NCCN 11th Annual Congress:
Hematologic Malignancies™

ALL: New Options for Relapsed Disease

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Relapsed and Refractory ALL

- Although over 80% of adults with ALL will achieve complete remission (CR), the majority will ultimately relapse
- Approximately 20% will have resistant disease
- Relapsed and refractory (R/R) ALL has 5 year overall survival of <10%
- Recent advances in immunotherapies are challenging this dismal prognosis

Immunotherapies in ALL

MONOCLONAL ANTIBODIES

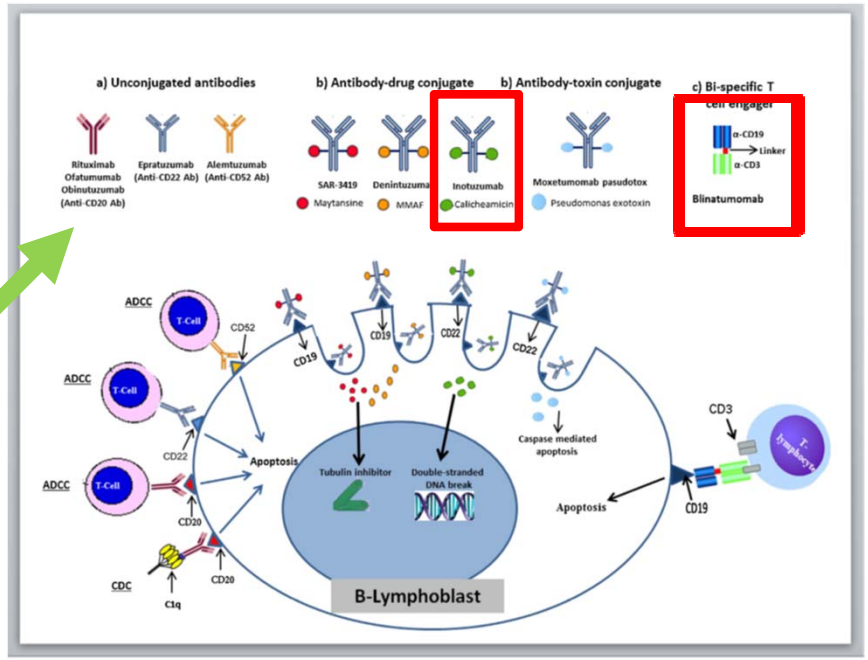
- Blinatumomab
- Inotuzumab ozogamicin

CHIMERIC ANTIGEN RECEPTOR T CELLS

- MSKCC
- UPENN
- NCI

Monoclonal Antibodies

- Three primary targets: CD19, CD20, CD22
- Include unconjugated, antibody-drug conjugates, antibody-toxin conjugates, and b-specific T cell engaging antibodies



Farhadfar N, et al. Leukemia Research 2016;49: 13-21

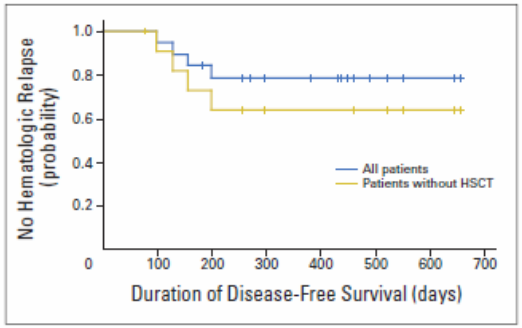
Blinatumomab – GMALL MRD study

- Bi-specific T-cell engager (BiTE) antibody with CD19 and CD3 specificity
- Binds CD3+ cytotoxic T cells and CD19+ B cells -> activated T cells induce B cell death via pore-forming perforin system
- Patients with MRD persistence or relapse after induction and consolidation chemotherapy
- Primary objective: efficacy of converting to MRD-
- Open label, Phase II
- Blinatumomab 15 µg/m^2/24 hrs over 4 weeks with 2 week rest (6 weeks = 1 cycle) up to 4 cycles

