# Recent Advances in the Treatment of Hematologic Malignancies

Developed in collaboration

Med-IQ DukeHealth

## Learning Objectives

Upon completion, participants should be able to:

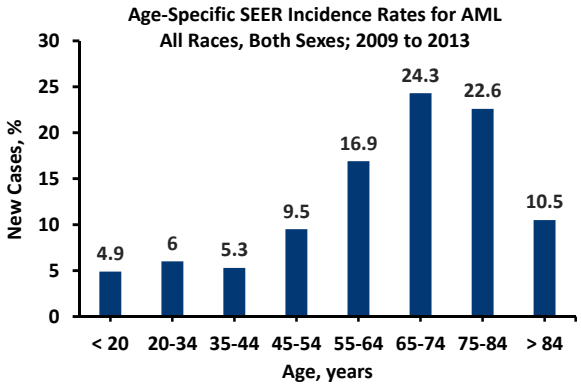
- Describe recent clinical data supporting the use of novel agents that target FLT3 for the treatment of AML
- Identify aspects of current and emerging CAR T-cell therapies, including targets, activity, and toxicity

# Update in AML:
# ASCO and EHA 2018 Annual Congresses
## Targeting the Biologic Drivers of AML: Focus on FLT3

**Harry P. Erba, MD, PhD**

# AML: Basic Facts

- Estimated new cases annually = 19,520[a]
- Most patients diagnosed after age 60 years[a]
- Heterogeneous based on disease- and patient-related features[b]
- Therapy is adapted accordingly[c]
- 5-year OS = 27%[a]
- Outcomes have improved in younger patients but remain suboptimal
- Outcomes have not improved as much for older patients; 5-year OS for AML patients older than 65 years = 5%[a]




[a]PDQ® Adult Treatment Editorial Board. PDQ adult acute myeloid leukemia treatment. www.ncbi.nlm.nih.gov/pubmedhealth/PMH0032612; [b]Medinger M, et al. *Leuk Res Rep*. 2016;6:39-49; [c]O'Donnell MR, et al. *J Natl Compr Canc Netw*. 2017;15:926-57.

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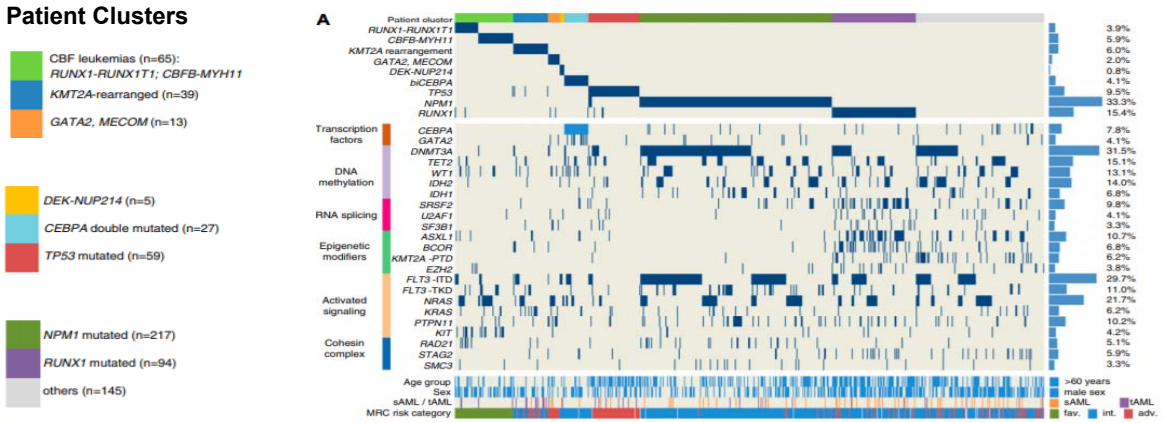
# The Molecular Heterogeneity of AML




Metzeler KH, et al. *Blood*. 2016;128:686-96.

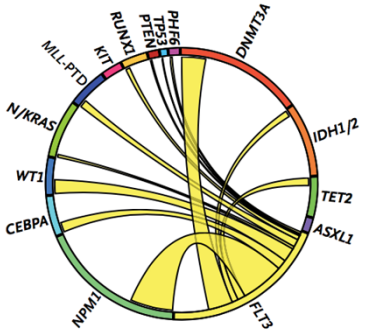
# *FLT3* Mutations in AML

- Three types of *FLT3* mutation:
  - ITD
    - 20%-30%
    - Disrupts the auto-inhibitory function of the JM region
    - The receptor is still dependent on the presence of FLT3 ligand for complete activation
  - TKD point mutation
    - 5%-10%
    - Activates FLT3 kinase directly
  - JM domain point mutation (1%)

Nakao M, et al. *Leukemia*. 1996;10:1911-8; Yamamoto Y, et al. *Blood*. 2001;97:2434-9; Reindl C, et al. *Blood*. 2006;107:3700-7; Fröhling S, et al. *Cancer Cell*. 2007;12:501-13; Patel JP, e al. *N Engl J Med*. 2012;366:1079-89.

# Characteristics of *FLT3* Mutation–Positive AML

**Higher incidence of *NPM1* and *DNMT3A* mutations**




**Higher WBC and BM blasts %**

| Karyotype characteristics | ITD neg/ TKD wt n (%) | ITD pos n (%) | TKD mut n (%) | ITD pos + TKD mut n (%) |
|---|---|---|---|---|
| All patients | 721 (73.6) | 183 (18.7) | 58 (5.9) | 17 (1.7) |
| Karyotype not available | 59 (8.2) | 22 (12.0) | 2 (3.4) | 0 (0) |
| Normal (XX,XY) | 282 (39.1) | 119 (65.0) | 35 (60.3) | 15 (88.2) |
| Aberrant | 380 (52.7) | 42 (23.0) | 21 (36.2) | 2 (11.8) |
| Individual aberrations t(8;21) | 38 (5.3) | 2 (1.1) | 1 (1.7) | 0 (0) |
| t (15;17) | 26 (3.6) | 13 (7.1) | 4 (6.9) | 0 (0) |
| inv(16);t(16;16) | 36 (5) | 1 (0.6) | 5 (8.6) | 1 (4.8) |
| t(6;9) | 1 (0.1) | 9 (4.9) | 0 (0) | 0 (0) |
| t(3;3), inv(3q) | 10 (1.4) | 1 (0.6) | 0 (0) | 0 (0) |
| +8 | 69 (9.6) | 6 (3.3) | 6 (10.3) | 0 (0) |
| t(9;11);t(9;22) | 14 (1.9) | 0 (0) | 0 (0) | 0 (0) |
| +11/+13/+21/+22 | 75 (10.4) | 1 (0.6) | 4 (6.9) | 1 (4.8) |
| -5/5q- | 75 (10.4) | 2 (1.1) | 0 (0) | 0 (0) |
| -7/7q- | 86 (11.9) | 0 (0) | 5 (8.6) | 0 (0) |
| Other monosomies | 94 (13.3) | 3 (1.6) | 1 (1.7) | 0 (0) |
| Multiple aberrations | 132 (18.3) | 3 (1.6) | 5 (8.6) | 1 (4.8) |

Thiede C, et al. *Blood*. 2002;99:4326-35;
Patel JP, et al. *N Engl J Med*. 2012;366:1079-89.

