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2021 Updates in Leukemia

UNC Lineberger Cancer Network
17 November 2021

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2021 Leukemia Update Outline

- Acute Myeloid Leukemia—improving outcomes for older adults, high risk groups, approval of oral therapies
- Acute Lymphoblastic Leukemia--CAR-T cells approved for adults
- Chronic Myeloid Leukemia—a new class of drug approved
- Leukemia in the COVID-19 pandemic

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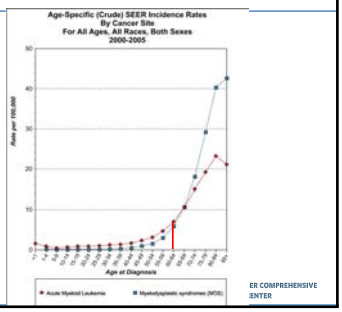
Myeloid disease in the elderly

- Median age of AML/MDS at diagnosis:
  - 65-70 years

(Estey E. JCO 2007; 25(14):1908-15)

- Standard definition of elderly in AML is >/= 60 y.o.



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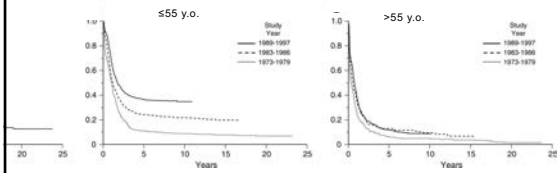
Lack of progress in older patients



Tallman, M. S. et al. Blood 2005;106:1154-1163

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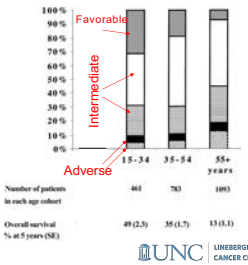
Older patients have higher risk AML

- Frequency of favorable cytogenetics:
  - <55yo: 24%
  - >/=55yo: 7%
- Complex:
  - <55yo: 6%
  - >/=55yo: 13%



Grimwade, D. et al. Blood 2001;98:1312-1320

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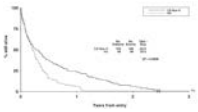
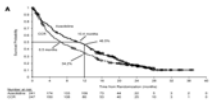
For the frailer patients…something is better than nothing…..

- **LDAC:**
  - **CR in 18%**
  - **Median time to CR 114 days**
  - **26% 2 month mortality**



Burnett AK et al. Cancer 2007;109:1114–24.

- Azacitidine:
  - CR 19.5%%, CR+CRi 27.8%
  - 7.5% early death



Dombret H et al. Blood. 2015;126(3):291-299.

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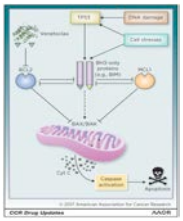
Now we know for many, more may be better…Venetoclax—BCL2 inhibitor



Roberts AW et al. Clin Cancer Res; 23(16); 4527-33.

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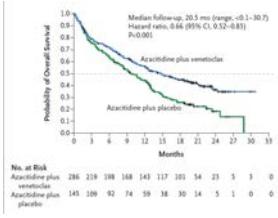
Azacitidine-venetoclax phase 3



-CR+Cri:
- -Aza-ven: 66.4%
- -Aza: 28%
- (p<.001)

-RBC transfusion independence:
- -Aza-ven: 59.8%
- -Aza: 35.2%

-platelet transfusion independence:
- -Aza-ven: 68.5%
- -Aza: 49.7%

DiNardo CD et al. *N Engl J Med* 2020;383:617-29.

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Select toxicities more frequent with aza-ven

Event	Azacitidine–Venetoclax Group (N=283)		Azacitidine–Placebo Group (N=144)	
	All Grades†	≥Grade 3‡	All Grades†	≥Grade 3‡
	number of patients (percent)			
Hematologic adverse events	236 (83)	233 (82)	100 (69)	98 (68)
Thrombocytopenia	130 (46)	126 (45)	58 (40)	55 (38)
Neutropenia	119 (42)	119 (42)	42 (29)	41 (28)
Febrile neutropenia	118 (42)	118 (42)	27 (19)	27 (19)
Infections	239 (84)	180 (64)	97 (67)	74 (51)
Pneumonia	65 (23)	56 (20)	39 (27)	36 (25)
Serious adverse events§	235 (83)	232 (82)	105 (73)	102 (71)
Febrile neutropenia	84 (30)	84 (30)	15 (10)	15 (10)
Anemia	14 (5)	14 (5)	6 (4)	6 (4)
Neutropenia	13 (5)	13 (5)	3 (2)	3 (2)
Atrial fibrillation	13 (5)	10 (4)	2 (1)	2 (1)
Pneumonia	47 (17)	46 (16)	32 (22)	31 (22)
Sepsis	16 (6)	16 (6)	12 (8)	12 (8)

DiNardo CD et al. *N Engl J Med* 2020;383:617-29.

