Targeted Alpha-Particle Therapy for Acute Myeloid Leukemia

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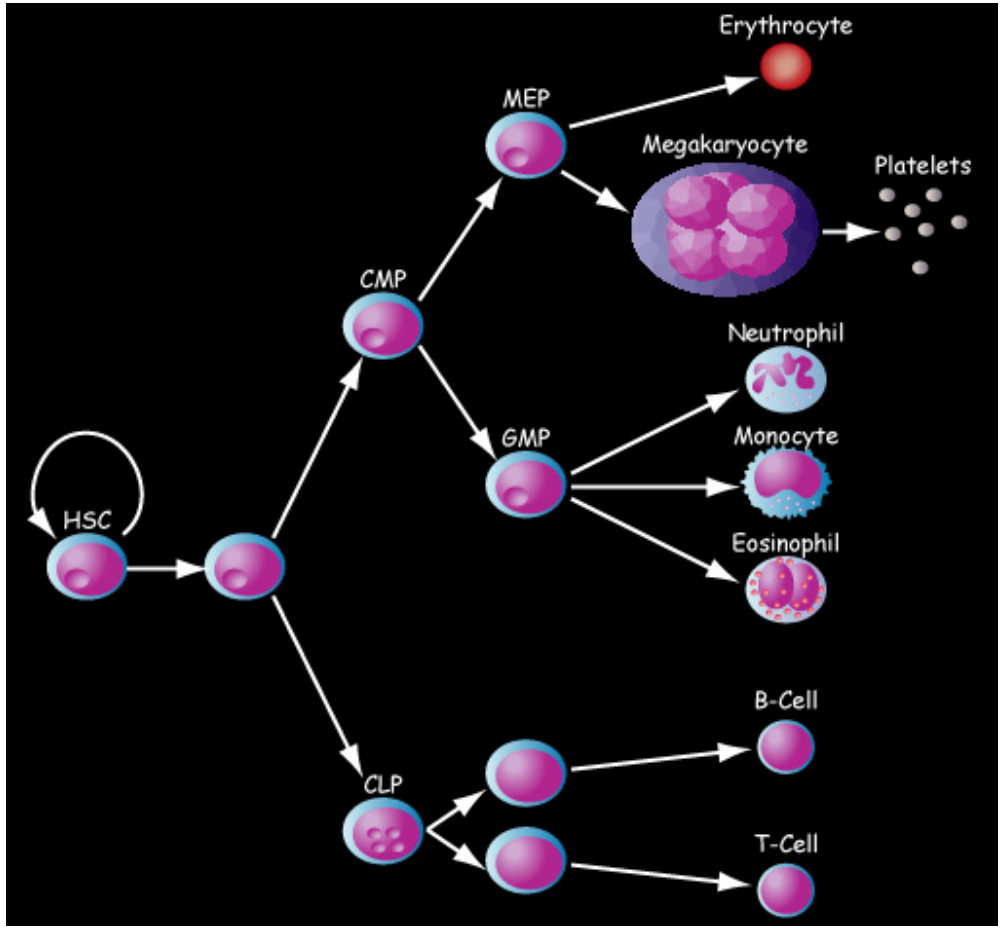
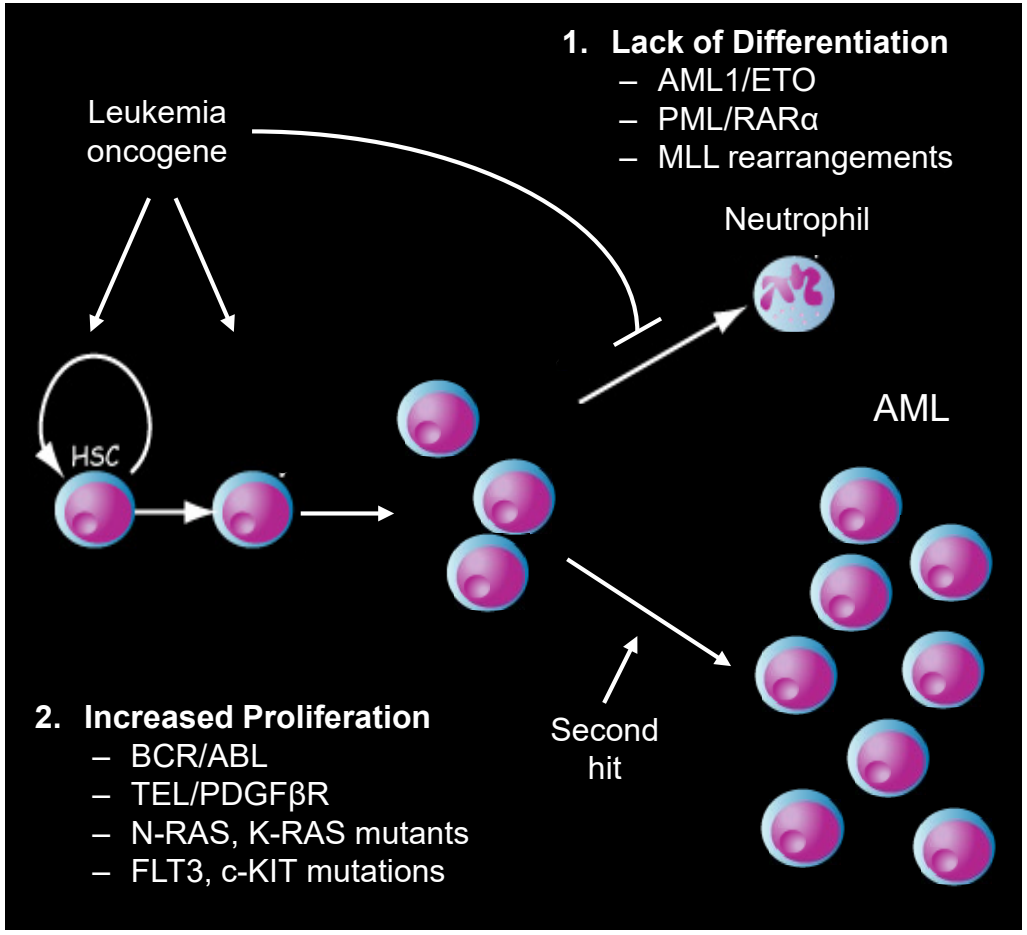
^{225}Ac-lintuzumab is an investigational agent currently in development for use in AML and MDS.

