Other Novel Agents and Investigational Strategies for Patients with Acute Myeloid Leukemia

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Research To Practice
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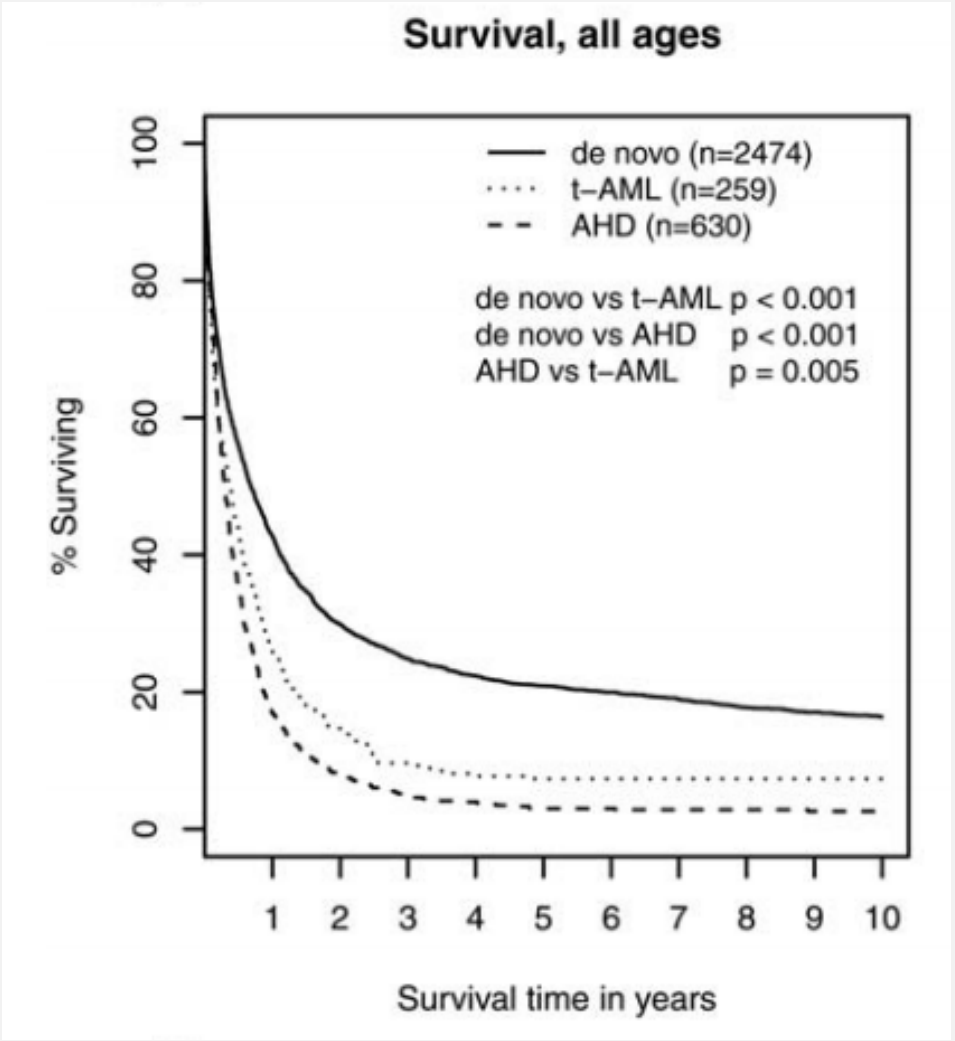
Definition of Secondary AML

- AML from an antecedent hematological disorder
  - Most commonly MDS (1/3 of MDS patients will develop AML)
  - Could also be from MPN or a non-malignant antecedent disorder (e.g. aplastic anemia)
- Treatment-related AML
  - WHO defined as history of exposure to alkylating agents and/or topoisomerase II inhibitors and/or ionizing radiation to large fields including bone marrow
  - Other implicated therapies include antimetabolites or antitubulin agents but their relationship is less certain.

Greenberg et al, Blood 1997
Arber et al, Blood 2016

De Novo AML vs Secondary AML

- Secondary AML patients are older, have more adverse biological risk factors (cytogenetics/TP53)
- Lower response rates to conventional treatments
- Worse overall survival
- Incurable without an allogeneic stem cell transplantation

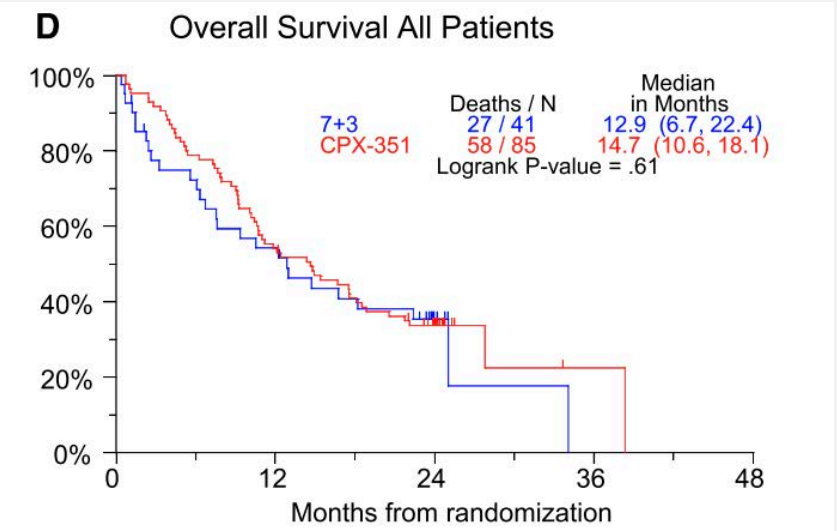


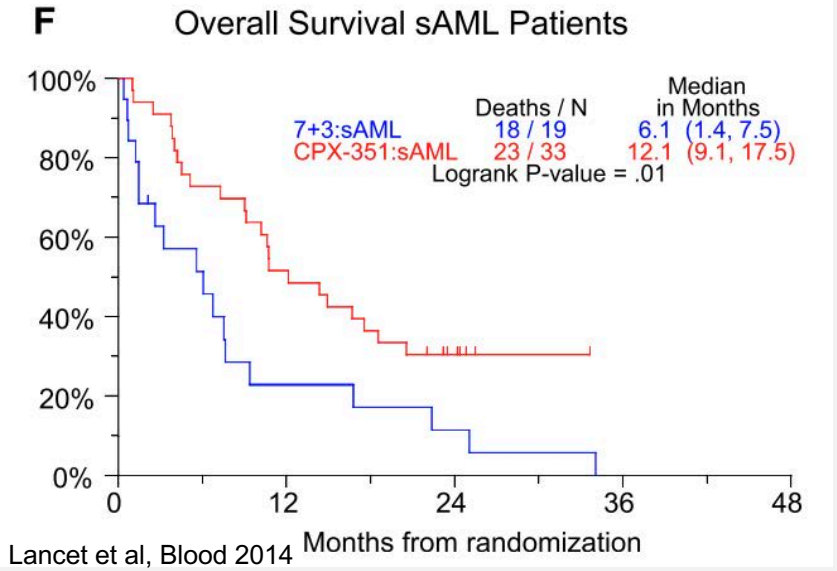
Courtesy of Daniel A Pollyea, MD, MS

Hulegardh et al, AJH 2015

Treatment Consideration for Secondary AML: Liposomal Daunorubicin and Cytarabine (CPX-351)