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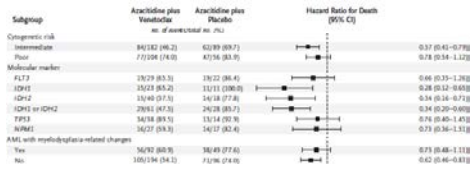
Aza-ven preferentially benefits certain subgroups



DiNardo CD et al. *N Engl J Med* 2020;383:617-29.

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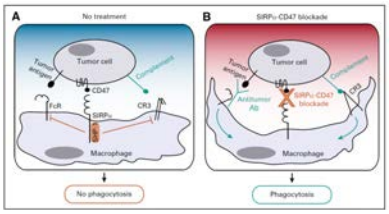
Hope on the horizon for TP53 mutant MDS and AML?



Veillette A and Tang Z. *J Clin Oncol* 2019 Apr 20;37(12):1012-1014

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Magrolimab (anti-CD47) in TP53 mutated AML and MDS

- **In a phase 1b study presented at ASH 2020:**
  - **Among a subset of 21 TP53 mutant AML patients treated with azacitidine and magrolimab:**
    - **67% CR + CRi**
    - **89% of patients maintained response at 6 months**
    - **Median survival of 12.9 months**
- **Ongoing studies of magrolimab in:**
  - **AML with mutated TP53**
  - **MDS**

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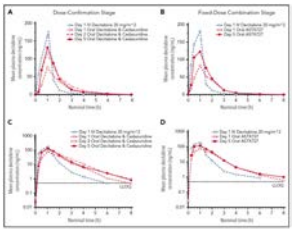
Will future AML patients be treated with oral therapies?

- DNA methyltransferase inhibitors are administered by IV or subcutaneous injections, over 5-7 consecutive days per month.
- Oral versions have long been sought to improve patient burden
- Unstable due to GI/hepatic cytidine deaminase (CDA).
- Decitabine with the CDA inhibitor cedazuridine tested in bioequivalence study



Garcia-Manero G et al. *Blood*. 2020;136(6):674-683.

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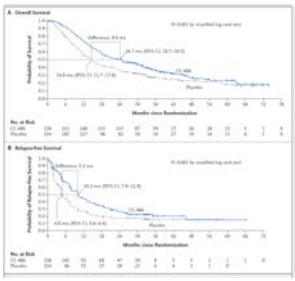
Oral azacitidine as maintenance therapy



Wei A et al. *N Engl J Med* 2020;383:2526-37.

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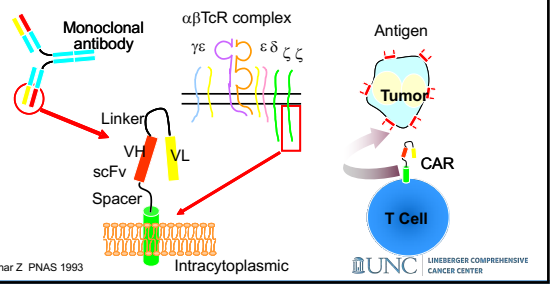
What is a "CAR-T" cell?



Eshhar Z PNAS 1993

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Theoretical advantages of CAR-T cells over other immunotherapies

- Single dose
- Persistence:
  - Single T cell may be "serial killer" and target multiple cancer cells
- Expansion:
  - Burden of cancer antigens can drive expansion of the cell "dose" after initial administration

