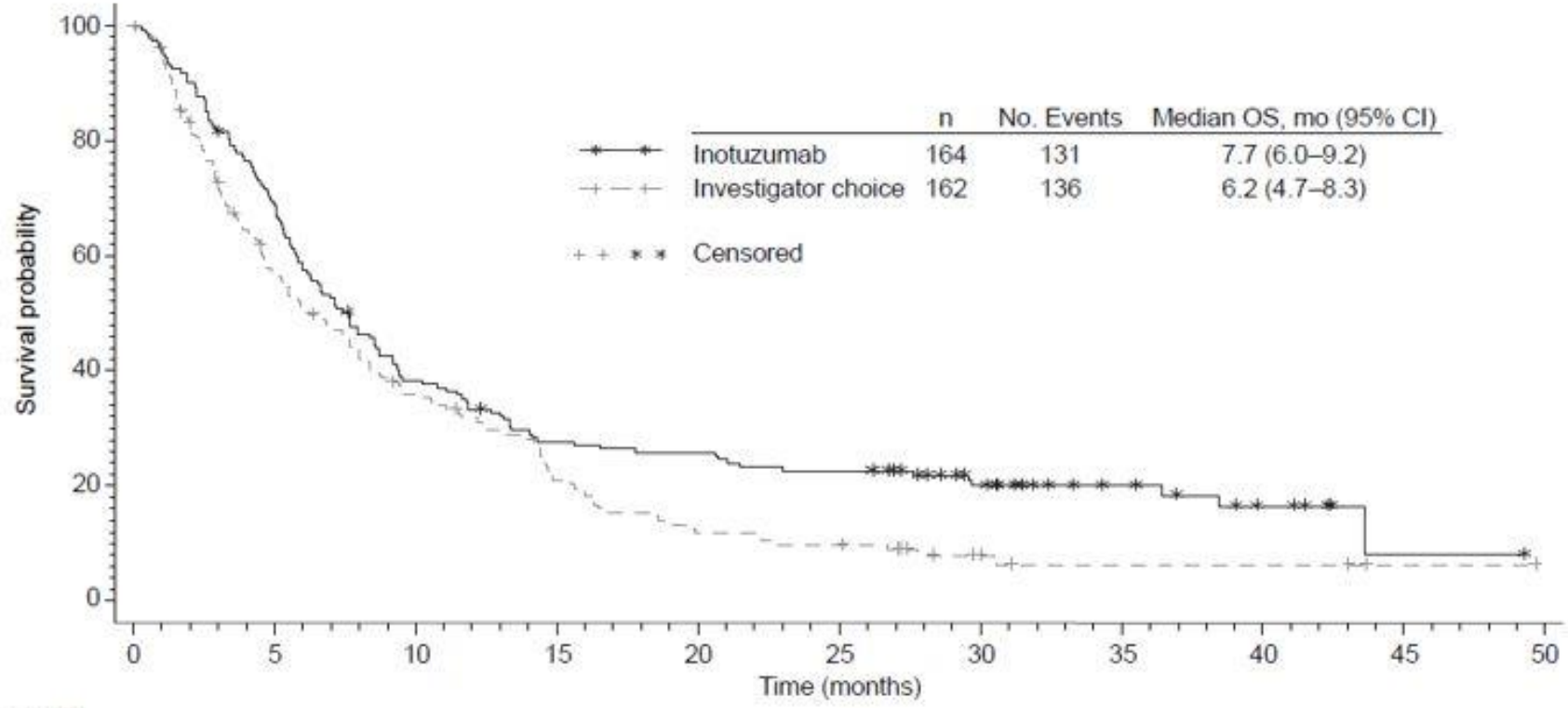
# INO-VATE: Subgroup Analysis of OS

| | Events, n | | Median OS, Mos | | HR (97.5% CI) |
|---|---|---|---|---|---|
| | InO | SoC | InO | SoC | |
| **All pts** | 164 (122) | 162 (130) | 7.7 | 6.7 | 0.77 (0.57-1.02) |
| **Duration of CR1** | | | | | |
| <12 mos | 109 (89) | 107 (89) | 6.6 | 5.3 | 0.83 (0.59-1.17) |
| ≥12 mos | 55 (33) | 55 (41) | 11.1 | 9.4 | 0.59 (0.34-1.00) |
| **Salvage status** | | | | | |
| 1 | 108 (75) | 107 (87) | 8.6 | 7.1 | 0.65 (0.46-0.93) |
| 2 | 56 (47) | 55 (43) | 6.2 | 5.2 | 0.97 (0.60-1.56) |
| **Age at randomization** | | | | | |
| < 55 yrs | 104 (70) | 103 (79) | 8.6 | 8.0 | 0.68 (0.47-0.98) |
| ≥ 55 yrs | 60 (52) | 59 (51) | 5.6 | 5.3 | 0.90 (0.58-1.41) |
| **Cytogenetics** | | | | | |
| Ph+ | 22 (18) | 28 (22) | 8.7 | 7.7 | 0.99 (0.48-2.02) |
| Ph- | 142 (104) | 134 (108) | 7.4 | 5.9 | 0.71 (0.52-0.97) |
| Complex | 27 (22) | 22 (18) | 7.2 | 3.9 | 0.61 (0.30-1.25) |
| Normal with ≥ 20 metaphases | 35 (24) | 34 (28) | 8.6 | 8.9 | 0.64 (0.34-1.19) |
| **Prestudy transplant** | | | | | |
| Yes | 28 (23) | 29 (20) | 8.5 | 13.1 | 1.31 (0.66-2.61) |
| No | 136 (99) | 133 (110) | 7.1 | 5.5 | 0.67 (0.49-0.91) |
| **BM blasts** | | | | | |
| < 50% | 53 (37) | 48 (42) | 7.4 | 9.1 | 0.69 (0.41-1.15) |
| ≥ 50% | 109 (84) | 113 (87) | 7.7 | 5.5 | 0.77 (0.55-1.09) |