Pathogenesis of Acute Myeloid Leukemia

Normal Hematopoiesis



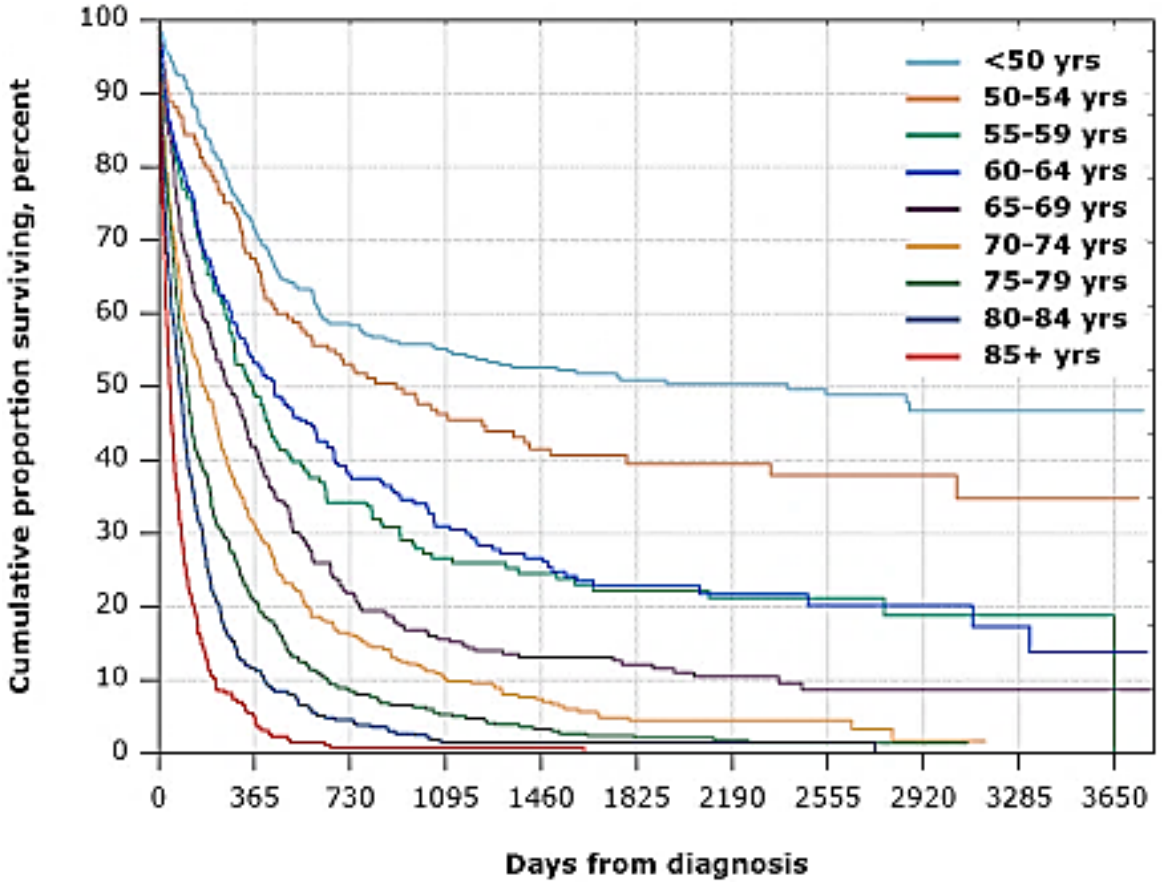
Leukemogenesis



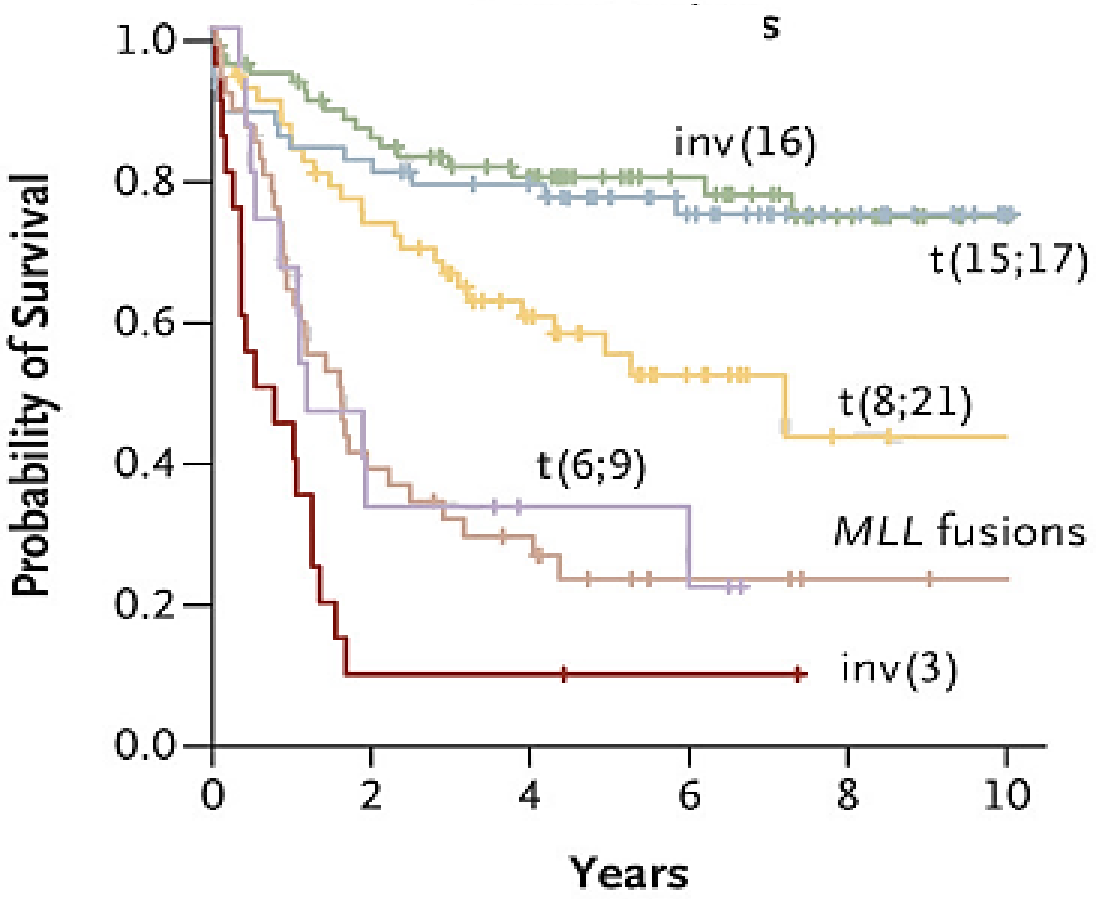
Gilliland DG. *Curr Opin Hematol* 2001; 8:189-191.