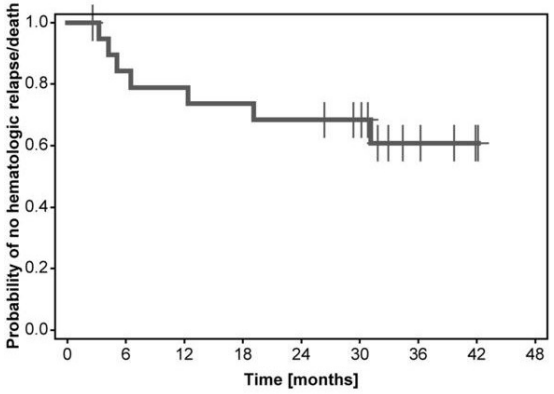
Topp MS, et al. JCO 2011; 29:2493-5498
Topp MS, et al. Blood 2012;120: 5185-5187

Blinatumomab – GMALL MRD study

- N=21 (20 evaluable for MRD response)
- 16/20 converted to MRD-; all responses at end of first cycle
- Ph- MRD response 13/15; Ph+ MRD response 3/5
- 12 responders had never achieved MRD negativity
- 9/10 patients with high MRD load (≥ 10^{-2}) became MRD-



Median follow up 13.5 months



Median follow up 33 months

Topp MS, et al. JCO 2011; 29:2493-5498
Topp MS, et al. Blood 2012;120: 5185-5187

Blinatumomab – Relapsed/refractory disease

	DOSE FINDING STUDY[1]	CONFIRMATORY STUDY[2]
No. patients	36	189
Disease	Ph- B-ALL; Ph+ B-ALL if not eligible for dasatinib or imatinib	Ph- B-ALL only
Dosing	Dose finding	9 µg/d for 7 days then 28 µg/d
Schedule	4 weeks with 2 week rest	4 weeks with 2 week rest
CR/CRi	69%	43%
Allogeneic SCT	52%	40%
Median RFS	7.6 months (9.7 month median follow up)	5.9 months (8.9 month median follow up)

[1]Topp MS, et al. JCO 2014; 32: 4134-4140
[2]Topp MS, et al. Lancet Oncol 2015 57-66

Blinatumomab Adverse Events

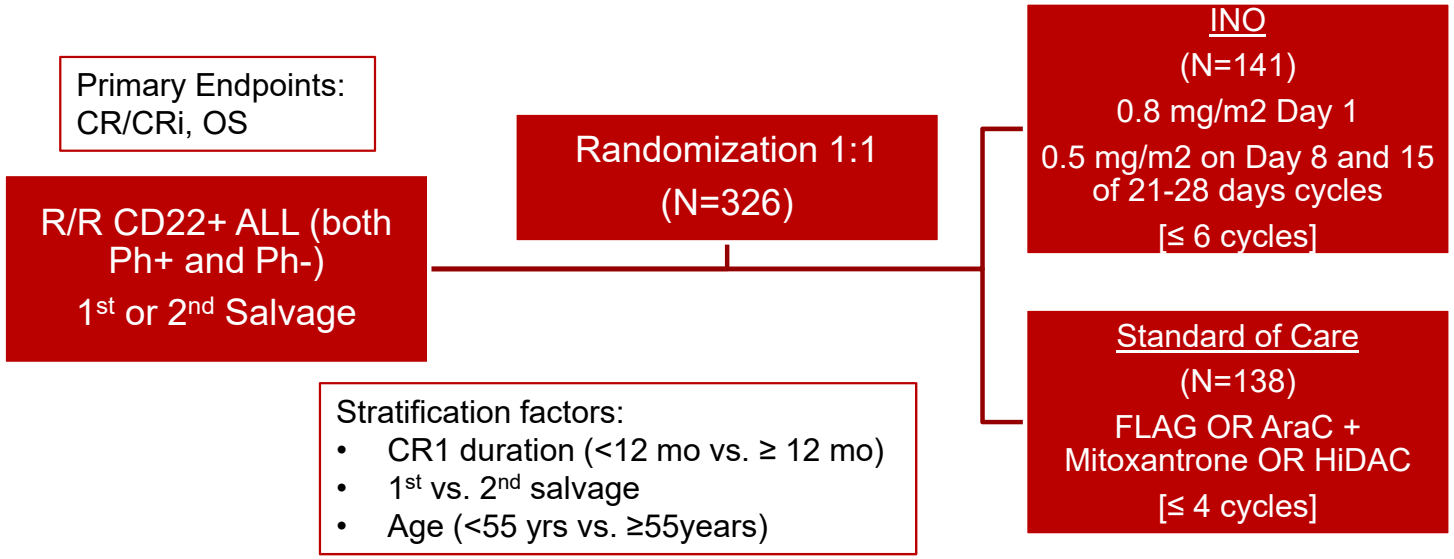
- Most common: Grade 3/4 Lymphopenia (33%)
- All grades: fever, chills, headache, fatigue, hypogammaglobinemia, hypokalemia
- Cytokine release syndrome (CRS): greatest risk 1st day of 1st cycle
  - Incidence Grade 3/4: 0-6%
  - Incidence and severity increases with increasing disease burden
  - Preventive strategy: pretreatment with steroids/chemo to reduce circulating disease burden; dose escalation with 1st cycle
  - Dexamethasone during initiation and dose escalation