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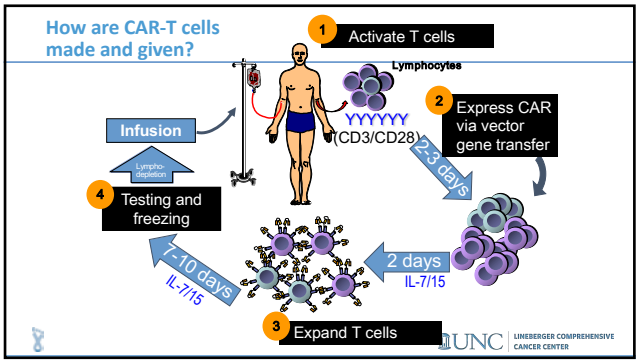
How are CAR-T cells made and given?
1 Activate T cells
Lymphocytes
2 Express CAR via vector gene transfer
YYYYYY
(CD3/CD28)
2-3 days
Infusion
Lympho-depletion
4 Testing and freezing
7-10 days
IL-7/15
2 days
IL-7/15
3 Expand T cells
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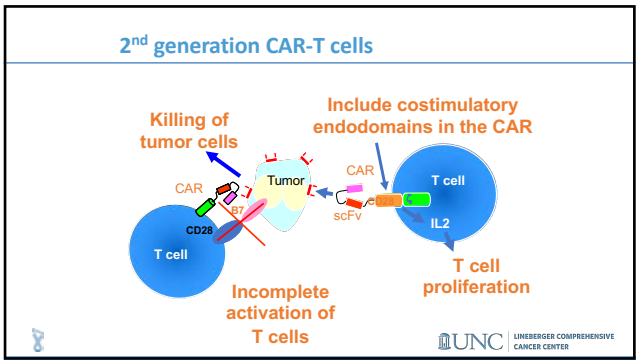
2nd generation CAR-T cells
Killing of tumor cells
Include costimulatory endodomains in the CAR
CAR
Tumor
B7
CD28
T cell
CAR
scFv
T cell
IL2
T cell proliferation
Incomplete activation of T cells
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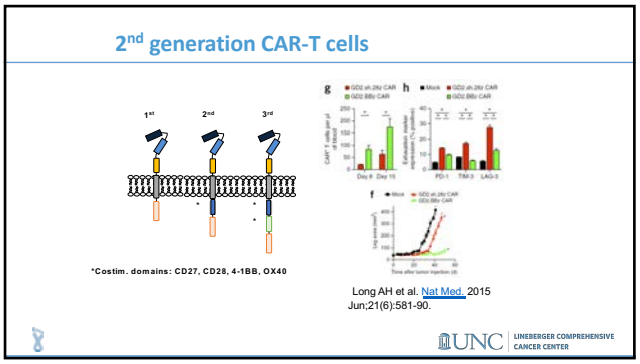
2nd generation CAR-T cells
1st
2nd
3rd
*Costim. domains: CD27, CD28, 4-1BB, OX40
Long AH et al. Nat Med. 2015 Jun;21(6):581-90.
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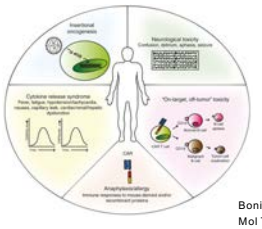
Toxicities of CAR-T Therapy



Bonifant et al.,
Mol Ther Oncolytics, 2016

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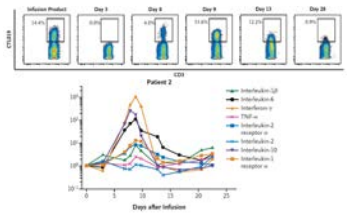
Cytokine release syndrome



Grupp SA et al. N Engl J Med. 2013 Apr 18;368(16):1509-1518.

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CRS: Symptoms

- Fever- usually first presenting symptom and occur in most patients with CRS
  - Instructed to call if fever > 38 C
- Timing
  - Can occur within 24 hours of infusion but usually occurs within a few days to more than a week after infusion
  - Does not usually occur past 3 weeks post-infusion
- Presence of CRS seems to correlate with CAR-T efficacy
- Severity of CRS does not correlates with anti-tumor efficacy
  - Many patients with mild CRS show effective anti-tumor responses

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ICANS

- Headaches, confusion, alterations in wakefulness, hallucinations, dysphasia, ataxia, apraxia, facial nerve palsy, tremor, dysmetria, seizures
- Can occur at different times than CRS or in absence of other CRS toxicities
- Symptoms almost always reversible
- Not associated with disease response
- Cerebral edema may be fatal

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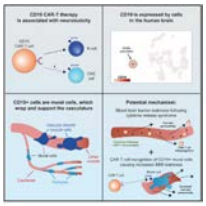
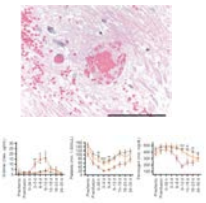
Potential mechanisms for ICANS