Prognostic Factors for AML

Survival by Age[1]

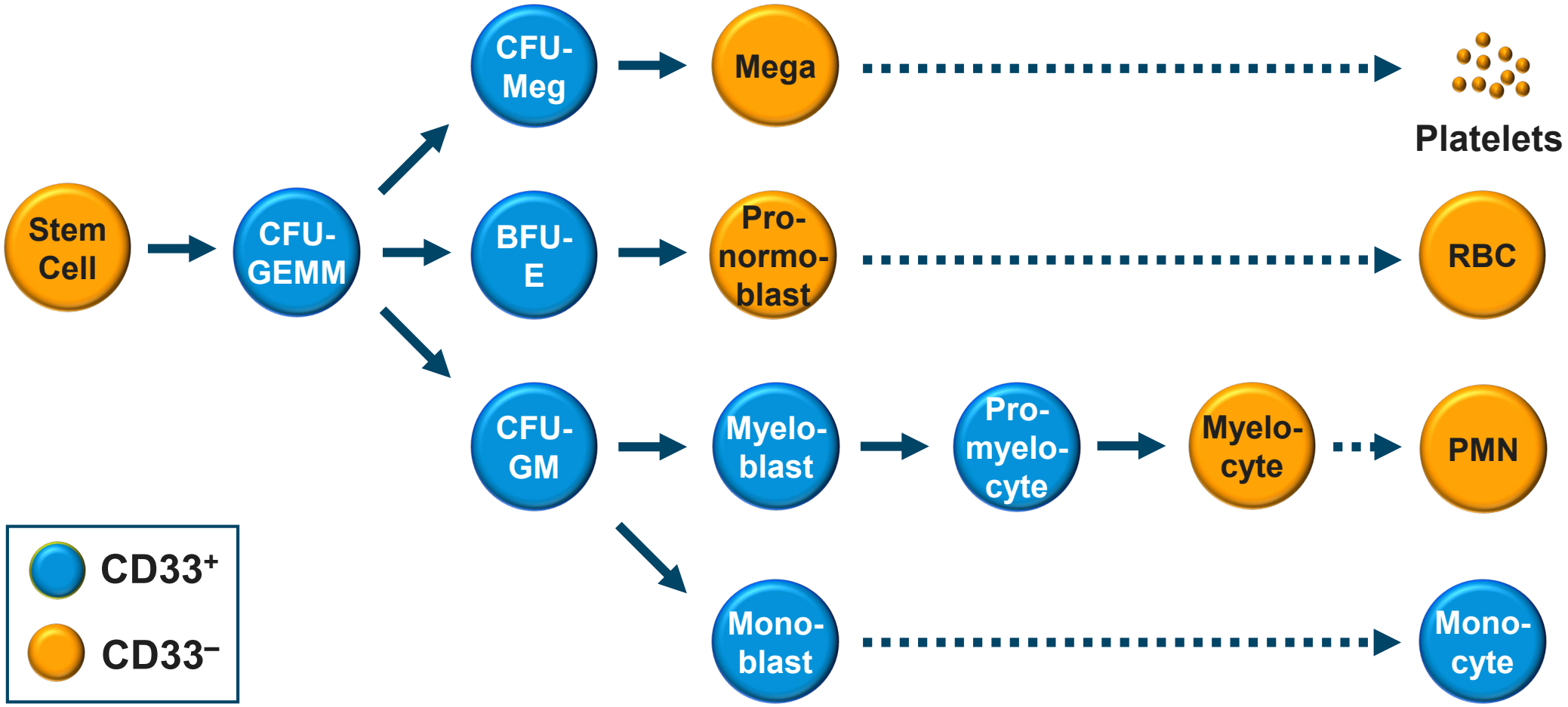


Survival by Karyotype[2]



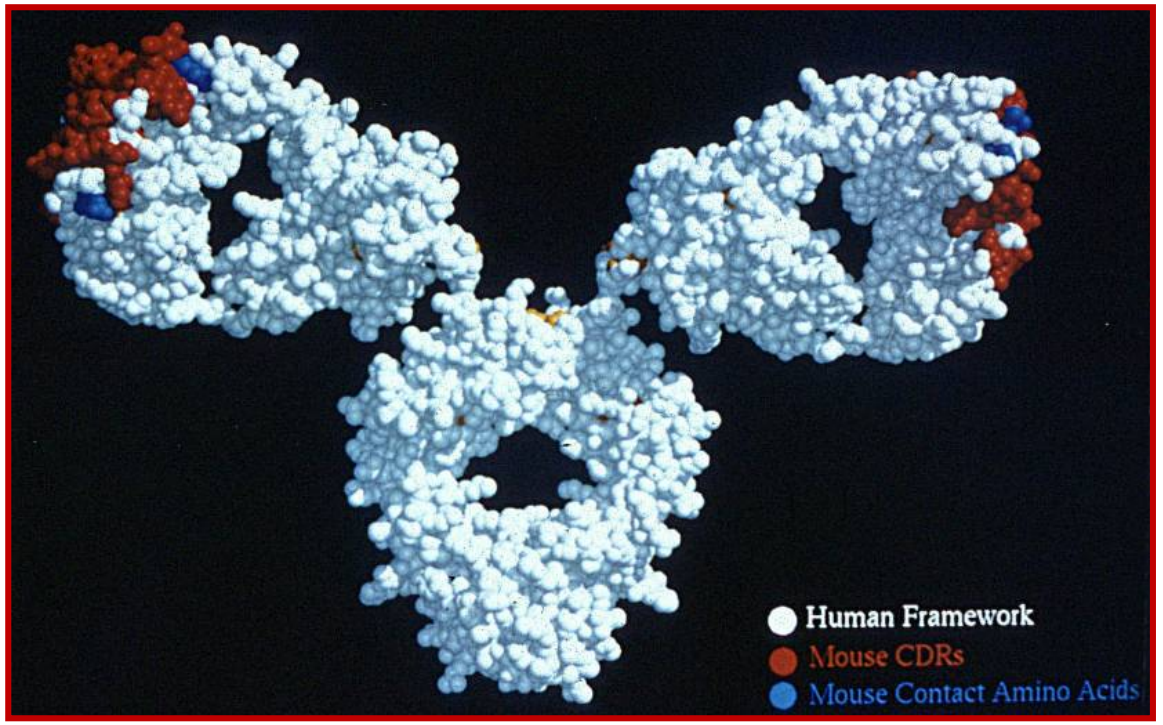
[1]Juliusson G *et al. Blood* 2009;113:4179-4187.
[2]Papaemmanuil E *et al. N Engl J Med* 2016; 2209-2221.