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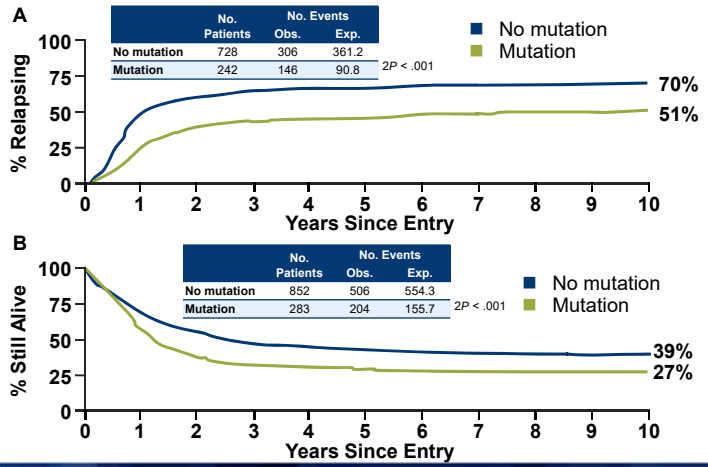
# Effect of *FLT3*-ITD Mutation on Outcome (UK NCRI AML 10 and AML 12)

**283/1,135 (25%) non-APL AML are *FLT3*-ITD pos**

**_FLT3_-ITD pos: CR 86%**
**_FLT3_-ITD neg: CR 85%**




Gale RE, et al. *Blood*. 2005;106:3658-65.

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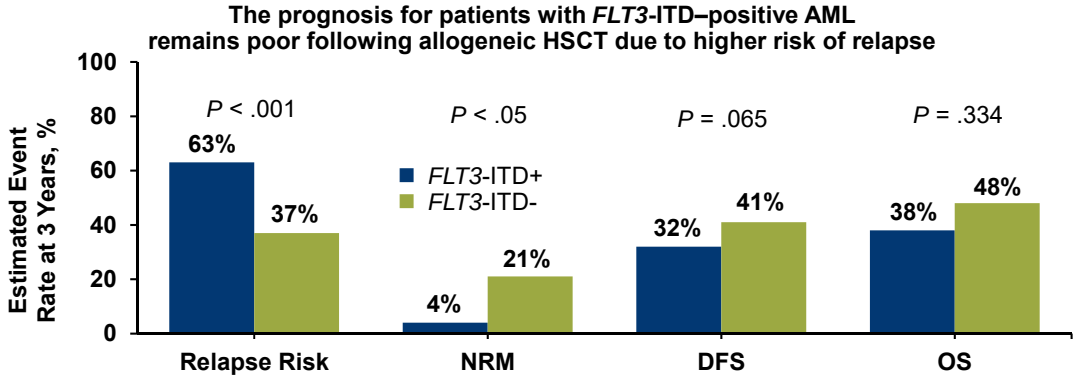
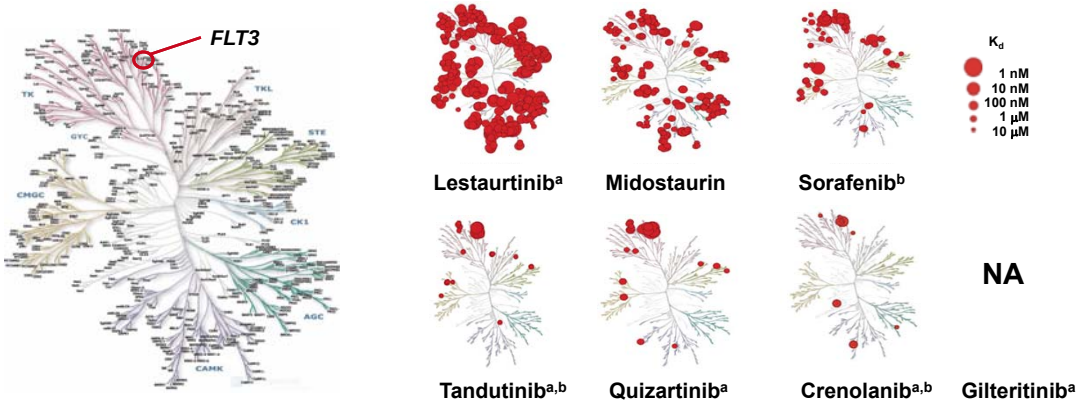
# Outcome of *FLT3*-ITD–Positive AML Following Allogeneic HSCT




Song Y, et al. *Bone Marrow Transplant.* 2016;51:511-20.

# Selectivity of FLT3 Inhibitors




[a]Investigational.
[b]Off-label use.
Zarrinkar PP, et al. *Blood.* 2009;114:2984-92.

# Lestaurtinib in First-Line Chemotherapy for *FLT3*-Mutated AML

| | AML 15 (median age, 47 years) | AML 17 (median age, 50 years) |
|---|---|---|
| | 1,007 pts were recruited | 1,708 pts were recruited |
| | 825 *FLT3* status tested | 1,633 *FLT3* status tested |
| Selection Bias: 81% | 215 tested positive | 406 tested positive |
| | 175 randomly assigned | 325 randomly assigned |

| AML 15 and 17 | Lestaurtinib n = 300 | Standard n = 200 | *P* Value |
|---|---|---|---|
| *FLT3*-ITD alone, n (%) | 220 (73) | 150 (75) | |
| CR/CRi, % | 92 | 94 | .4 |
| Survival at 5 y | 51 | 56 | .4 |

| AML 17 | Lestaurtinib | Standard | *P* Value |
|---|---|---|---|
| 5-y OS: No azole | 60 | 55 | .03 |
| 5-y OS: Azole | 40 | 60 | |
| By FLT3 inhibition (n = 83) | | | |
| > 85% | 60 | | .04 |
| ≤ 85% | 33 | | |

AEs included nausea, emesis, constipation, diarrhea, and elevated alkaline phosphatase.
Knapper S, et al. *Blood*. 2017;129:1143-54.

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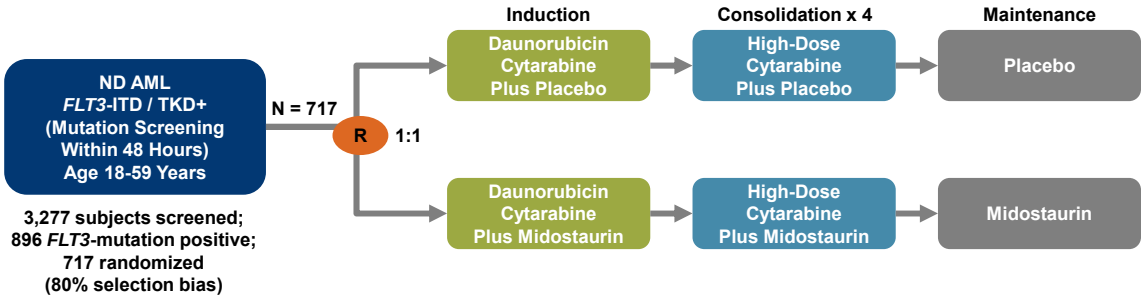
# RATIFY (CALGB 10603): Chemotherapy + Midostaurin or Placebo in Newly Diagnosed Patients < 60 Years With *FLT3*-Mutated AML




3,277 subjects screened;
896 *FLT3*-mutation positive;
717 randomized
(80% selection bias)

- Collaboration with 13 international cooperative groups; 225 sites from 17 countries
  - Alliance, SWOG, ECOG, NCIC, NCCTG, GIMEMA, EORTC, AMLSG, SAL, OSHO, PETHEMA, CETLAM, ALSG
  - 9 academic FLT3 screening laboratories worldwide

Stone RM, et al. *N Engl J Med*. 2017;377:454-64.