# Long-Term Results of the Phase 3 INO-VATE Study

**Figure 1.** Overall Survival.



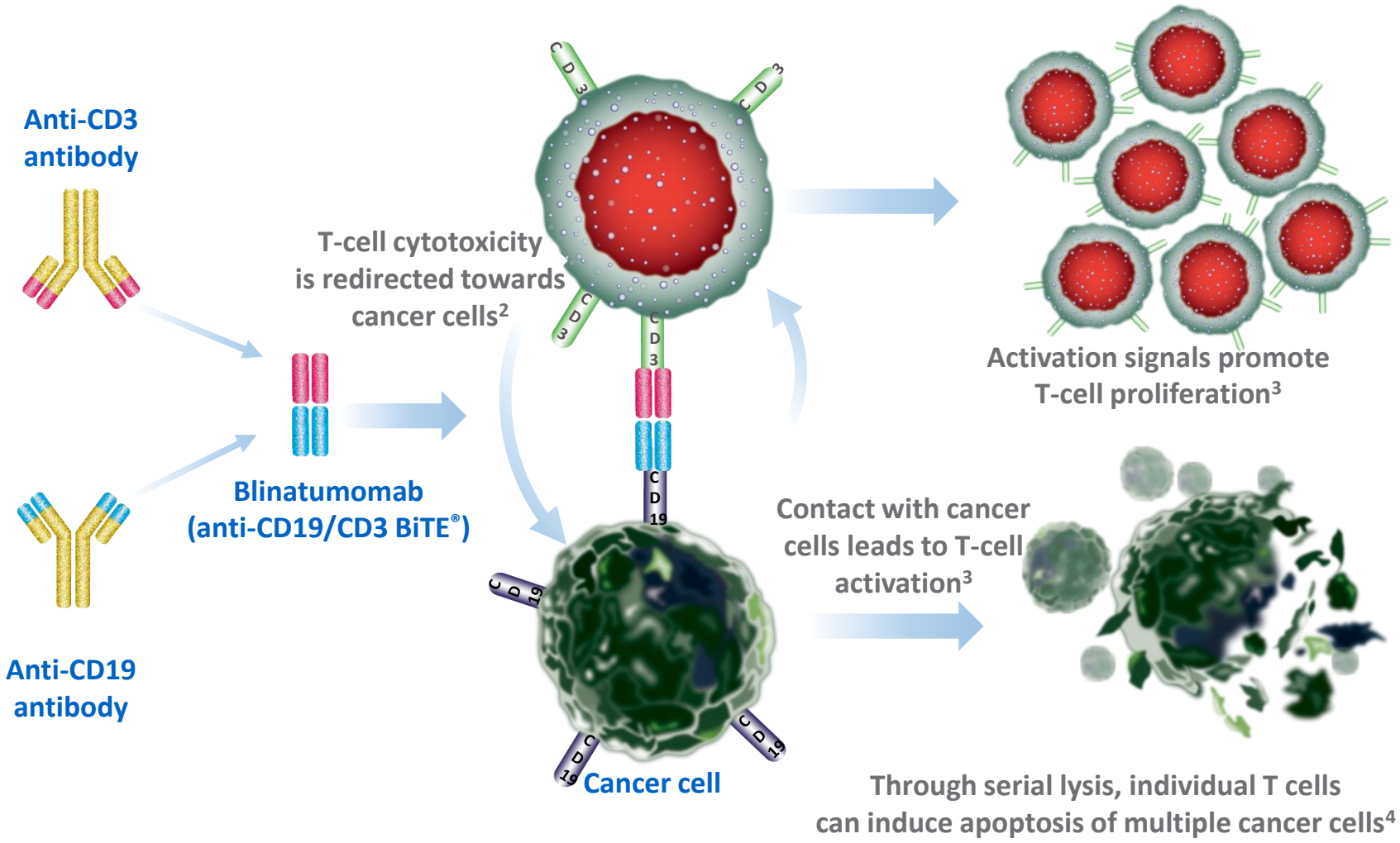

| # at Risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Inotuzumab | 164 | 112 | 62 | 44 | 41 | 36 | 23 | 13 | 7 | 1 | 0 |
| Investigator choice | 162 | 85 | 51 | 30 | 17 | 14 | 5 | 3 | 3 | 1 | 0 |

# INO-VATE: SOS Among Inotuzumab-Treated Pts

| Parameter | InO | SoC |
|---|---|---|
| Overall SOS incidence, % (n/N) | 13 (22/164) | 1 (1/162) |
| SOS incidence during study treatment, % (n/N) | 3 (5*/164) | -- |
| Post-study HSCT, % (n/N) | 47 (77/164) | 20 (33/162) |
| Post-HSCT SOS, % (n/N) | 22 (17†/77) | -- |
| Median time to post-HSCT SOS, days (range) | 15 (3-57) | -- |