- Liposomal formulation of 7+3
- Fixed molar ratio of daunorubicin to cytarabine (1:5)
- No improvement in OS compared to 7+3 for all comers AML
- Statistically significant improvement for the secondary AML subgroup
- Confirmed in a follow-up study…



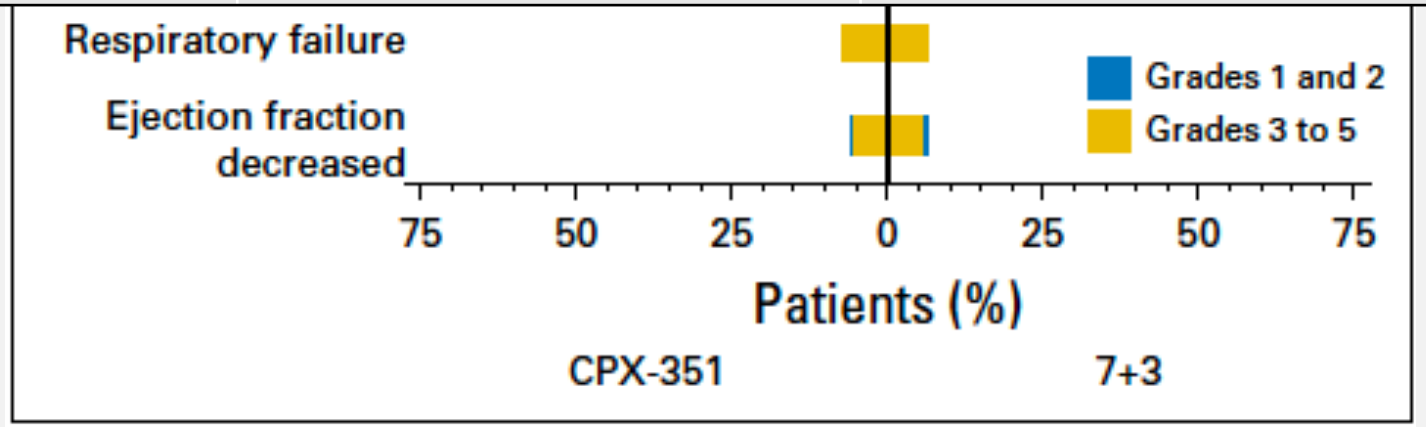


Courtesy of Daniel A Pollyea, MD, MS

Lancet et al, Blood 2014

Secondary Endpoints Included Safety Data and Response Rates

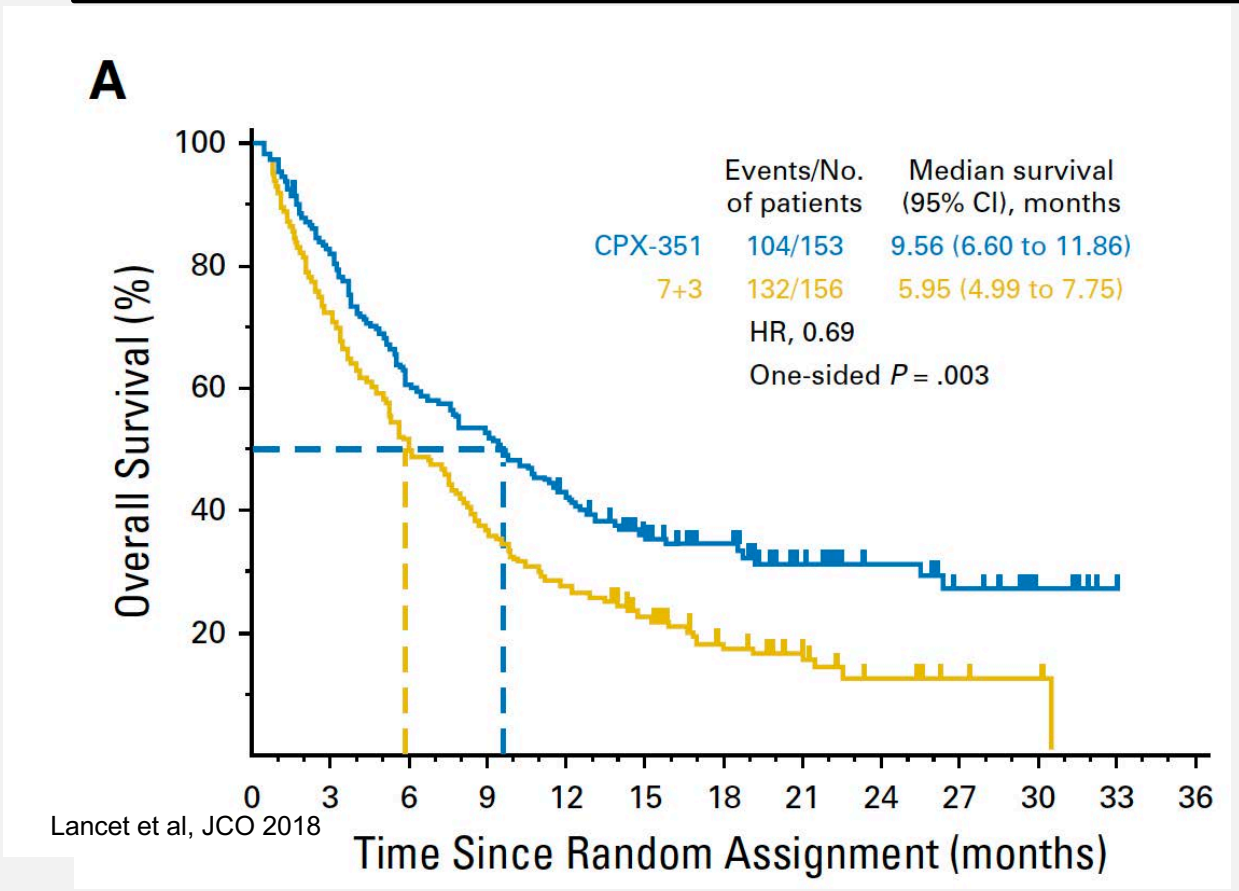
Best Response Rates			
Response	CPX-351, No (%)	7+3, No (%)	OR (95% CI)
Number of patients	153	156	
CR + CRi	73 (47.7)	42 (33.3)	1.77 (1.11 to 2.81)
CR	57 (37.3)	40 (25.6)	1.69 (1.03 to 2.78)