CD33 Surface Antigen Expression



Lintuzumab (HuM195, SGN-33)

- Humanized anti-CD33 monoclonal antibody
- Kills target cells by ADCC and fixes complement[1]
- Rapidly targets leukemia cells in patients without immunogenicity[2]
- Has modest activity in relapsed AML[3]
- Can eliminate large leukemic burdens when labeled with the β-emitters ^{131}I and ^{90}Y[4,5]

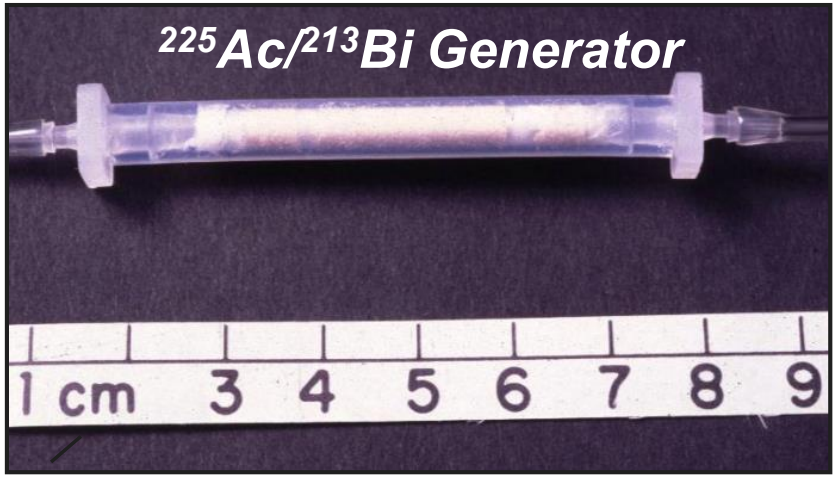


[1]Caron PC *et al. Cancer Res* 1992; 52:6761-6767.
[2]Caron PC *et al. Blood* 1994; 83:1760-1768.
[3]Raza A *et al. Leuk Lymph* 2009; 50:1336-1344.
[4]Burke JM *et al*. *Bone Marrow Transplant*. 2003; 32:549-556.
[5]Jurcic JG *et al. Proc ASCO* 2000; 19:8a.

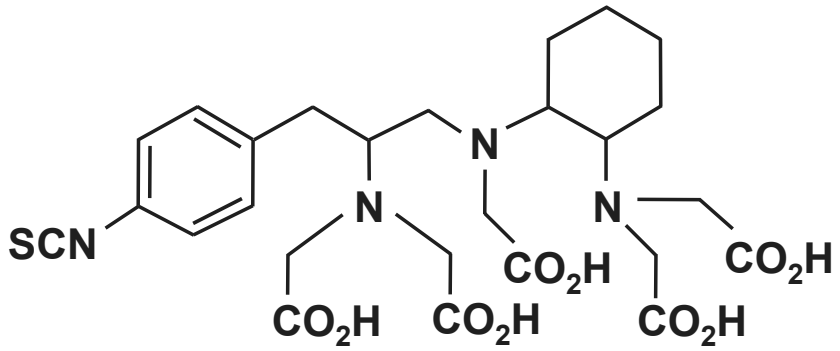
^{213}Bi-Lintuzumab: A 1st Generation α-Emitting Conjugate

^{225}Ac —α, 10 days→ ^{221}Fr —α, 4.9 min→ ^{217}At —α, 0.032 sec→ ^{213}Bi —α, 46 min→ Stable Isotopes

- 10.36-37 MBq/kg delivered in 3-7 fractions over 2-4 days
- Myelosuppression lasted 12-41 days (median, 22 days)
- Transient liver function abnormalities seen in 6 patients
- MTD was not reached
- 14/18 patients had reductions in marrow blasts



SCN-CHX-A-DTPA



Jurcic JG *et al. Blood* 2002; 100:1233-1239.

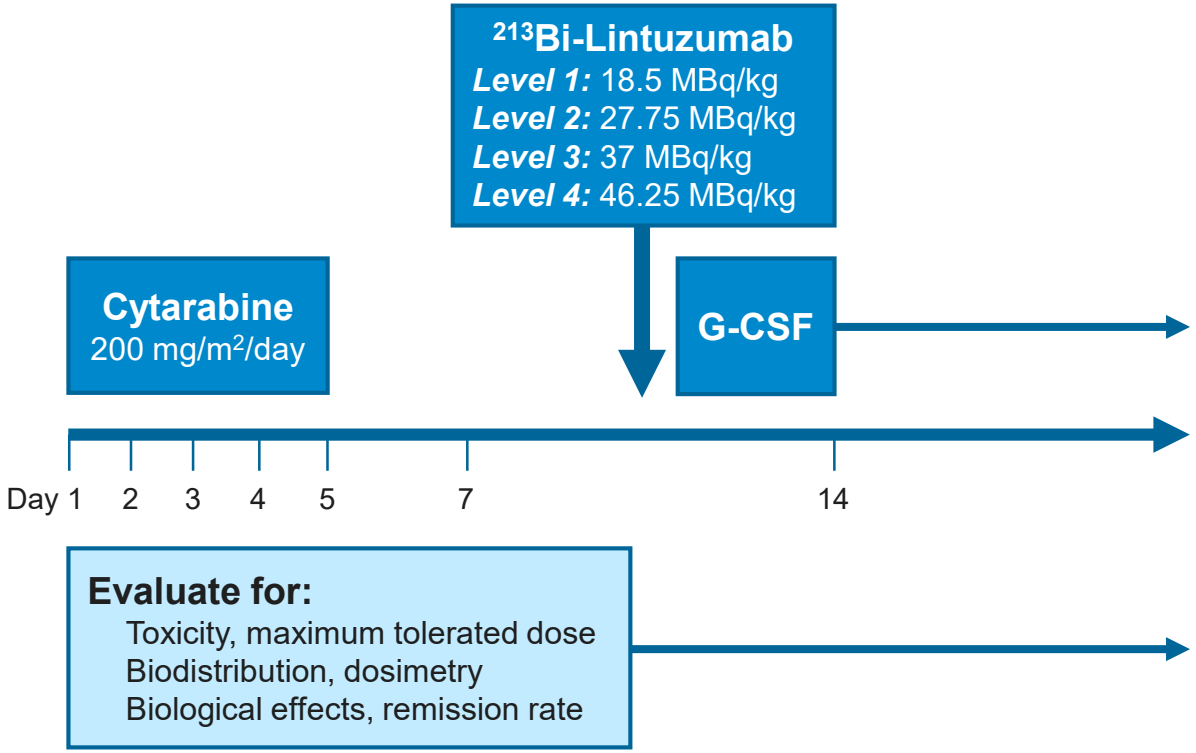
Comparison of ^{131}I, ^{90}Y, and ^{213}Bi Dosimetry for Lintuzumab

Isotope	Mean Absorbed Dose (mSv/MBq)			Marrow/ Whole Body Ratio
	Marrow	Liver	Whole Body	
^{131}I	2.7	0.8	0.16	14.4
^{90}Y	6.8	4.0	0.49	13.9
^{213}Bi	9.8	5.8	0.0004	27,300

Jurcic JG *et al. Blood* 2002; 100:1233-1239.