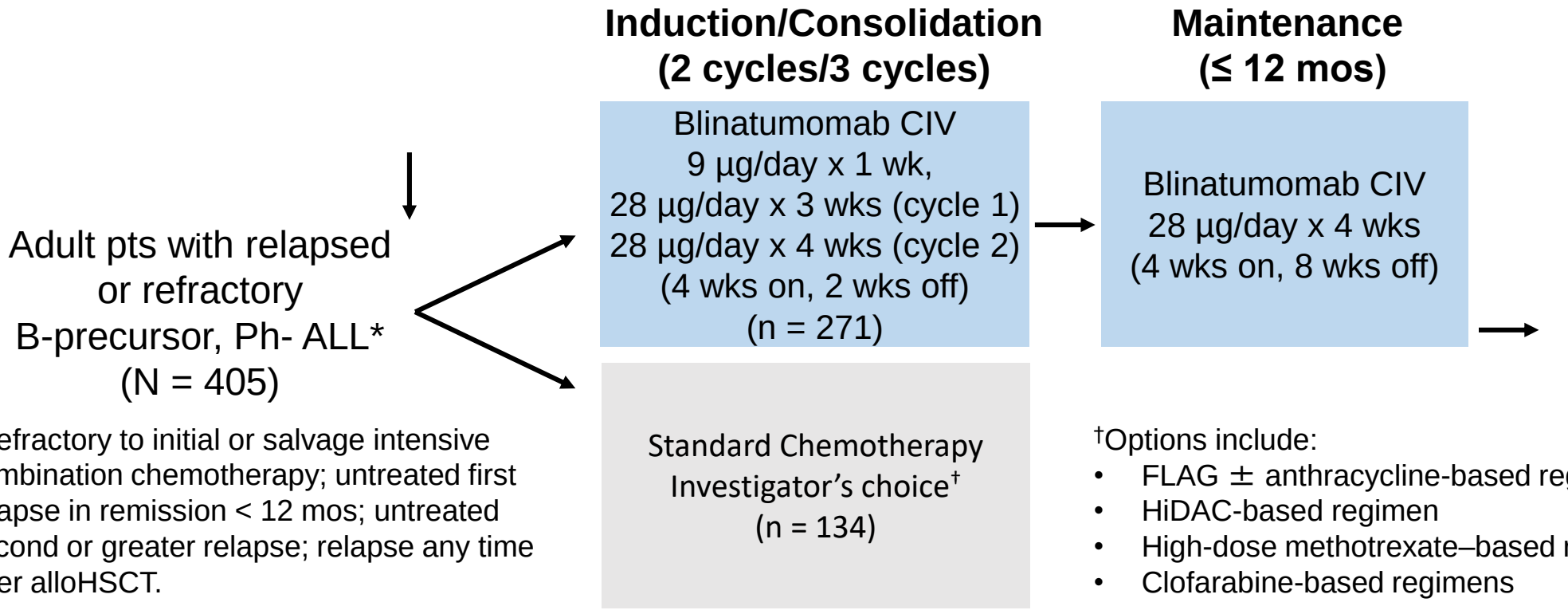
| Factors Associated With Post-HSCT SOS | OR (95% CI) | P Value |
|---|---|---|
| Alkylator conditioning: dual vs single | 7.6 (1.7-33.8) | .008 |
| Age: ≥ 55 yrs vs < 55 yrs | 4.8 (1.0-22.0) | .043 |

# Redirecting T cells to hematological malignancies with bispecific antibodies: Blinatumomab



# Phase III TOWER: Blinatumomab in Relapsed/Refractory, B-Precursor, Ph- ALL

- Multicenter, randomized, open-label phase III study




*Refractory to initial or salvage intensive combination chemotherapy; untreated first relapse in remission < 12 mos; untreated second or greater relapse; relapse any time after alloHSCT.