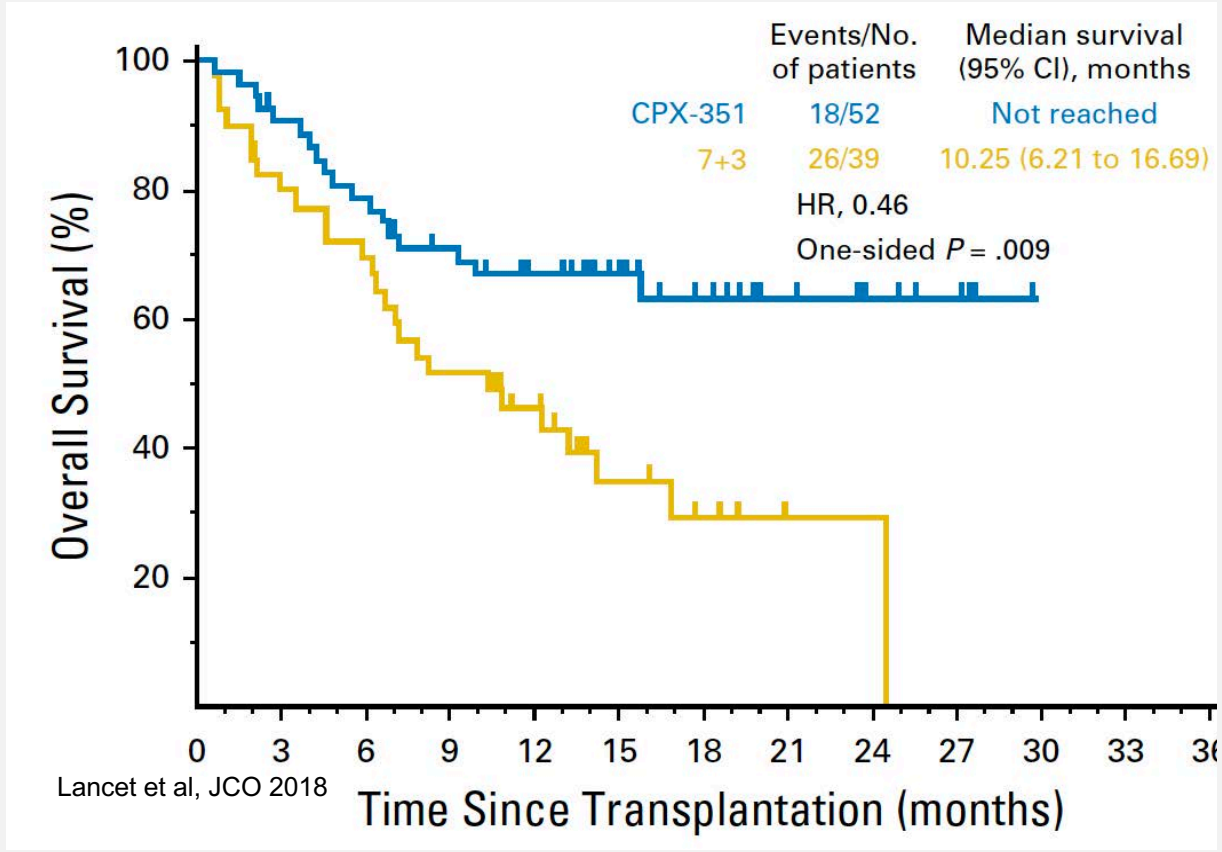
Lancet et al, JCO 2018

Courtesy of Daniel A Pollyea, MD, MS

Phase III Study 301: CPX-351 vs 7+3 for Older Patients with Newly Diagnosed Secondary AML



Lancet et al, JCO 2018



Lancet et al, JCO 2018

- Consider CPX-351 for newly diagnosed, *induction eligible* secondary AML patients, particularly if they would be suitable candidates for a transplant
- How can you tell if they have secondary AML? Probably OK to wait (up to 15 days) for marrow results (Rollig et al, Blood 2020)
- Caution if TP53+ (Lindsley et al, ASH 2019)