Parker et al. *Cell*, 2020; 183, 126-142



Gust et al. *Cancer Discov* 2017; 7(12): 1404-19

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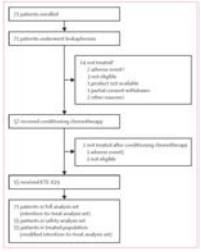
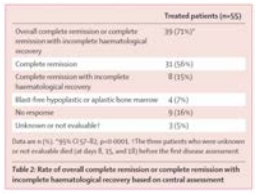
KTE-X19 (brexucabtagene autoleucel) in R/R B-ALL





	Treated patients (n=55)
Overall complete remission or complete remission with incomplete haematological recovery	39 (71%)*
Complete remission	31 (56%)
Complete remission with incomplete haematological recovery	8 (15%)
Blast-free hypoplastic or aplastic bone marrow	4 (7%)
No response	9 (16%)
Unknown or not evaluable†	3 (5%)

Data are n (%). *95% CI 57·82; p<0·0001. †The three patients who were unknown or not evaluable died (at days 8, 15, and 18) before the first disease assessment.

Table 2: Rate of overall complete remission or complete remission with incomplete haematological recovery based on central assessment

Shah BD et al. *Lancet* 2021;398:491-502.

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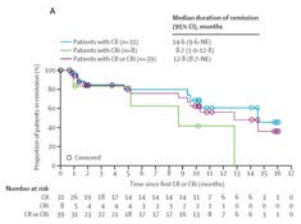
KTE-X19 (brexucabtagene autoleucel) in R/R B-ALL



Shah BD et al. *Lancet* 2021;398:491-502.

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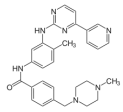
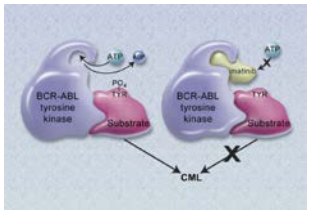
Seminal tyrosine kinase inhibitor to treat CML--imatinib





Druker B. Blood 2008 112: 4808-4817

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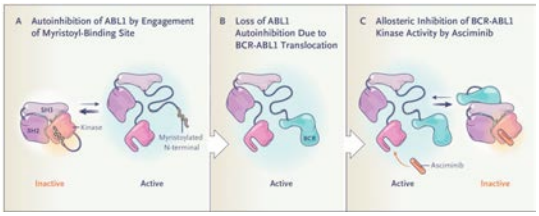
Mechanism of a new class of CML drug--asciminib



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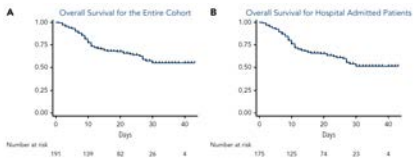
High rates of morbidity and mortality with COVID19 infection



Mato A et al. Blood. 2020; 136(10):1134-1143.

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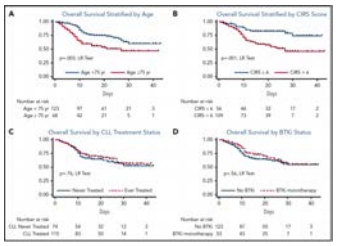
High rates of morbidity and mortality with COVID19 infection



Mato A et al. Blood. 2020; 136(10):1134-1143.

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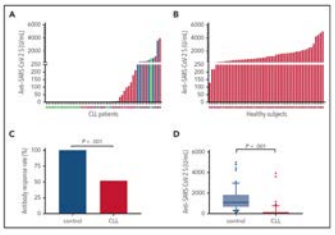
CLL patients have poor response to COVID vaccines



Herishanu Y et al. *Blood* (2021) 137 (23): 3165–3173.

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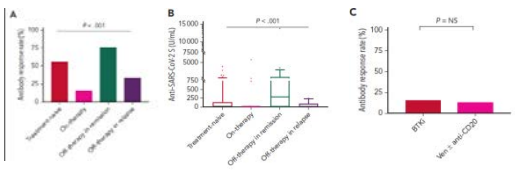
Even untreated CLL patients have poor responses



Herishanu Y et al. *Blood* (2021) 137 (23): 3165–3173.

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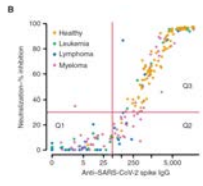

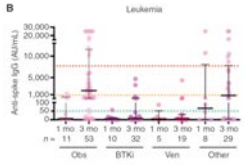

Chung D el atl. *Blood Cancer Discov* 2021;2:1-9.

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Thank you!

Contact me with any questions:
matthew_foster@med.unc.edu

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