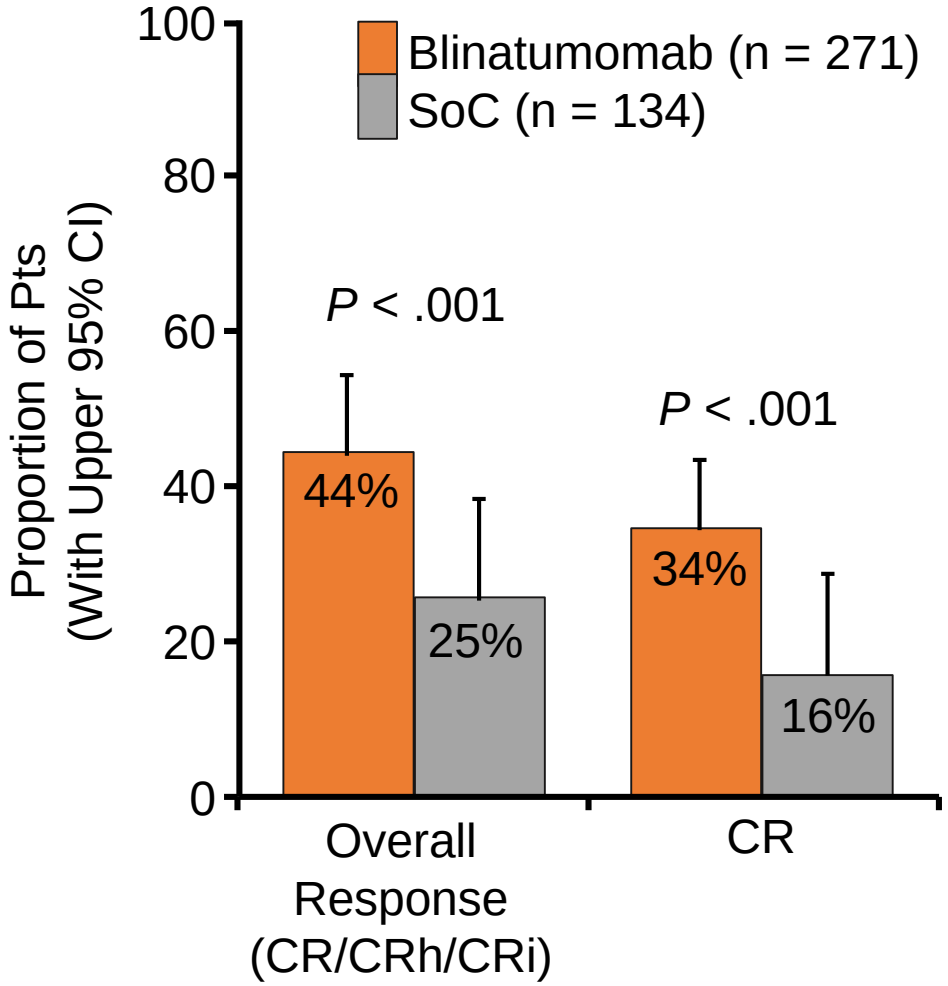
†Options include:
- FLAG ± anthracycline-based regimen
- HiDAC-based regimen
- High-dose methotrexate–based regimen
- Clofarabine-based regimens