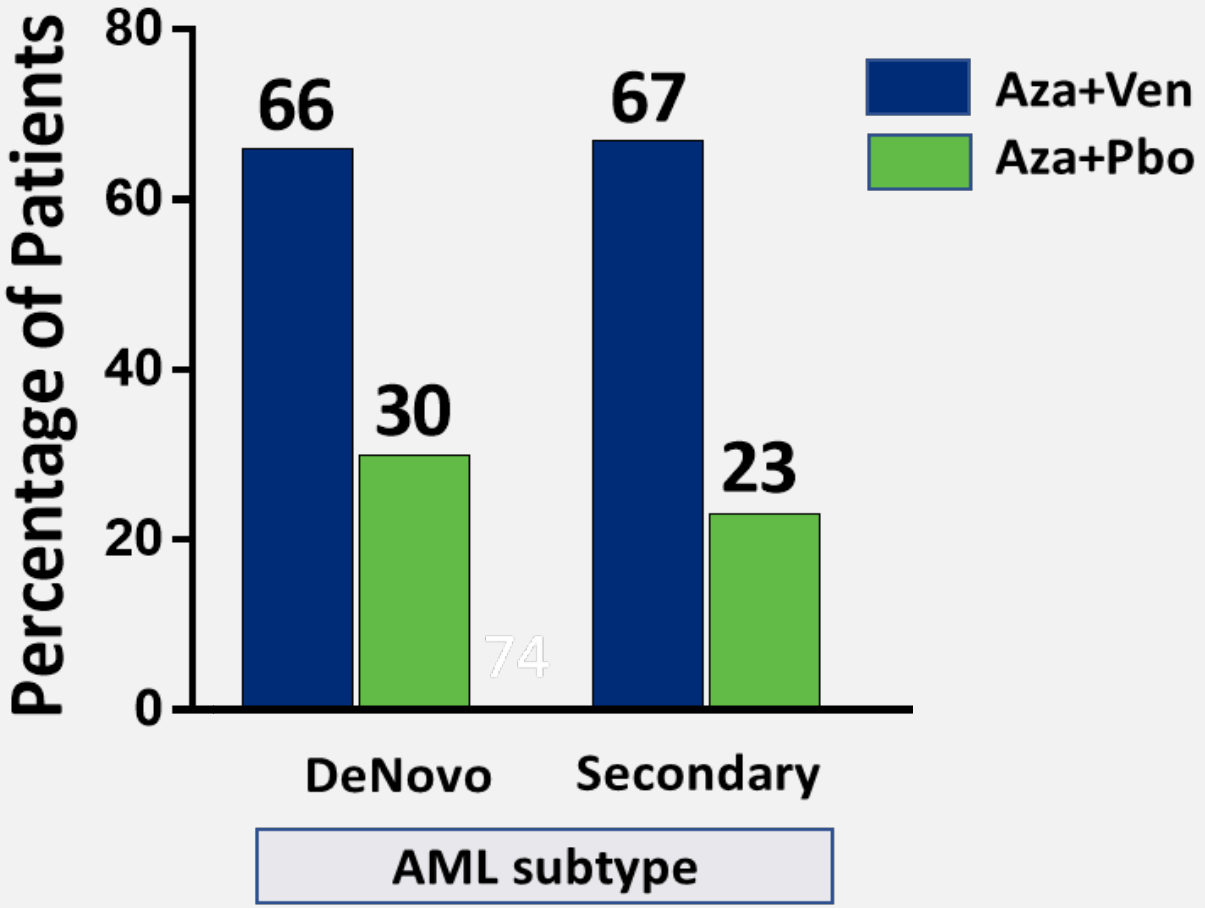
Courtesy of Daniel A Pollyea, MD, MS

Other Investigations Related to CPX-351 in Myeloid Malignancies

Disease Setting and/or Drug Combination	ClinicalTrials.gov Study Number
First line AML with venetoclax	NCT04038437
First line AML with palbociclib	NCT03844997
First line FLT3+ AML with quizartinib	NCT04128748
First line AML with glasdegib	NCT04231851
Relapsed FLT3+ AML with quizartinib	NCT04209725
Relapsed IDH2+ AML with enasidenib	NCT03825796
Relapsed AML with gemtuzumab	NCT03904251
Hypomethylator failure MDS	NCT03957876 and NCT04109690
First line high risk MDS	NCT03572764
With ruxolitinib for advanced phase MPNs	NCT03878199

Courtesy of Daniel A Pollyea, MD, MS

Secondary AML Patients Unfit for Intensive Chemotherapy

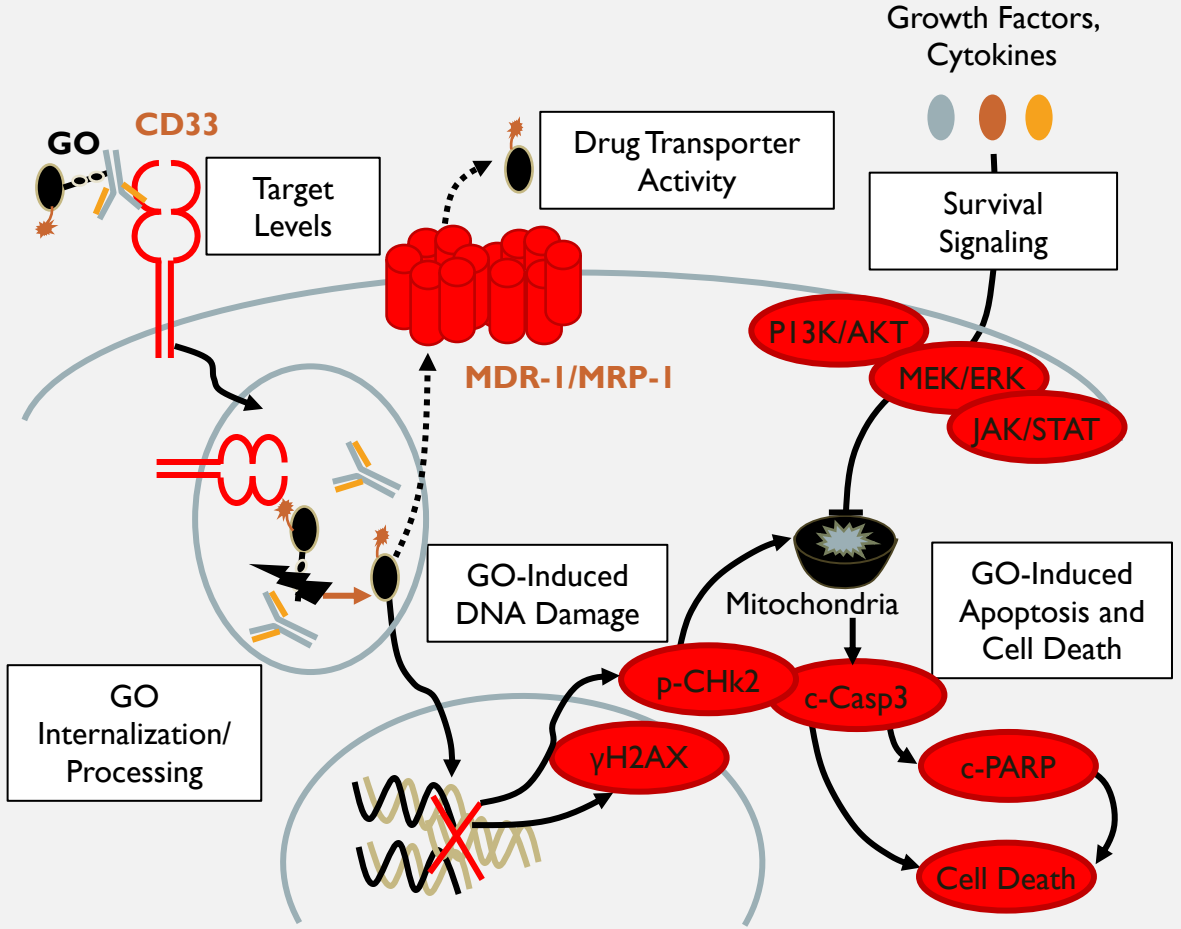


DiNardo et al, EHA 2020

Courtesy of Daniel A Pollyea, MD, MS

CD33 Antibody Drug Conjugate: Gemtuzumab Ozogamicin

- Monoclonal anti-CD33 antibody linked to calicheamicin
- Internalized and cleaved in lysosomes to release calicheamicin
- Calicheamicin enters nucleus and interacts with DNA causing double-strand breaks initiating apoptosis
- Approved in 2000 based on 30% ORR in R/R AML



Rosen DB, et al. *PLoS One.* 2013;8:e53518.

