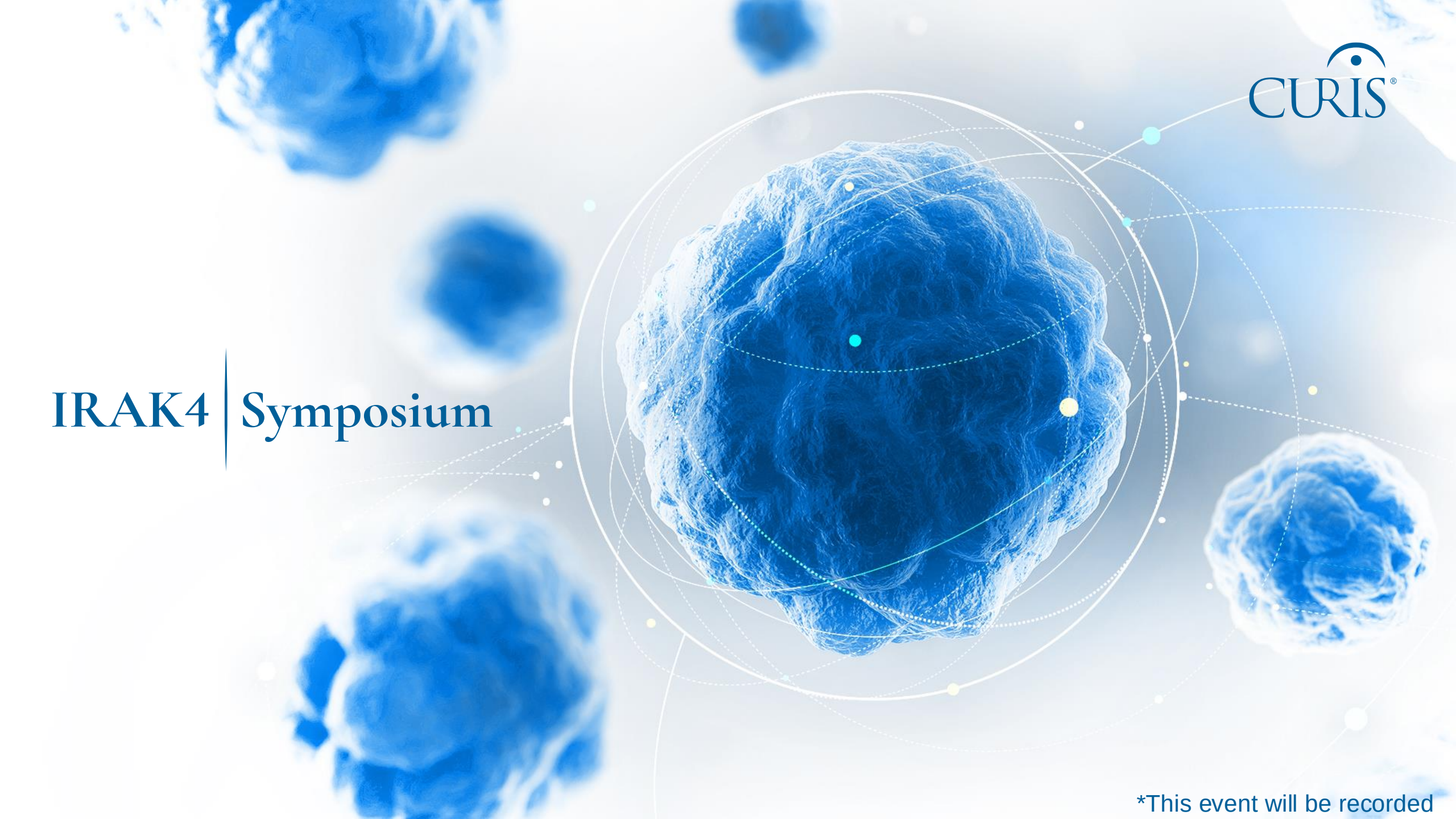

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*This event will be recorded

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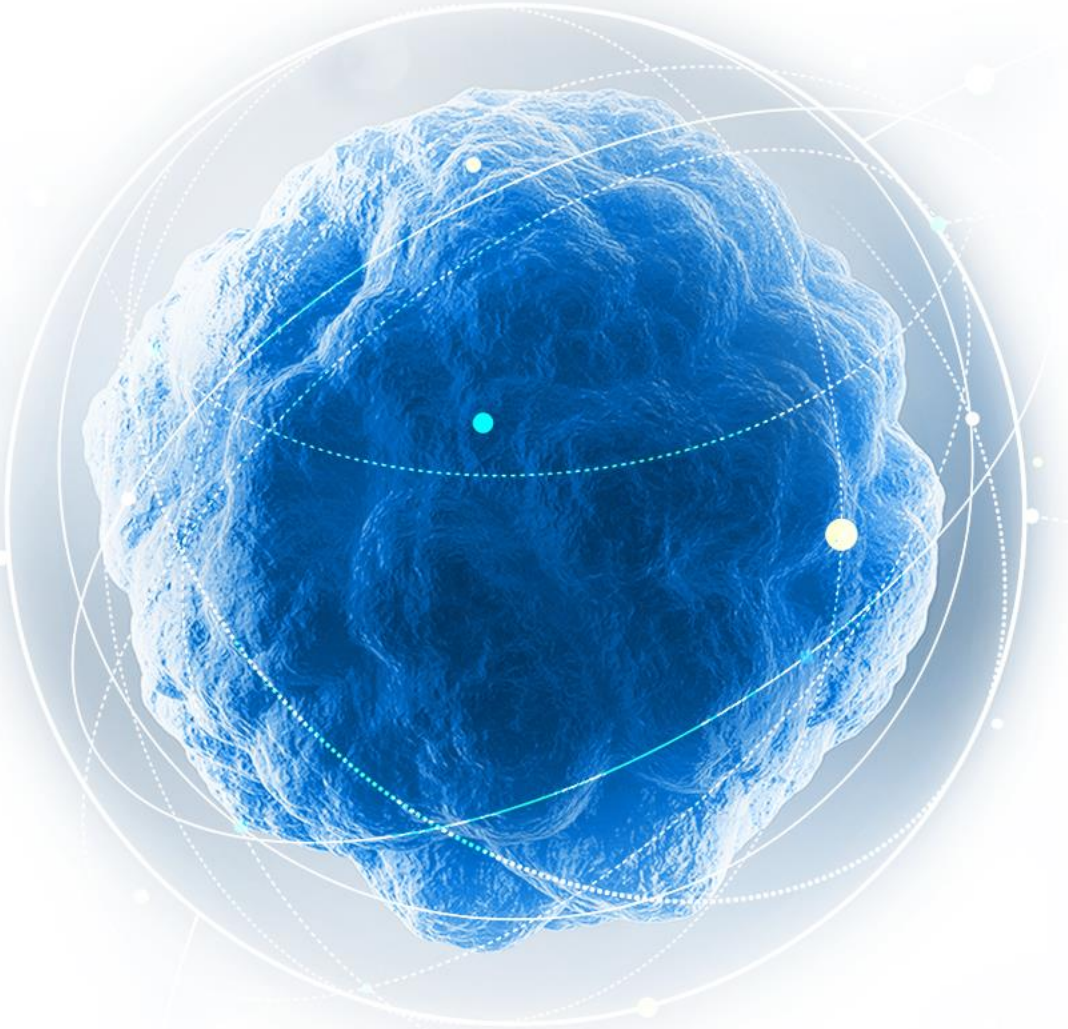
Mechanisms of BCL2i resistance in myeloid malignancies and the potential for emavusertib+ venetoclax synergy



Marina Konopleva, MD, PhD

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Albert Einstein College of Medicine and Montefiore Medical Center

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Disclosures

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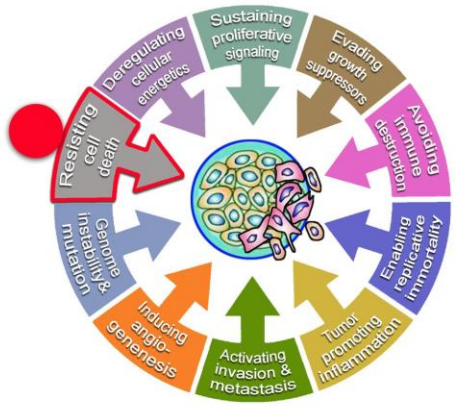
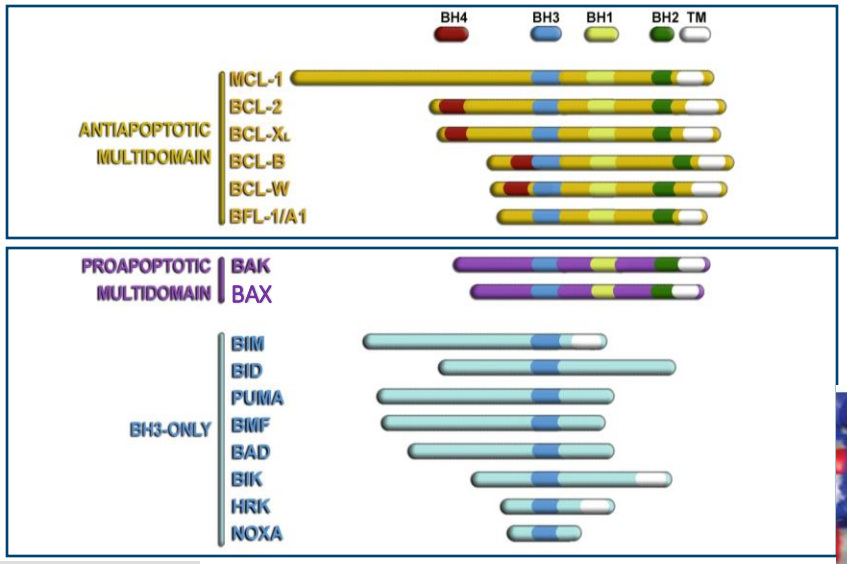
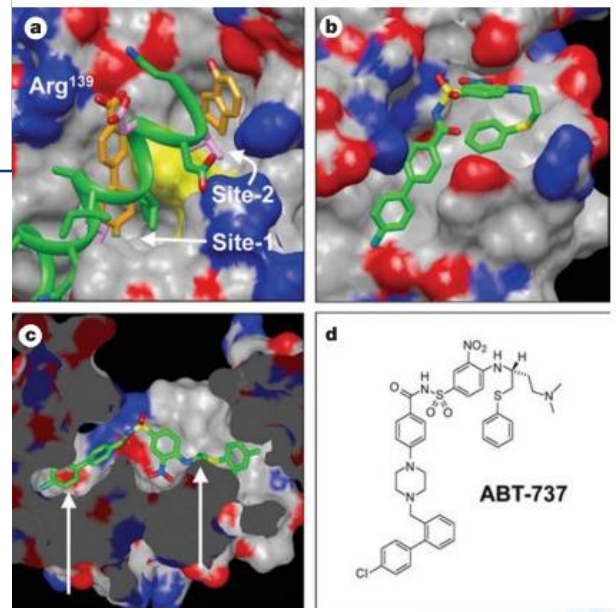
Reata Pharmaceutical

Resisting apoptosis is a hallmark of cancer and a primary cause of cancer resistance to therapy







nature

LETTERS

An inhibitor of Bcl-2 family proteins induces regression of solid tumours

Tilman Oltersdorf[1]*, Steven W. Elmore[2]*, Alexander R. Shoemaker[2]*, Robert C. Armstrong[1], David J. Augeri[2], Barbara A. Belli[1], Milan Bruncko[2], Thomas L. Deckwerth[1], Jurgen Dinges[2], Philip J. Hajduk[2], Mary K. Joseph[2], Shinichi Kitada[3], Stanley J. Korsmeyer[4,5], Aaron R. Kunzer[2], Anthony Letai[5], Chi Li[6], Michael J. Mitten[2], David G. Nettesheim[2], ShiChung Ng[2], Paul M. Nimmer[2], Jacqueline M. O'Connor[2], Anatol Oleksijew[2], Andrew M. Petros[2], John C. Reed[3], Wang Shen[2], Stephen K. Tahir[2], Craig B. Thompson[6], Kevin J. Tomaselli[1], Baole Wang[2], Michael D. Wendt[2], Haichao Zhang[2], Stephen W. Fesik[2] & Saul H. Rosenberg[2]

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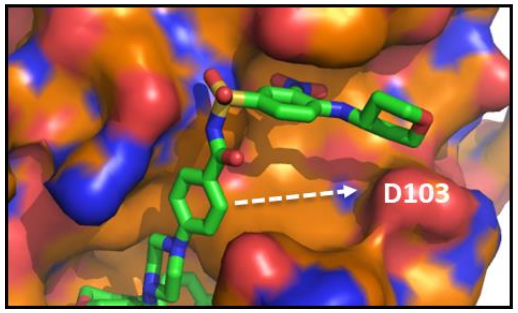
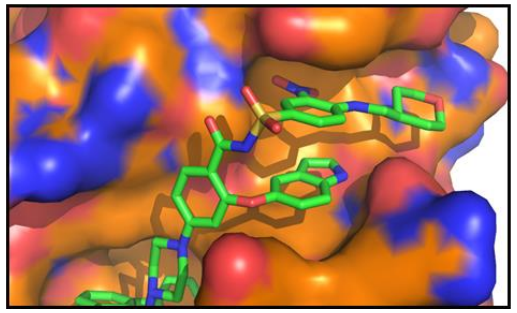
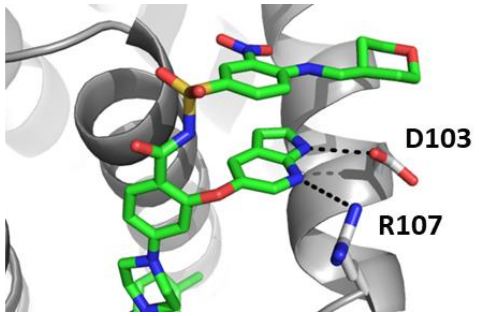
Structure-Based Design of BCL-2-Selective Inhibitor

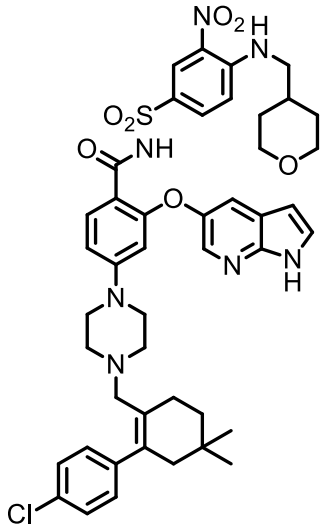






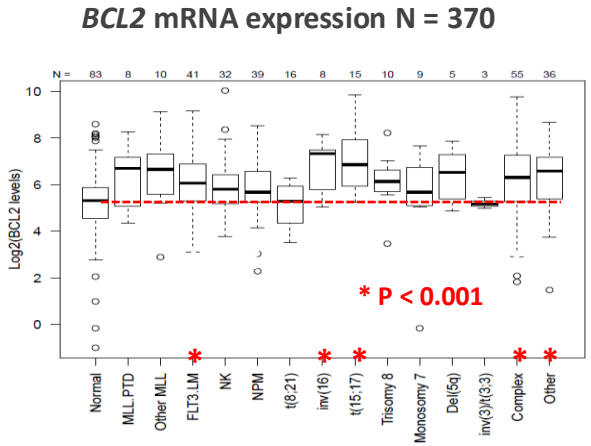
Insights from X-ray crystal structures drove the design of first-in-class BCL-2-selective inhibitor, venetoclax

- Selective, high affinity for BCL-2
- Kills tumor cells but spares platelets
- Orally bioavailable



Venetoclax

BCL-2 as a therapeutic target in AML



- BCL-2 is highly expressed in AML blasts and stem /progenitor cells;
- Venetoclax effectively kills AML cells *in vitro* and *in vivo*
- **BCL2 targeting toxic to AML > CD34+ cells**

Souers, et al. *Nature Medicine.* 2013

Konopleva, *Cancer Cell* 2006
Pan, et al. *Cancer Discovery.* 2014

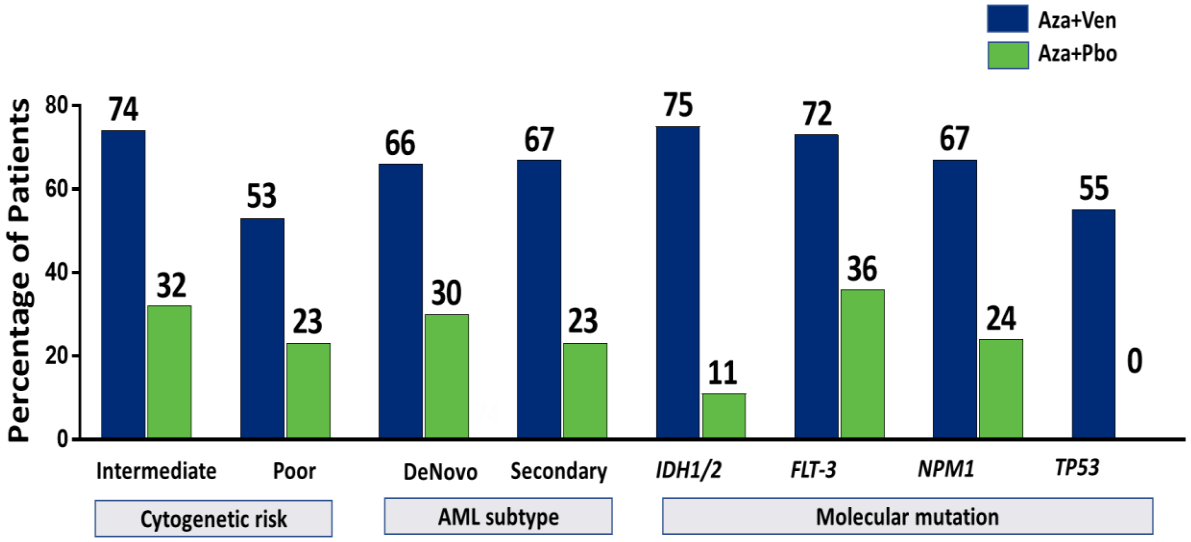
Phase 3 trials validate BCL2 as a therapeutic target in AML

CR rate: 36.7% vs 17.9% (*P* < .001)

CR/CRi rate: 66.4% vs 28.3% (*P* < .001)

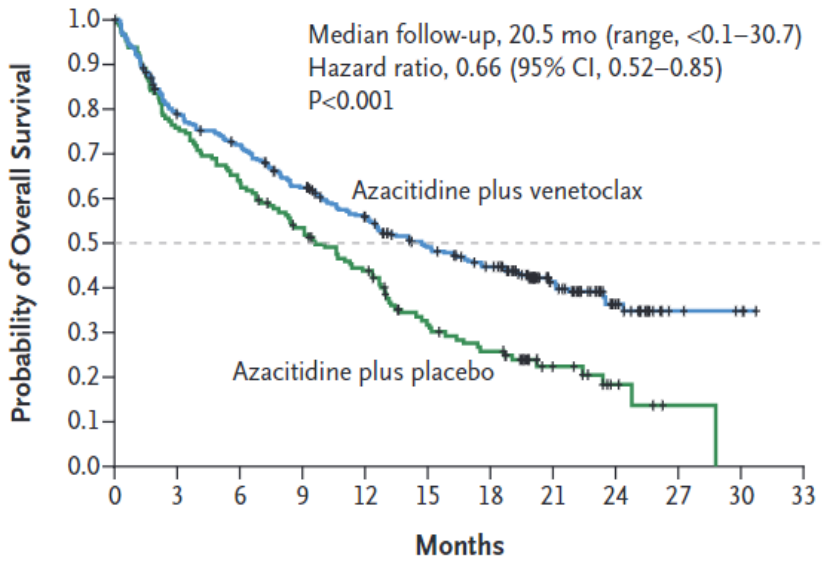
Median time to response: 1 vs 3 cycles (*P* < .001)

Improved responses occurred ***independent*** of **high risk genomics**



Significant OS improvement with venetoclax/azacitidine

	Median OS, mo (95% CI)
VEN + AZA	14.7 (11.9-18.7)
AZA + placebo	9.6 (7.4-12.7)



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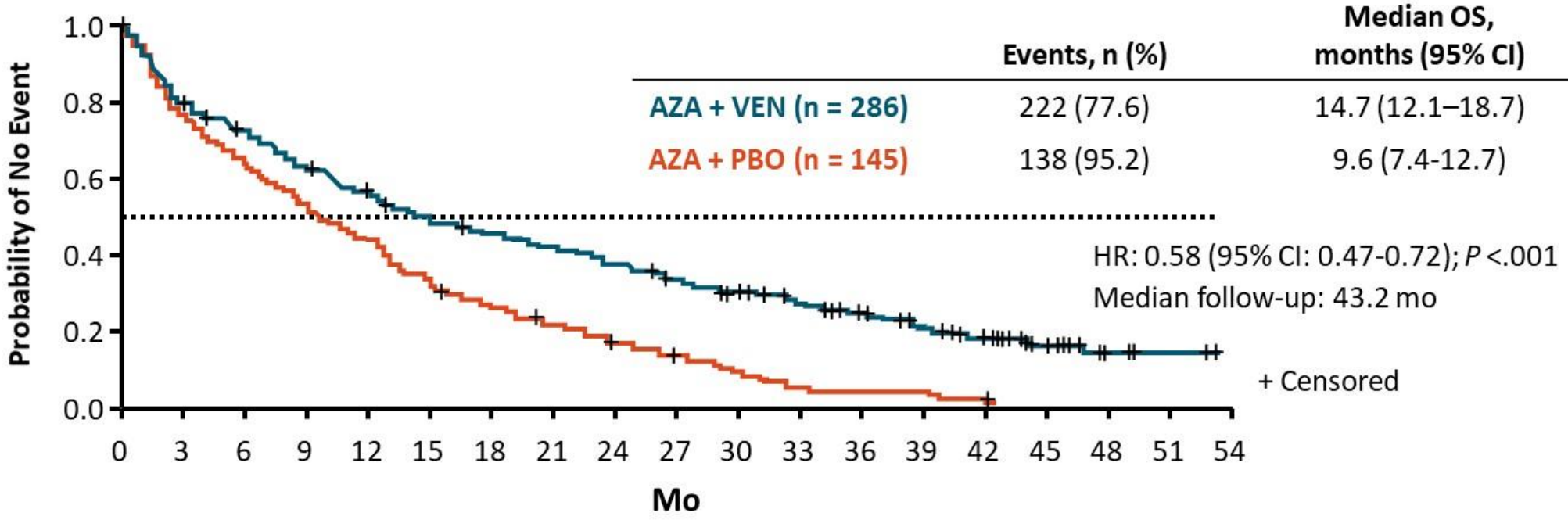
DiNardo C, et al. *N Engl J Med*. 2020;383:617-629.

Long-Term VIALE-A Follow Up: Cure remains rare and elusive



	Events, n (%)	Median OS, months (95% CI)
AZA + VEN (n = 286)	222 (77.6)	14.7 (12.1–18.7)
AZA + PBO (n = 145)	138 (95.2)	9.6 (7.4-12.7)

Patients at Risk, n

AZA + PBO	145	109	92	77	63	47	37	30	22	17	12	6	5	5	3	0			
AZA + VEN	286	220	199	173	153	133	122	113	101	89	78	67	57	45	34	18	6	2	0

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Pratz. ASH 2022. Abstr 219.