- Primary endpoint: OS

# TOWER: Prior Treatment

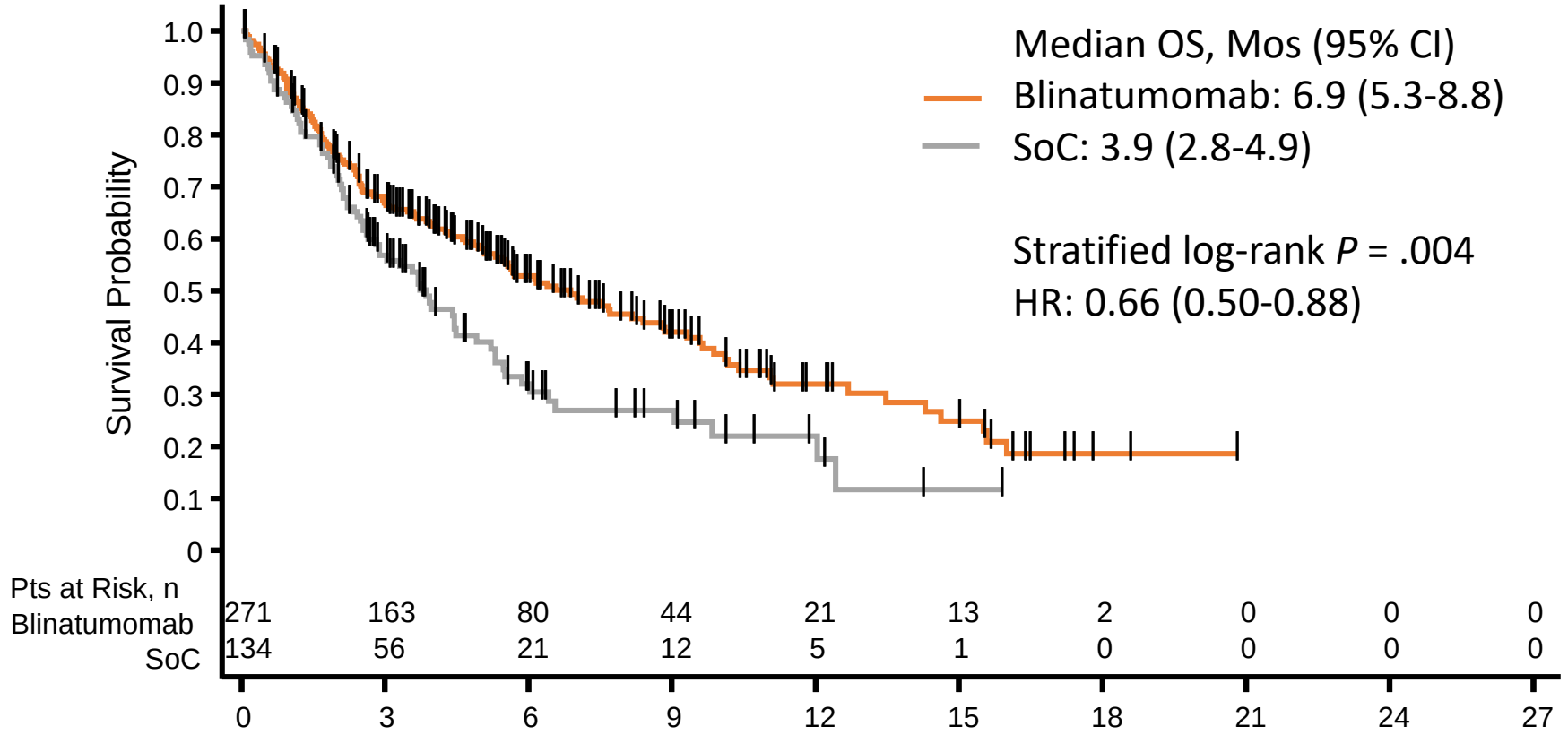
| Characteristic, n (%) | Blinatumomab ITT (n = 271) | SoC ITT (n = 134) |
|---|---|---|
| Prior salvage regimens | | |
| ▪ None | 114 (42) | 65 (49) |
| ▪ 1 | 91 (34) | 43 (32) |
| ▪ 2 | 45 (17) | 16 (12) |
| ▪ ≥ 3 | 21 (8) | 10 (7) |
| Prior alloHSCT | 94 (35) | 46 (34) |
| Primary refractory | 46 (17) | 27 (20) |
| Refractory to salvage | 87 (32) | 34 (25) |

# TOWER: Hematologic Response During Induction




- HR for EFS: 0.55 (95% CI: 0.43-0.71; *P* < .001)

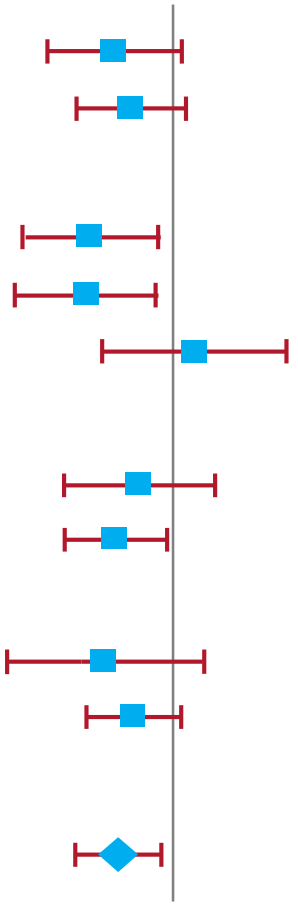
# TOWER: OS (Censoring for AlloHSCT)




| | Blinatumomab (n = 271) | SoC (n = 134) |
|---|---|---|
| AlloHSCT postbaseline, n (%) | 65 (24)<br>95% CI: 19-30 | 32 (24)<br>95% CI: 17-32) |