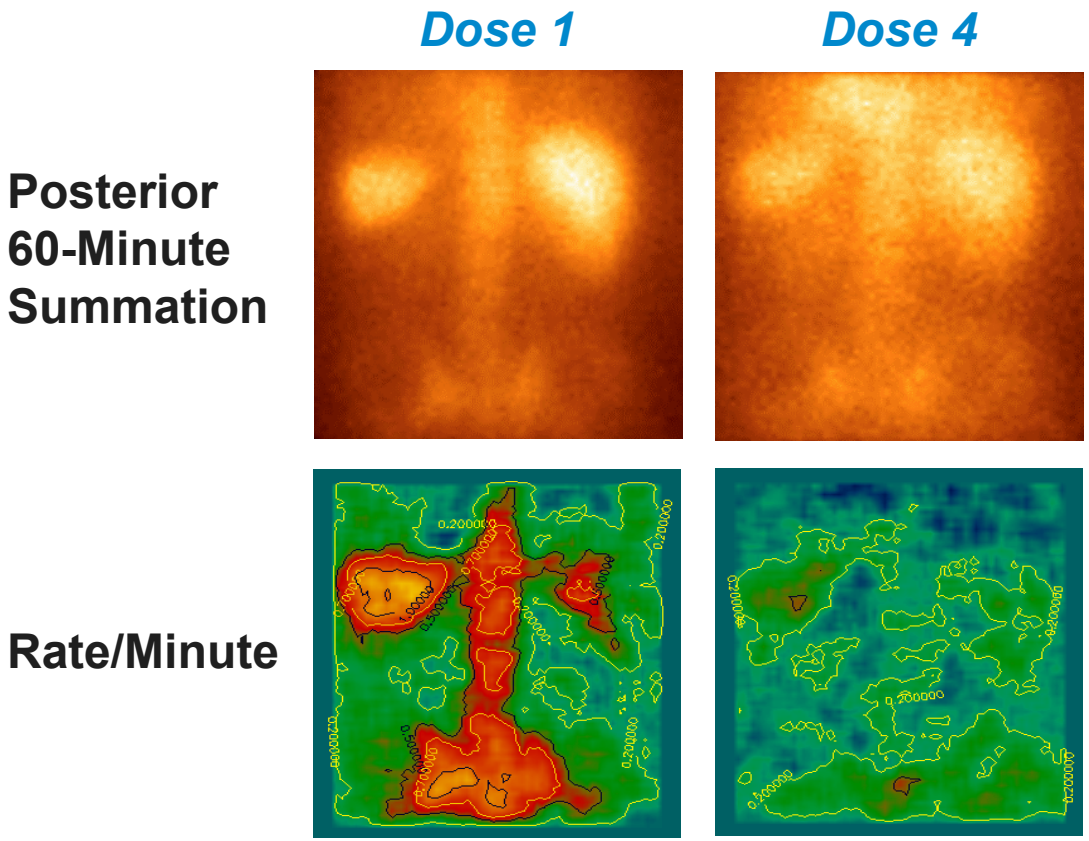
^{213}Bi-Lintuzumab for Cytoreduced Disease
Rationale and Study Design

- The short range and high LET make α-particles best suited for treatment of small-volume disease.
- Given the number of CD33 binding sites in AML and achievable specific activity, it is difficult to target adequate numbers of ^{213}Bi atoms to each leukemia cell.
- **Hypothesis:** Cytoreduction with cytarabine should decrease tumor burden by 1-2 logs and increase the ratio of ^{213}Bi atoms to target cells.



Rosenblat TL *et al. Clin Cancer Res* 2010; 16:5303-5311.

^{213}Bi-Lintuzumab for Cytoreduced Disease
Biodistribution and Clinical Outcomes



Results by Disease Status for Doses ≥ 37 MBq/kg

Disease Status	No. of Patients	CR	CRp	PR	Overall Response
Untreated AML, Untreated relapse	18	2	2	2	6 (33%)
1° refractory, Refractory relapse	7	0	0	0	0

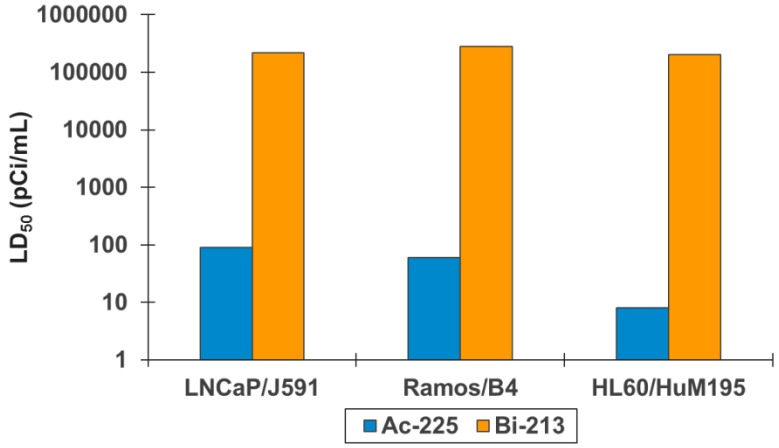
Abbreviations: CR, complete remission; CRp, CR with incomplete platelet recovery; PR, partial remission.

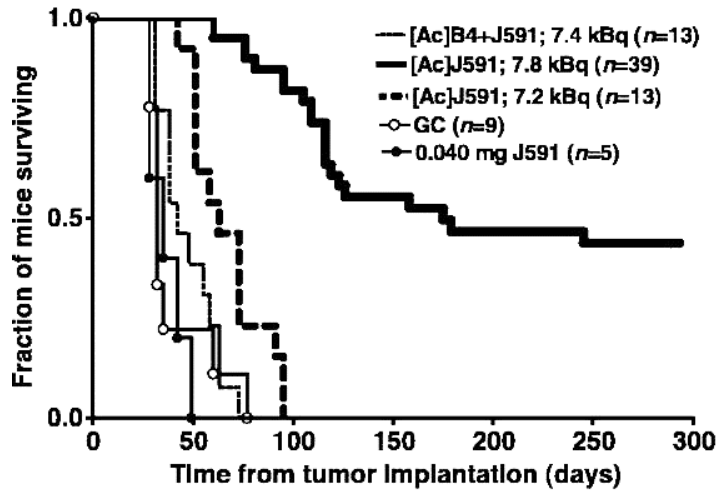
Rosenblat TL *et al. Clin Cancer Res* 2010; 16:5303-5311.