Multi-factorial Venetoclax Resistance in AML

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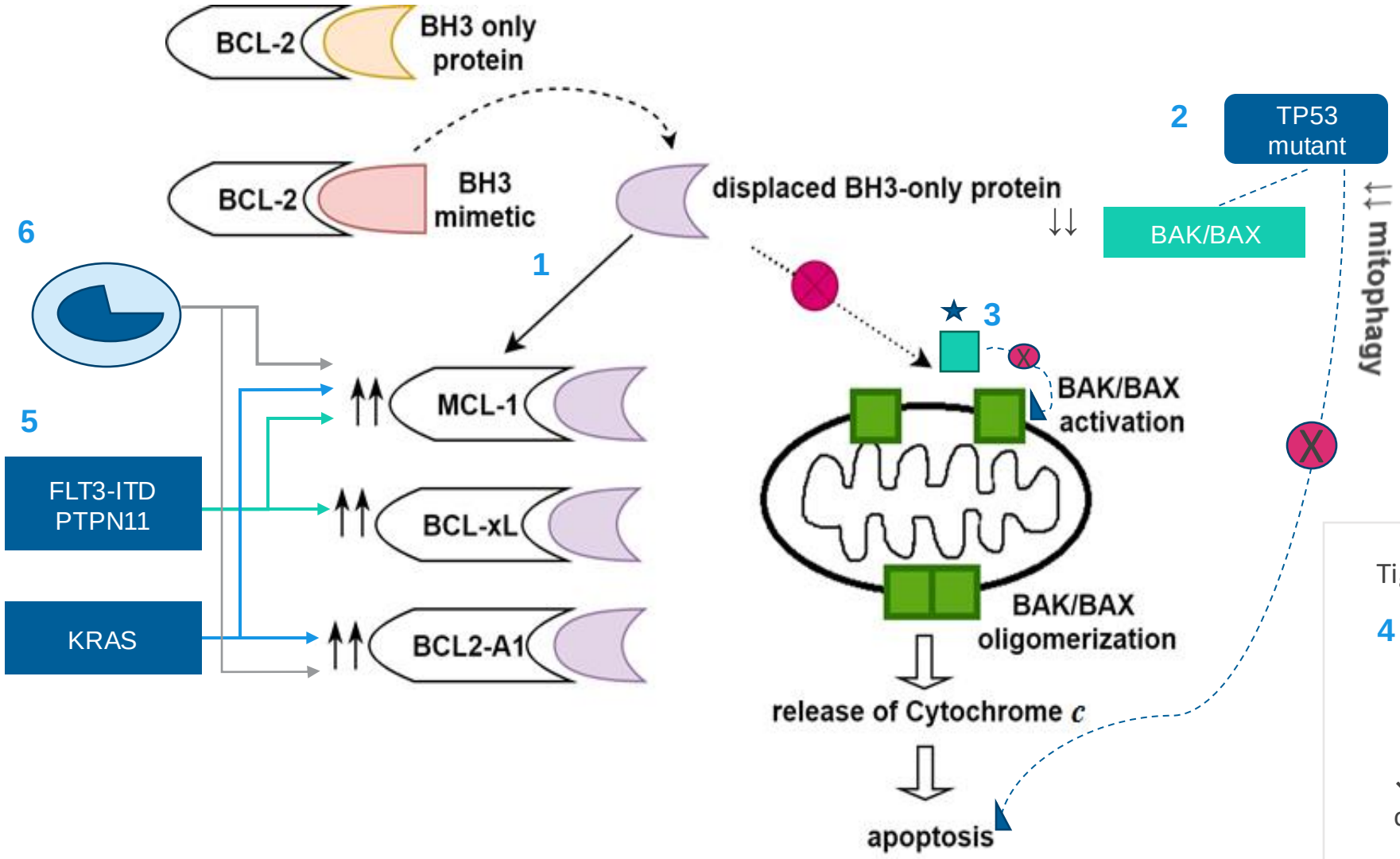

1. Other anti-apoptotic BCL-2 family proteins
2. TP53 mutation
3. BAX mutation
4. Mitochondrial aberration
5. Mutations in activating kinases
6. Monocytic differentiation

Tighter mitochondrial cristae lumen

↓ Opening of cristae junction → ↓ Cytochrome *c* release → ↓ apoptosis

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Modified from Ong et al. *Cancer Drug Resistance* 2022

FLT3-mut AML: Subset Analysis Phase Ib and VIALE-A

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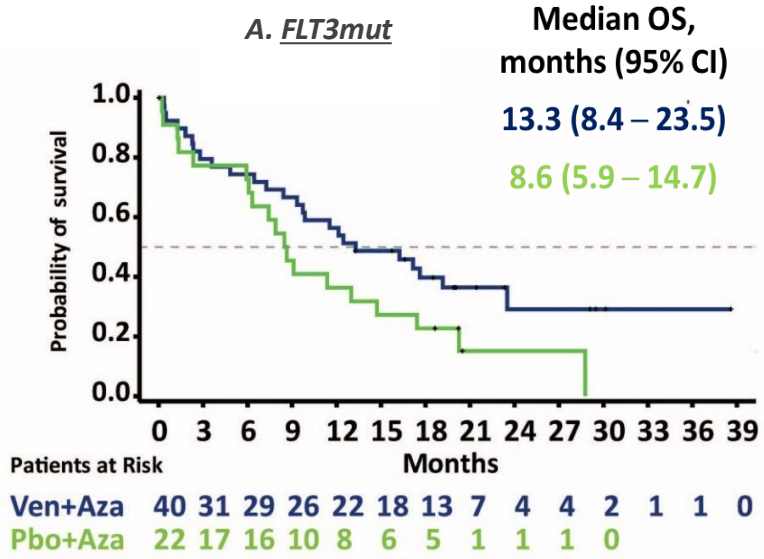

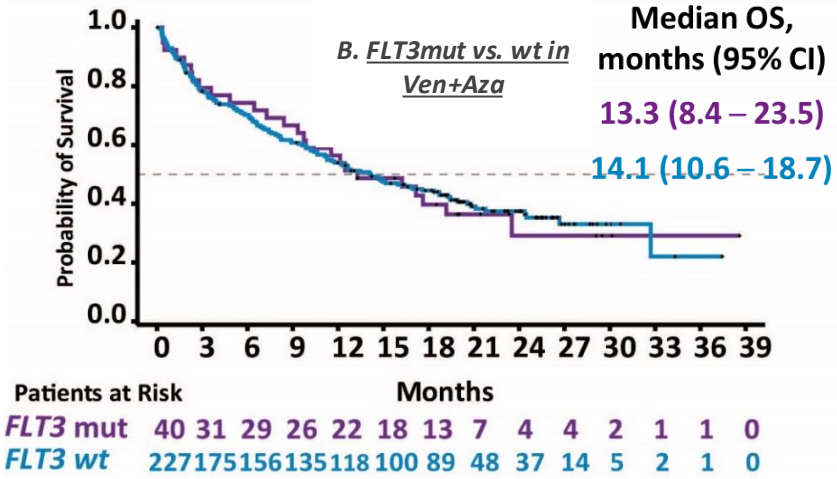

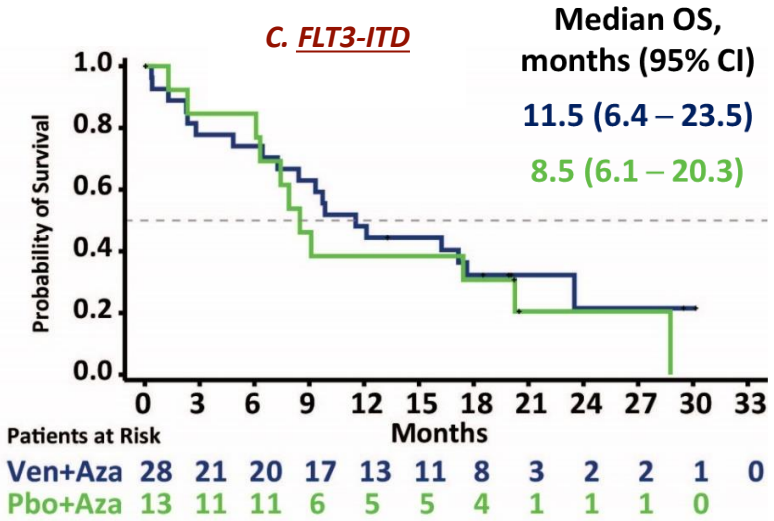

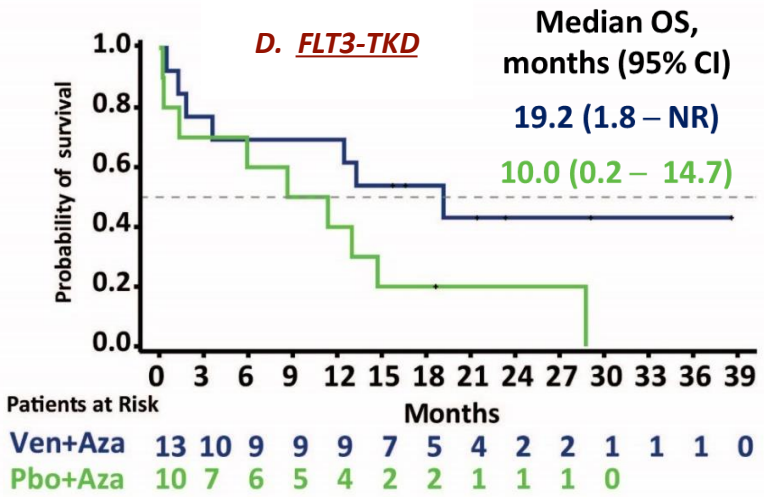

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Konopleva, et al. *Clin Cancer Res*. 2022:28-2744.

FLT3-ITD AML: Primary Refractory or Early Relapse

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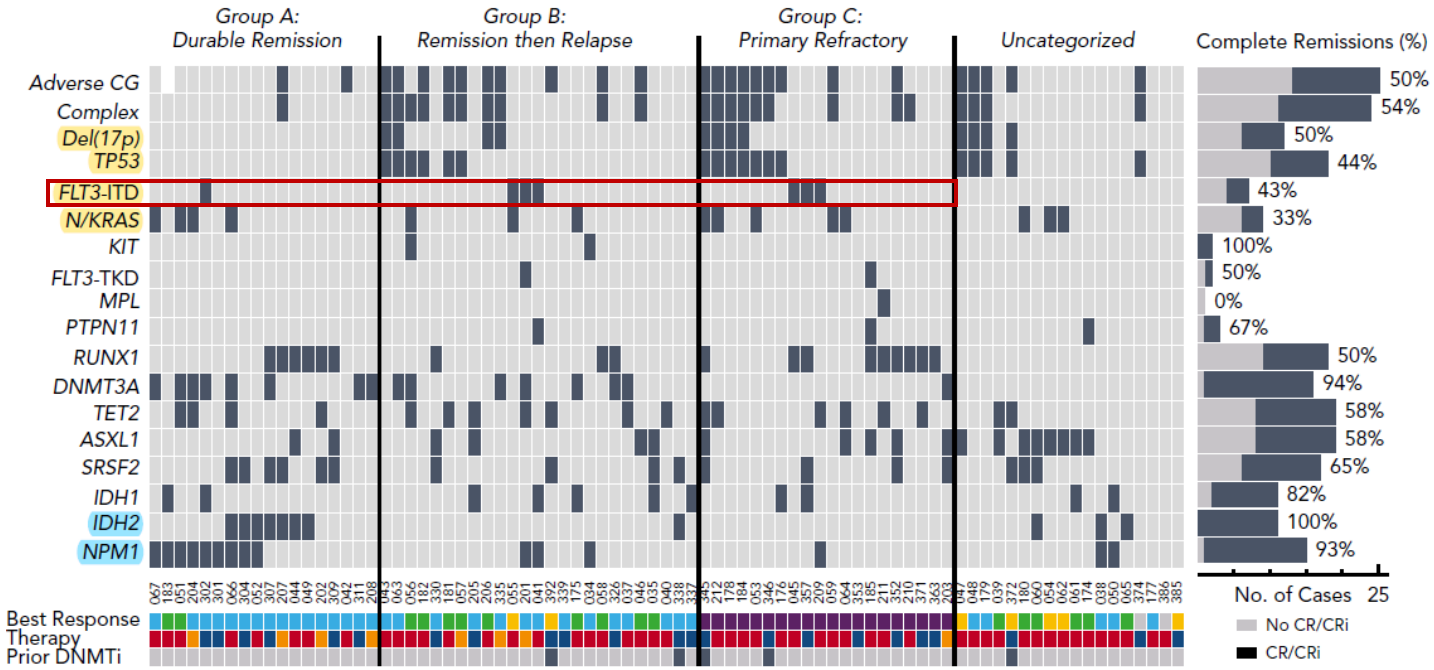
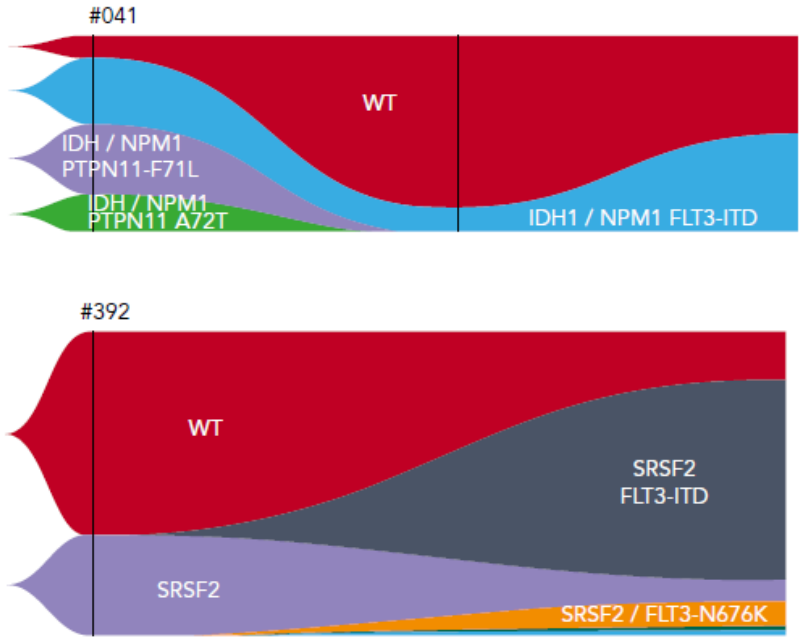
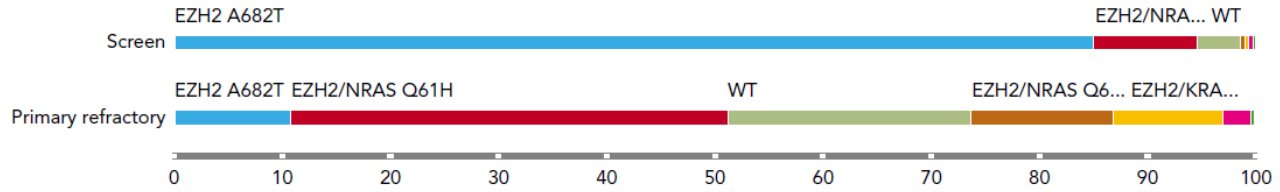




Patients treated at MDACC and The Alfred (n=81)

#064

Sample	Date	Blast%	EZH2	EZH2/NRAS Q61H	WT	EZH2/NRAS Q61K	EZH2/KRAS Q61H	EZH2/KRAS G13D	EZH2/NRAS Q61R
Screen	03/31/2017	24	85.02%	9.57%	3.99%	0.59%	0.16%	0.55%	0.12%
Refractory	05/03/2017	53	10.85%	40.35%	22.52%	13.18%	10.12%	2.57%	0.41%



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DiNardo CD, Tiong I, ... Konopleva M, Wei A, *Blood*. 2020

Ven+Aza: Genotype-specific Prognostic Model

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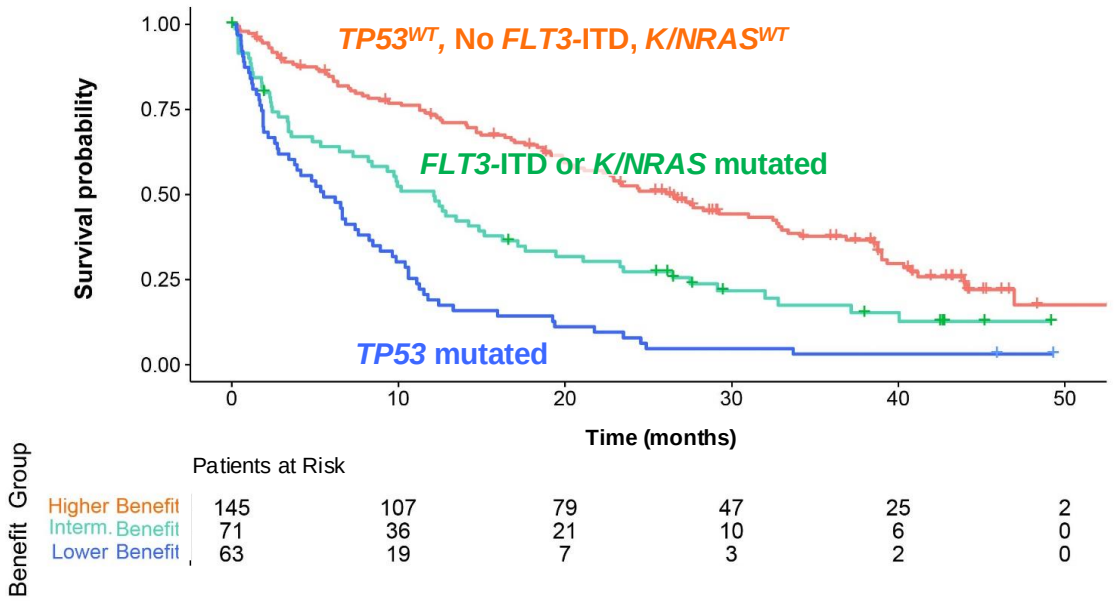
- First a higher benefit group was identified, with a median OS > 24 months
- Subsequently a lower benefit group was determined, with a median OS < 6 months
- Patients fitting neither criteria were categorized as the intermediate benefit group, with a median OS of 12 months



Ven + Aza (N = 279)	n	Events	Median OS, months (95% CI)
Higher Benefit	145	96	**26.51** (20.24, 32.69)
Intermediate Benefit	71	57	**12.12** (7.26 – 15.15)
Lower Benefit	63	61	**5.52** (2.79 – 7.59)

- Majority of patients in the Ven+Aza arm are in the higher benefit group: 52% (145/279)
- The remainder of the patients are distributed equally between the intermediate and lower benefit groups: 25.4% (71/279) and 22.6% (63/279), respectively

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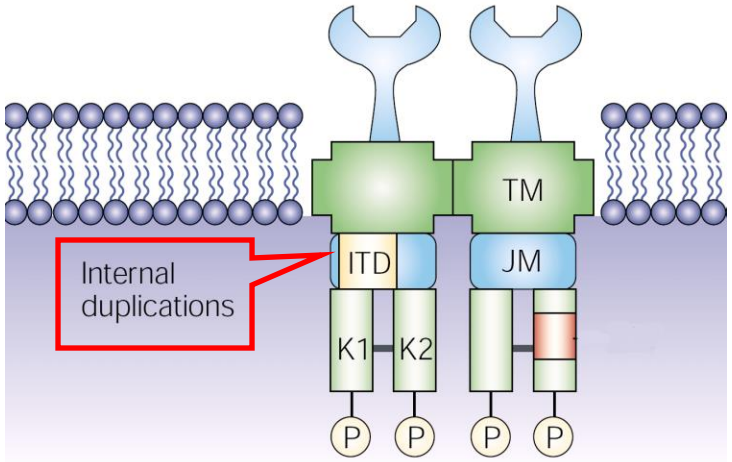
Dohner H et al, ASH 2022

Mutant FLT3: Oncogenic Signaling and MCL-1

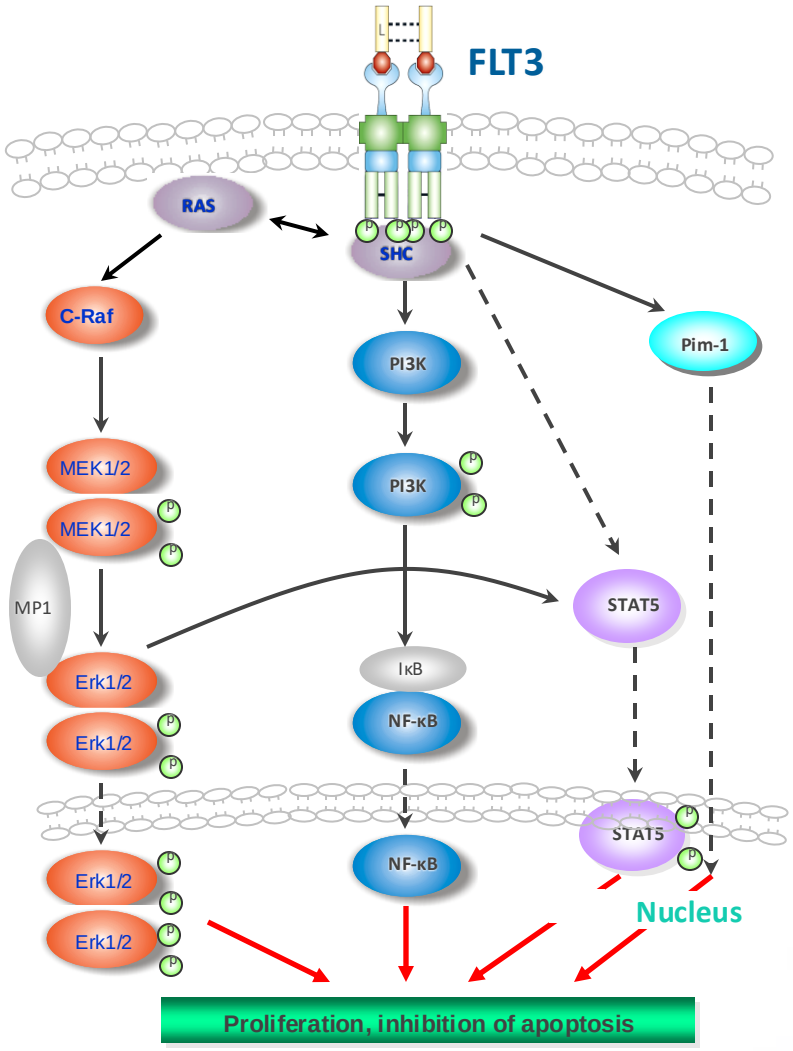


FLT3-ITD **24%**

FLT3-D835Y
FLT3-D835G **7%**

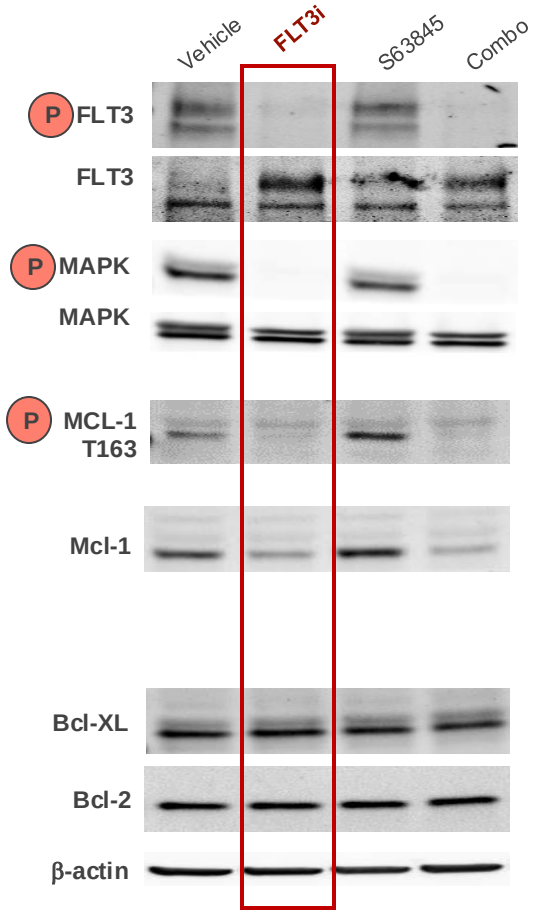
Sorafenib
Quizartinib
Gilteritnib
Midostaurin