# TOWER: OS by Subgroup

| Subgroup | Blinatumomab, n/N (%) | SoC, n/N (%) | HR (95% CI) |
|---|---|---|---|
| **Age** | | | |
| < 35 yrs | 68/123 (55.3) | 34/60 (56.7) | 0.70 (0.46-1.06) |
| ≥ 35 yrs | 96/148 (64.9) | 53/74 (71.6) | 0.77 (0.55-1.08) |
| **Prior salvage therapy** | | | |
| S0 | 53/114 (46.5) | 39/65 (60.0) | 0.60 (0.39-0.91) |
| S1 | 61/91 (67.0) | 32/43 (74.4) | 0.59 (0.38-0.91) |
| S2+ | 50/66 (75.8) | 16/26 (61.5) | 1.13 (0.64-1.99) |
| **Prior alloHSCT** | | | |
| Yes | 58/94 (61.7) | 26/46 (56.5) | 0.81 (0.51-1.29) |
| No | 106/177 (59.9) | 61/88 (69.3) | 0.70 (0.51-0.96) |
| **Baseline BM blasts** | | | |
| < 50% | 31/69 (44.9) | 16/30 (53.3) | 0.66 (0.36-1.20) |
| ≥ 50% | 132/201 (65.7) | 71/104 (68.3) | 0.78 (0.58-1.04) |
| Unknown | 1/1 (100.0) | 0/0 (0.0) | NE |
| **Overall** | **164/271 (60.5)** | **87/134 (64.9)** | **0.71 (0.55-0.93)** |



*NE = not estimable.

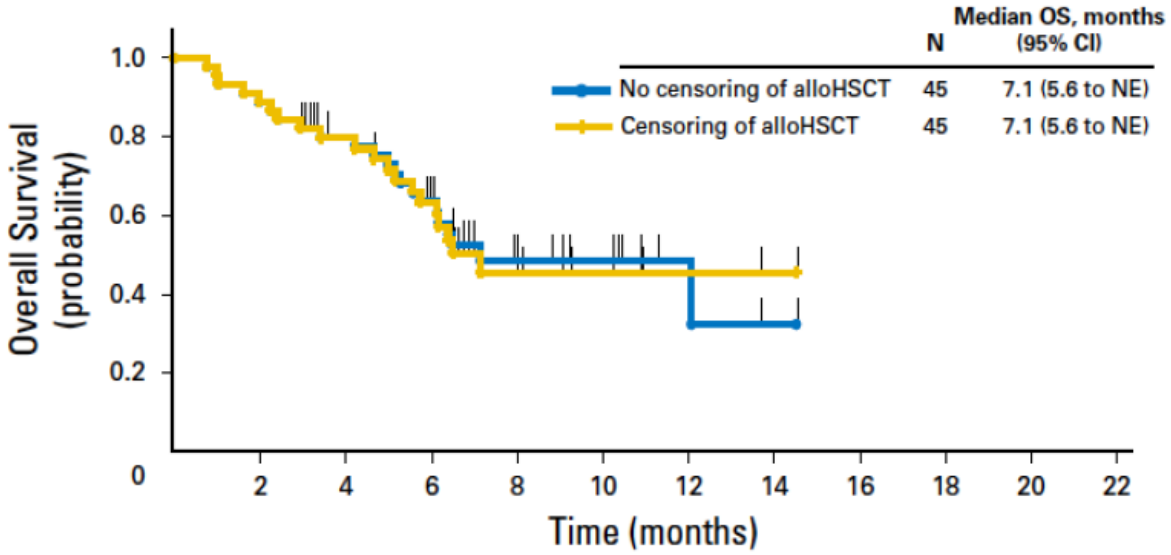
0.1 1 10

← Favors Blinatumomab Favors SoC →

# Ongoing Chemoimmunotherapy Combination Trials in ALL

| Study Description | Pt Population | Planned N | Study Arms | Primary Endpoint |
|---|---|---|---|---|
| Phase III ECOG 1910[1] | Newly diagnosed adult Ph- B-lineage ALL | 360 | Induction chemotherapy ± blinatumomab | OS |
| Phase II MD Anderson[2] | Newly diagnosed adult Ph- B-lineage ALL | 60 | Hyper-CVAD in sequential combination with blinatumomab | RFS |
| Phase II SWOG 1318[3] | Pts ≥ 65 yrs of age with:<br>▪ Cohort 1: newly diagnosed Ph- B-precursor ALL | 44 | ▪ Cohort 1: blinatumomab + maintenance chemotherapy (POMP) | Toxicity, OS |
| | ▪ Cohort 2: newly diagnosed Ph+ or R/R DSMKF | | ▪ Cohort 2: Dasatinib, prednisone followed by blinatumomab + dasatinib | |
| Phase I S1312[4] | Relapsed/refractory adult CD22+ acute leukemia | 38 | Inotuzumab + combination chemotherapy (CVP) | Safety |