Blinatumomab Adverse Events

- Neurotoxicity was dose limiting: encephalopathy, seizures, coordination/speech difficulties, confusion, dysphasia, impaired cognition
- Median onset, 7 days; reversible
- Local cytokine release by activated T cells in the CNS
- Higher rates in elderly patients
- Incidence all grades may be as high as 50%
- Grade 3/4 events: 13-22%
- Management includes:
  - Interrupt infusion for Grade 3 (potentially rechallenge) and Grade 4 (permanent discontinuation)
  - Dexamethasone
  - Anti-epileptics for seizures

INO-VATE: Inotuzumab in Relapsed ALL

- Inotuzumab ozogamicin (INO): anti-CD22 antibody conjugated to calicheamicin
- Phase 3: 19 countries at 117 sites



Kantarjian HM, et. Al. N Engl J Med 2016; 375(8):740-753

INO-VATE: Inotuzumab in Relapsed ALL

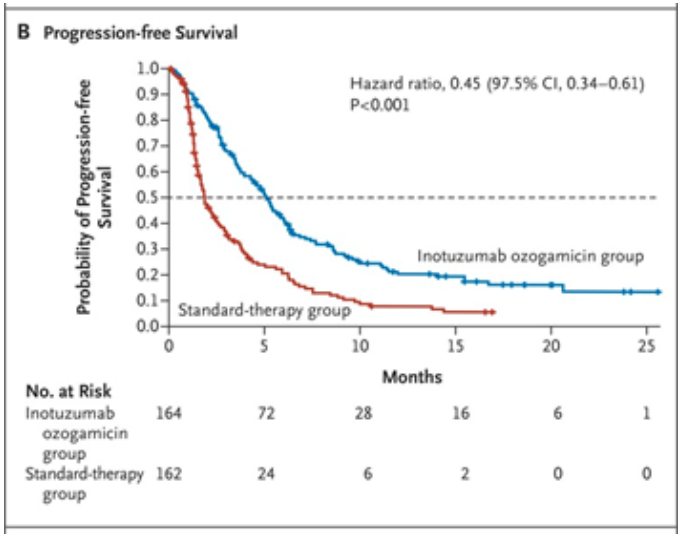
- CR/CRi: independent blinded external adjudication of first 218 patients randomized (Oct 2014)
- Intention to treat analysis

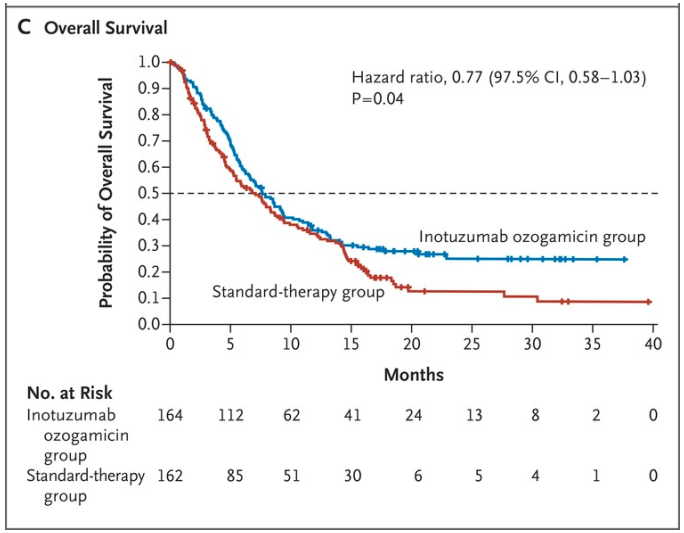
Response, n (%)	INO (n=109)	SOC (n=109)	1-sided P value
CR/CRi	88 (80.7)	32 (29.4)	<0.0001
MRD neg (in CR/CRi pts)	69 (78.4)	9 (28.1)	<0.0001
Proceed to allogeneic SCT	45 (41)	12 (11)	<0.0001