Actinium-225: An Alpha-Particle Nanogenerator

^{225}Ac —α, 10 days→ ^{221}Fr —α, 4.9 min→ ^{217}At —α, 0.032 sec→ ^{213}Bi —α, 46 min→ Stable Isotopes

- Short half-life and need for on-site generator limit use of ^{213}Bi.
- ^{225}Ac can be stably conjugated to antibodies using DOTA.
- ^{225}Ac-labeled antibodies are 1,000-10,000 times more potent *in vitro* compared to ^{213}Bi analogs.
- Nanocurie doses of ^{225}Ac-labeled antibodies prolong survival of mice in xenograft models.

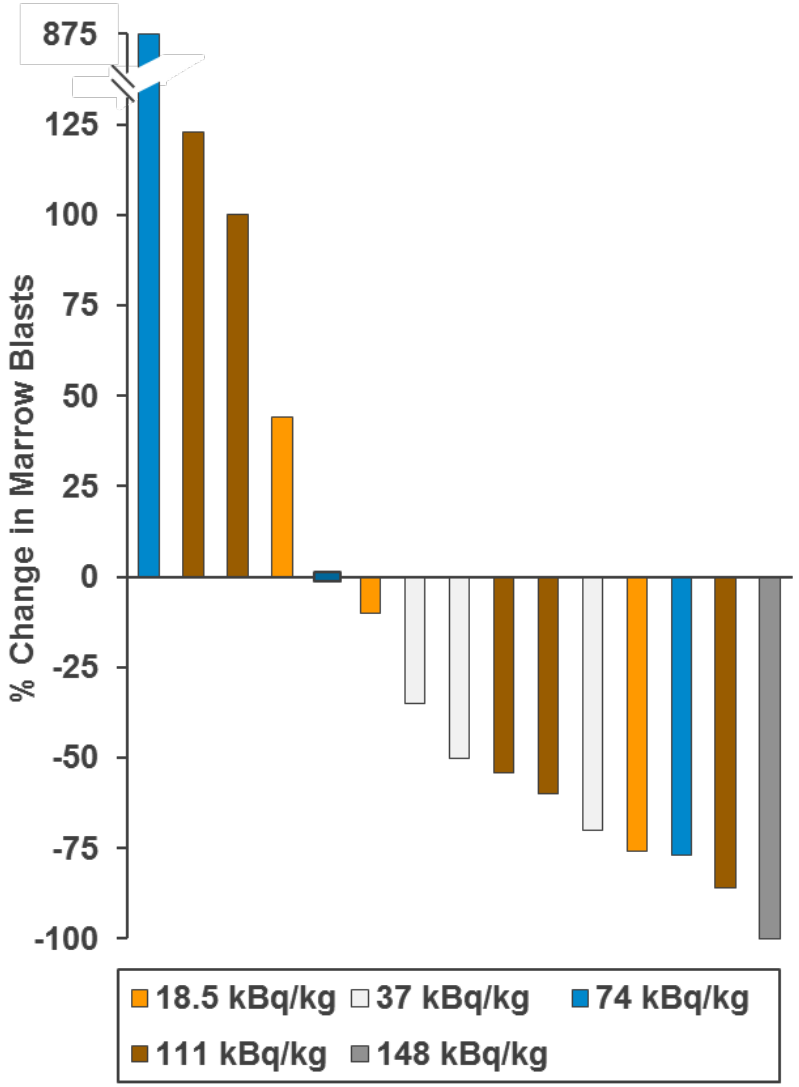




McDevitt MR *et al. Science* 2001; 294:1537-1540.

Phase I Trial of ^{225}Ac-Lintuzumab

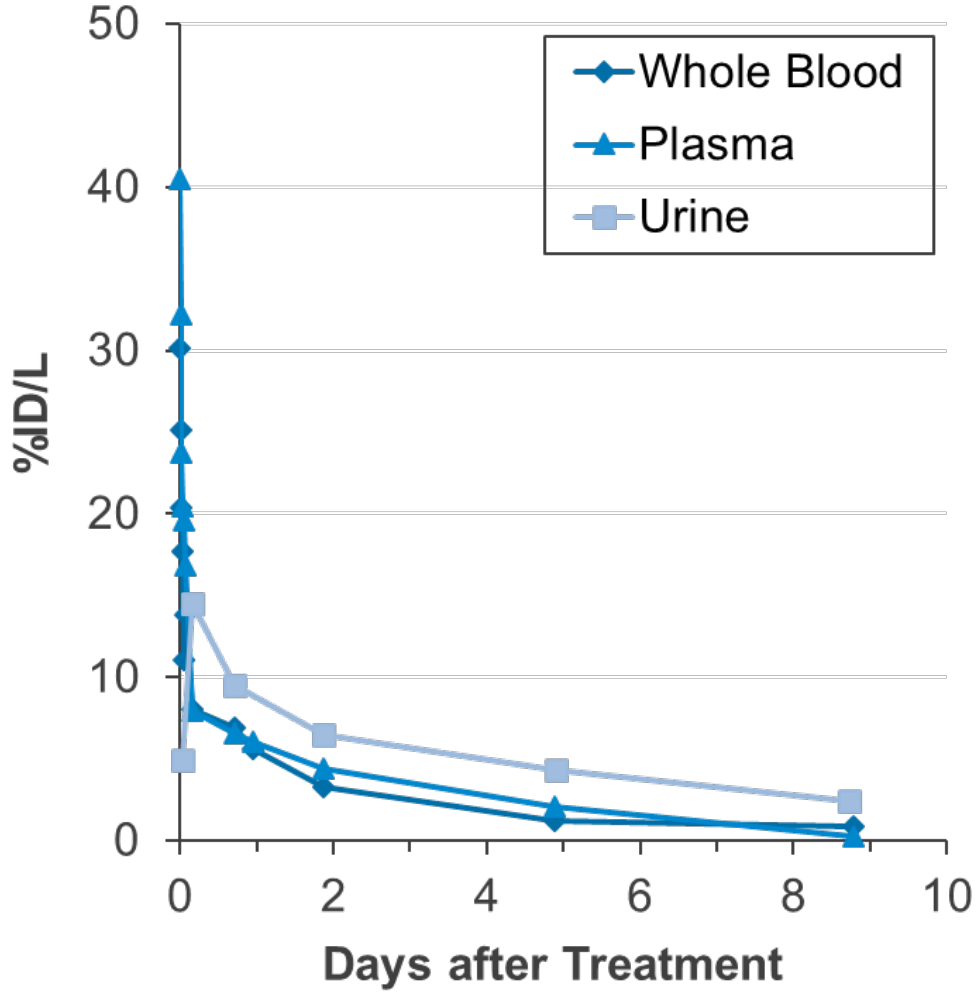
- 18 patients with R/R AML received a single dose of 18.5-148 kBq/kg
- DLT was myelosuppression
- No renal toxicity was seen
- MTD was 111 kBq/kg
- Bone marrow blasts were reduced in 10/15 (67%) evaluable patients
- 8 patients (53%) had marrow blast reductions of ≥ 50%
- 3 patients achieved ≤ 5% marrow blasts at doses of 37, 111, and 148 kBq/kg



Updated from Jurcic JG *et al. Blood* 2011; 118:768.