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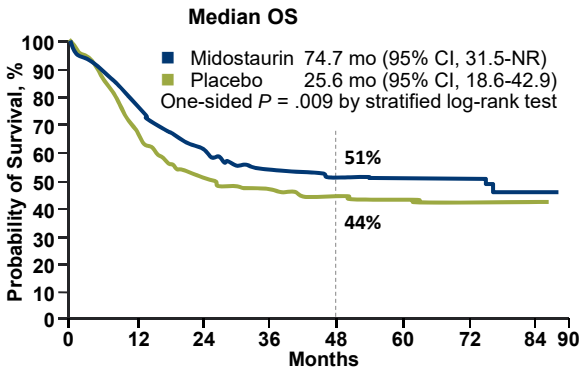
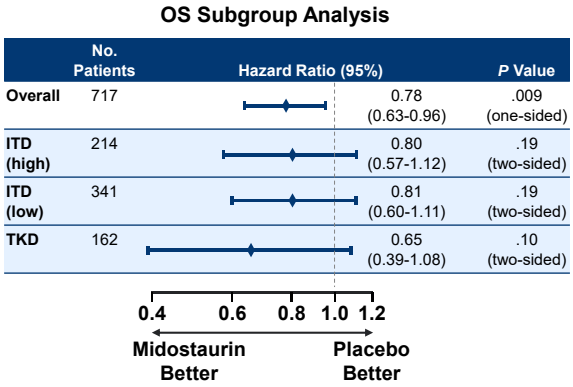
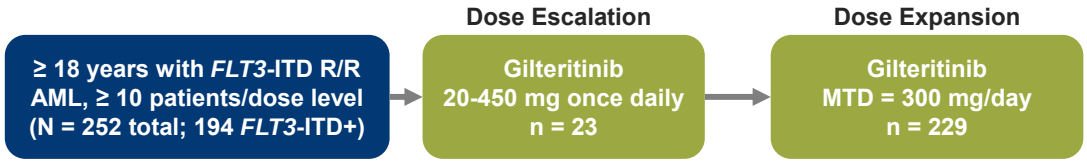
# RATIFY (CALGB 10603): OS




Stone RM, et al. *N Engl J Med*. 2017;377:454-64.

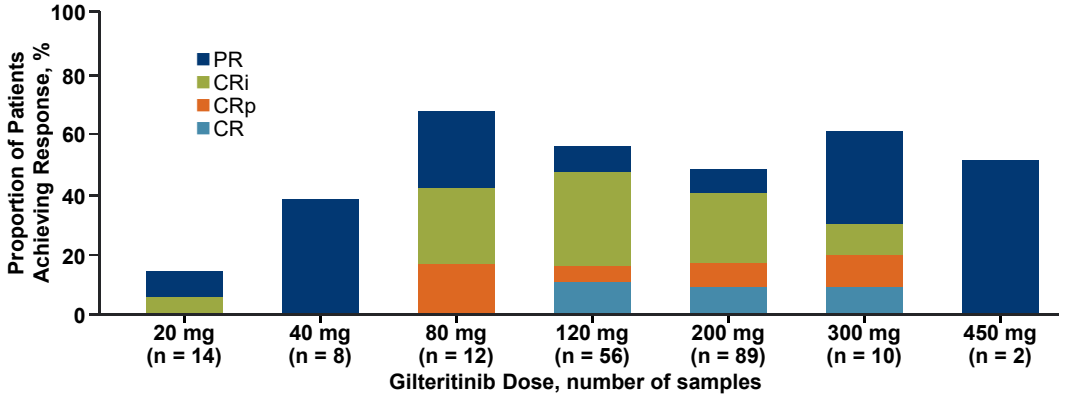
# Gilteritinib in *FLT3*-Mutated R/R AML Phase 1/2 Study (CHRYSALIS)




- Induction failure or relapsed AML
- 7 dose escalation (n = 23) or expansion (n = 229) cohorts
- Primary endpoints: safety, tolerability, PK
- Doses of 80 mg/day or higher led to 90% phosphorylation inhibition by day 8

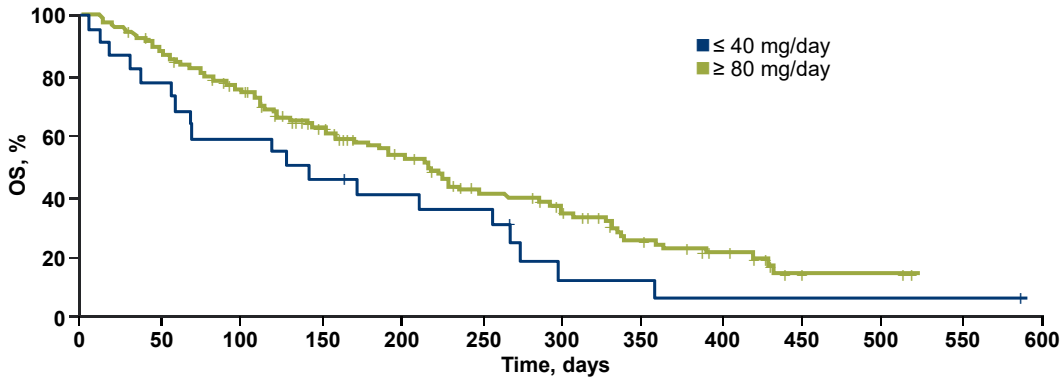
Perl AE, et al. *Lancet Oncol*. 2017;18:1061-75.

# Gilteritinib in *FLT3*-Mutated R/R AML: Clinical Response by Dose



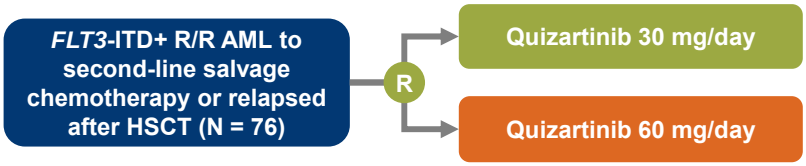

Perl AE, et al. *Lancet Oncol*. 2017;18:1061-75.

# Gilteritinib in *FLT3*-Mutated R/R AML: OS




Common AEs included diarrhea, fatigue, and abnormal liver enzyme tests.
NDA filed 2018.
Perl AE, et al. *Lancet Oncol*. 2017;18:1061-75.