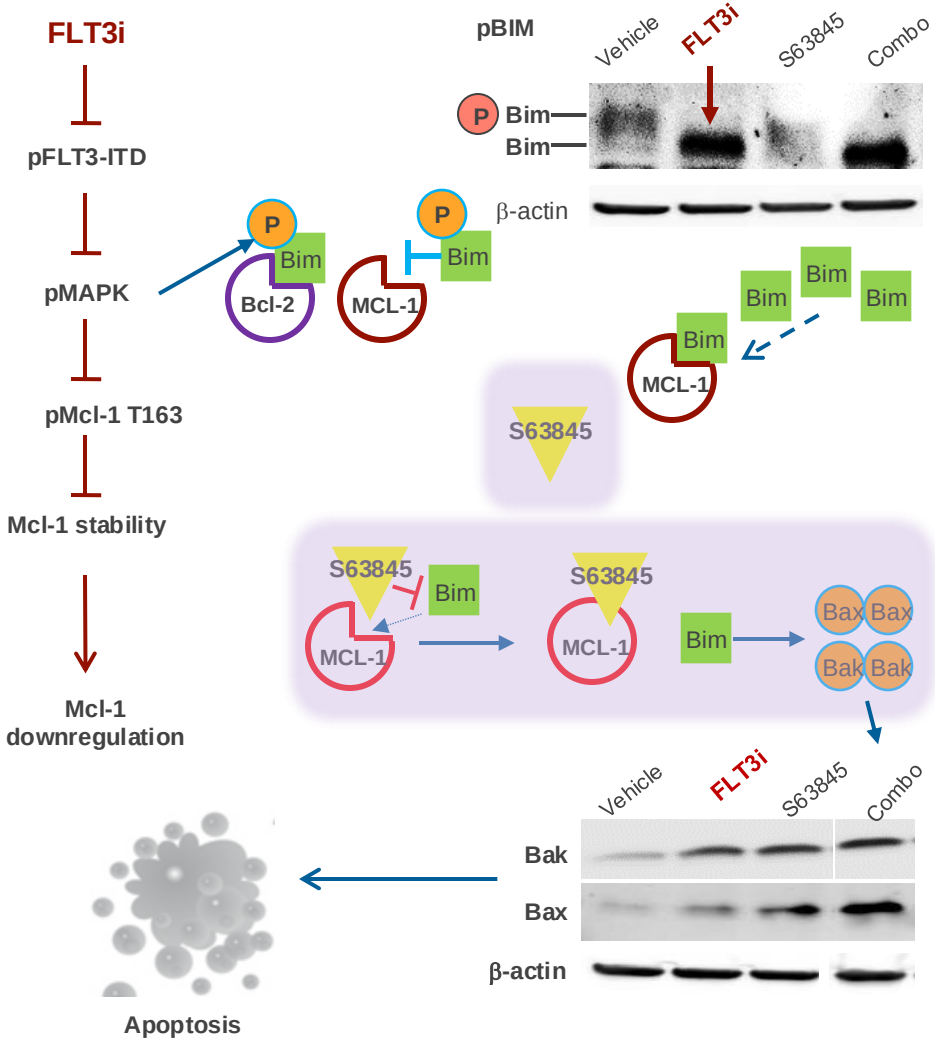
Phospho-FLT3 & its cascades



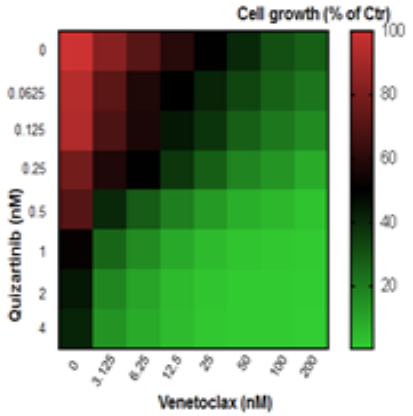
↑ **MCL-1**

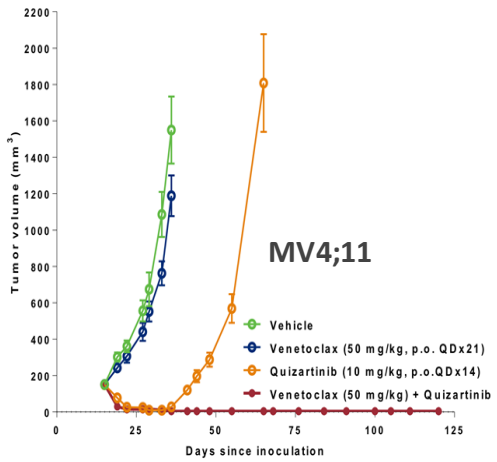
FLT3 inhibitor Targets both MCL-1 and BIM: Synergy with BCL-2 or MCL-1 inhibitors

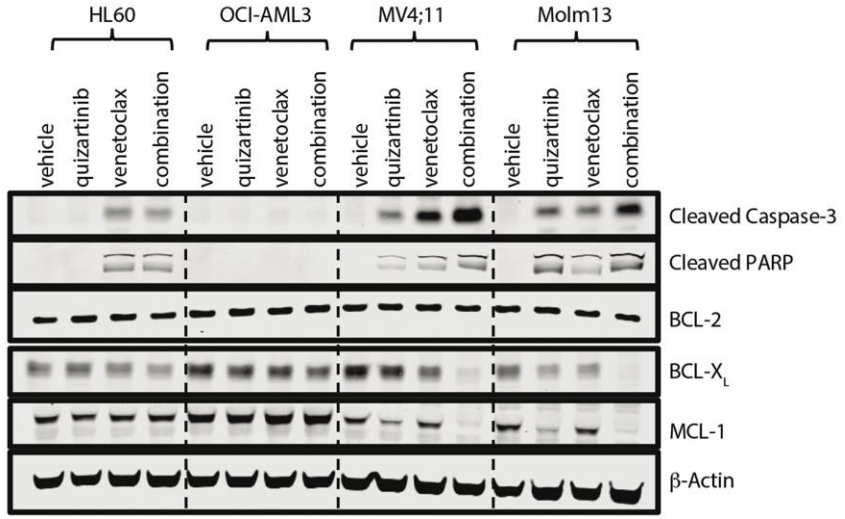


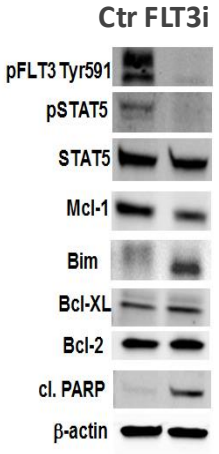


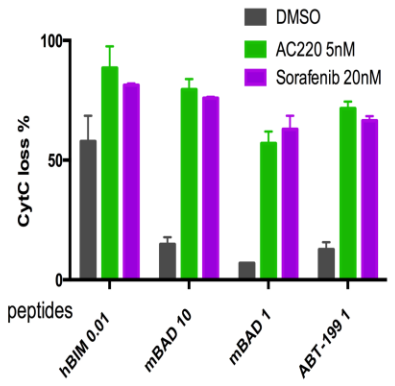
FLT3 Inhibitors and Venetoclax: Synergy and Priming



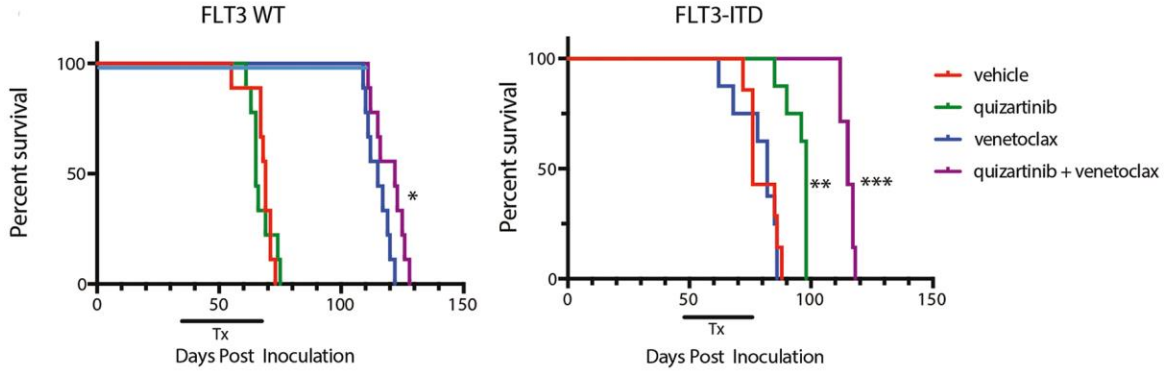






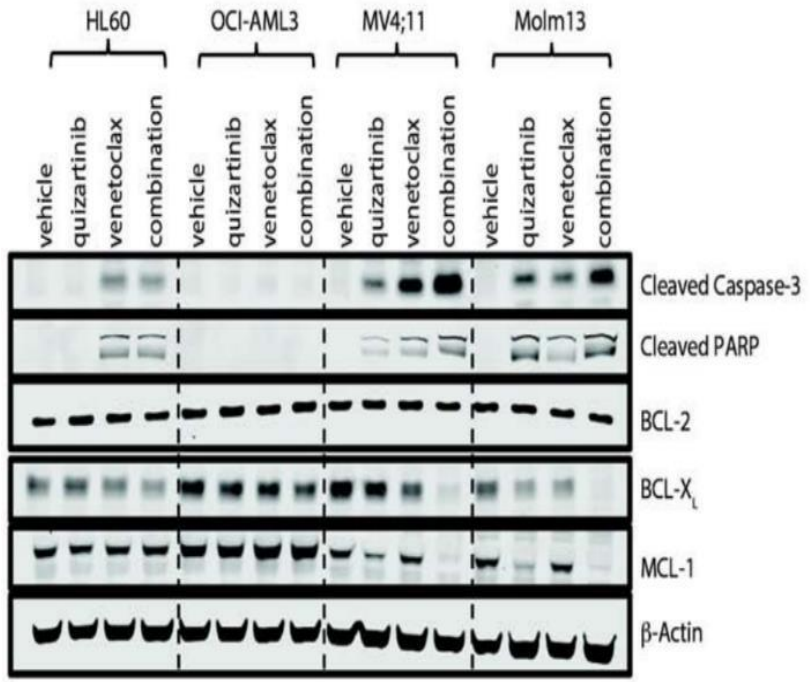


Dynamic BH3 profiling *in vitro*



Chyla et al. *Am H Hematol* 2018.
Mali R et al. *Haematologica* 2021

Venetoclax Combines Synergistically With FLT3i's



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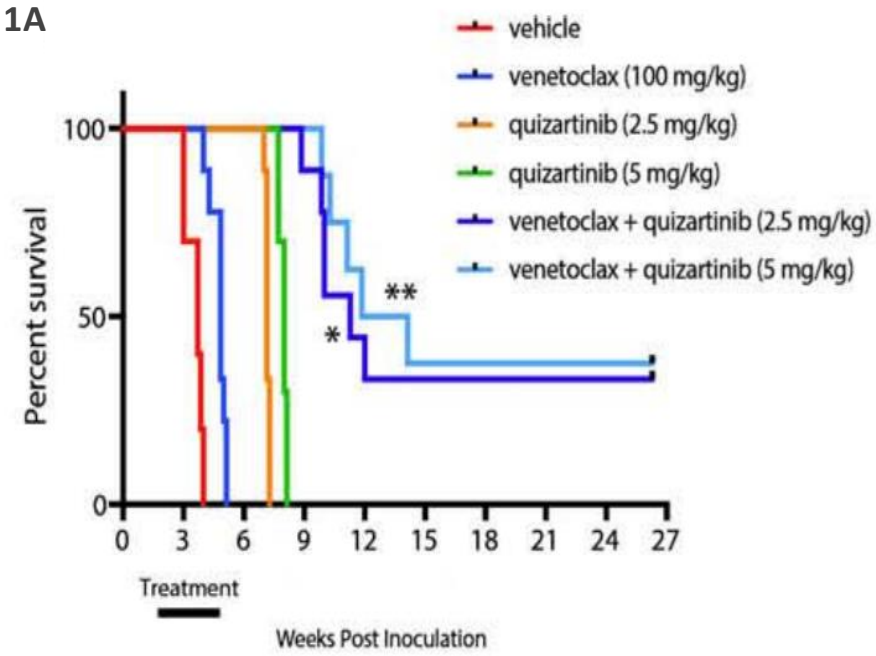
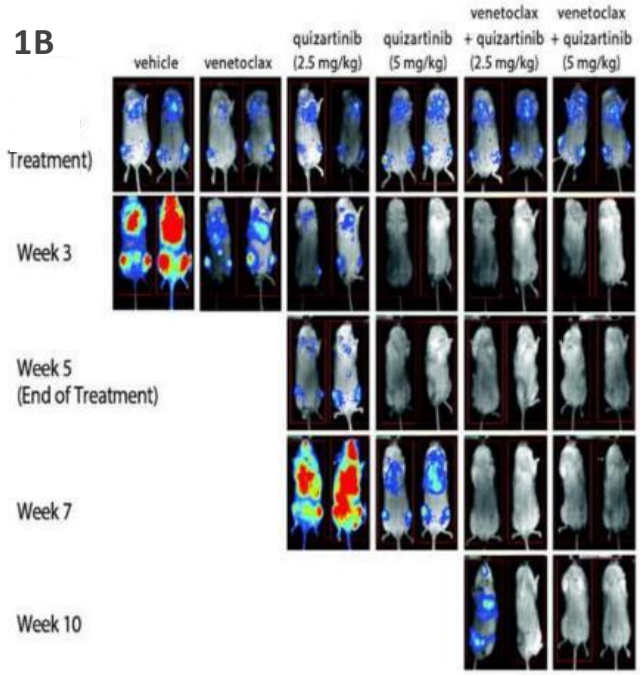


1B



Cell lines were treated with combination –↓ MCL-1, ↓ BCL-X_L

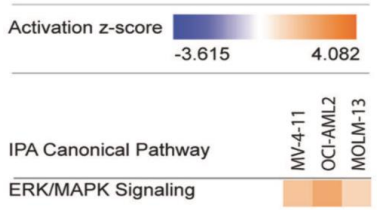
Venetoclax combined with quizartinib prolonged survival and reduced tumor burden in FLT3-ITD+ xenograft models

Singh Mali R, et al. *Haematologica*. 2021;106:1034-1046.

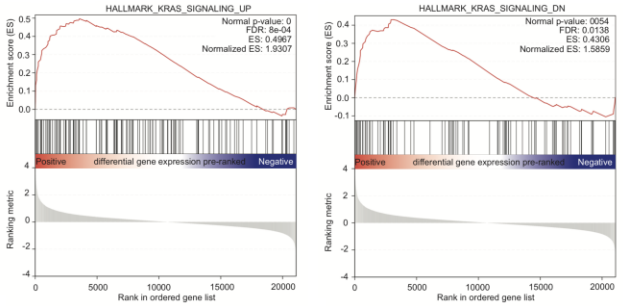
Adaptive Venetoclax Resistance in FLT3m AML: Activation of RAS/MAPK pathway and MCL-1 stabilization

VEN-RE cells have enriched ERK/MAPK pathway

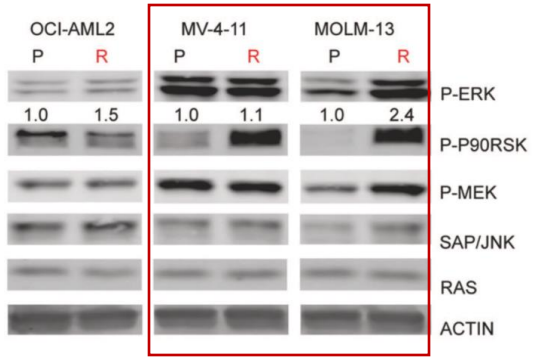
IPA



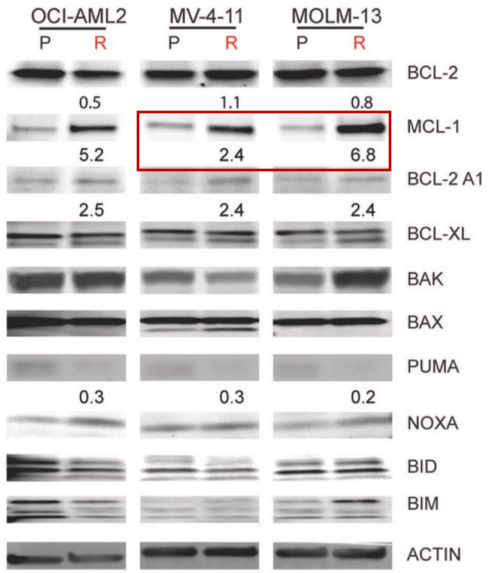
GSEA



WB

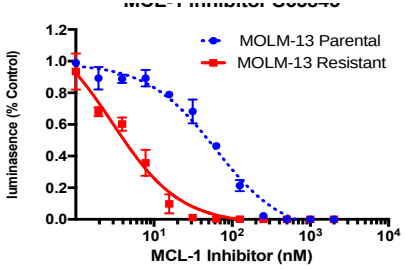


Increased MCL-1 expression

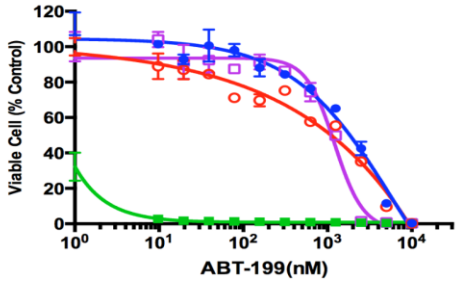


VEN-RE cells are sensitive to MCL-1 inhibition

MCL-1 inhibitor S63845

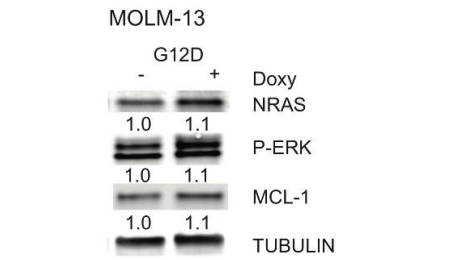


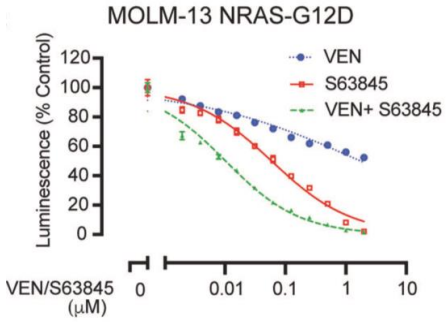
shMCL-1

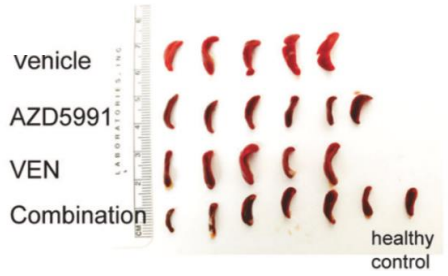


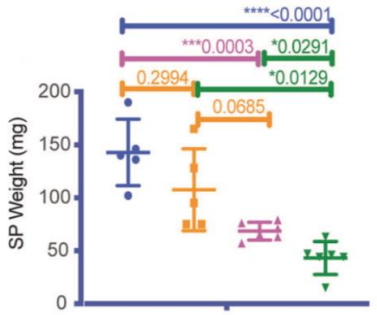
Zhang Q. *Signal Transduct Target Ther.* 7(1):51, 2022.