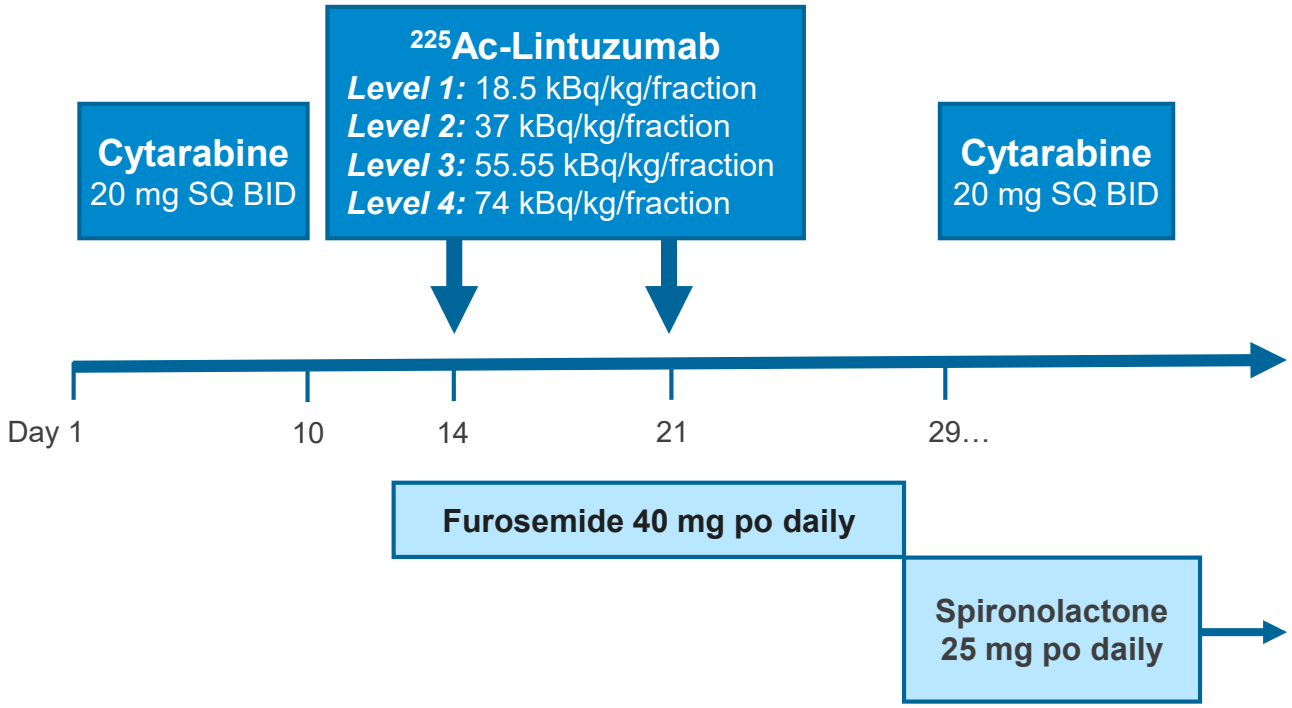
Pharmacokinetics of ^{225}Ac-Lintuzumab

- Determined by γ counting at energy windows for:
  - ^{221}Fr (185-250 KeV)
  - ^{213}Bi (360-480 KeV)
- Two-phase elimination kinetics were seen:
  - Mean plasma $t_{½}$-α = 1.9 hrs
  - Mean plasma $t_{½}$-β = 38 hrs
- Similar to ^{131}I- and ^{90}Y- but distinct from ^{213}Bi-lintuzumab



Updated from Jurcic JG *et al. Blood* 2011; 118:768.

Low-Dose Cytarabine Plus ^{225}Ac-Lintuzumab



Objective Responses

Response	Dose Level (kBq/kg/fraction)				Total (N=18)
	18.5 (n=3)	37 (n=6)	55.5 (n=3)	74 (n=6)	
CR	0	0	1 (33%)	0	1 (6%)
CRp	0	1 (17%)	0	1 (17%)	2 (11%)
CRi*	0	0	1 (33%)	1 (17%)	2 (11%)
Overall	0	1 (17%)	2 (67%)	2 (33%)	5 (28%)

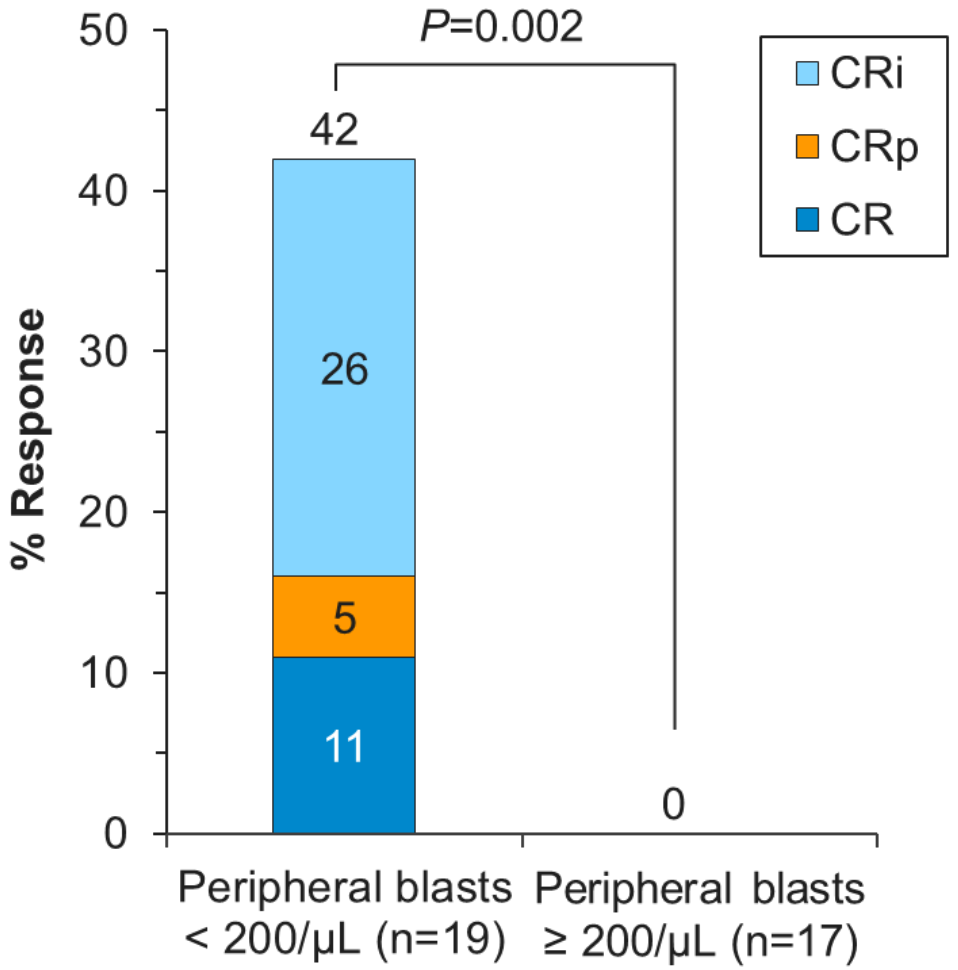
Abbreviations: CR, complete remission; CRp, CR with incomplete platelet recovery; CRi, CR with incomplete blood count recovery.