Sievers et al, JCO 2001

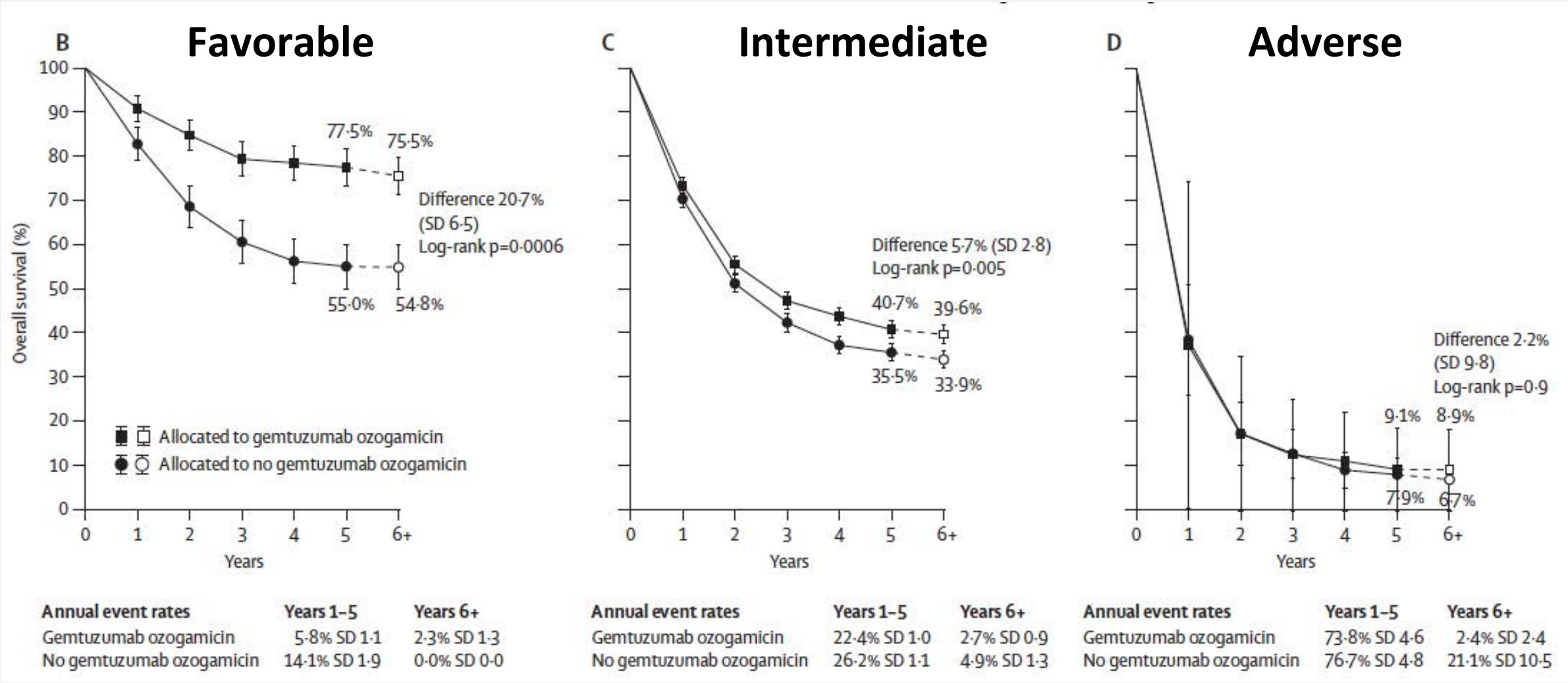
Courtesy of Daniel A Pollyea, MD, MS

Gemtuzumab in AML: Select Phase III Results

Study	N	Treatment	Results of GO vs Comparator
MRC/NCRI AML1 (2011)	1113	GO (3 mg/m^2) + either ADE, DA, or FLAG-IDA	▪ Improved 5-yr OS for favorable-risk group ▪ No difference in ORR, TRM, relapse, survival
ALFA 0701 (2012)	280	GO (3 mg/m^2) + DA	▪ Improved 2-yr EFS, RFS, OS ▪ No difference in ORR or mortality
MRC/NCRI AML (2012)	1115	GO (3 mg/m^2) + either DA or DCLo	▪ Reduced 3-yr relapse risk, and superior DFS and OS ▪ No difference in TRM
SWOG S0106 (2013)	637	GO (6 mg/m^2) + DA induction vs DA	▪ No difference in CR, DFS, OSs

Courtesy of Daniel A Pollyea, MD, MS

Meta Analysis of Gemtuzumab with Induction Chemotherapy



Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	5·8% SD 1·1	2·3% SD 1·3
No gemtuzumab ozogamicin	14·1% SD 1·9	0·0% SD 0·0

Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	22·4% SD 1·0	2·7% SD 0·9
No gemtuzumab ozogamicin	26·2% SD 1·1	4·9% SD 1·3

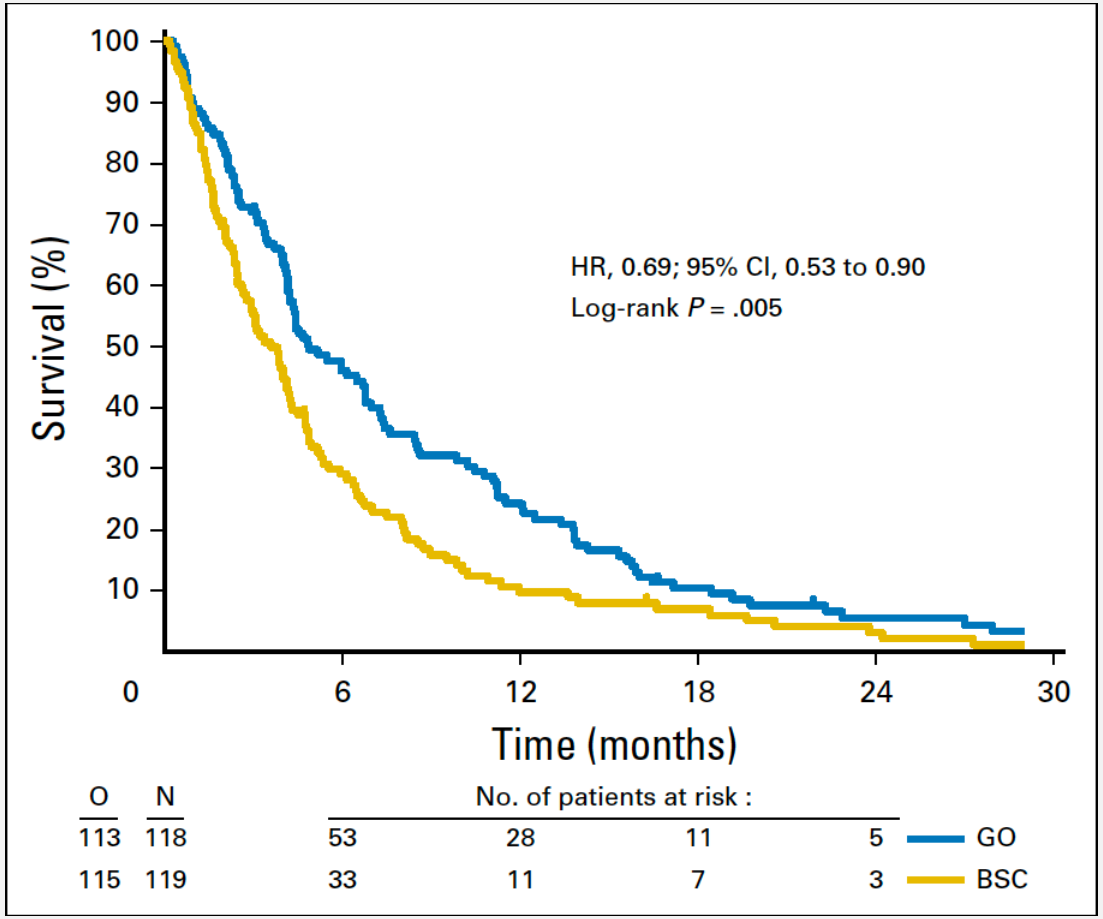
Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	73·8% SD 4·6	2·4% SD 2·4
No gemtuzumab ozogamicin	76·7% SD 4·8	21·1% SD 10·5