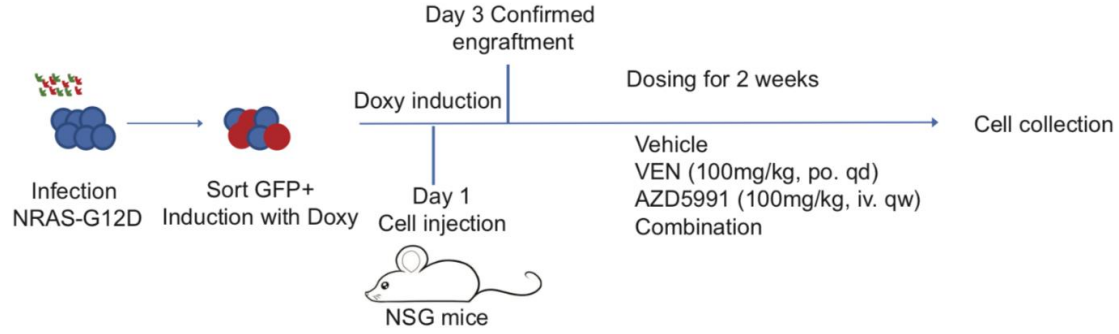
VEN combined with MCL-1 inhibitor in VEN-resistant FLT3-ITD/NRASG12D AML in vivo

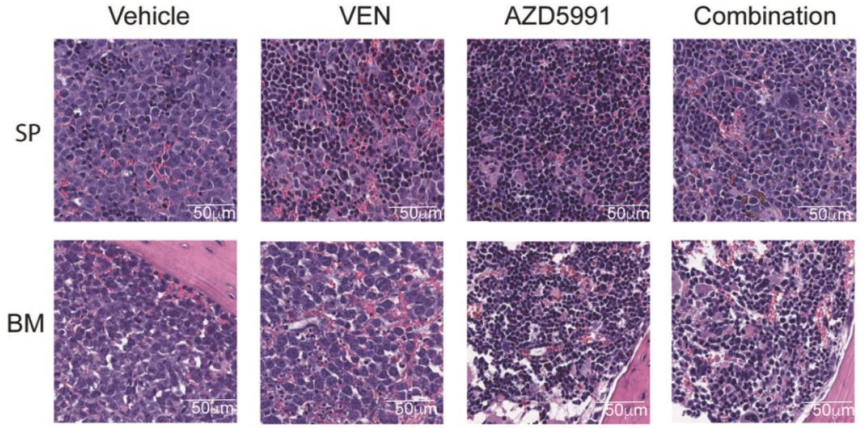








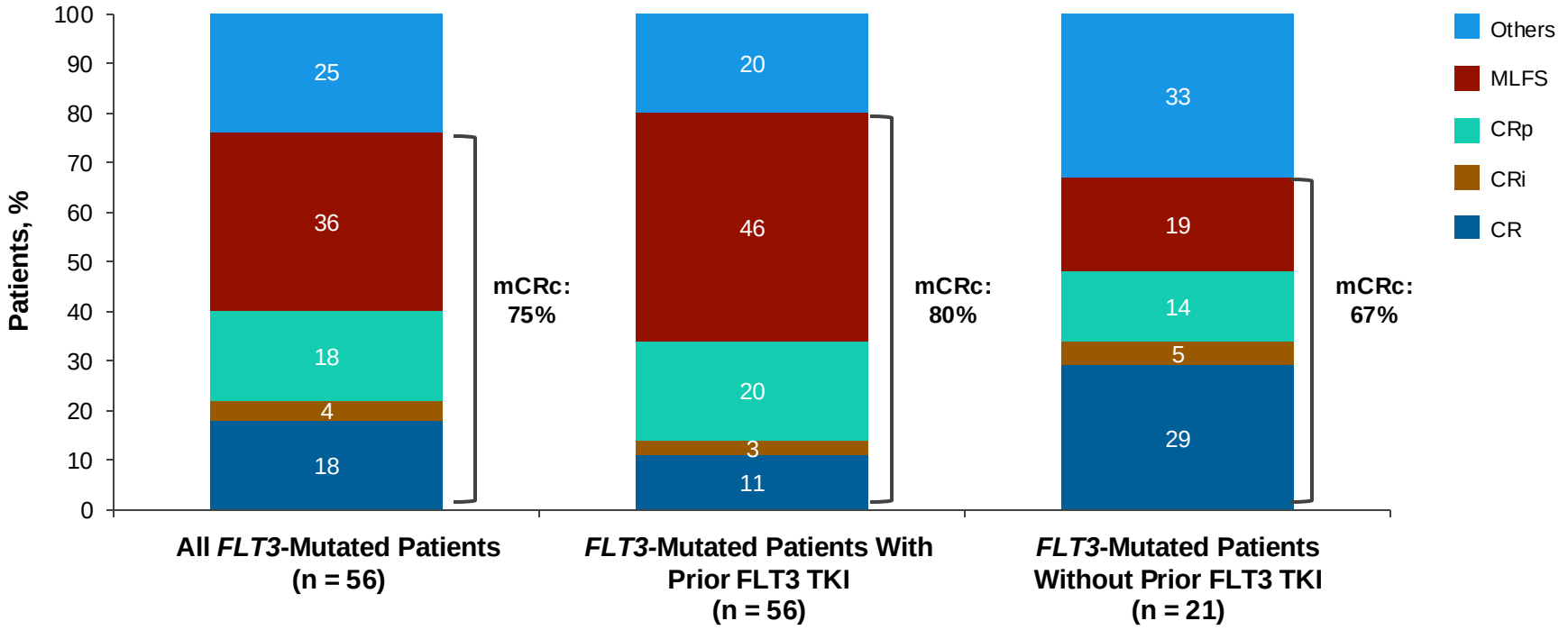




Zhang Q. *Signal Transduct Target Ther.* 7(1):51, 2022.

VEN + GILT: A Backbone to Build a Frontline Triplet [1,2]

IRAK4 | Symposium



Median salvage 2-3

Prior FLT3 TKI exposure: 60%

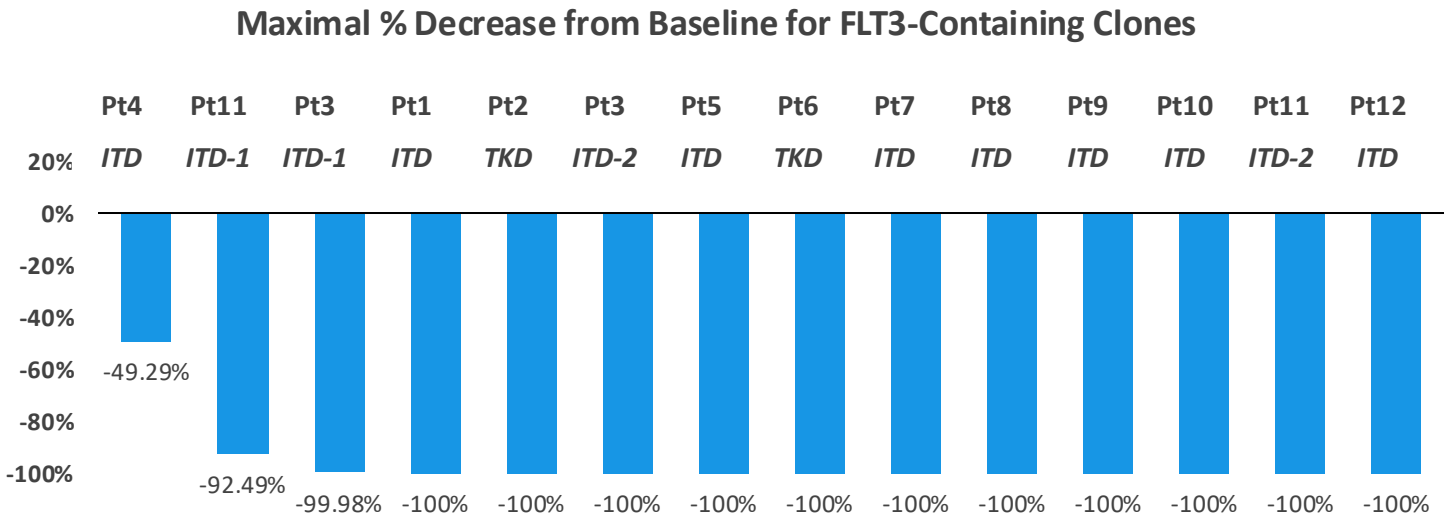
The mCRc rate in this study was 75%, whereas the CRc rate in the ADMIRAL phase 3 study for single-agent GILT was **54.3%** (using the same response parameters)

CURIS

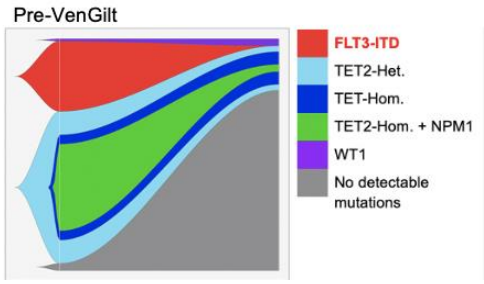
1. Daver N et al. *J Clin Oncol*. 2022;40:4048-4059. 2. Perl AE et al. *N Engl J Med*. 2019;381:1728-1740.

Decrease of *FLT3* clones with VenGilt treatment

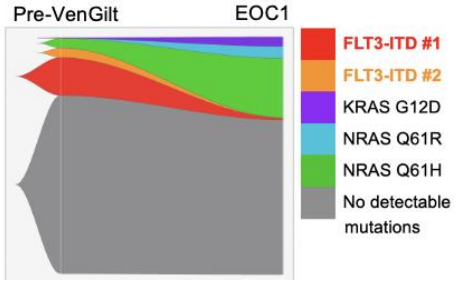
IRAK4 | Symposium



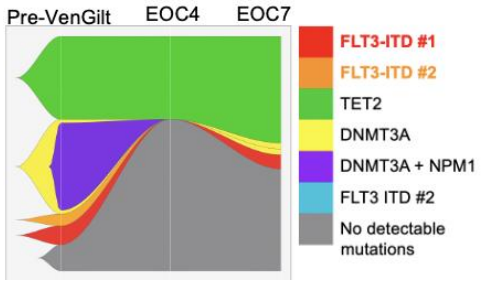
Decrease of FLT3-ITD to undetectable levels



Decrease but not elimination of FLT3-ITD



Decrease and subsequent rise of FLT3-ITD



- **All 14** *FLT3*^{mut} clones decreased in size on therapy
- **11 clones from** in 9 patients decreased to an undetectable level at maximum response
- **2 clones** returned at a later timepoint
- Response was frequently rapid, with maximal decrease of FLT3 by cycle 1 day 28 of therapy in 5 of 8 evaluable patients
- 7 patients had matching timepoints where FLT3-ITD was evaluated by MyFLT3 specific MRD assay. Sensitivity of decrease ranged between 10^{-2} to 10^{-6}

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VenGilt, venetoclax and gilteritinib.
Kennedy V…..Smith C. ASH 2022. Abst 933

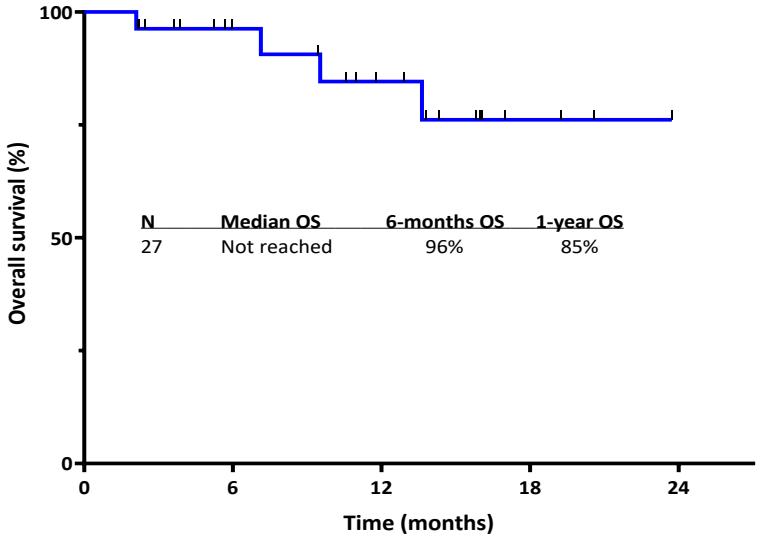
Aza+Ven+Gilteritinib in Frontline FLT3-mutated AML: Healthier marrow, potentially more curative and better tolerated

Induction

Azacitidine
75 mg/m² IV/SC on D1-7
Venetoclax R/U to goal 400mg D1-14
Gilteritinib 80 mg on D1-14
(--if blasts <5% on D14, hold both GV
--if blasts >5% on D14 continue GV and repeat BM in 1 week)

Consolidation (up to 24 cycles)

Azacitidine 75 mg/m² IV/SC on D1-5
Venetoclax 400mg on D1-7
Gilteritinib 80 mg on D1-28

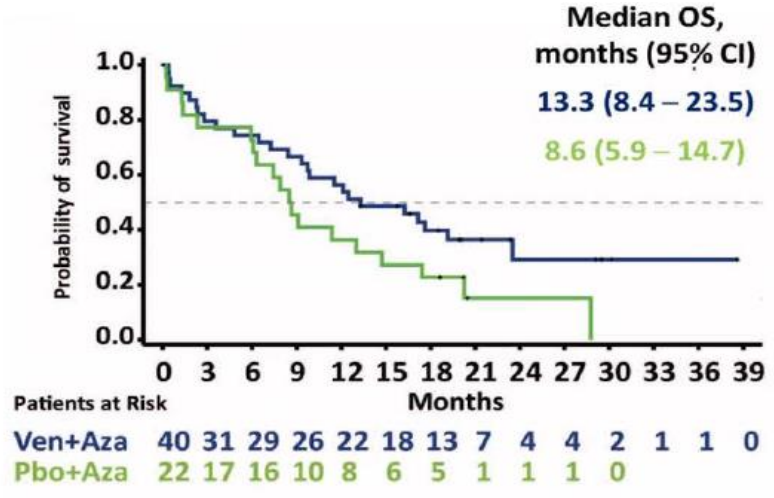


N=30

CR 92%
CRi 4%
CR+CRi: 96%

Recovery:
ANC ≥0.5 37d
Plt ≥50 25d

Historical perspective (Konopleva M et al CCR 2023)
AZA+VEN in FLT3m frontline AML (N=40)



CURIS

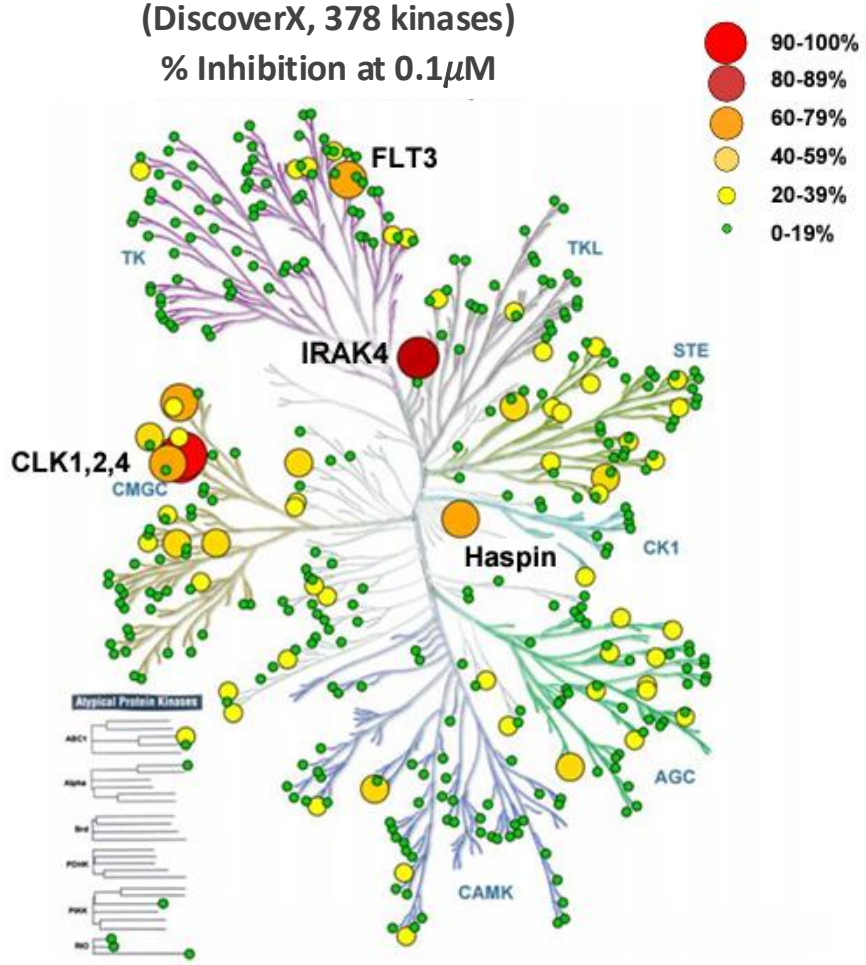
Short N, Daver N, et al. *J Clin Oncol*. Jan 2024

Emavusertib (CA-4948)

IRAK4 | Symposium

A Small Molecule Kinase Inhibitor

Active-site binding
(DiscoverX, 378 kinases)
% Inhibition at 0.1μM



CA-4948 Binding Affinity Activity

	DiscoverX
Kinase	K_d (nM)
IRAK4	23
IRAK1	12,000
IRAK2	>20,000
IRAK3	8,500

Other top hits:

CLK1	10
CLK4	14
CLK2	20
FLT3	31
DYRK1A	25
Haspin (GSG2)	32
TrkA	130

- First-in-class IRAK4 and FLT3 inhibitor for cancer patients currently being investigated in Phase 1/2 dose-escalation trials
- Binds with high affinity to **IRAK4, FLT3, CLK** and **DYRK1A**
- Multi-kinase inhibitor with strong preclinical evidence to over come Venetoclax resistance.
- CA-4948 targets **transcriptional and post-translational regulation of MCL-1**

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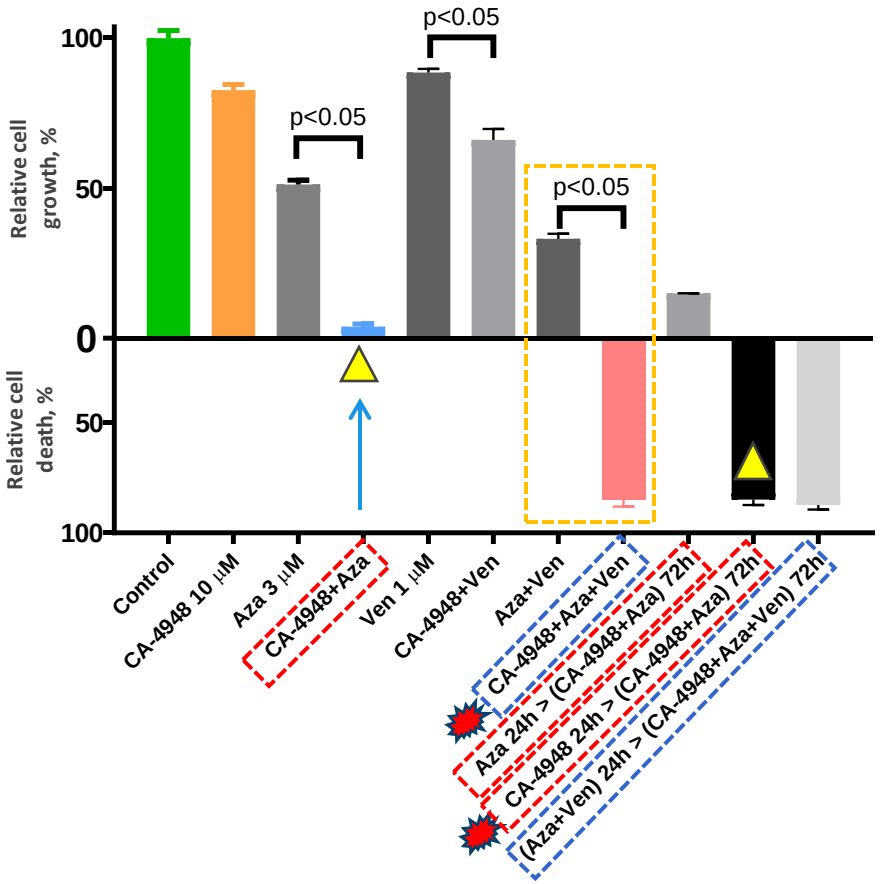
Kinome illustration reproduced courtesy of Cell Signaling Technology

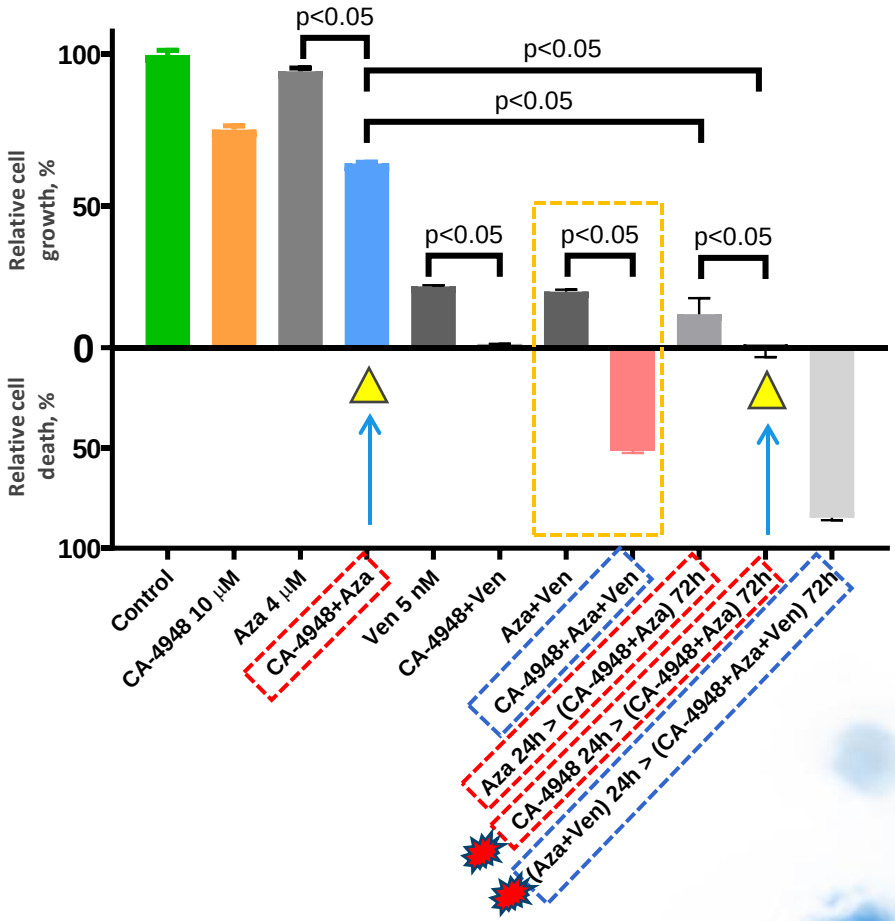
CA-4948

Combination of CA-4948 with azacitidine and venetoclax in FLT3-WT AML cell lines

THP-1 (venetoclax resistant)



OCI-AML2 (azicitidine resistant)



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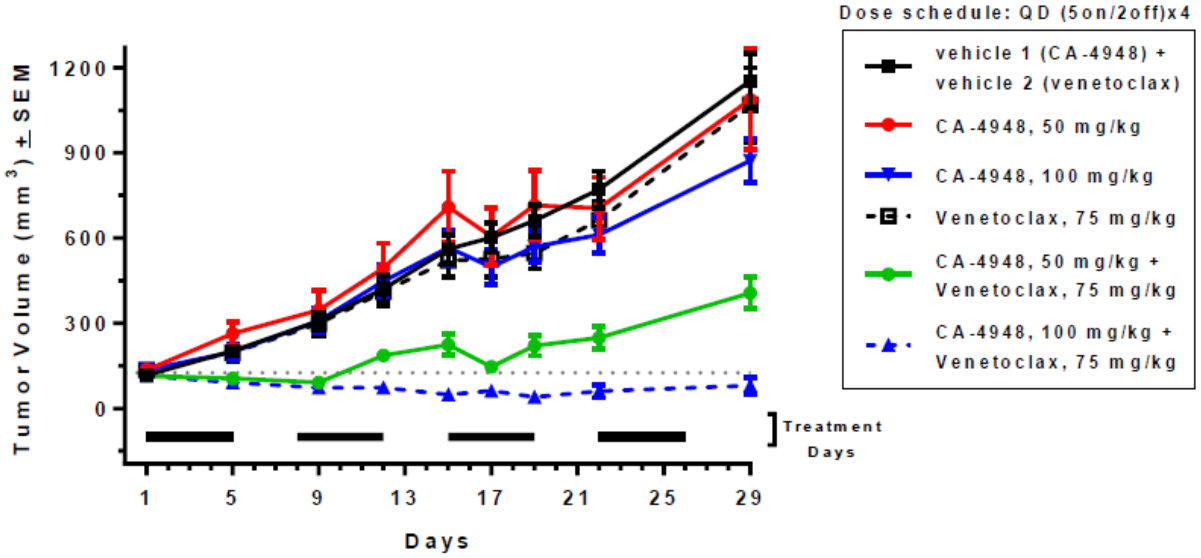
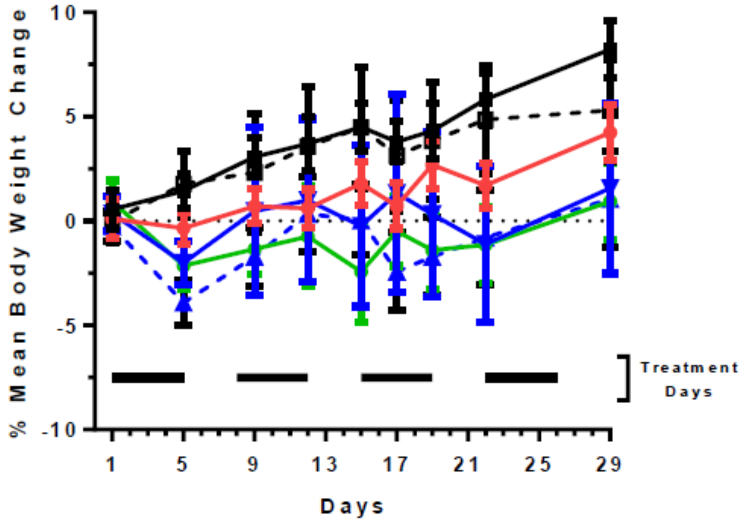
Efficacy of CA-4948 + Venetoclax Combination Dosed 5on/2off in the DLBCL OCI-LY10 (ap1) Model

OCI-LY (ap1) Tumor Growth



Body Weight



- OCI-Ly10 (ap1) cells: DLBCL-ABC, *MYD88*-L265P, *CD79A*
- CA-4948 + venetoclax combination on a 5on/2off dose schedule induced tumor stasis and regression with CA-4948 at low and high dose, respectively
- The CA-4948 + venetoclax combination was tolerated with the 5on/2off schedule, but minor skin/fur/rough coat signs were present in 50 and 100 mg/kg CA-4948 (single and combinations) treated animals on days 17 and 17/19, respectively.