Kantarjian HM, et. Al. N Engl J Med 2016; 375(8):740-753

INO-VATE: Inotuzumab in Relapsed ALL

- OS: prespecified boundary of *P*=0.0104; included all 326 randomized patients after ≥248 events (March 2016)





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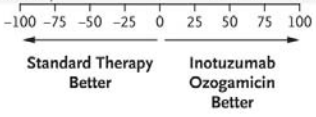
INO-VATE: Inotuzumab in Relapsed ALL

B Rate According to Patient Characteristics at Baseline

Subgroup	No. of Patients: Inotuzumab Ozogamicin Group	No. of Patients: 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
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



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INO-VATE: Inotuzumab in Relapsed ALL

Table 3. Serious Adverse Events That Occurred during Treatment.*

Serious Adverse Event	Inotuzumab Ozogamicin Group (N=139)		Standard-Therapy Group (N=120)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Any event	67 (48)	64 (46)	55 (46)	52 (43)
Febrile neutropenia	16 (12)	15 (11)	22 (18)	21 (18)
Veno-occlusive disease	15 (11)	13 (9)	1 (1)	1 (1)
Sepsis	3 (2)	3 (2)	6 (5)	6 (5)
Pyrexia	4 (3)	2 (1)	3 (2)	1 (1)
Disease progression	5 (4)	5 (4)	2 (2)	2 (2)
Pneumonia	5 (4)	5 (4)	1 (1)	0
Neutropenic sepsis	3 (2)	3 (2)	3 (2)	3 (2)
Respiratory failure	1 (1)	1 (1)	4 (3)	4 (3)
Abdominal pain	3 (2)	2 (1)	1 (1)	1 (1)
Septic shock	2 (1)	2 (1)	1 (1)	1 (1)
Escherichia sepsis	1 (1)	1 (1)	2 (2)	2 (2)
Multiorgan failure	1 (1)	1 (1)	2 (2)	2 (2)
Hyperbilirubinemia	0	0	3 (2)	2 (2)
Hypotension	0	0	3 (2)	2 (2)
Stomatitis	2 (1)	2 (1)	1 (1)	1 (1)
Bacteremia	2 (1)	2 (1)	1 (1)	1 (1)
Clostridium difficile colitis	2 (1)	2 (1)	1 (1)	1 (1)
Nausea	2 (1)	2 (1)	0	0
Influenza	2 (1)	2 (1)	0	0
Asthenia	2 (1)	2 (1)	0	0
Pancytopenia	0	0	2 (2)	2 (2)
Tumor lysis syndrome	2 (1)	1 (1)	0	0
Acute renal failure	2 (1)	1 (1)	0	0
Klebsiella infection	0	0	2 (2)	2 (2)
Fungal pneumonia	0	0	2 (2)	2 (2)