# Quizartinib in *FLT3*-ITD–Positive R/R AML: Randomized Phase 2 Study




- *FLT3*-ITD–positive R/R AML after one second-line salvage or HSCT
- N = 76
- Prior FLT3 inhibitor allowed
- Primary objective: CR rate
- Secondary objectives: OS, duration of CRc, rate of bridging to HSCT, safety

Cortes JE, et al. *Blood*. 2018. [Epub ahead of print]

# Quizartinib in *FLT3*-ITD–Positive R/R AML: Efficacy

| | 30-mg arm (n = 38) | 60-mg arm (n = 38) | Total (N = 76) |
|---|---|---|---|
| **ORR, CRc, and PR, %** | 60.5 | 71.1 | 65.8 |
| **CRc, %** | 47.4 | 47.4 | 47.4 |
| **Median duration CRc, wk** | 4.2 | 9.1 | 5.4 |
| **Bridge to HSCT, %** | 32 | 42 | 37 |
| **Median OS, wk** | 20.9 | 27.3 | 22.6 |

AEs included febrile neutropenia, anemia, thrombocytopenia, neutropenia, pneumonia, increased bilirubin, and pyrexia.
Cortes JE, et al. *Blood*. 2018. [Epub ahead of print]

# Quizartinib significantly prolongs overall survival in patients with FLT3-ITD–mutated relapsed/refractory AML in the phase 3, randomized, controlled QuANTUM-R trial

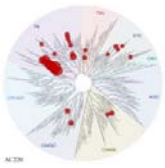
Jorge E. Cortes, Samer Khaled, Giovanni Martinelli, Alexander E. Perl, Siddhartha Ganguly, Nigel Russell, Alwin Krämer, Hervé Dombret, Donna Hogge, Brian A. Jonas, Anskar Yu-Hung Leung, Priyanka Mehta, Pau Montesinos, Markus Radsak, Simona Sica, Meena Arunachalam, Melissa Holmes, Ken Kobayashi, Ruth Namuyinga, Nanxiang Ge, Antoine Yver, Yufen Zhang, Mark J. Levis

Presented at the 23rd Congress of the European Hematology Association; June 16, 2018; Stockholm, Sweden. Abstract LB2600.

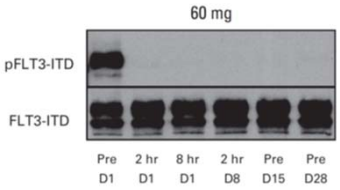
# Quizartinib (AC220): A Highly Potent and Selective FLT3 Inhibitor

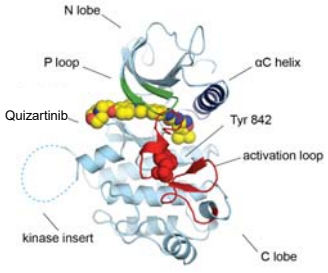
Lestaurtinib[a] Midostaurin[a] Sorafenib[a]

First-generation multikinase inhibitors[b]



Quizartinib[a]
Second-generation FLT3 inhibitor[c]



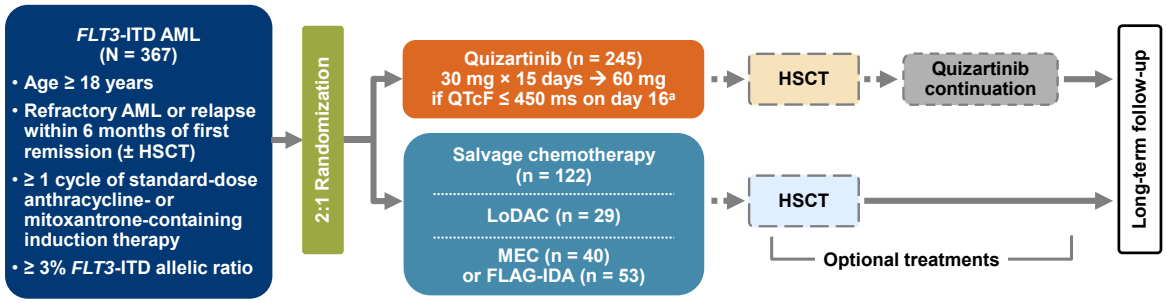




**Quizartinib properties:**

- **Oral, highly potent, selective[c]**
- **Nanomolar affinity (1.6 ± 0.7 nM) against FLT3[c] and complete suppression of FLT3 phosphorylation in ex vivo PIA assays[d]**
- **Highly selective for FLT3 when screened against 402 human kinases (other kinases with $K_d$ within 10-fold that of FLT3 were closely related RTKs [eg, KIT])[c]**

[a]Davis MI, et al. *Nat Biotechnol.* 2011;29:1046-51; [b]Stone R, et al. *N Engl J Med.* 2017;377:454-64; [c]Zarrinkar P, et al. *Blood.* 2009;114:2984-92; [d]Cortes JE, et al. *J Clin Oncol.* 2013;31:3681-7.

# QuANTUM-R Study Design




- Primary endpoint: OS (ITT population)
- Secondary endpoint: event-free survival (ITT population)
- Select exploratory endpoints: CRc rate, duration of CRc, and transplant rate
- Enrollment dates: May 2014 (first patient) to September 2017 (last patient); data cutoff: February 2018

[a]20 mg × 15 days → 30 mg if concomitantly taking CYP3A4 inhibitors.
Cortes JE, et al. *Blood*. 2018. [Epub ahead of print]

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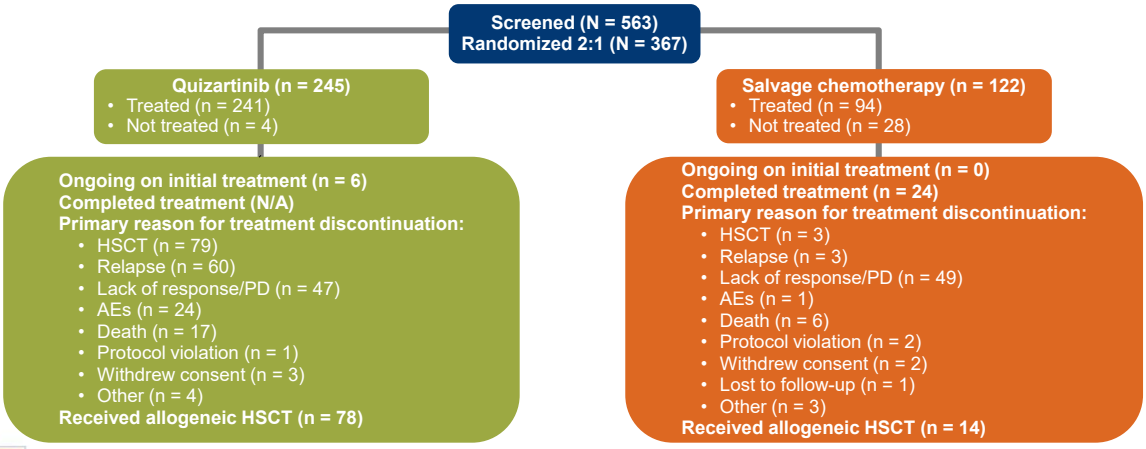
# QuANTUM-R CONSORT Diagram




Cortes JE, et al. *Blood*. 2018. [Epub ahead of print]