Hills RK, et al. *Lancet Oncology. 2014*

Courtesy of Daniel A Pollyea, MD, MS

Single Agent Gemtuzumab

Compared with best supportive care for older untreated patients



Amadori et al, JCO 2016

Response rates in relapsed patients

Type of Remission	No. of Patients (N – 142)	%	95% CI
CR	23	16	11-23
CR_p	19	13	8-20
OR*	42	30	22-38

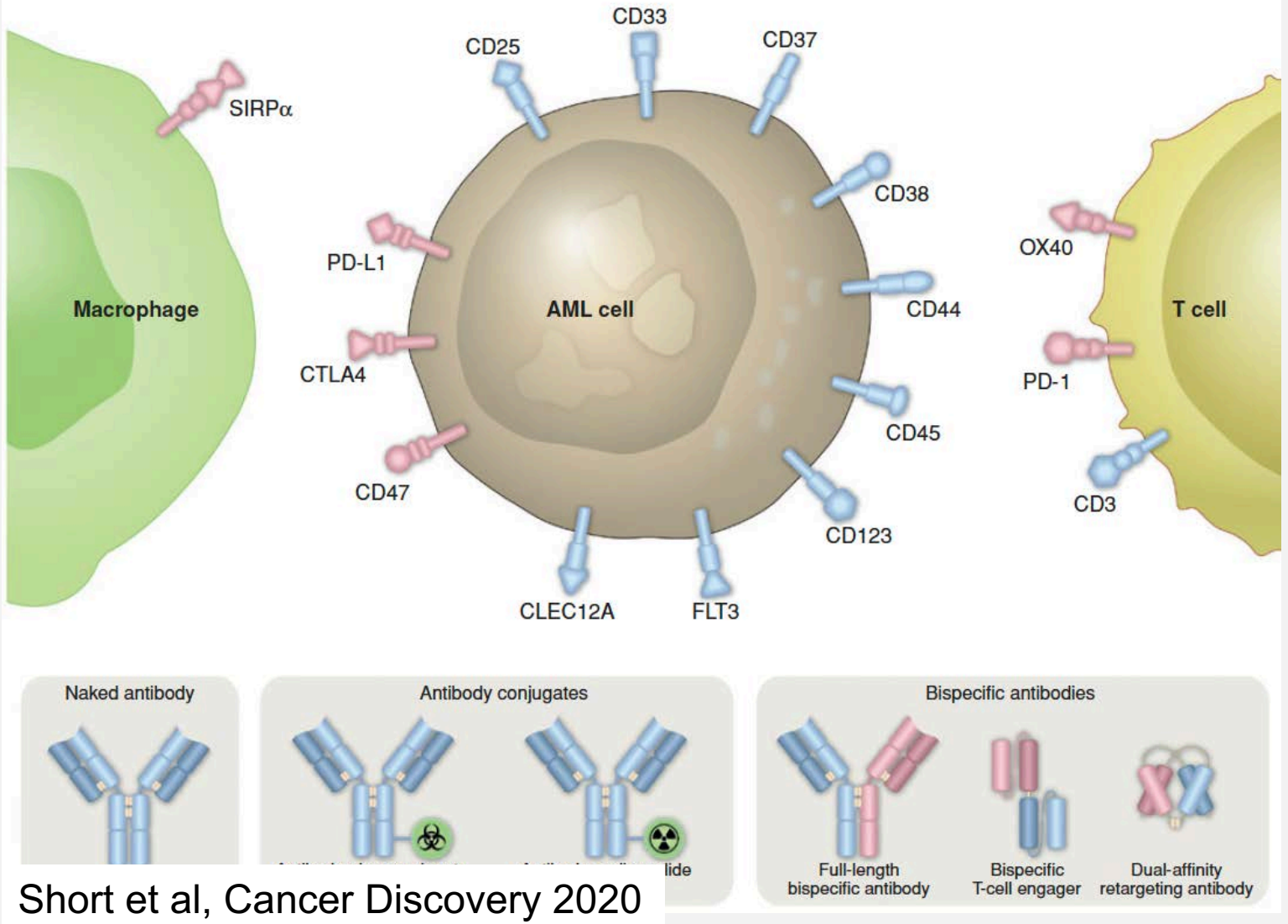
*OR = CR + CR_p.

Sievers et al, JCO 2001

Courtesy of Daniel A Pollyea, MD, MS

Immunotherapeutic Approaches in AML

- Antibody-drug conjugates
- T-cell based therapies
  - Multi-valent antibodies
  - Immune checkpoint (T-cell *and* macrophage based)
  - CAR-T therapies



Short et al, Cancer Discovery 2020

Courtesy of Daniel A Pollyea, MD, MS

Antibody-Drug Conjugates

Target	Drug(s)	Clinical Experience	Citation
CD33	Gemtuzumab ozogamicin	Extensive, previously reviewed	Multiple
	IMG779	Modest activity	Cortes et al, Blood 2018
CD123	IMGN632	Blast reduction and modest response rates	Daver et al, ASH 2019
	SGN-CD123A	Not reported	
CD25	Camidanlumab tesirine	Minimal responses, manageable toxicity	Goldberg et al, Leukemia Research 2020
CD30	Brentuximab vedotin	Used with chemotherapy for R/R AML; ~40% ORR	Narayan et al, Cancer 2020
CLL-1	Several	Pre-clinical	