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EXP-18-AA1856

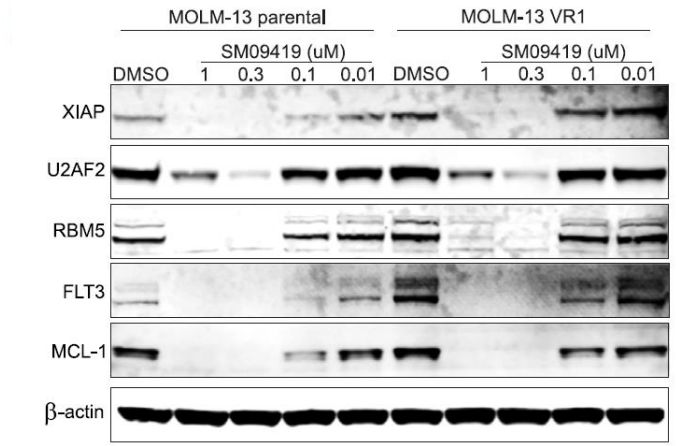
* Data from Curis

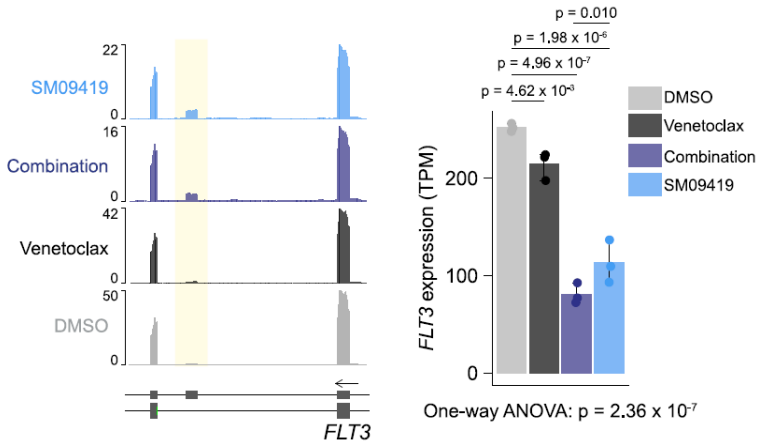
Modulation of RNA splicing enhances response to BCL2 inhibition in leukemia

IRAK4 Symposium

Cancer Cell

CLK inhibition induces splicing alterations of key survival genes in AML





- CLK inhibition is associated with splicing changes by increased intron retention within the transcripts of RNA splicing factors - **SRSF5, U2AF2, RBM17, and RBM5**
- CLK inhibition promoted inclusion of an exon with an in-frame stop codon (a ‘‘poison exon,’’ whose inclusion renders the transcript NMD sensitive) in the receptor tyrosine kinase FLT3
- CLK inhibition in AML cells led **to downregulation of MCL-1, XIAP and FLT3 levels** that confer resistance to BCL2 inhibitors
- Additional CLK inhibition targets are:
  1. SMYD2 (a lysine methyltransferase recognized as a therapeutic target in AML)
  2. DHODH (a metabolic enzyme and recent AML therapeutic target)
  3. ATAD3A (a metabolic enzyme whose expression has been included in leukemia stem cell signatures)
  4. MYC target gene **CDC16**
  5. RNA processing genes **SRPK3, TRA2A, and DDX51**

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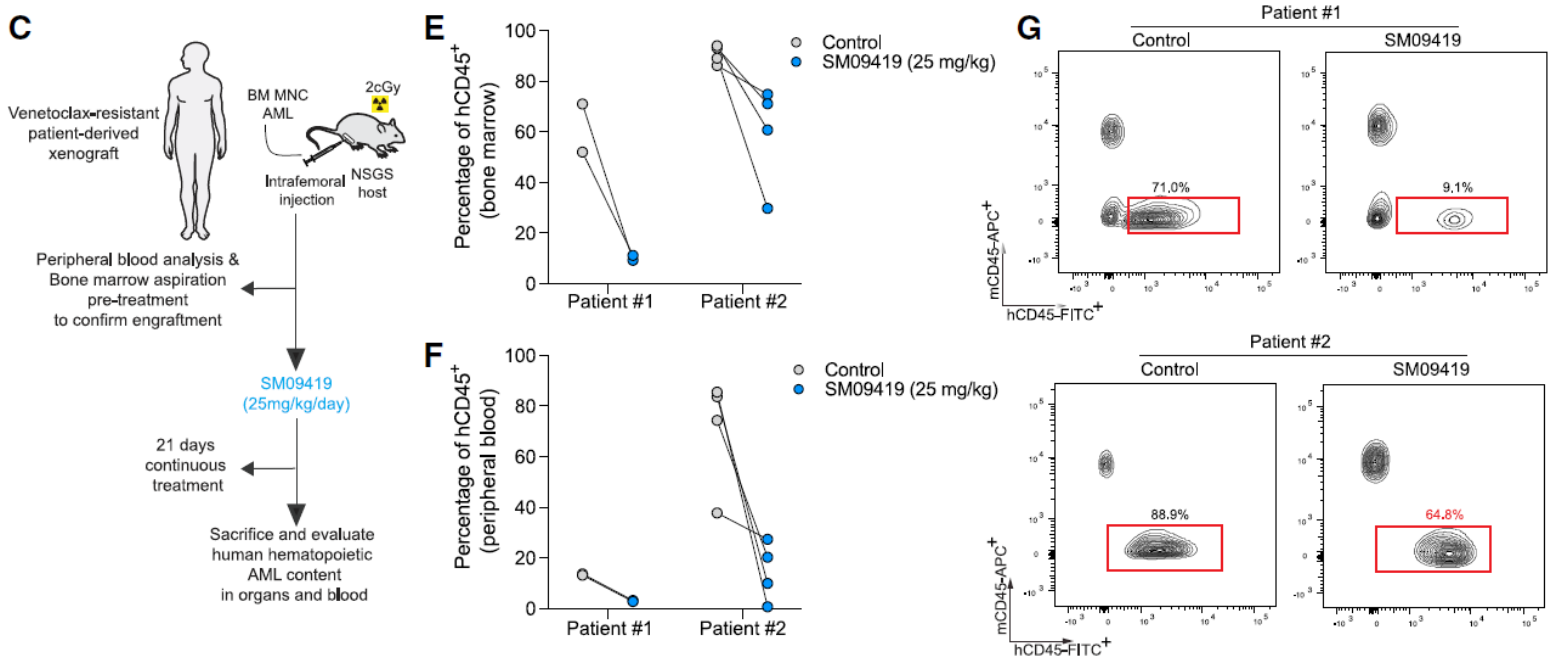
Wang E, et al. *Cancer Cell*. 2023 Jan 9;41(1):164-180.e8.

Modulation of RNA splicing enhances response to BCL2 inhibition in leukemia

CLK inhibition circumvents therapeutic resistance to venetoclax



Patient	Prior therapies	Reponse	Start of venetoclax	End of venetoclax	Sample date	Genetic alterations
1	VEN+Azacytidine	Primary refractory	01/18/2019	02/27/2019	06/05/2020	RUNX1, PTPN11, FLT3, SF3B1, STAG2
2	VEN+Low-dose Cytarabine	Primary refractory	01/03/2017	04/06/2017	04/10/2017	RUNX1, DNMT3A, IDH2

Wang E, et al. *Cancer Cell*. 2023 Jan 9;41(1):164-180.e8.

Summary

IRAK4 | Symposium

- Resistance to BCL2i is multifactorial, commonly associated with TP53 and “signaling” mutations and differentiation state:
    - Deficit of activator (BAX expression/mutations) or/and
    - Switch to other anti-apoptotics (MCL-1/BCL-xL)
- Inhibition of FLT3 signaling by FLT3 inhibitors or emavusertib reduces BCL-xL and MCL-1 expression via PI3K-AKT, RAS-MAPK and STAT5 pathways and sensitizes FLT3-mutated cells to venetoclax
- Inhibition of CLK (CDC like kinases) and DYRKs (dual-specificity tyrosine-regulated kinases) by emavusertib can overcome venetoclax resistance and shows strong potential to synergize with venetoclax
- Emavusertib in combination with azacitidine and venetoclax demonstrated significant antileukemic effects in all AML cell lines, including azacitidine- or venetoclax-resistant cell lines (Ugolkov EHA 2021)

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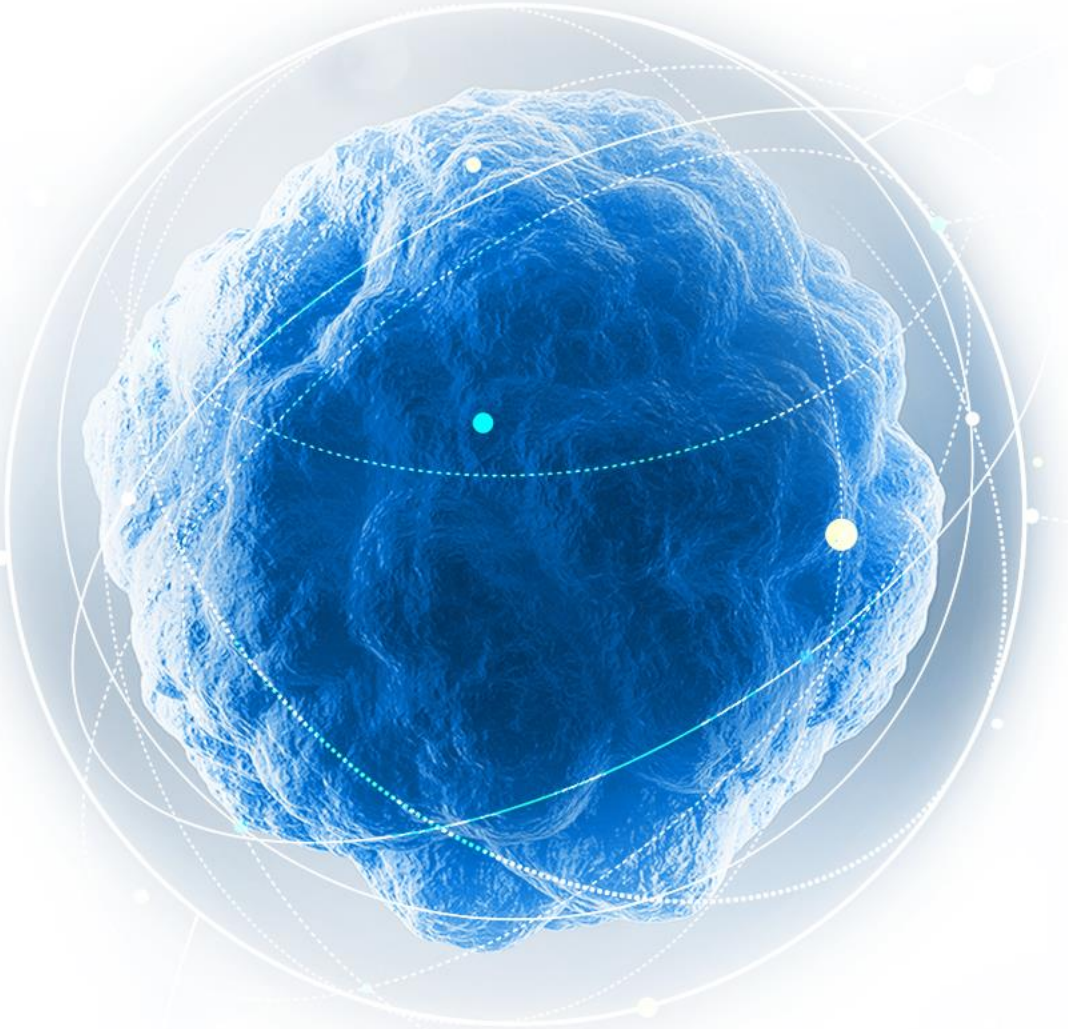
IRAK4 | Symposium

Incorporating IRAK inhibition in the treatment of myeloid disease



Guillermo Garcia-Manero MD
McCredie Professor
Chief, Section of MDS
Department of Leukemia
MD Anderson Cancer Center
Houston, TX

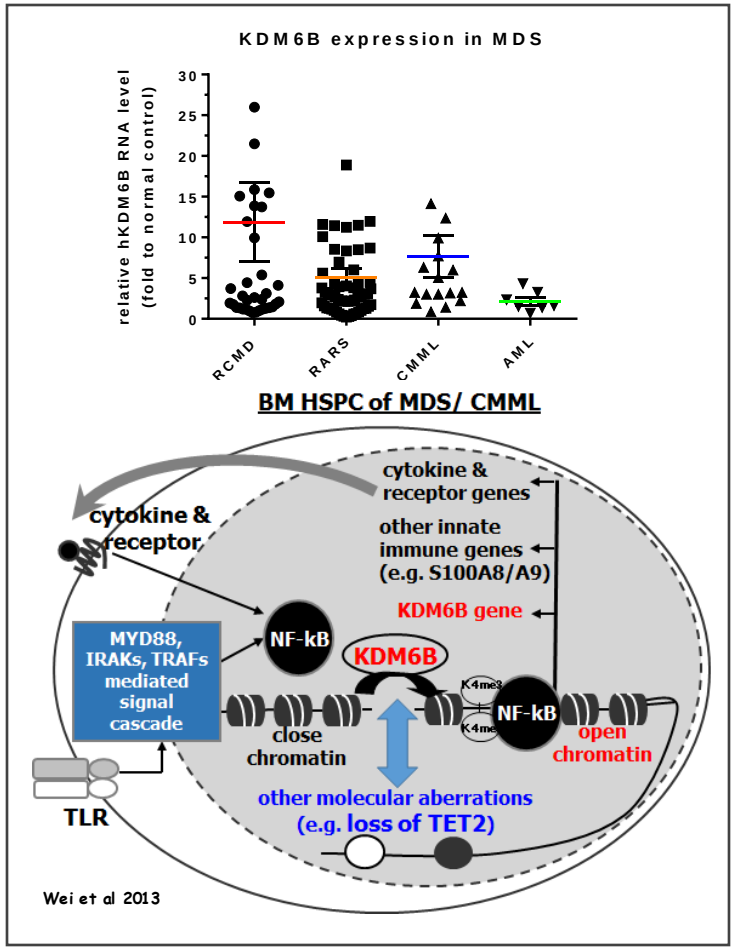
CURIS®

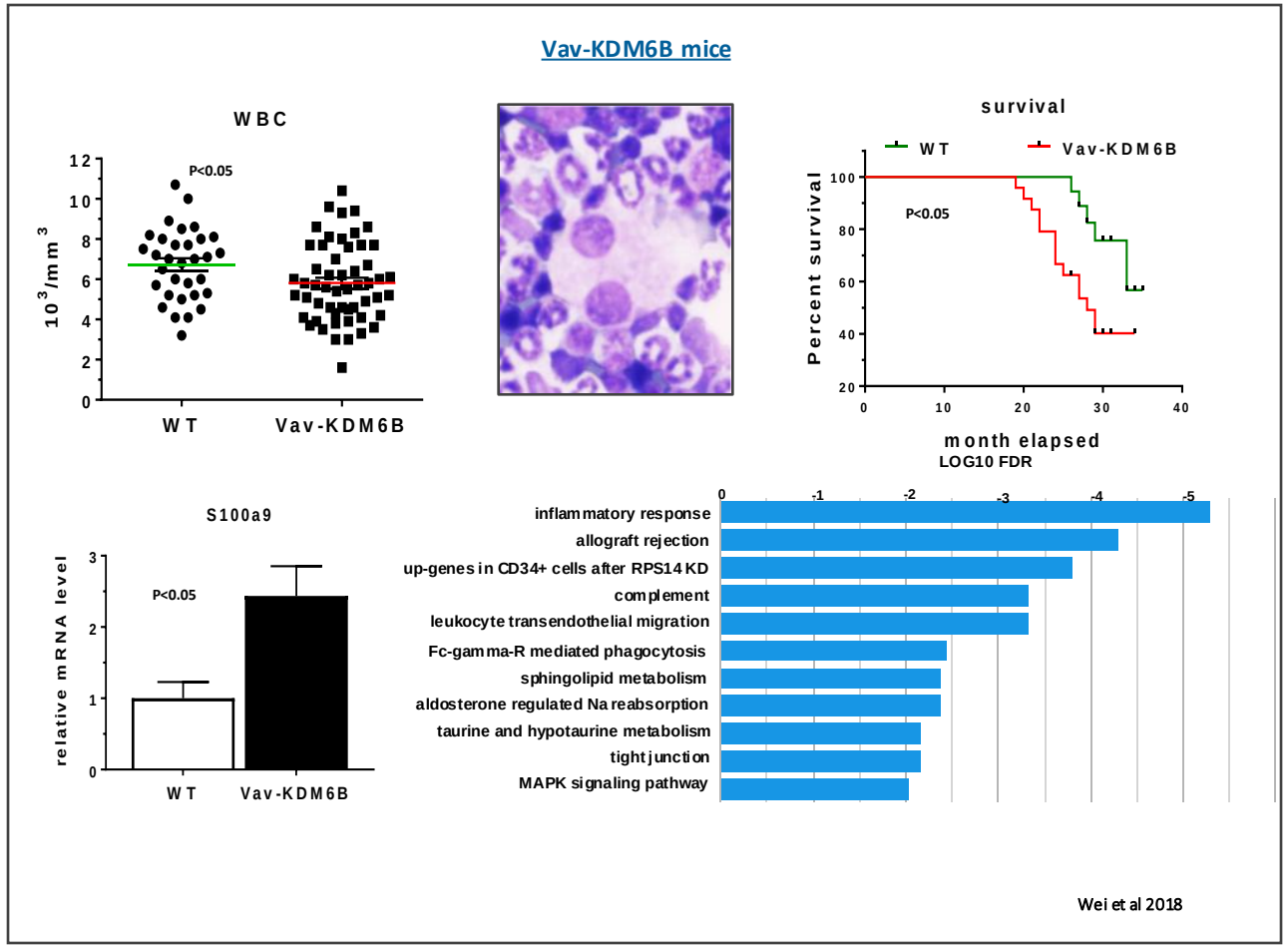
Agenda

- Discuss basic concepts of MDS
- Review clinical activity of CA4849 in RR MDS and AML
- Discuss potential role of IRAK inhibition in MDS
- Discuss potential role of IRAK inhibition in AML

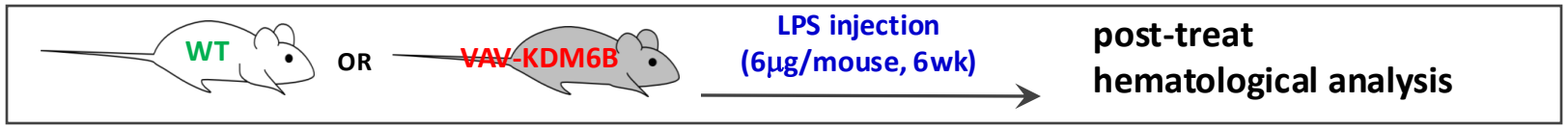
Souers, et al. *Nature Medicine.* 2013

Innate Immune Signal Deregulation including Overexpression of KDM6B Drives Pathogenesis of MDS/ CMML

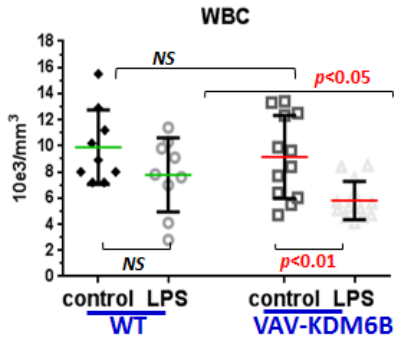


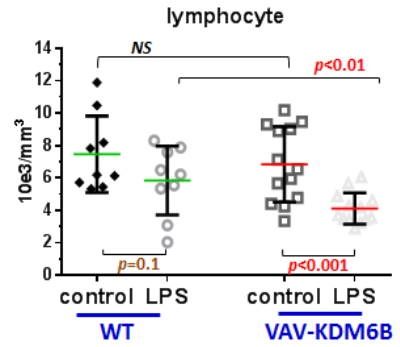


Vav-KDM6B(JMJD3)-Tg mice display MDS-like phenotype, particularly after exposure to chronic innate immune stimulation

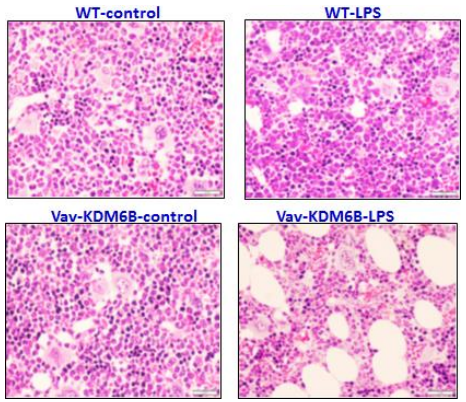


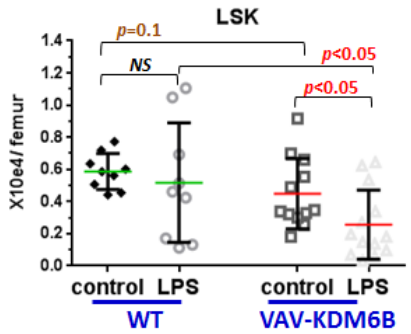
#PB: significantly lowered white cell counts