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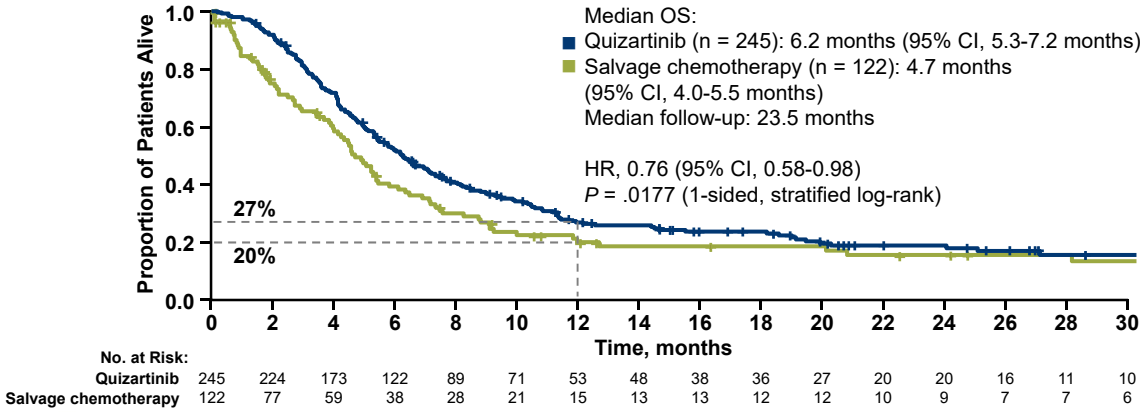
# QuANTUM-R Primary Endpoint: OS by Kaplan-Meier Method




| No. at Risk: | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Quizartinib | 245 | 224 | 173 | 122 | 89 | 71 | 53 | 48 | 38 | 36 | 27 | 20 | 20 | 16 | 11 | 10 |
| Salvage chemotherapy | 122 | 77 | 59 | 38 | 28 | 21 | 15 | 13 | 13 | 12 | 12 | 10 | 9 | 7 | 7 | 6 |

# QuANTUM-R: Best Response

| Characteristic | Percentage (95% CI) Quizartinib n = 245 | Salvage Chemotherapy n = 122 |
|---|---|---|
| **Best response** | | |
| **CRc[a]** | 48 (42-55) | 27 (19-36) |
| **CR** | 4 (2-7) | 1 (0-5) |
| **CRp** | 4 (2-7) | 0 (0-3) |
| **CRi** | 40 (34-47) | 26 (19-35) |
| **PR** | 21 (16-27) | 3 (1-8) |
| **ORR (CRc + PR)** | 69 (63-75) | 30 (22-39) |
| **No response** | 25 (20-31) | 37 (28-46) |
| **Nonevaluable** | 5 (3-9) | 33 (25-42) |

[a]Nominal *P* = .0001 for between-group comparison of CRc.
Cortes JE, et al. *Blood*. 2018. [Epub ahead of print]

# QuANTUM-R: Duration of CRc and Transplant Rate

| Characteristic | Quizartinib n = 245 | Salvage Chemotherapy n = 122 |
|---|---|---|
| **Duration of CRc (95% CI), weeks** | | |
| **Median** | 12.1 (10.4-27.1) | 5.0 (3.3-12.6) |
| **Transplant, %** | | |
| **Transplant rate[a]** | 32 | 12 |

[a]Nominal *P* < .0001 for between-group comparison of transplant rate.
Cortes JE, et al. *Blood*. 2018. [Epub ahead of print]



# QuANTUM-R: Conclusions

- Single-agent quizartinib significantly prolonged OS of patients with *FLT3*-ITD–mutated R/R AML compared with salvage chemotherapy
  - OS: HR, 0.76 (95% CI, 0.58-0.98; *P* = .0177)
- Single-agent quizartinib was well tolerated
  - Grade ≥ 3 QTcF prolongation was uncommon
  - Investigator choice and quizartinib associated with similar rates of TEAE
- QuANTUM-R: first phase 3 trial to demonstrate that an FLT3 inhibitor improved OS compared with standard chemotherapy in patients with *FLT3*-ITD–mutated R/R AML
- QuANTUM-First: ongoing phase 3 study of standard chemotherapy plus placebo versus quizartinib in patients with newly diagnosed *FLT3*-ITD–mutated AML

Cortes JE, et al. *Blood*. 2018. [Epub ahead of print]

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# Targeting FLT3 in AML: Closing Thoughts

1. Single-agent inhibitors of FLT3 are active in AML, but response rates are low despite the presence of the biomarker and inhibition of the target in all subjects
   - Predictors of response are needed
2. Combination of a kinase inhibitor with chemotherapy improves the survival of patients with *FLT3*-mutated AML
   - OS benefit with midostaurin is less than impressive
   - Biological basis of survival benefit is not certain (ie, inhibition of FLT3 or other kinases)
   - Will more specific inhibitors further improve outcome with chemotherapy?
3. FLT3 is a late event in leukemogenesis and is likely present only in a subclone
4. Combination of FLT3 inhibitors with agents that target cellular apoptosis (eg, BCL2 inhibitors, MDM2 inhibitors) or target the leukemic stem cell (eg, Hedgehog inhibitors, anti-CD123 antibody drug conjugates) may further improve efficacy of this class of drugs

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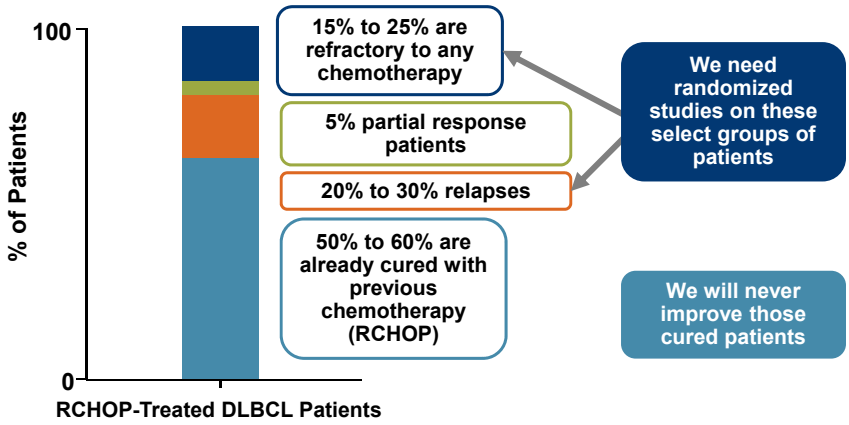
# CAR T-Cell Therapy for R/R DLBCL