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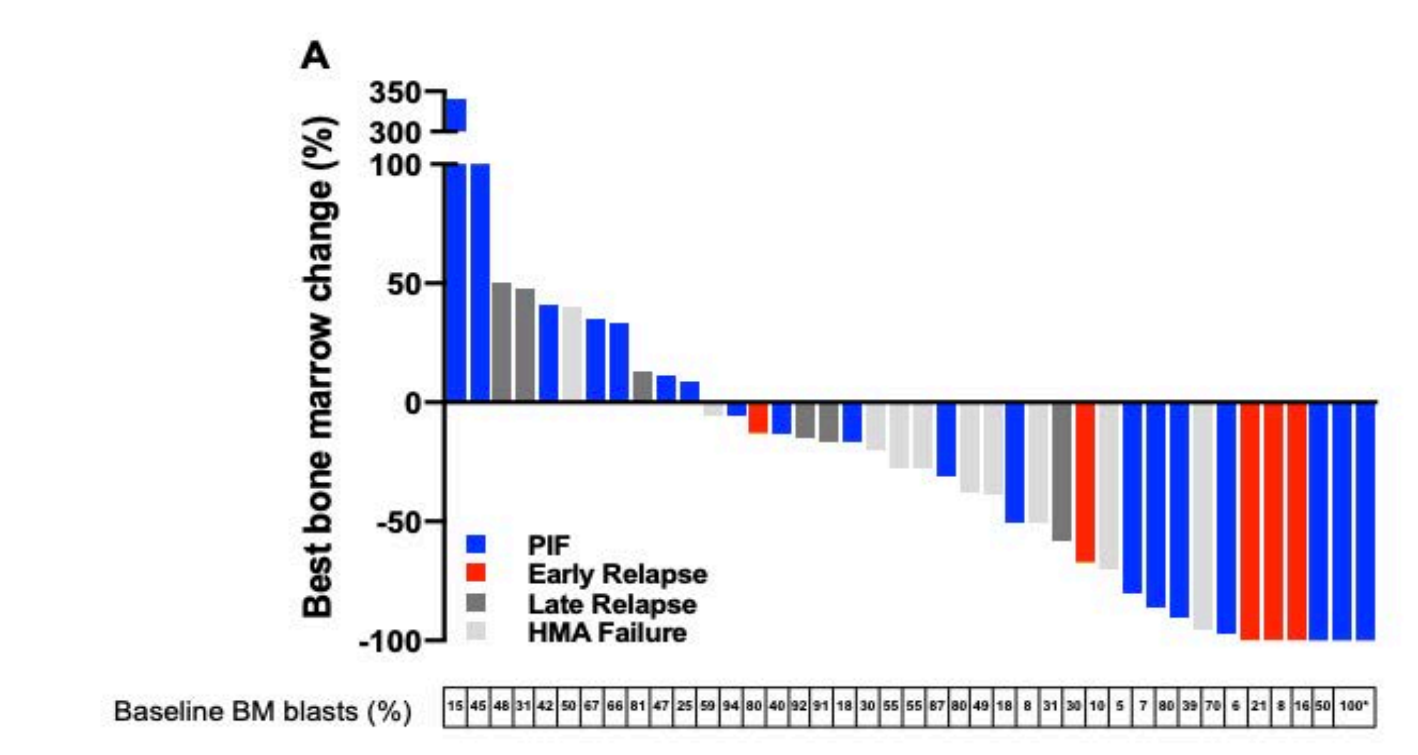
Multi-Valent Antibodies

- Conjugate an AML antibody of interest (CD123, CD33) with a T-cell engager (CD3) or NK-cell engager (CD16)
- Flotetuzumab (C123, CD3) for R/R AML



Uy et al, Blood 2020

Courtesy of Daniel A Pollyea, MD, MS

Immune Checkpoint Inhibitors

- PD-1/PD-L1 inhibitors with azacitidine in R/R AML

Best response	Azacitidine/nivolumab
Overall response rate	23 (33)
CR	4 (6)
CRi/CRp	11 (16)
PR	1 (1)
HI[a] (6 months+)	7 (10)
Stable disease (6 months+)[b]	6 (9)
Nonresponders	41 (58)
Median cycles to response	2 (1–13)
Median follow-up, in months	13.3 (8.2–25.5)

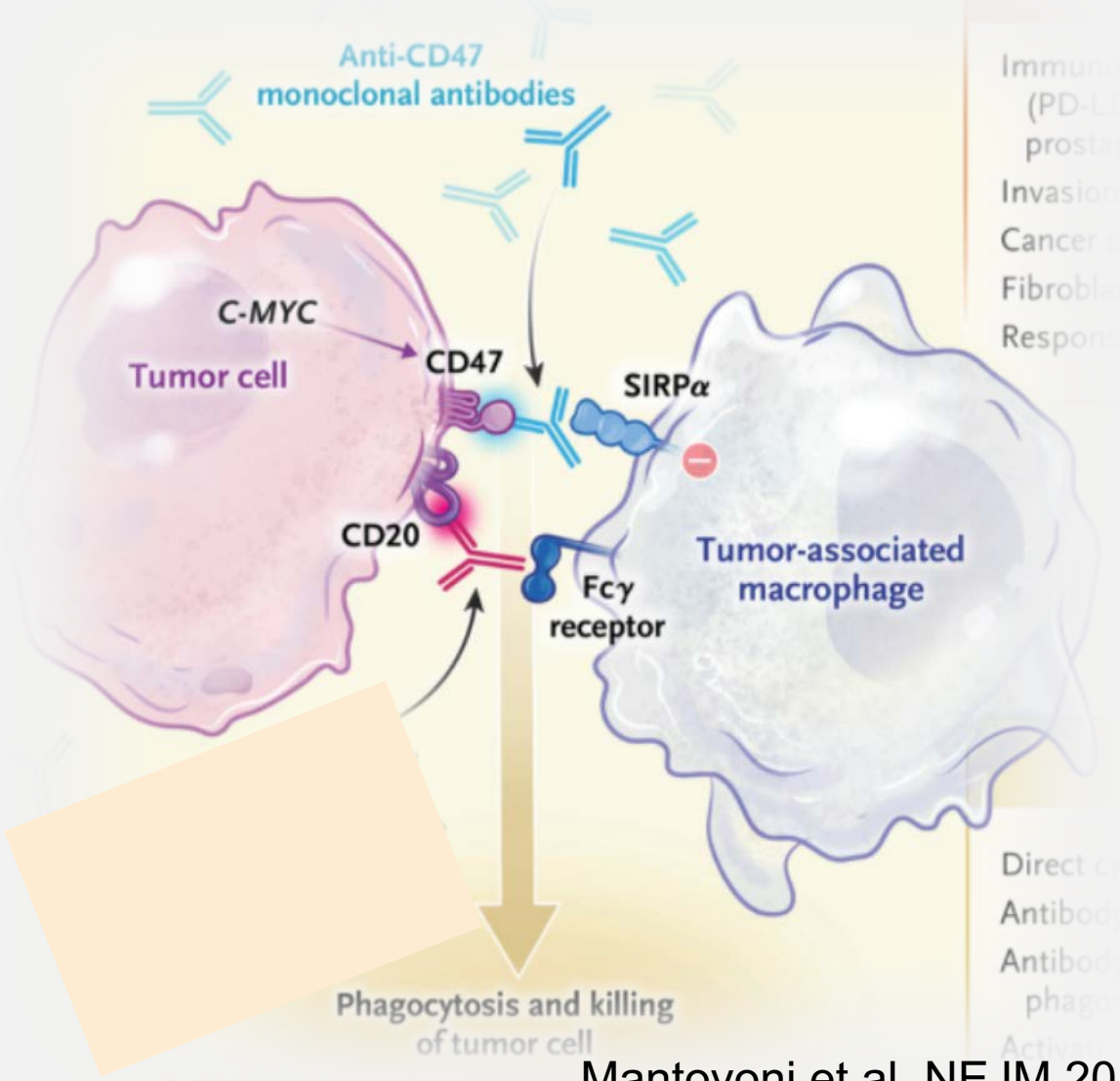
Daver et al, Cancer Discovery 2019

- Ongoing work with pembrolizumab and durvalumab in combinations and in various settings…