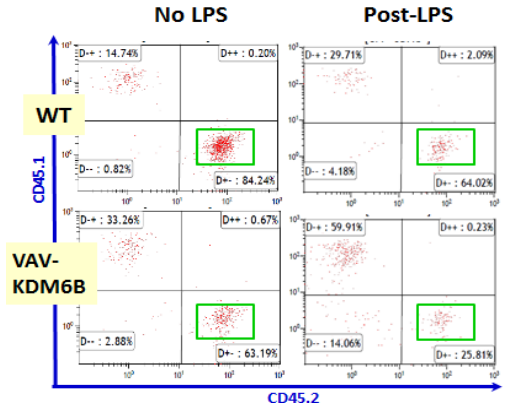


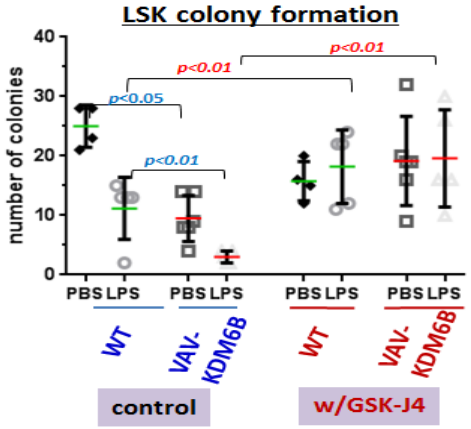
#BM: significantly lowered BM cellularity & HSC (LSK)



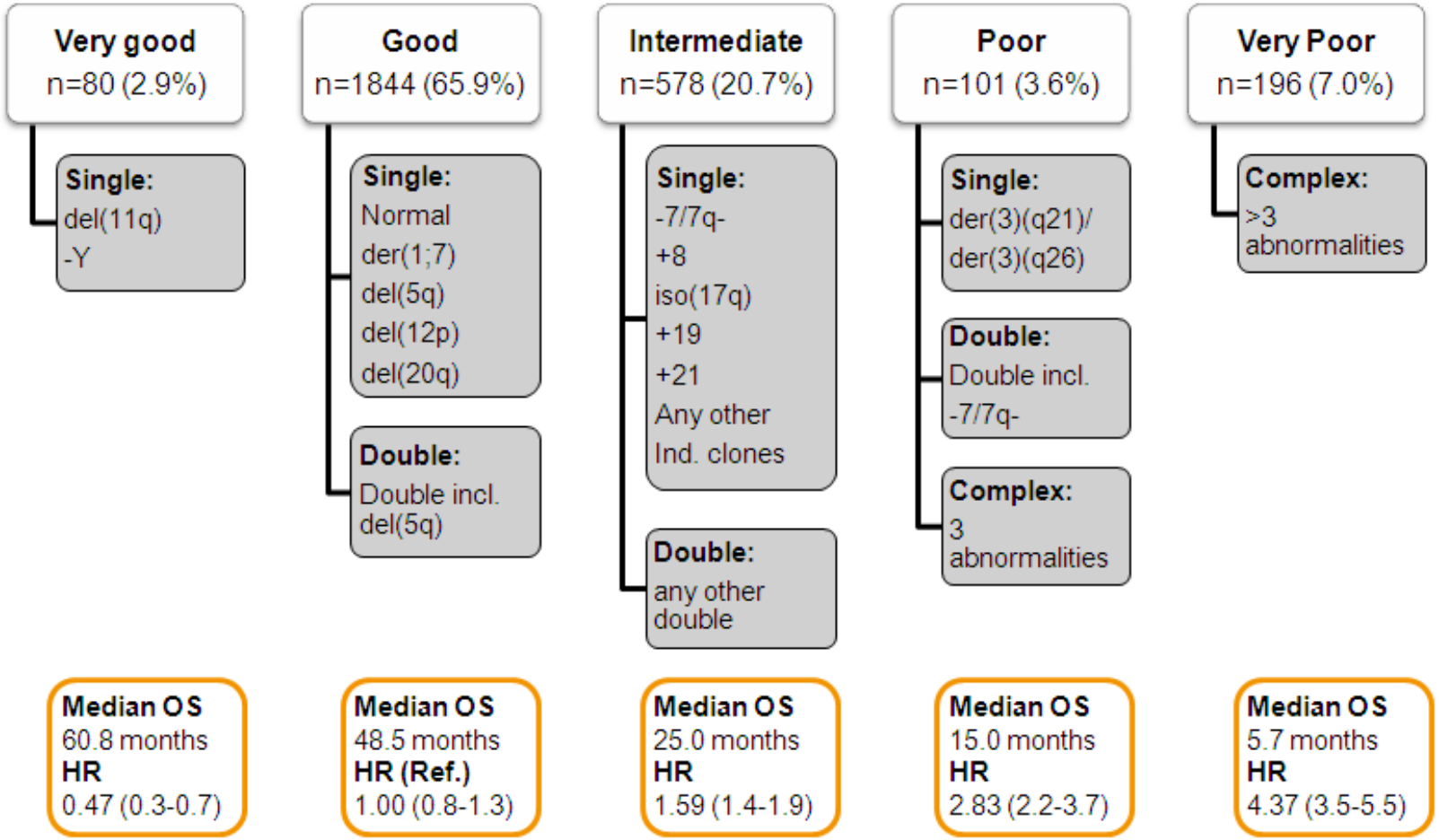


#HSC function: significantly reduced repopulating; can potentially be rescued by KDM6B inhibitor



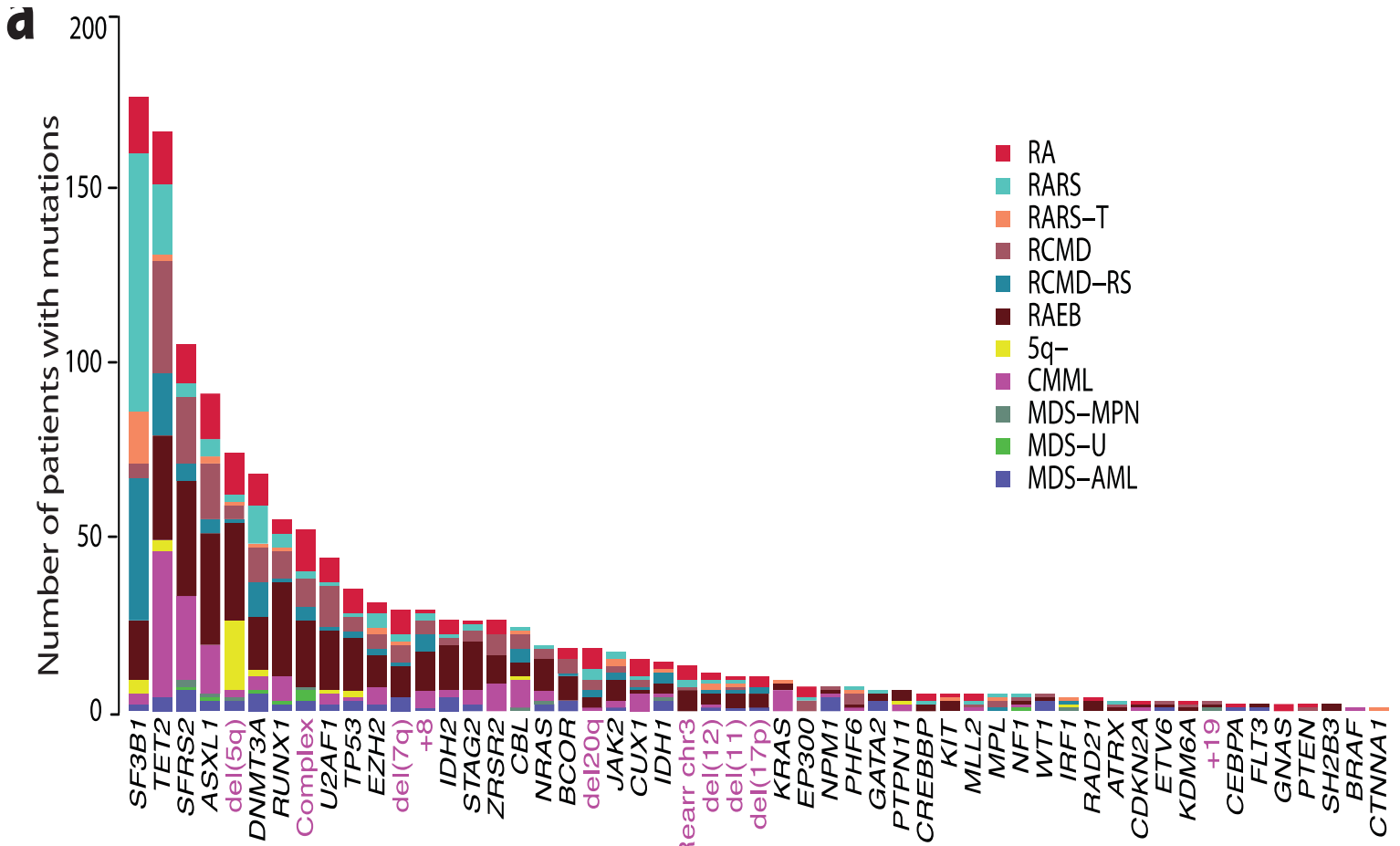


Cytogenetic Scoring System in MDS



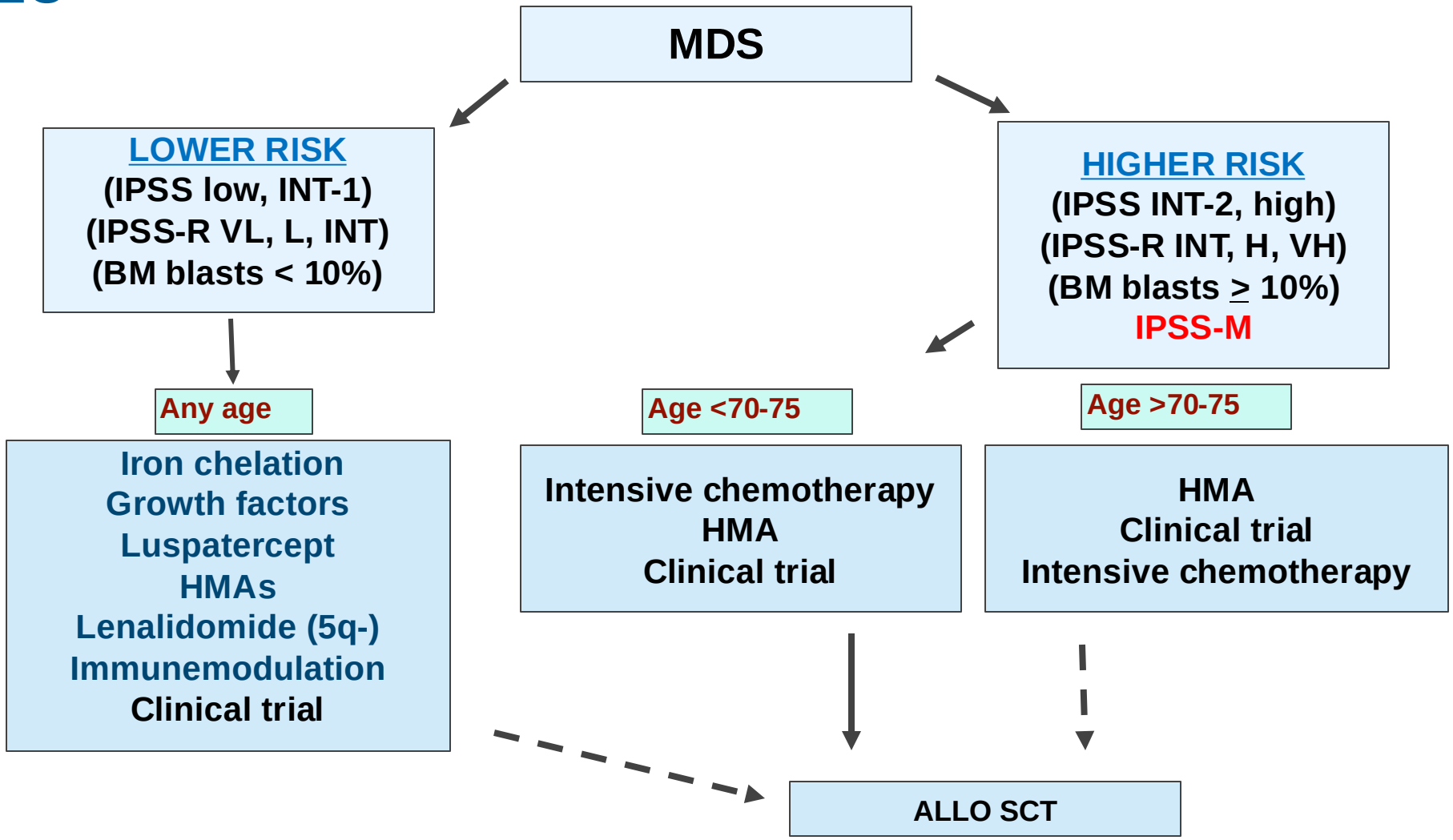
Schanz et al., JCO, 2011

Genomics of MDS



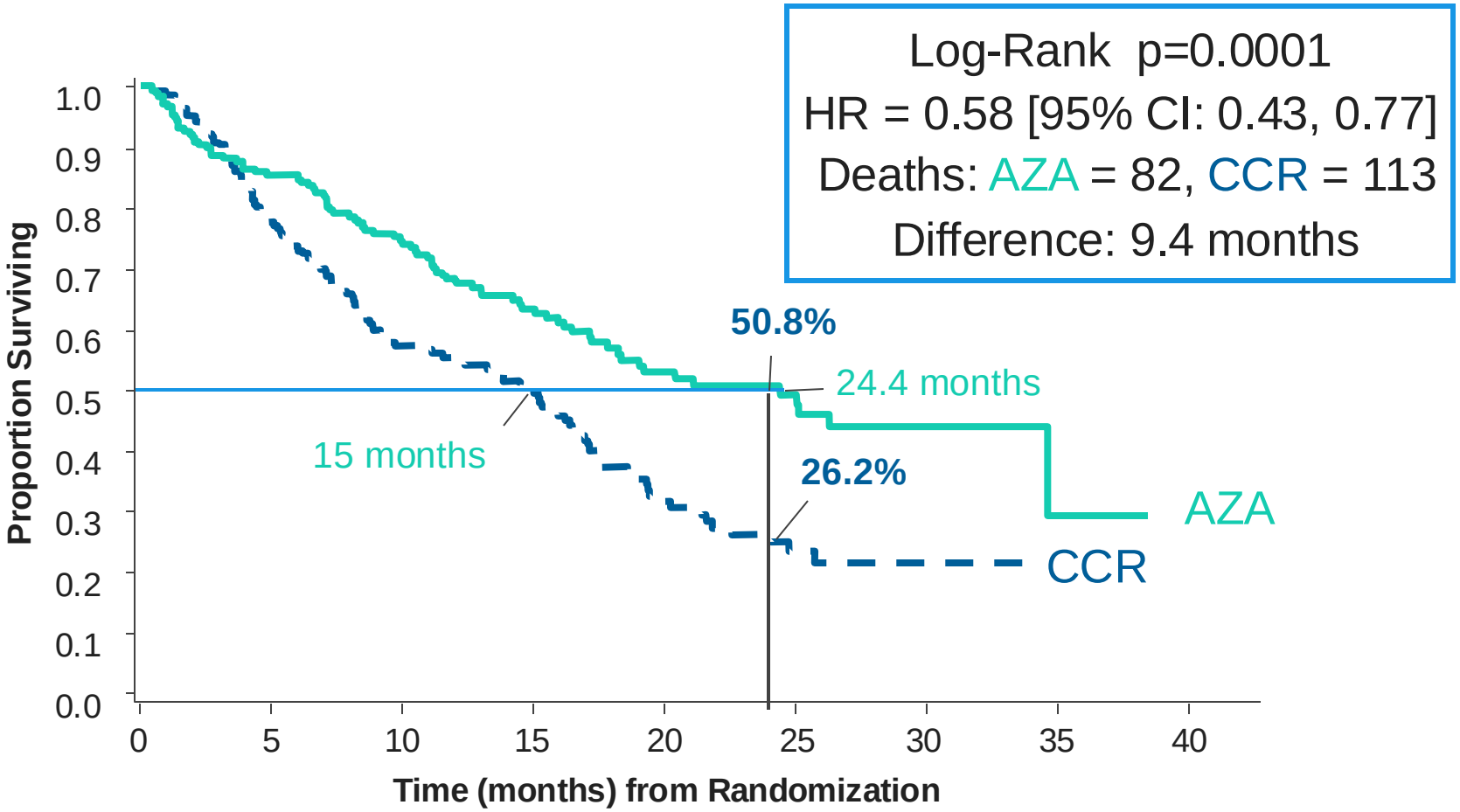
Papaemmanuil et al Blood 2013;122:3616-27

Proposed treatment algorithm for patients with MDS 2023



Garcia-Manero et al AJH 2023

SOC: Azacitidine



Fenaux et al. Lancet Oncology 2010

Doublets in Higher Risk MDS

IRAK4 | Symposium

- **Panther (P-3001): azacytidine +/- pevonedistat**
- **Azacytidine + APR-246 for p53 mutated MDS**
- **HMA+ anti CD47**
- **HMA + venetoclax**
- **HMA + sabatolimab**

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A phase 1 study of azacitidine combined with venetoclax for myelodysplastic syndrome and chronic myelomonocytic leukemia

Alexandre Bazinet, MD, MSc, FRCPC

Leukemia Fellow

Updated EHA 22 P757

Lancet Hematology 2022

Department of Leukemia

University of Texas MD Anderson Cancer Center

Phase I Azacitidine and Venetoclax for High-Risk MDS and CMML

Responses (N = 23 ITT analysis)

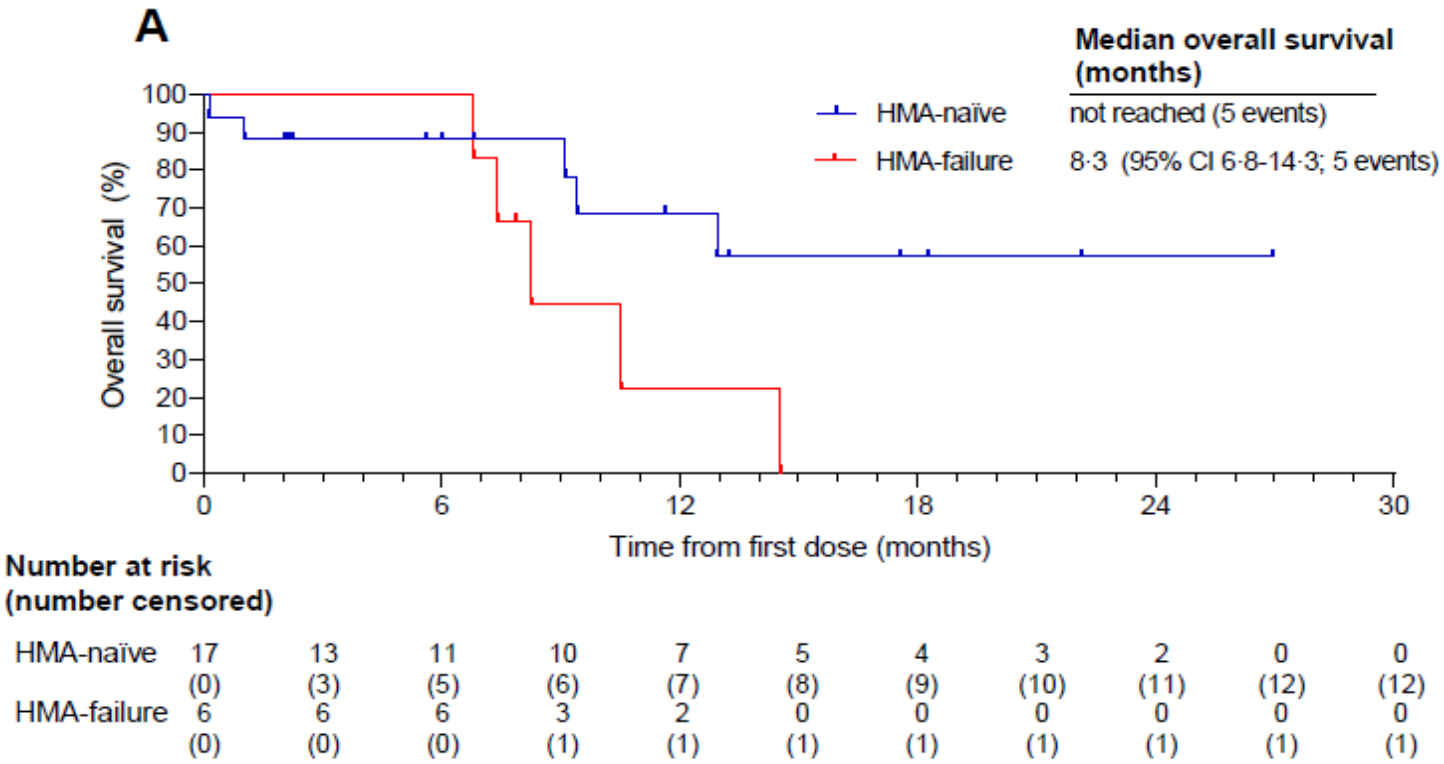
Response (Modified IWG)	All (n = 23) n (%) or median [range]	HMA-naïve (n = 17) n (%) or median [range]	HMA-failure (n = 6) n (%) or median [range]
ORR	20 (87)	14 (82)	6 (100)
CR	3 (13)	3 (18)	0 (0)
mCR	17 (74)	11 (65)	6 (100)
mCR + HI	5 (22)	5 (29)	0 (0)
mCR alone	12 (52)	6 (35)	6 (100)
Median DOR (months)		12.2	5.4
Median cycles given	3 [1–11]	3 [1–11]	5 [2–8]
Median cycles to response	1 [1–2]	1 [1–2]	1 [1–2]

Cytogenetic response rate in patients with baseline abnormality: 17% (2/12)

Phase I Azacitidine and Venetoclax for High-Risk MDS and CMML

Overall survival (N = 23)

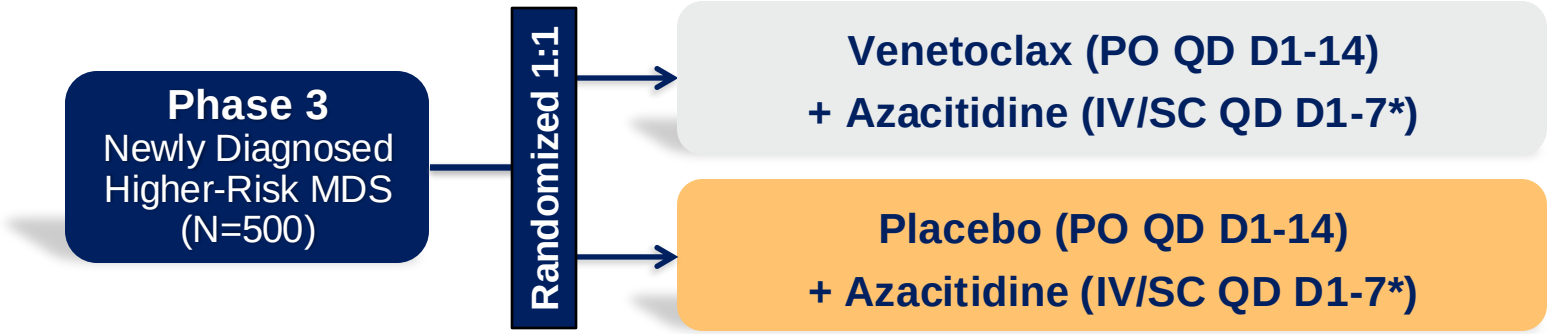
Median follow-up: 13.2 months



Phase 3 VERONA (NCT04401748)