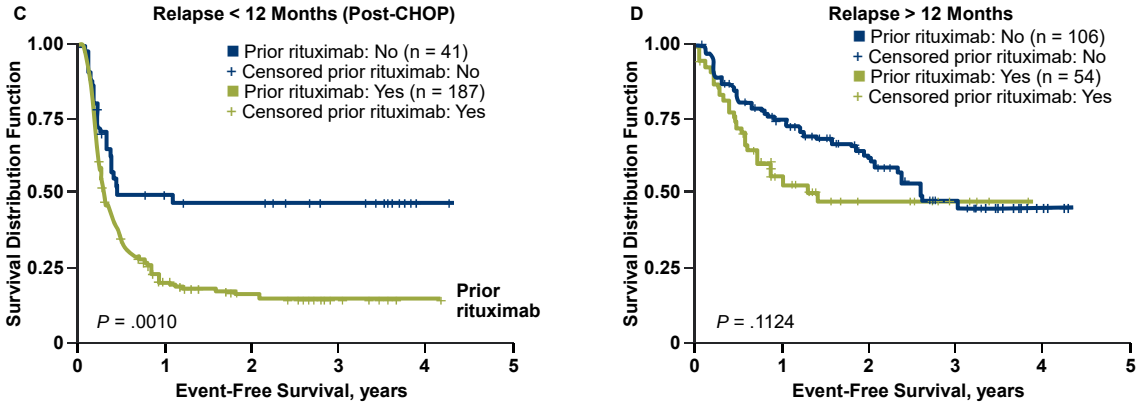
**Matthew McKinney, MD**

# Refractoriness and Relapses: The Fundamental Issue in DLBCL



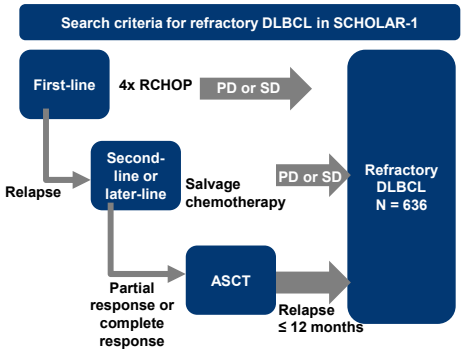

Coiffier, et. al. ASH education program. 2016.

# "Traditional" Salvage Chemotherapy in DLBCL




Gisselbrecht C, et al. *J Clin Oncol.* 2010;28:4184-90.

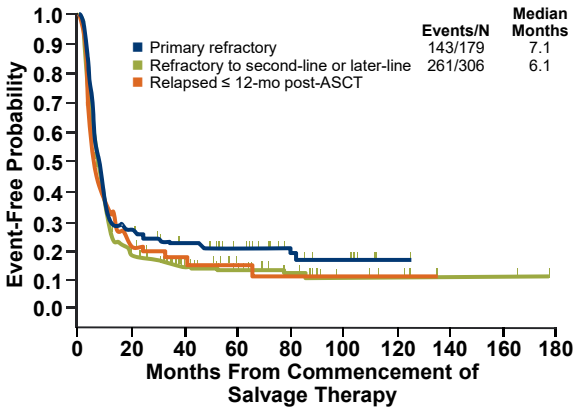
# SCHOLAR-1 Dataset

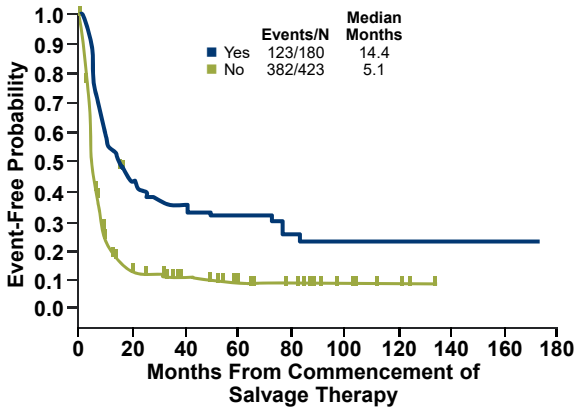



| | MDACC (n = 165) | IA/MC (n = 82) | LY-12 (CCTG) (n = 219) | CORAL (LYSARC) (n = 170) | Pooled (N = 636) |
|---|---|---|---|---|---|
| Patients evaluated for survival, n | 165 | 72 | 196 | 170 | 603 |
| **Survival from commencement of salvage therapy** | | | | | |
| Deaths | 89 | 92 | 80 | 80 | 84 |
| Median (95%, CI), mo | 6.6 | 5.0 | 6.6 | 6.5 | 6.3 (5.9, 7.0) |
| 1-y survival rate | 28 | 18 | 31 | 30 | 28 (25, 32) |
| 2-y survival rate | 17 | 10 | 23 | 22 | 20 (16, 23) |
| **Primary refractory** | | | | | |
| Deaths | -- | 90 | 76 | 85 | 80 |
| Median (95% CI), mo | -- | 6.1 | 7.9 | 7.3 | 7.1 (6.0, 8.1) |
| 1-y survival rate | -- | 26 | 30 | 27 | 29 (22, 36) |
| 2-y survival rate | -- | 21 | 27 | 16 | 24 (18, 30) |
| **Refractory to ≥ second-line therapy** | | | | | |
| Deaths | 88 | 92 | 86 | 77 | 85 |
| Median (95% CI), mo | 6.6 | 4.7 | 5.3 | 6.1 | 6.1 (5.2, 7.0) |
| 1-y survival rate | 29 | 9 | 24 | 30 | 26 (22, 31) |
| 2-y survival rate | 19 | 6 | 14 | 22 | 17 (13, 22) |
| **Relapse ≤ 12-mo post-ASCT** | | | | | |
| Deaths | 94 | 94 | 86 | 80 | 86 |
| Median (95% CI), mo | 5.9 | 4.2 | 7.0 | 6.5 | 6.2 (5.2, 7.6) |
| 1-y survival rate | 19 | 25 | 38 | 34 | 32 (24, 41) |
| 2-y survival rate | 6 | 6 | 21 | 26 | 19 (12, 27) |

Crump M, et al. *Blood.* 2017;130:1800-8.

# SCHOLAR-1 Long-Term Outcomes and ASCT



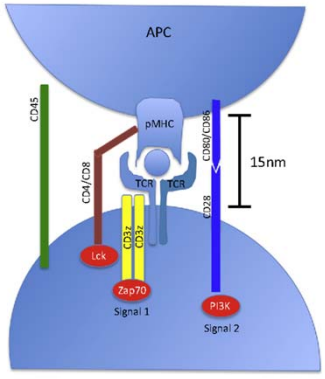

Crump M, et al. *Blood.* 2017;130:1800-8.

## Outcomes are poor…
## how do you move the needle?

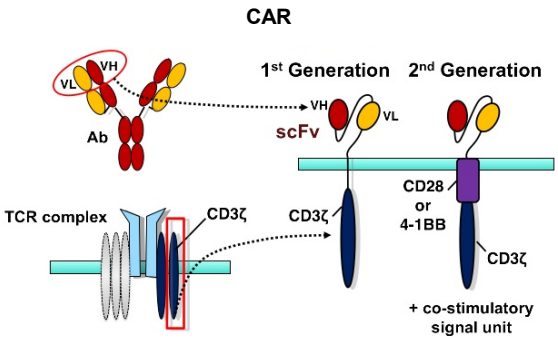
## Rationale for Immunotherapy in DLBCL (and Other B-Cell NHLs)

- Chemorefractory DLBCL has a very poor outcome
- Immunotherapy of B-cell markers has already improved survival
- Acquired B-cell aplasia is remarkably well tolerated in adults

Chavez JC, et al. *Clin Haematol.* 2018;31:135-46.