Courtesy of Daniel A Pollyea, MD, MS

Targeting CD47: Macrophage Immune Checkpoint Inhibitor

- Magrolimab
  - Anti-CD47 monoclonal antibody
  - Allows for the elimination of target cells via macrophage phagocytosis



Courtesy of Daniel A Pollyea, MD, MS

Mantovoni et al, NEJM 2018

Magrolimab + Azacitidine in Newly Diagnosed Unfit AML Patients

Efficacy: Response

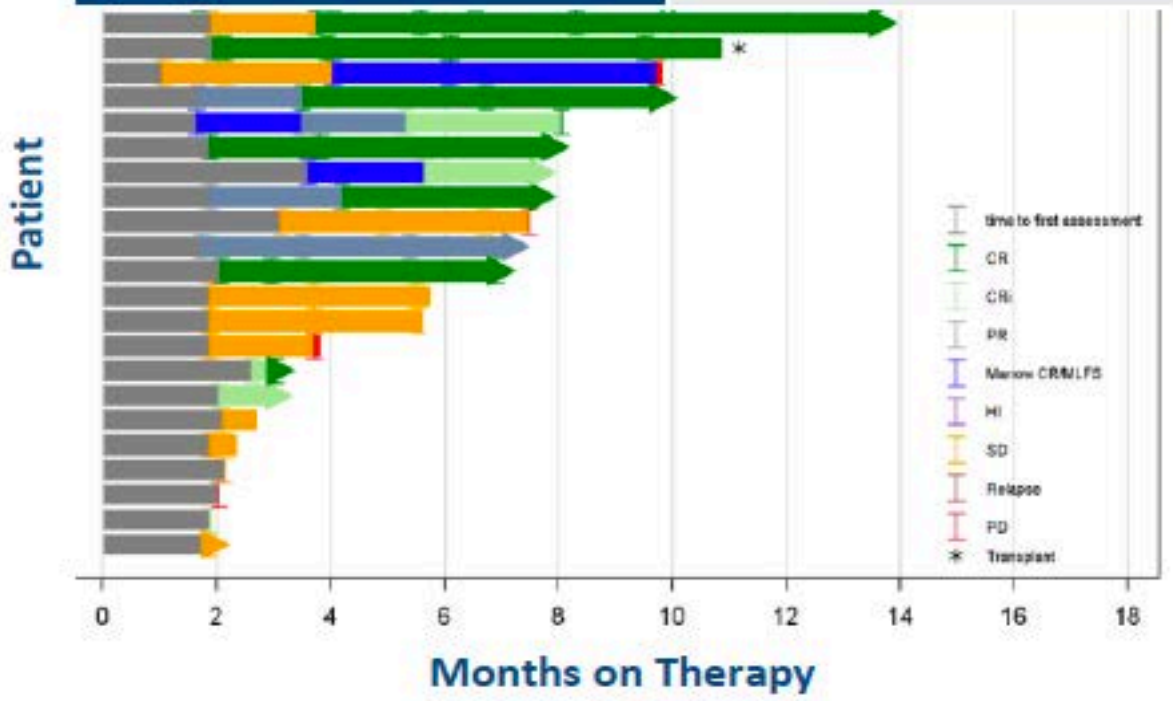
Best Overall Response	1L AML N=25	TP53 Mutant N=12
ORR	16 (64%)	9 (75%)
CR	10 (40%)	5 (42%)
CRi	4 (16%)	4 (33%)
PR	1 (4%)	0
MLFS	1 (4%)	0
SD	8 (32%)	2 (17%)
PD	1 (4%)	1 (8%)
MRD negativity[1]	8/16 (50%)	4/9 (44%)

onders

Daver et al, EHA 2020

Efficacy: Durability

Median DOR in mos (range)	Not reached (0.03+ – 15.1+)
Median follow-up in mos (range)	9.4 (1.9–16.9)



Courtesy of Daniel A Pollyea, MD, MS

CAR T-Cell Therapies in AML

- Multiple potential approaches and targets
- No published data yet

Courtesy of Daniel A Pollyea, MD, MS

Unique Toxicities of Immunotherapies

- Antibody-drug conjugates
  - Specific to target (CD33 can cause prolonged cytopenias and veno-occlusive disease)
- Multi-valent antibodies
  - Specific to target; CRS-like symptoms
- Checkpoint inhibitors
  - Multi-organ, auto-immune; can be subtle
- CD47
  - Hemolytic anemia
- CAR T-Cell Therapies
  - CRS-like symptoms

Courtesy of Daniel A Pollyea, MD, MS

Case 1

79 year old healthy male with newly diagnosed AML. Had intermediate cytogenetics with a trisomy 8 and mutations in ASXL1, BCORL1, TET2 and RUNX1. He started venetoclax + azacitidine and experienced a CRi after cycle 1. He continued therapy and after 10 cycles had a routine bone marrow biopsy that showed 10% blasts. No new mutations on repeat sequencing. He stopped venetoclax and azacitidine and had two cycles of decitabine; a repeat bone marrow biopsy showed 30% blasts. No new mutations on repeat sequencing; he was CD33+. He had a course of gemtuzumab ozogamicin (three doses over 28 days) and a repeat bone marrow biopsy now showed 50% blasts. No new mutations on repeat sequencing. The patient opted for hospice and passed away 3 weeks later.

Courtesy of Daniel A Pollyea, MD, MS

Case 2

67 year old woman with hyperlipidemia and hypothyroidism, 4 year history of low grade MDS that was followed expectantly, presents with 2 weeks of fatigue, weakness, easy bruising and dyspnea. Bone marrow biopsy shows AML with complex, monosomal karyotype and mutations in TP53 and PTPN11. She was a suitable candidate for induction chemotherapy and so received CPX-351 on days 1, 3 and 5. Experienced CR with MRD after prolonged count recovery (day 43). While contemplating a transplantation in first remission patient was admitted for neutropenic fever and passed away from sepsis, 10 weeks after initial diagnosis.

Courtesy of Daniel A Pollyea, MD, MS


Thank You!