Study Design and Endpoint

VERONA Study Design



*7 days within the first 9 calendar days/28 day cycle

Select Inclusion Criteria

- \+ ≥18 years old with newly diagnosed MDS according to 2016 WHO classification
- \+ <20% BM blasts
- \+ ECOG PS 0-2
- \+ IPSS-R score of >3 (Intermediate, High, Very High)
- \+ No planned HSCT at the time of C1D1

Select Exclusion Criteria

- – Prior therapy for MDS with HMA, chemotherapy, or allo-HSCT
- – Prior diagnosis of therapy-related MDS, MDS evolved from MPN, MDS/MPN including CMML, aCML, JMML, and unclassifiable MDS/MPN

End Points

Primary: *CR, OS*

Secondary: *mOR, TI, ORR, fatigue score, physical functioning score, time to deterioration in physical functioning*

aCML=Atypical Chronic Myeloid Leukemia. allo-HSCT=Allogeneic Hematopoietic Stem Cell Transplant. AML=Acute Myeloid Leukemia. BM=Bone Marrow. C=Cycle. CMML=Chronic Myelomonocytic Leukemia. CR=Complete Remission. D=Day. ECOG PS=Eastern Cooperative Oncology Group Performance Status. HMA=Hypomethylating Agent. HSCT=Hematopoietic Stem Cell Transplantation. IPSS-R=Revised International Prognostic Scoring System. IV=Intravenous. JMML=Juvenile Myelomonocytic Leukemia. MDS=Myelodysplastic Syndrome. mOR=Modified Overall Response. MPN=Myeloproliferative Neoplasm. ORR=Overall Response Rate. OS=Overall Survival. PO=Oral. QD=Daily. SC=Subcutaneous. TI=Transfusion Independence. WHO=World Health Organization. 1. ClinicalTrials.gov. NCT04401748. https://clinicaltrials.gov/ct2/show/NCT04401748. Accessed July 2021

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Targeted options in MDS

- **IDH-2 (5-10%): enasidenib, venetoclax**
- **IDH-1 (5%): ivosidenib, venetoclax**
- **Flt-3 (15%): multiple agents**
- **TP53 (10%): anti-CD47 ?**
- **NPM1 (1%): ara-C based**
- **Splicing: IRAK4, H3BIO, Clk**

Enasidenib in MDS: Response Rates

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	Response Evaluable (N = 46)	Arm A (Untreated) AZA + ENA (N = 25)	Arm B (HMA-failure) ENA (N = 21)
sponse rate (ORR), n (%)	**30 (68)**	**21 (84)**	**9 (43)**
te remission (CR)	11 (24)	6 (24)	5 (24)
l remission (PR)	3 (7)	2 (8)	1 (5)
row CR (mCR)	12 (26)	11 (44)	1 (5)
ical improvement (HI) only	4 (9)	2 (8)	2 (10)
ponse (NR), n (%)	**16 (35)**	**4 (16)**	**12 (57)**
le disease (SD)	14 (30)	4 (16)	10 (48)
ssive disease (PD)	2 (4)	0 (0)	2 (10)

Response (Modified IWG)	All (n = 23) n (%) or median [range]	HMA-naïve (n = 17) n (%) or median [range]
ORR	20 (87)	14 (82)
CR	3 (13)	3 (18)
mCR	17 (74)	11 (65)
mCR + HI	5 (22)	5 (29)
mCR alone	12 (52)	6 (35)
Median DOR (months)		12.2
Median cycles given	3 [1–11]	3 [1–11]
Median cycles to response	1 [1–2]	1 [1–2]

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DiNardo et al Blood Advances 2022


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HYBRID JUNE 9-17 VIENNA

TAKEAIM LEUKEMIA- A PHASE 1/2A STUDY OF THE IRAK4 INHIBITOR EMAVUSERTIB (CA-4948) AS MONOTHERAPY OR IN COMBINATION WITH AZACITIDINE OR VENETOCLAX IN RELAPSED/REFRACTORY AML OR MDS

Guillermo Garcia-Manero, MD[1], Eric S. Winer, MD[2], Daniel J. DeAngelo, MD, PhD[2], Stefano Tarantolo, MD[3], David A. Sallman, MD[4], James Dugan, MD[5], Stefanie Groepper, MD[6], Aristoteles Giagounidis, MD[6], Katharina Götze, MD[7], Klaus H. Metzeler, MD[8], Chia-Cheng Li, DDS, DMSc[9], Li Zhou, PhD[9], Elizabeth Martinez, PhD[9], Maureen Lane, PhD[9], Reinhard von Roemeling, MD[9], Matthias Böhme, MD[8], Anne Sophie Kubasch, MD[8], Amit Verma, MBBS[10], and Uwe Platzbecker, MD[8]

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Date: June 11, 2022

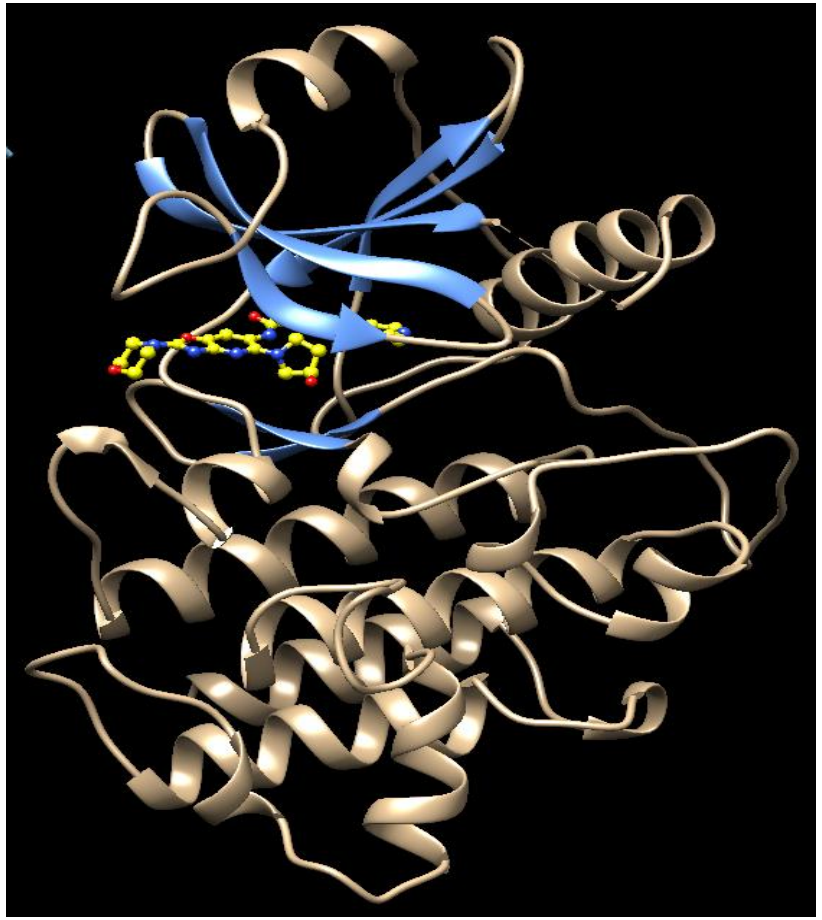
Session Title: Novel insights into AML treatment

Abstract: S129

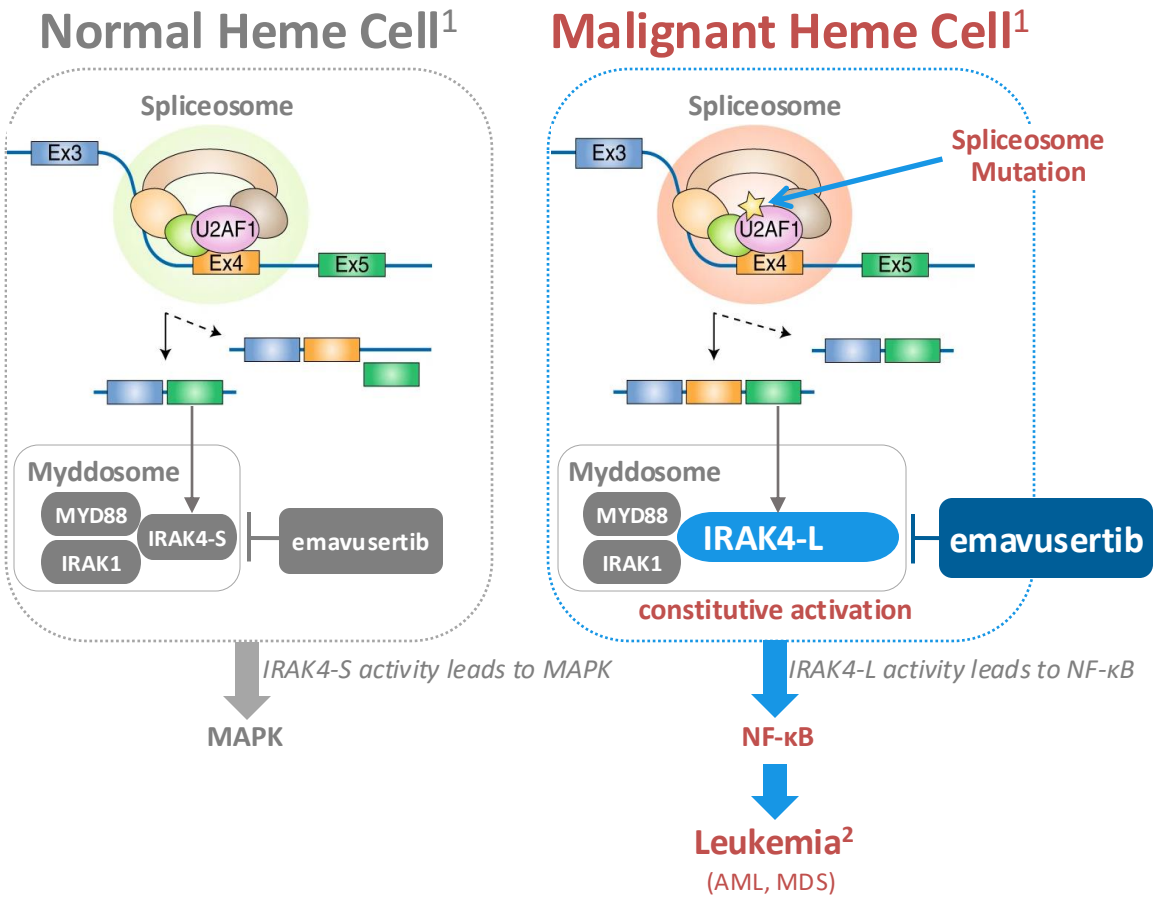
Emavusertib, An Oral IRAK4 Inhibitor

- Emavusertib:
  - Selective, small molecule inhibitor of IRAK4
  - ATP-competitive, type 1 inhibitor, reversible
  - Excellent drug-like properties:
    - Orally bioavailable (>100% dog/mouse)
    - Moderate plasma binding (77% human)
    - Stable in plasma, liver microsomes, hepatocytes
    - No inhibition of 7 major CYP450s
    - No significant metabolism in vitro
    - Humans: rapid absorption/clearance, T1/2 6 hr, no accumulation with QD dosing

IRAK4/Emavusertib Co-crystal Structure



2.4Å resolution

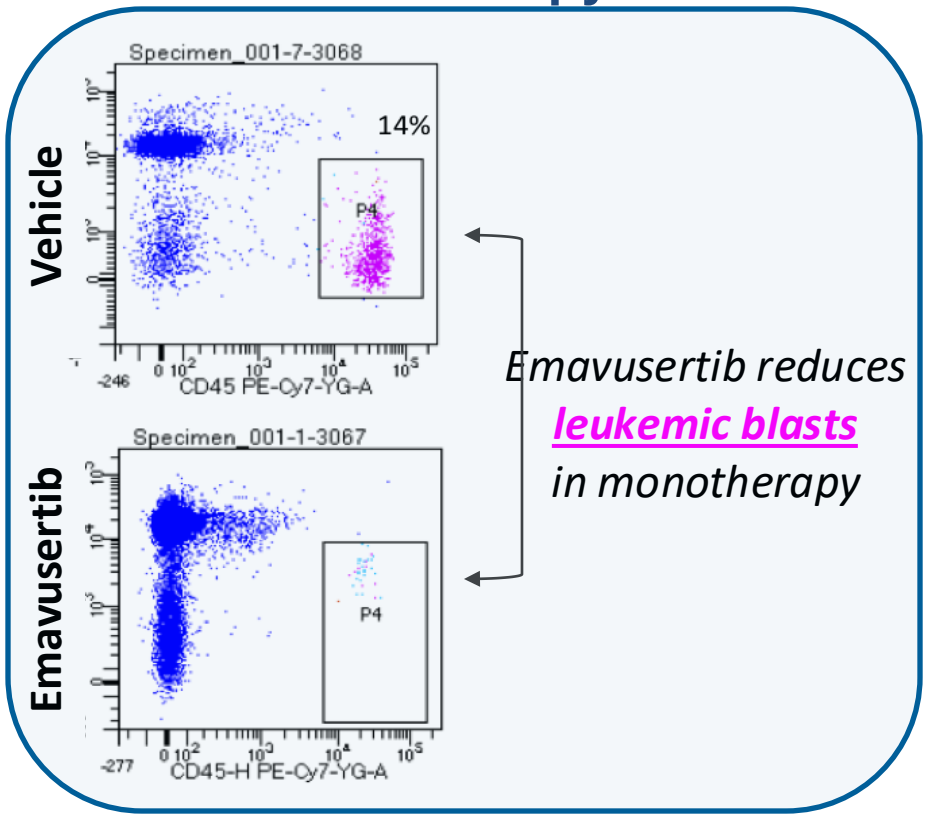


- Emavusertib (CA-4948), a novel oral IRAK4 inhibitor has potential anti-leukemia activity
- Specific genetic mutations (*SF3B1*, *U2AF1*) in the spliceosome drive overexpression of IRAK4 long isoform (IRAK4-L)
- IRAK4-L then causes constitutive activation of the myddosome, leading to overactivity of NF-κB
- Therefore, this drug can target patients with splicing mutations
- Emavusertib also targets FLT3 and has shown potential synergetic activity with other drugs

1)Guillamot et al. Nat Cell Biol 2019.
2)Smith et al. Nat Cell Biol 2019.

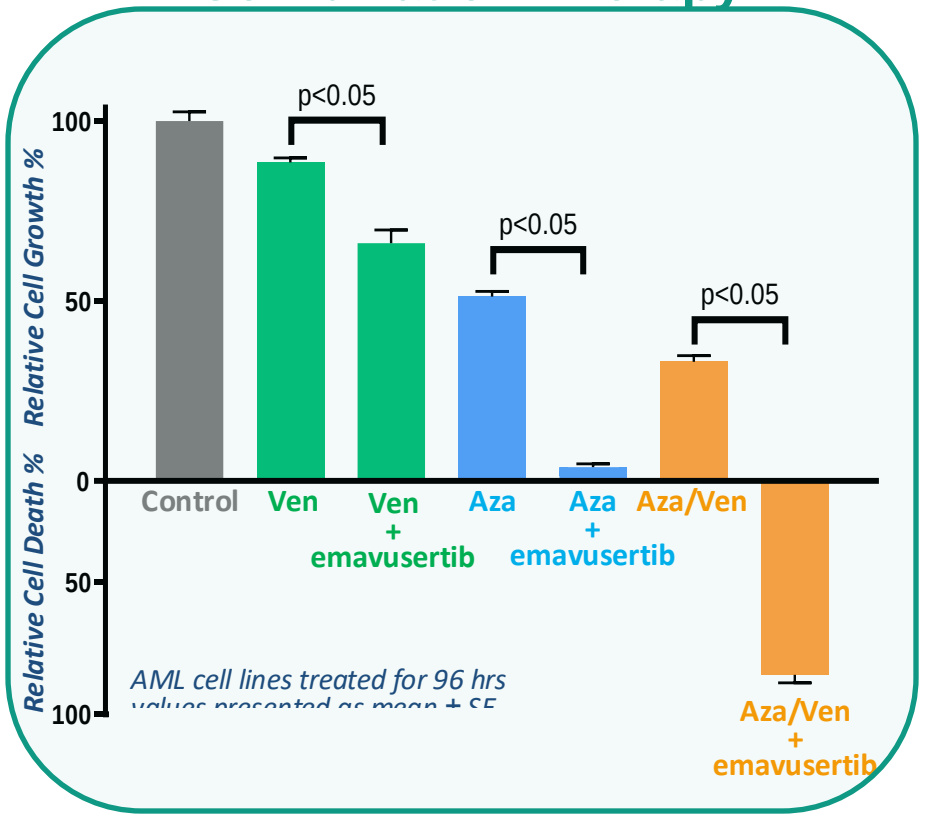
Emavusertib: Preclinical Activity in AML and MDS

Monotherapy



Emavusertib demonstrates monotherapy activity in patient-derived xenografts[1]

Combination Therapy



Emavusertib demonstrates synergy with both azacitidine and venetoclax in THP-1 model[2]

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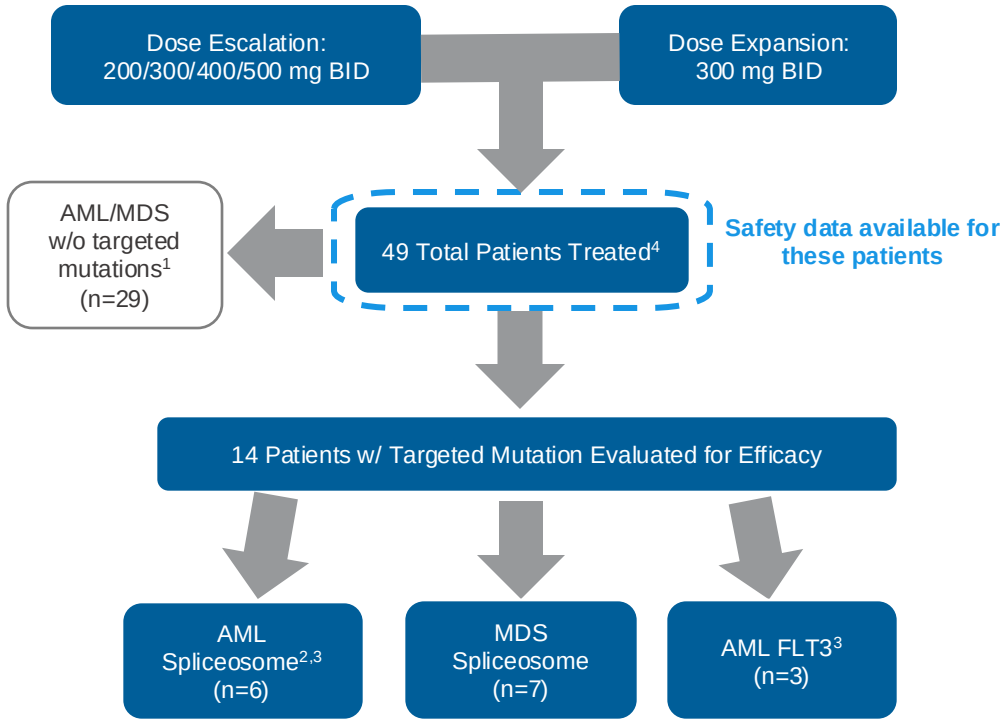
1. Choudhary et al. AACR 2017; 2. Curis AML MDS poster, EHA 2021

Emavusertib: Study Design

TakeAim Leukemia (NCT #04278768): Open-label, single arm, Phase 1/2 dose escalation and expansion 3+3 study design in R/R AML or high-risk MDS (HR-MDS)



Study Objectives

1°: Determine maximum tolerated dose
Determine recommended Phase 2 dose

2°: Pharmacokinetic (PK) profile
Preliminary anti-cancer activity

Dosing

- Oral, BID Dosing
- 28-day cycles

Study Population

- Relapsed/Refractory AML or high-risk MDS
- ECOG performance Status of ≤ 2
- Age ≥ 18 years

All the data was extracted on Dec 16, 2021. Patients began enrollment into the combination therapy portion of the study in November 2021.

1. These are non-targeted patients, due to lack of spliceosome or *FLT3* mutation, this population will be addressed in the combination therapy study
2. One patient was not response evaluable because of discontinuation due to patient decision
3. Two AML patients have both a spliceosome and *FLT3* mutation and are included in both populations (there are 13 total evaluable patients with spliceosome or *FLT3* mutation)
4. Six patients did not start treatment by September 30th, 2021, which did not allow 2 on-study disease assessments

Emavusertib: Baseline Characteristics

		All patients (n=49)	AML/MDS Subsets		
			AML Spliceosome[1] (n=6)	MDS Spliceosome (n=7)	AML FLT3[1] (n=3)
Female n (%) : Male n (%)		16 (33) : 33 (67)	0 (0) : 6 (100)	5 (71) : 2 (29)	0 (0) : 3 (100)
Age (yrs): median (range)		74 (32, 87)	76 (60, 84)	74 (61, 80)	80 (78, 87)
ECOG: n 0/1/2		11/30/8	0/4/2	2/5/0	0/1/2
Median platelets (10^3/mm^3) (range)		30 (4, 275)	28 (21, 80)	16 (7, 146)	21 (9, 23)
Median ANC (10^3/mm^3) (range)		0.64 (0, 14.75)	0.23 (0, 3.3)	1.85 (0.15, 11.0)	0.05 (0, 0.11)
Median bone marrow blasts (%) (range)		-	33 (20, 95)	8 (3, 12)	60 (39, 95)
Median lines of prior therapy (range)		2 (1, 5)	2.5 (1, 4)	2 (1, 4)	2 (1, 4)
Prior therapy, n (%)	HMA[2]	-	6 (100)	7 (100)	3 (100)
	Chemotherapy[3]	-	3 (50)	0 (0)	1 (33)
	Venetoclax	-	4 (67)	1 (14)	3 (100)

1. Two AML patients have both a spliceosome and FLT3 mutation and are included in both populations (there are 13 total evaluable patients with spliceosome or FLT3 mutation)
2. HMA includes azacitidine, decitabine, and guadecitabine
3. Chemotherapy includes cytarabine

Emavusertib: Toxicities Profile

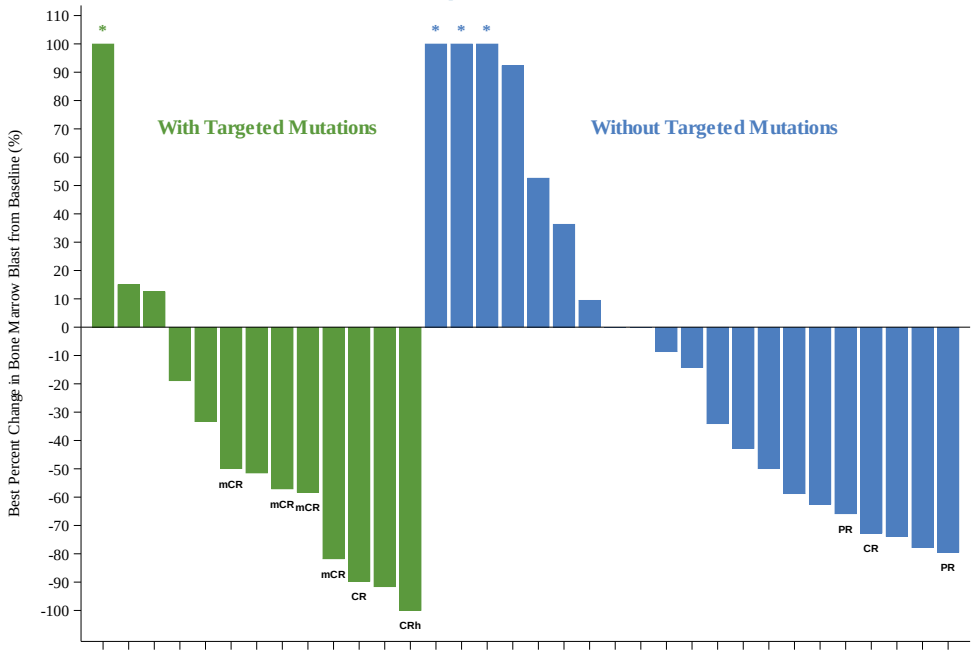
- During the initial dose escalation phase, no DLT was observed in 200-400 mg BID dose levels. Additional patients were enrolled at 300 mg and 400 mg BID to further explore the safety profile.