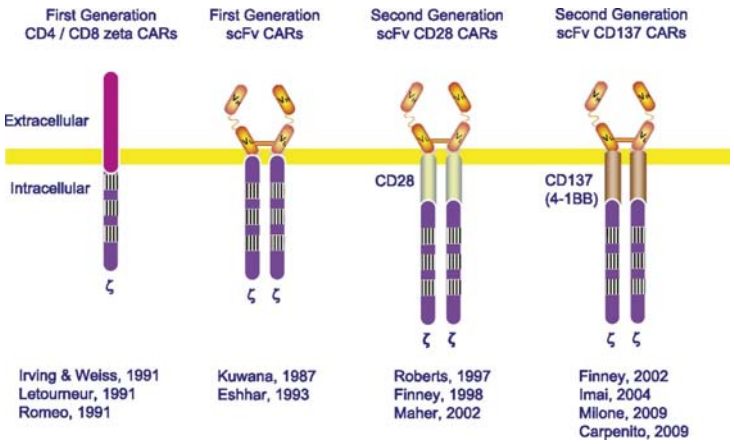

Conventional T Cell




CARs are hybrid proteins consisting of an extracelluar single chain fragment of variable region (scFv) fused to co-stimulatory signaling domains CD28 or 4-1BB (CD137), coupled with CD3ζ to mediate T-cell activation.

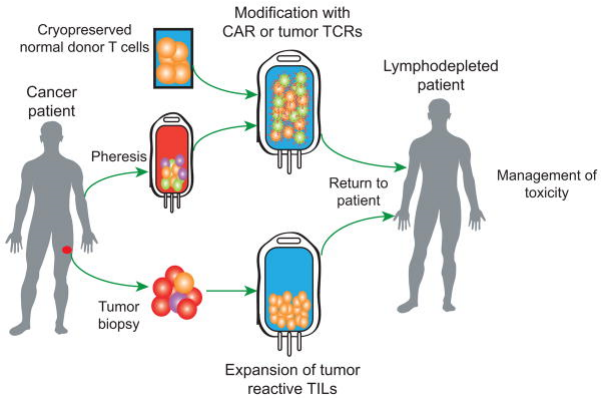
Chavez JC, et al. *Clin Haematol.* 2018;31:135-46.

# Molecular Aspects of CAR T-Cell Constructs




Barrett DM, et al. *J Immunol.* 2015;195:755-61.

# CTL019[a] Is Designed to Hunt and Destroy CD19-Positive B-Cell Cancers in Patients




Cellular reprogramming and ex vivo expansion are conducted at a cell-processing facility.
[a]Off-label.
Barrett DM, et al. *J Immunol.* 2015;195:755-61.

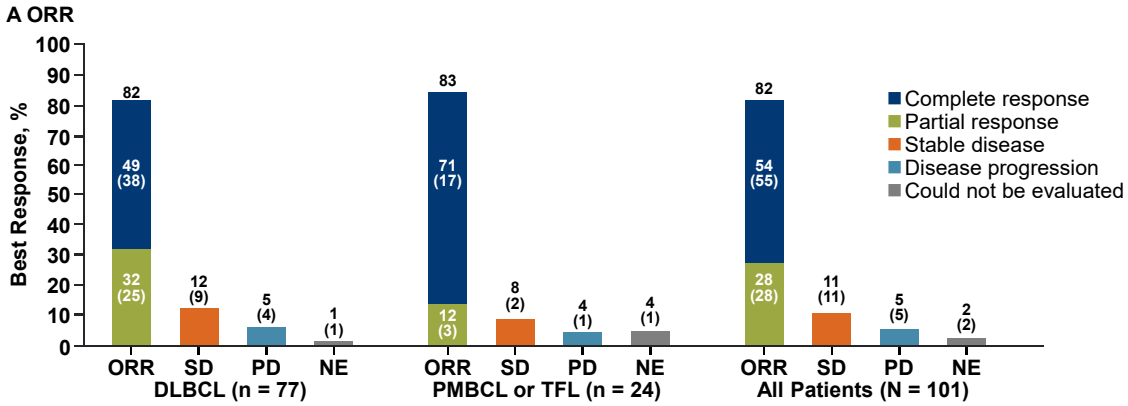


# Aspects of Most Studied CD19 CAR T-Cell Constructs—The Models

| Academic Group | Company (Drug) | Costimulatory Domain | Vector Delivery | Indications |
|---|---|---|---|---|
| **UPenn** | **Novartis (CTL019)** | 4-1BB | Lentiviral | **ALL**, CLL, **DLBCL**, FL |
| **MSKCC** | Juno (JCAR 015) | CD28 | Retroviral | ALL, CLL, various B-cell malignancies |
| **Fred Hutchinson** | Juno (JCAR 017) | 4-1BB | Lentiviral | |
| **NCI (NIH)** | **Kite Pharma (KTE- C19)** | CD28 | Retroviral | **DLBCL** |
| **Baylor** | Bluebird/Celgene | CD28 | Retroviral | ALL, CLL |
| **MDACC** | Ziopharm/Intrexon | CD28 → 4-1BB | Transposon/transposase | Adjuvant, pre-/post-transplant |
| **Institut Pasteur** | Cellectis/Pfizer (UCART19[a]) | 4-1BB | Lentiviral | ALL, CLL,AML, MM |
| **Baylor** | Bellicum (BPX-401[a]) | MyD88 + CD40 | Retroviral | Various |
| **Dartmouth** | Cardio3 | DAP-10 transmembrane | Retroviral | AML, MDS, MM |

**FDA-approved indication.**
[a]Off-label and investigational.
www.clinicaltrials.gov.

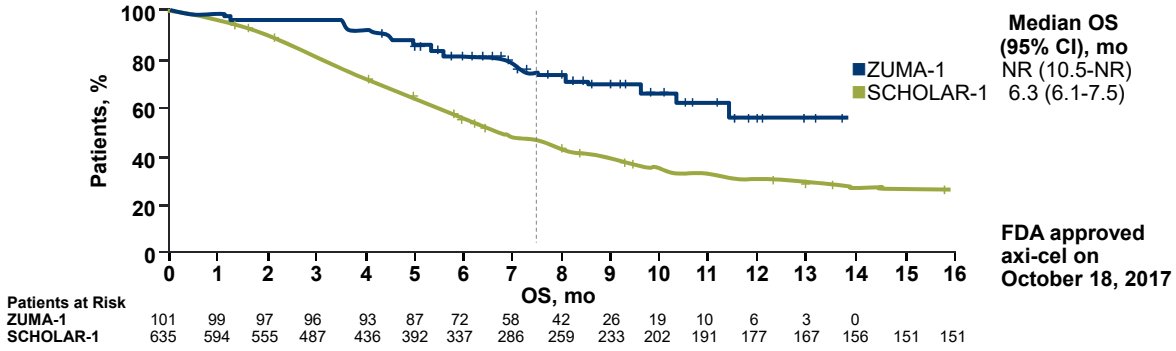
# Axicabtagene Ciloleucel (axi-cel) in R/R DLBCL




Neelapu SS, et al. *N Engl J Med.* 2017;377:2531-44.