# ALCANTARA: Blinatumomab for Relapsed/Refractory Ph+ ALL

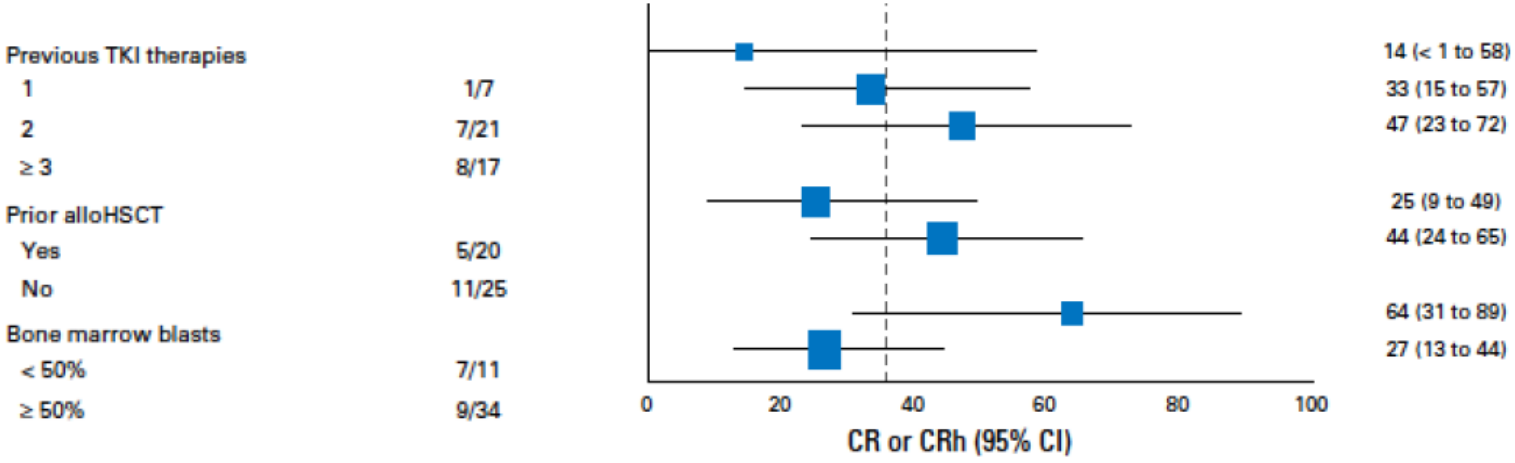



**Open-label phase II study of adults relapsed/refractory to second-generation TKI and/or intolerant of TKI**

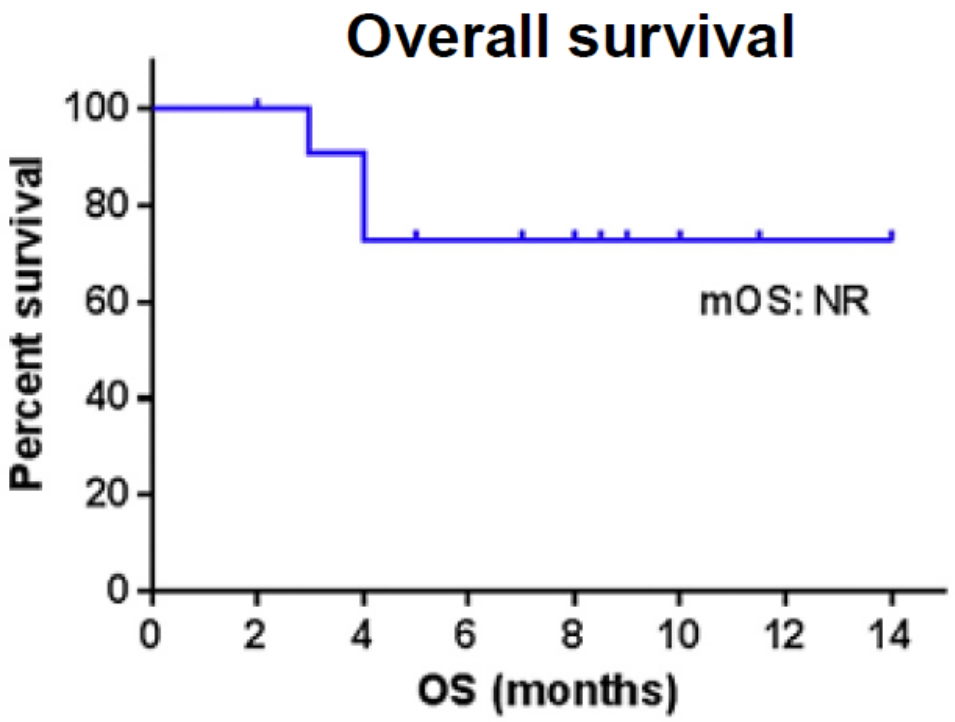
**45 patients Rx blinatumomab monotherapy**
**36% CR/CRi after 2 cycles**
**88% of responders achieved MRD response**