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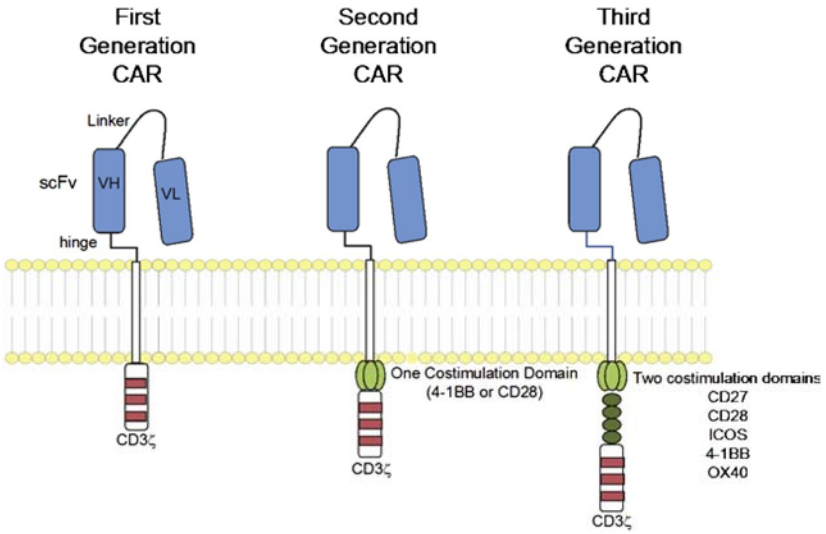
- Hepatic toxicity more frequent with INO
- VOD reported in 10/48 patients who proceeded with allogeneic stem cell transplant
- Dual vs. single alkylator containing conditioning associated with VOD

CHIMERIC ANTIGEN RECEPTOR T CELLS

- Reprogram T cells to recognize and eliminate malignant cells
- Constructs include extracellular antigen-recognition domain linked to intracellular signaling domains of TCR
- Gene vector can vary



Shannon L. Maude et al. Blood 2015;125:4017-4023

CAR-Ts in ALL: Phase I trials

	MSKCC[1]	UPENN[2]	NCI[3]
CAR Design	19-28z	19-BBz	19-28z
No. patients	16	30	21
Median age (yr)	50	14	13
CR (%)	88	90	67
MRD negative (%)	75	79	57

[1]Davila ML, et al. Sci Transl Med 2014; 6: 224ra25
[2]Maude SL, et al. NEJM 2014; 371: 1507-17
[3]Lee DW, et al. Lancet 2015; 385: 517-28

Cytokine Release Syndrome with CAR-T

- Most common acute toxicity
- Cytokines directly produced by infused cells or by other immune cells in response to these cytokines
- Implicated cytokines include IL-6, IFN-gamma, TNF, IL-2, IL2R-alpha, IL-8, IL-10
- Common initial symptoms include fever, tachycardia, hypotension
- CRS-mediated organ damage can include neurologic symptoms (seizures, encephalopathy, etc.), hepatitis, coagulopathies, cytopenias, hypoxia, myalgias/weakness, arrhythmias, tumor lysis syndrome, acute kidney injury, etc.

Cytokine Release Syndrome with CAR-T

- Supportive care includes acetaminophen, cooling blankets, IVF, vasopressors, empiric antibiotics, blood product support
- CRS CTCAE grading created for monoclonal antibodies, several alternative grading scales published
- Tocilizumab frontline therapy for CRS (off-label use) requiring interventions beyond supportive measures; criteria for initiation are protocol specific
- Avoidance of corticosteroids if at all possible; effective but inhibit CAR-T persistence and anti-cancer effects

Neurologic toxicity with CAR-T

- May occur with or without CRS
  - Variable incidence: 0-50%
- Headache, confusion, hallucinations, seizures, dysphasia, apraxia, ataxia, tremors, facial nerve palsies
- Anti-CD19 CAR-T cells and elevated levels of IL6 have been found in CSF; likely different mechanism than CRS
- Unclear if tocilizumab is beneficial, unlike with CRS
- Monoclonal antibodies unlikely to cross BBB
- Frontline treatment generally dexamethasone for any seizure or grade 4 toxicity

B-cell aplasia with CAR-T

- Generally universal and presents when CAR-Ts persist
- May persist even after circulating CAR-Ts are undetectable
- Immunoglobulin replacement when IgG< 400-500mg/dl

CONCLUSIONS

- Immunotherapies are offering great promise in managing relapsed and refractory ALL, and support of **clinical trials** is critical for ongoing progress
- Cytokine release syndromes and neurologic toxicities represent the predominant unique toxicities to these immunotherapies
- Monoclonal antibodies are generally well tolerated with significant response rates, but questions remain regarding durability
- Early impressive responses with CAR-T cells highlight ongoing challenges with tolerability and persistence of CAR-T cells

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