All responses seen after Cycle 1.

Jurcic JG *et al.* SNMMI 2017; abstract 456.

Effect of Peripheral Blasts on Response

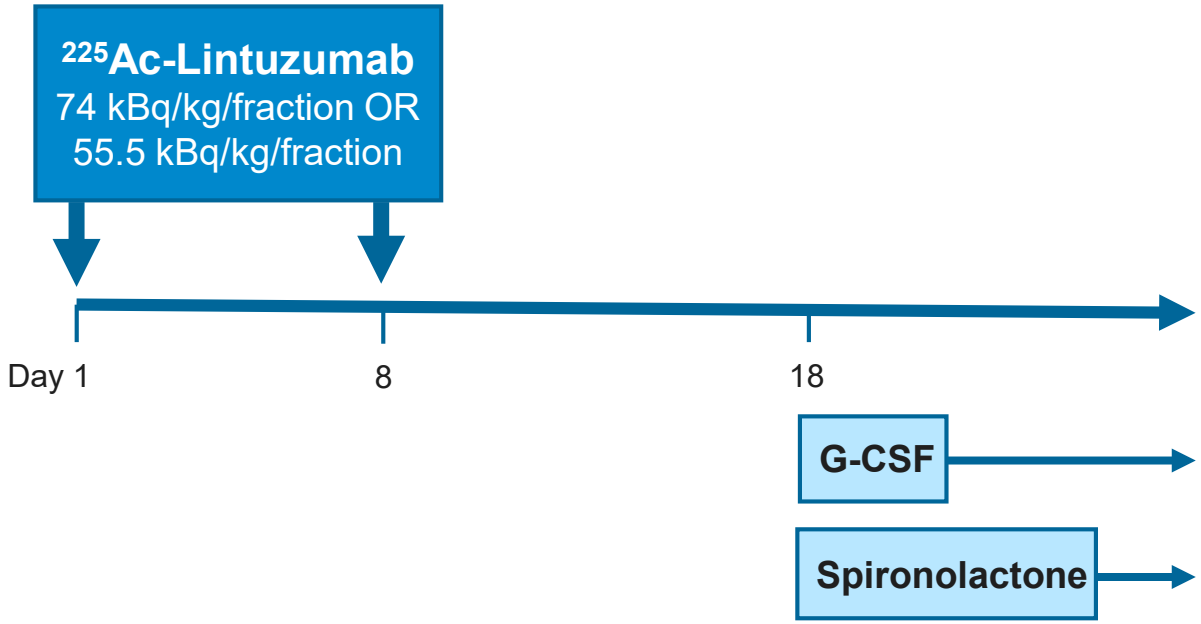
- 36 patients from initial 2 trials analyzed for response by:
  - Age
  - Disease characteristics
    - Newly diagnosed vs. relapsed
    - *De novo* vs. secondary AML
    - Genetic risk category
  - Disease burden
    - Bone marrow blast percentage
    - Peripheral blood blast count
  - Treatment regimen
    - Administered activity
    - Single vs. fractionated dose
    - Monotherapy vs. prior LDAC
- Only significant predictor of response was peripheral blood blast count
  - Circulating blasts may alter biodistribution leading to decreased delivery of isotope to marrow



Berger M *et al.* Proc TAT 10 2017.

Phase II Trial of ^{225}Ac-Lintuzumab Monotherapy

Study Design and Clinical Outcomes

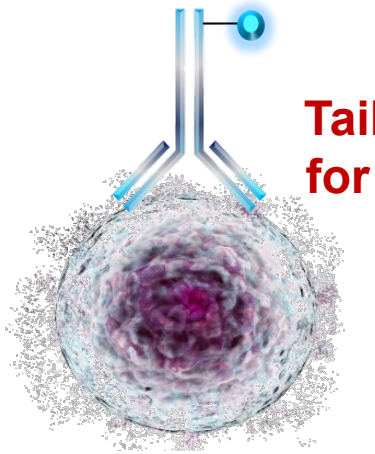


Dose (kBq/kg)	Response Rate	Patients with Gr 4 Thrombocytopenia > 6 weeks	Patients with Gr 4 Neutropenia > 6 weeks
74 (n=13)	69% 1 CR, 2 CRp, 6 CRi	46%	38%
55.5 (n=27)	22% 3 CRp, 3 CRi	30%	40%

Abbreviations: CR, complete remission; CRp, CR with incomplete platelet recovery; CRi, CR with incomplete blood count recovery.

Finn LE *et al. Blood* 2017; 130:2638; Atallah EL *et al. Blood* 2018; 130:1457; Berger M *et al.* TAT 11 2019; poster 61.

Future Development of ^{225}Ac-Lintuzumab in AML/MDS



Tailored ^{225}Ac dose for specific clinical application

High-Dose

- Targeted Conditioning → Conditioning for HCT in High-Risk MDS

Low-Dose

- Combination Therapy → Combination with Venetoclax
- Combination Therapy → Combination with CLAG-M
- Combination Therapy → Combination with 7+3 Induction

- Single-Agent → Minimal Residual Disease in AML

Conclusions

- Early studies with ^{213}Bi-lintuzumab provided proof-of-principle that systemically administered targeted α-particle therapy is feasible.
- ^{225}Ac-lintuzumab is active against advanced AML.
- ^{225}Ac-lintuzumab has produced remissions in older patients with untreated AML as a single agent and in combination with LDAC.
- These studies provide the rationale for use of ^{225}Ac-lintuzumab in combination with other agents in AML and MDS.

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