**Median RFS = 6.7 mos**
**Median OS = 7.1 mos**

**44% to alloSCT**



# Blinatumomab + TKI for Relapsed Ph+ ALL




9 Ph+ ALL and 3 CML blast crisis
Failed ≥1 chemotherapy and ≥1 TKI

Treatment: blinatumomab plus ponatinib (n = 8), dasatinib (n = 3), bosutinib (n = 1)

- Complete hematologic response = 50%
- Cytogenetic response = 71%
- Molecular response = 75%

- 2 cases of cytokine release syndrome
- Median FU = 8 mo
- Median OS = not reached
- 1-year OS = 73%

# Relapsed Ph+ ALL: Selection of TKI Therapy

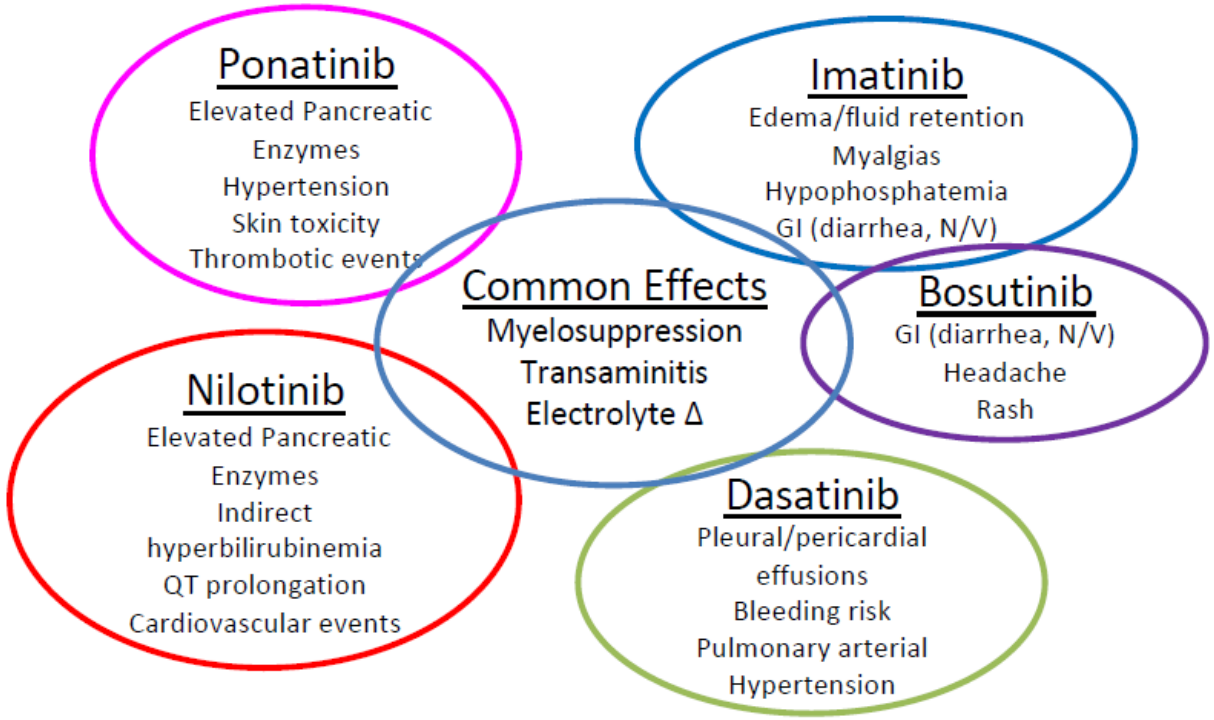
## BCR-ABL1 Resistance Mutations

| Mutation | Best TKI |
|---|---|
| *Y253H, E255KV, F359VCI* | Dasatinib |
| *F317LVIC, T315A, V299L* | Nilotinib |
| *E255KV, F317LVIC, F359VCL,T315A, Y253H* | Bosutinib |
| *T315I* | Ponatinib |

**CNS penetration**

- Imatinib < dasatinib levels in CSF

## Adverse Event Spectrum



# How I currently treat R/R ALL

## Ph- ALL

- < 24 months
- Post-HSCT
- Second relapse
- Primary refractory

→ BLINA (BM blasts < 50 %)

INO (leukocytosis or BM blasts > 50 %

→ HSCT

Late relapse > 24 months → CHT → Blina → MRD+ HSCT
MRD - HSCT ?

## Ph+ ALL

Ponatinib + mild intensity CHT → HSCT