# axi-cel CAR T-Cell Therapy and Outcomes

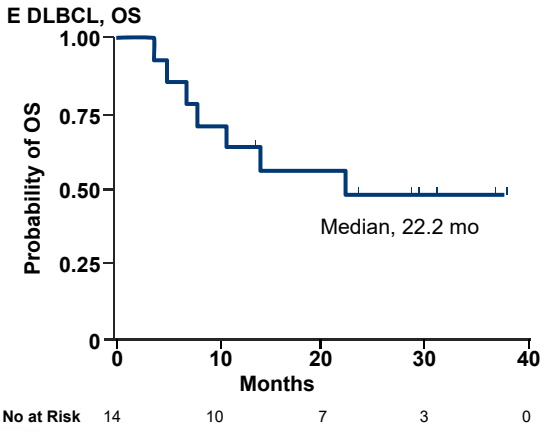
- 6-mo OS, ZUMA-1 vs SCHOLAR-1: 80% vs 55%

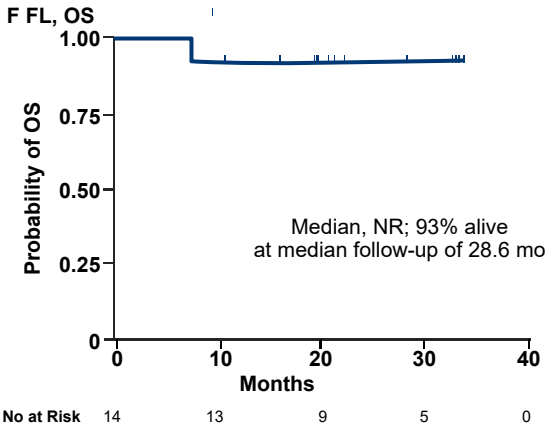



- Median follow-up: 8.7 mo

Neelapu SS, et al. *N Engl J Med.* 2017;377:2531-44.

# CTL 019 Results Comparison (DLBCL and FL)




Neelapu SS, et al. *N Engl J Med*. 2017;377:2531-44.

# Durable Response Rates With FDA-Approved CAR T-Cell Therapy

**JULIET study in DLBCL shows strong Duration of Response**

74% of responders were relapse-free at 6 months

**r/r DLBCL responses to therapy**

| Response | n | ORR | CR |
|---|---|---|---|
| Best overall response | 81 | **53%** | **40%** |
| Month 3 response | 81 | **38%** | **32%** |
| Month 6 response | 46 | **37%** | **30%** |

- 6-month probability of being relapse-free was 74%
- Median DOR and OS not reached
- 6-month probability of overall survival was 64.5%
- No patient who achieved a response (CR or PR) proceeded to allogenic- or auto-SCT

ASH December 9-12, 2017 Paper 577 Primary Analysis of Juliet: A Global, Pivotal, Phase 2 Trial of CTL019 in Adult Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma ORR - overall response rate, CR - complete response, DOR - duration of response, OS - overall survival, SCT - stem cell transplant

*Cancer Discov*. 2018;8:131-2.

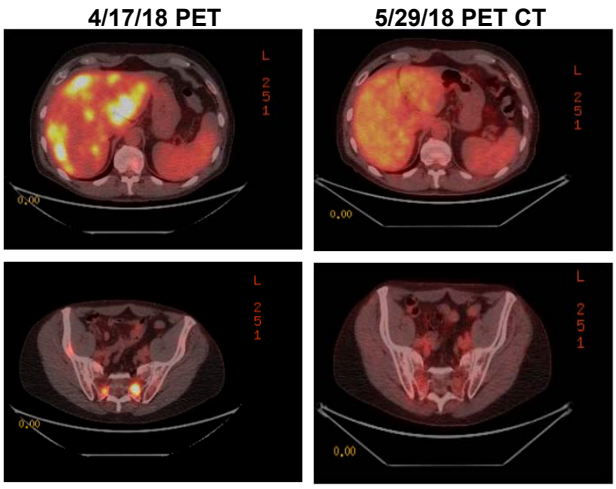
# CAR T Cells—Response at Cost of Toxicity

- Immunotherapy with CAR T cells with activation molecules not without collateral toxicity
- Cytokine release syndrome and neurologic toxicity can be severe/life-threatening
- Requires inpatient monitoring by dedicated expert staff

*Cancer Discov.* 2018;8:131-2.

# Patient Case

- 63-year-old with DLBCL
- Treated with:
  - Rituximab-EPOCH/MTX (complete response)
  - Rituximab-ICE (refractory)
  - 4/24/18 axi-cel infusion (post-collection/lymphodepletion)




Photos courtesy of Matthew McKinney, MD.

## Summary

- Outcomes in chemorefractory DLBCL have historically been dismal
- Current CAR modified T-cell technology offers new hope for R/R lymphomas and other B-cell malignancies
- Overcoming limitations associated with time to produce therapy, toxicity, and cost will be key to success of future therapies

## Contact Information

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Email info@med-iq.com

Please visit us online at www.Med-IQ.com
for additional activities provided by Med-IQ®.






**Hematologic Malignancies: Abbreviations and Acronyms**

AE = adverse event
ALL = acute lymphocytic leukemia
AML = acute myeloid leukemia
APC = antigen-presenting cell
APL = acute promyelocytic leukemia
ASCT = autologous stem cell transplantation
BCL2 = B-cell lymphoma 2
BM = bone marrow
CAR = chimeric antigen receptor
CBF = core-binding factor
CCTG = Canadian Cancer Trials Group
CLL = chronic lymphocytic leukemia
CR = complete remission
CRc = composite complete remission
CRi = complete remission with incomplete peripheral blood count recovery
CRp = complete remission with incomplete platelet recovery
CT = computed tomography
DFS = disease-free survival
DLBCL = diffuse large B-cell lymphoma
EPOCH = etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin
Exp = expected
FL = follicular lymphoma
FLAG-IDA = fludarabine, cytarabine, and idarubicin
FLT3 = fms-like tyrosine kinase-3
HSCT = hematopoietic stem cell transplantation
IA = Molecular Epidemiology Resource of the University of Iowa
ICE = ifosfamide, carboplatin, etoposide
ITD = internal tandem duplication
ITT = intention to treat
JM = juxtamembrane
LoDAC = low-dose cytarabine
LYSARC = Lymphoma Academic Research Organization
MC = Mayo Clinic Lymphoma Specialized Program of Research Excellence
MDACC = MD Anderson Cancer Center
MDS = myelodysplastic syndromes
MEC = mitoxantrone, etoposide, and cytarabine
MM = multiple myeloma
MSKCC = Memorial Sloan Kettering Cancer Center
MTD = maximum tolerated dose
MTX = methotrexate
NA = not available
N/A = not applicable
NCI = National Cancer Institute
NCRI = National Cancer Research Institute
ND = newly diagnosed
NDA = New Drug Application

NE = not evaluable
NHL = Non-Hodgkin lymphoma
NIH = National Institutes of Health
NR = not reached
NRM = nonrelapse mortality
Obs = observed
ORR = objective response rate
OS = overall survival
PD = progressive disease
PET = positron emission tomography
PIA = plasma inhibitory activity
PK = pharmacokinetics
PMBCL = primary mediastinal B-cell lymphoma
pMHC = peptide-major histocompatibility complex
PR = partial remission
QTcF = Fridericia-corrected QT interval
RCHOP = rituximab + cyclophosphamide/doxorubicin/vincristine/prednisone
R/R = relapsed or refractory
RTK = receptor tyrosine kinase
scFv = single-chain fragment of variable region
SD = stable disease
SEER = Surveillance, Epidemiology and End Results
TCR = T-cell receptor
TEAE = treatment-emergent adverse event
TFL = transformed follicular lymphoma
TIL = tumor-infiltrating lymphocyte
TKD = tyrosine kinase domain
WBC = white blood cell
wt = wild type