Grade 3+ Treatment-Related Adverse Event	200 mg BID (N = 3)	300 mg BID (N = 26)[1]	400 mg BID (N = 17)	500 mg BID (N = 3)
	n (%)	n (%)	n (%)	n (%)
Number of patients having grade 3+ TRAEs	1 (33.3)	6 (23.1)	6 (35.3)	2 (66.7)
Alanine aminotransferase increased	1 (33.3)			
Blood creatine phosphokinase increased		1 (3.8)		
Dizziness	1 (33.3)			
Dyspnoea			1 (5.9)	
Enterobacter infection			1 (5.9)	
Fatigue			1 (5.9)	
Gastrointestinal haemorrhage		1 (3.8)		
Hypophosphataemia		1 (3.8)		
Hypotension		1 (3.8)		
Lipase increased		2 (7.7)		
Platelet count decreased		1 (3.8)		
Presyncope			1 (5.9)	
Rhabdomyolysis		1 (3.8)	2 (11.8)	1 (33.3)
Syncope				1 (33.3)

1. 1. Data for the two patients that have escalated from 300 mg BID to 400 mg BID were included in the 400 mg BID dose group.
2. One death occurred after the data extraction date, currently under review.

Emavusertib: Single-agent Activity in AML and HR-MDS

All patients



Only evaluable patients with baseline and post-treatment bone marrow blast counts are included in the waterfall plot; among the patients w/o targeted mutations (*SF3B1* / *U2AF1* / *FLT3* mutation), 1 reached CR and 2 PR

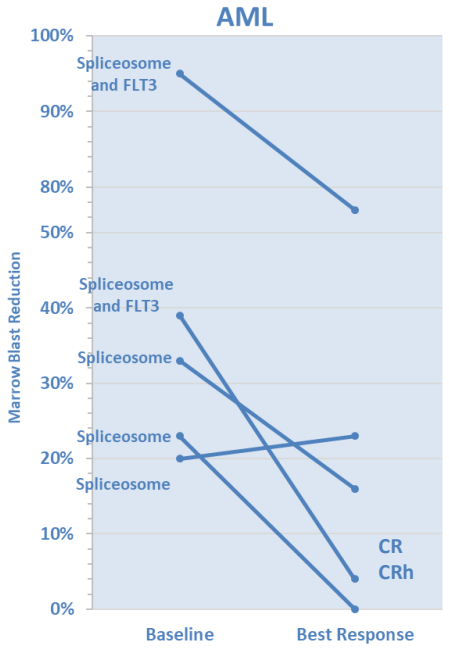
* Indicates the best percentage change from baseline >100%

Subset of patients with targeted mutations (*SF3B1* / *U2AF1* / *FLT3* mutation)

Best Response	Efficacy
Population #1: AML Spliceosome Patients[1, 2]	
CR/CRh Rate	2/5 (40%)
CR	*1/5 (20%)*
CRh	*1/5 (20%)*
Population #2: MDS Spliceosome Patients	
Objective Response Rate (ORR)	4/7 (57%)
CR	*0/7 (0%)*
mCR	*4/7 (57%)*
Population #3: AML FLT3 Patients[1]	
CR/CRh Rate	1/3 (33%)
CR	*1/3 (33%)*
CRh	*0/3 (0%)*

1. Two AML patients have both a spliceosome and *FLT3* mutation and are included in both populations (there are 13 total evaluable patients with spliceosome or *FLT3* mutation)
2. One patient was not response evaluable because of discontinuation due to patient decision

Emavusertib: Single-agent Activity in R/R AML with Spliceosome Mutation



Dose (BID)	Risk (ELN)	Baseline Molecular Mutations	# of Prior Therapies	Duration on emavusertib (mos)	Blasts Baseline	Blasts Best Response[1]	% Change
300 mg	Intermediate	SF3B1, RUNX1, WT1,	1	7	23	0	-100% (CRh)
300 mg	Intermediate	U2AF1, FLT3, BCOR, WT1	1	6+	39	4	-90% (CR)
300 mg	Intermediate	U2AF1, NRAS	4	2.5	33	16	-52%
300 mg	Adverse	FLT3, SF3B1, NRAS, PTPN11, RAD21, RUNX1, TET2, GATA, STAT3	4	2.6	95	77	-19%
400 mg	Adverse	SF3B1, DNMT3A, P53	1	2	20	23	15%

Data extraction date: Dec 16, 2021; "+" in Duration of Treatment indicates the patient remains on treatment as of the date of data extraction.
1. Two AML patients have both a spliceosome and *FLT3* mutation and are included in both populations (there are 13 total evaluable patients with spliceosome or *FLT3* mutation).

Emavusertib achieved 40% CR/CRh rate,
despite transformed AML being historically highly resistant to treatment

AML
Spliceosome
Mutation

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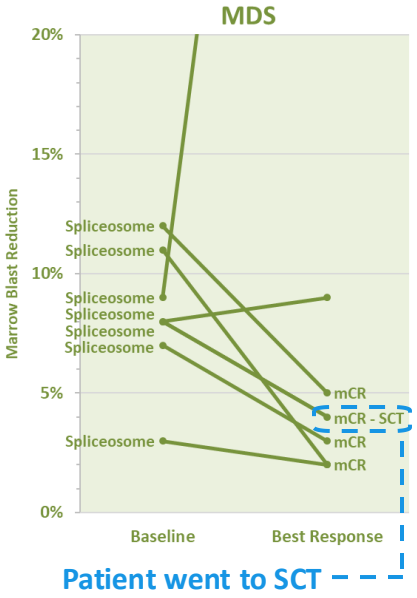
Emavusertib: Single-Agent Activity in R/R HR-MDS with Spliceosome Mutation



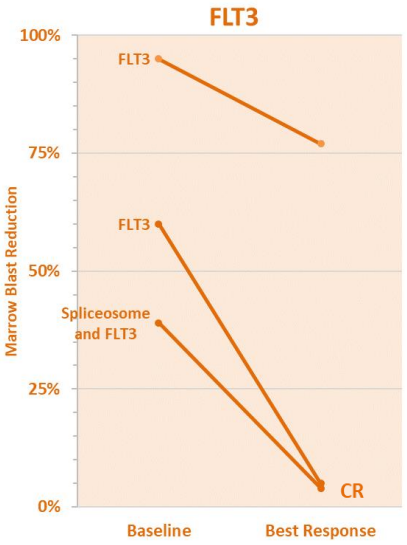
Dose (BID)	IPSS-R	Baseline Molecular Mutations	# of Prior Therapies	Duration on emavusertib (mos)	Blasts Baseline	Blasts Best Response	% Change
200 mg	Very High Risk	U2AF1 ,ASXL1, NF1, PHF6, GFI1, KDM6A, TET2	1	5.7	11	2	-82% (mCR)
300 mg	Very High Risk	U2AF1, DNMT3A, BCOR, STAG2, BCORL1, ETV6, SETBP1	1	3.3+	12	5	-58% (mCR)
400 mg	Very High Risk	SF3B1, RUNX1, NFE2	2	4.3	7	3	-57% (mCR)
300 mg	High Risk	SF3B1, DNMT3A, ASXL1, TET2, EZH2	2	0.9	8	4	-50% (mCR)
300 mg	High Risk	U2AF1, ASXL1	4	5.3+	3	2	-33%
300 mg	Very High Risk	SF3B1, ASXL1, NF1, SH2B3, RUNX1, PHF6, CBL, GFI1, EZH2	3	1.6	8	9	13%
400 mg	Very High Risk	U2AF1, ASXL1, BCOR, DNMTA, GATA2, SETBP1	1	1.2	9	62	>100%

Data extraction date: Dec 16, 2021; "+" in Duration of Treatment indicates the patient remains on treatment as of the date of data extraction.

Emavusertib achieved 57% ORR, including one patient who was able to proceed to transplant

MDS Spliceosome Mutation

Emavusertib: Single-agent Activity in R/R AML with FLT3 Mutation



Dose (BID)	Risk (ELN)	Baseline Molecular Mutations	# of Prior Therapies	Duration on emavusertib (mos)	Blasts Baseline	Blasts Best Response[1]	% Change
400 mg	Adverse	FLT3 ***(eradicated at C3D1)***, ASXL1, BCOR, CEBPA *(eradicated at C3D1)*, CSF3R, EZH2, NRAS, RUNX1 (X3), STAG2, TET2(X2,1) *(eradicated at C3D1)*	2	5.1	60	5	-92%
300 mg	Intermediate	FLT3 ***(eradicated at C4D1)***, BCOR *(eradicated at C4D1)*, U2AF1 *(decreased to 1.3 VAF at C4D1)*, WT1 *(eradicated at C4D1)*	1	6.2+	39	4	-90% (CR)
300 mg	Adverse	FLT3, SF3B1, NRAS, PTPN11, RAD21, RUNX1, TET2, GATA, STAT3	4	2.6	95	77	-19%

Data extraction date: Dec 16, 2021; "+" in Duration of Treatment indicates the patient remains on treatment as of the date of data extraction.
1. Two AML patients have both a spliceosome and *FLT3* mutation and are included in both populations (there are 13 total evaluable patients with spliceosome or *FLT3* mutation).

Emavusertib achieved 33% CR rate,
and FLT3 mutation eradicated in 2 out of 3 patients

AML
FLT3
Mutation

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Summary

- Emavusertib has a manageable safety profile
- Demonstrates oral, single-agent, anti-cancer activity in heavily pretreated AML and HR-MDS patients with targeted mutations (*U2AF1*, *SF3B1*, or *FLT3*)
- Potential candidate for use in combination therapy for all AML/HR-MDS patients, including patients without a targeted mutation

Next Steps:

- Correlative analysis ongoing
- Trials in lymphoma and solid tumors are being explored

We would like to thank the patients, their families and caregivers for their invaluable contribution and participation in this study.

Phase 2a Dose Expansion: Cohort 4

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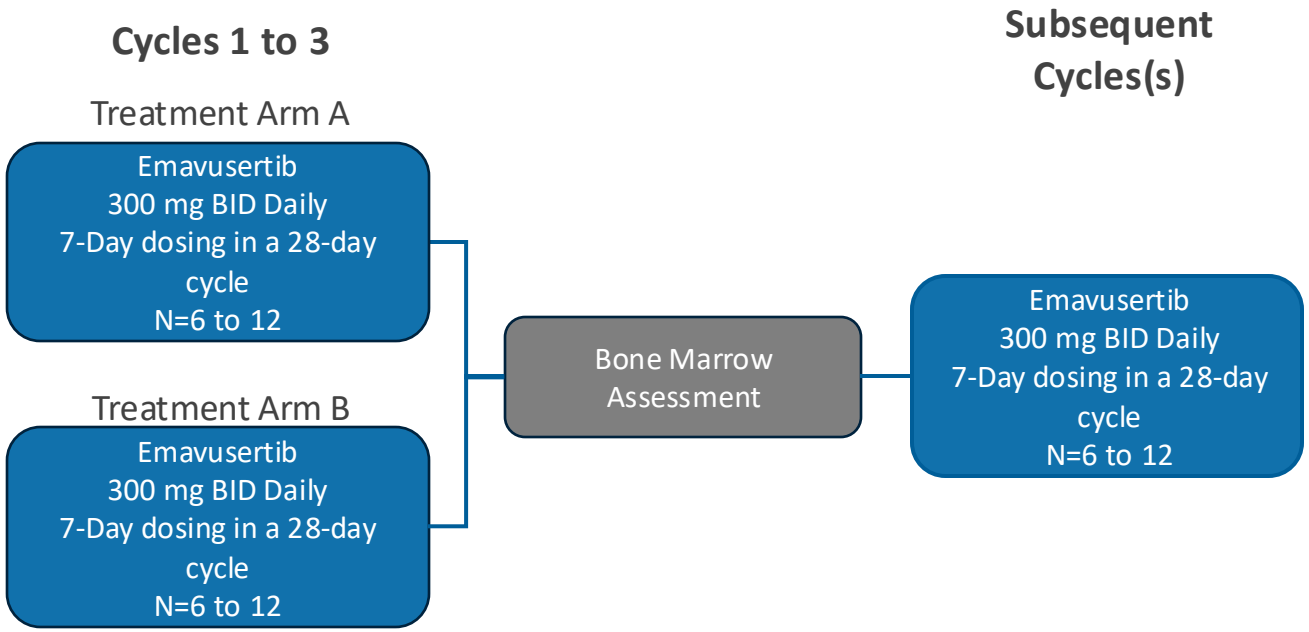
- Cohort 4 will include 2 treatment arms of orally administered CA-4948 as monotherapy to assess the safety, tolerability, and effect of 2 different dosing regimens of CA-4948 on the BM blast count and hematological parameters in patients with R/R hrMDS

Phase 2a Cohort 4: Adjusted Dosing Strategy for R/R hrMDS

Dose and Treatment Arms: Patients will receive 300 mg BID of CA-4948 with a shortened treatment duration of either 7 days (Arm A) or 14 days (Arm B) in a 28-day cycle, allowing for a drug holiday to promote normal hematological recovery.

Potential Benefits: This approach aims to maintain disease control while reducing transfusion needs and minimizing cytopenia-related AEs, potentially enhancing quality of life and prolonging survival.

Crossover Opportunity: After 3 cycles or 2 bone marrow assessments in Arm A, patients may switch to 14 days of treatment if early disease progression or lack of hematologic improvement is observed.



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Phase 2a Dose Expansion: Cohort 4

Objectives

Primary
assess safety and tolerability of the 2 different dosing regimens of CA-4948 in patients with R/R hrMDS

Secondary
assess the anti-cancer activity of the 2 different dosing regimens of CA-4948 in patients with R/R hrMDS

Exploratory
To further assess the anti-cancer activity of the 2 different dosing regimens of CA-4948 in patients with R/R hrMDS

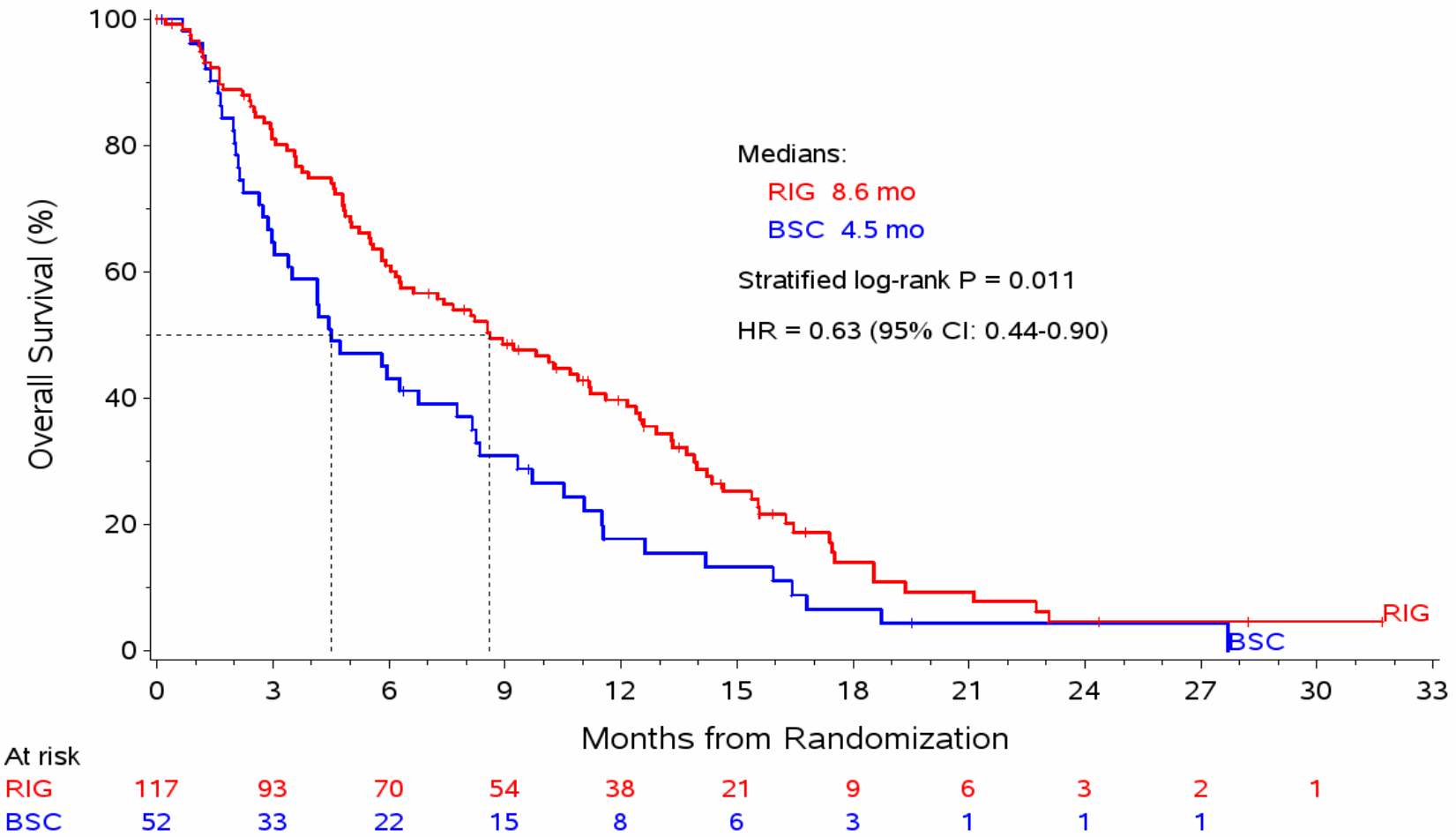
Endpoints

Primary
Safety measured by AEs, ECGs, chemistry and hematology laboratory values, vital signs, and physical examination

Secondary
Proportion of patients that achieve mCR or CR
- Reduction in frequency of transfusion versus baseline, including - Proportion of patients that achieve transfusion independence

Exploratory
- Proportion of patients that achieve HI: HI-E or HI-P or HI-N
- Proportion of patients who achieve CR, or PR, or mCR with HI
- DOR
- Time to responses
- OS

ONTIME Trial: Median Overall Survival for Pts with Primary HMA Failure - Blinded, Centralized Assessment



Garcia-Manero. Lancet Oncology 2016

Potential role of IRAK inhibition in MDS

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- **Examples HR MDS front line**
  - **Doublet HMA+ CA4948**
  - **Triplet HMA+venetoclax+ CA4948**
- **Monotherapy in HMA failure HR MDS**
- **Consider potential role in lower risk MDS**

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Potential role of IRAK inhibition in AML

- **Role as a Flt-3 inhibitor**
- **Similar path as in AML?**

Thank you

Guillermo Garcia-Manero

Section of MDS

Department of Leukemia

MD Anderson Cancer Center

ggarciam@mdanderson.org

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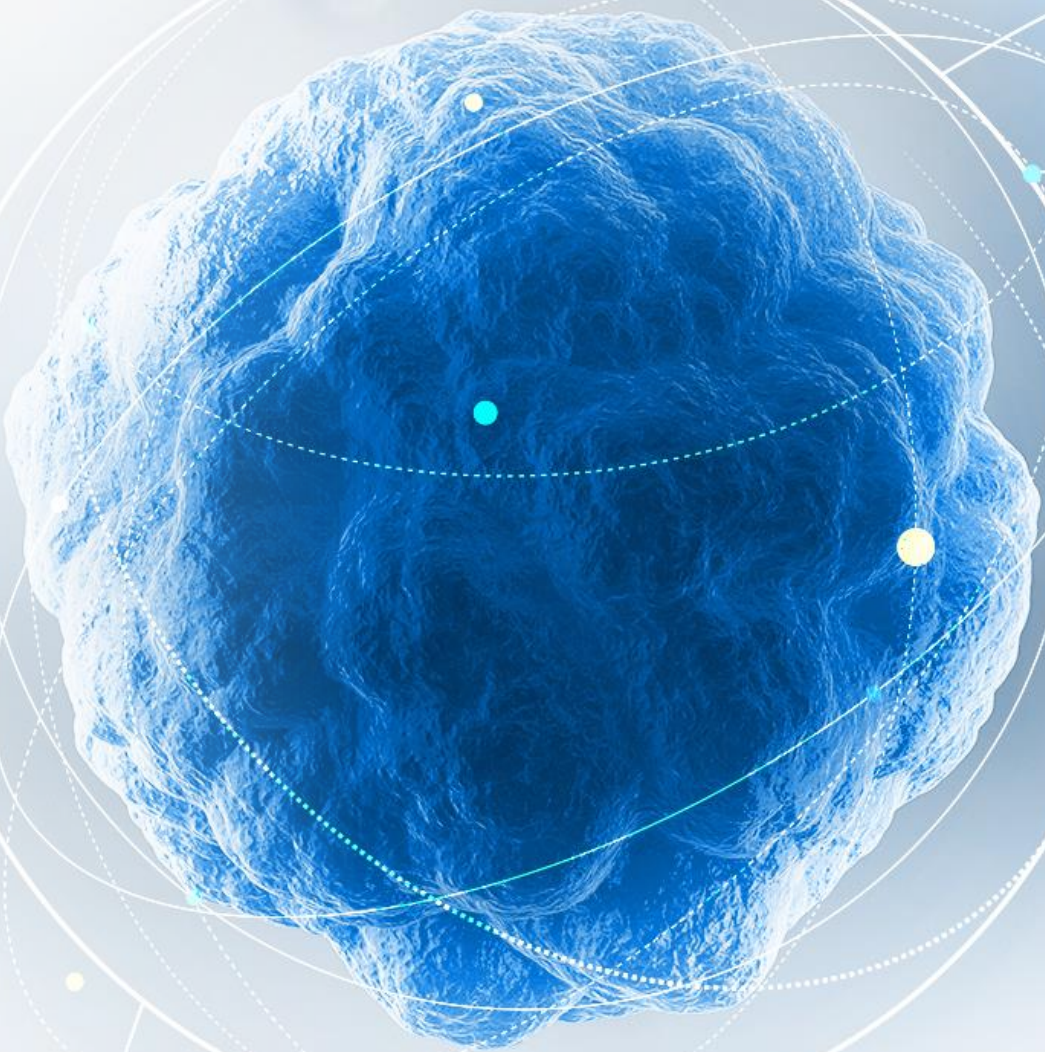
Questions?



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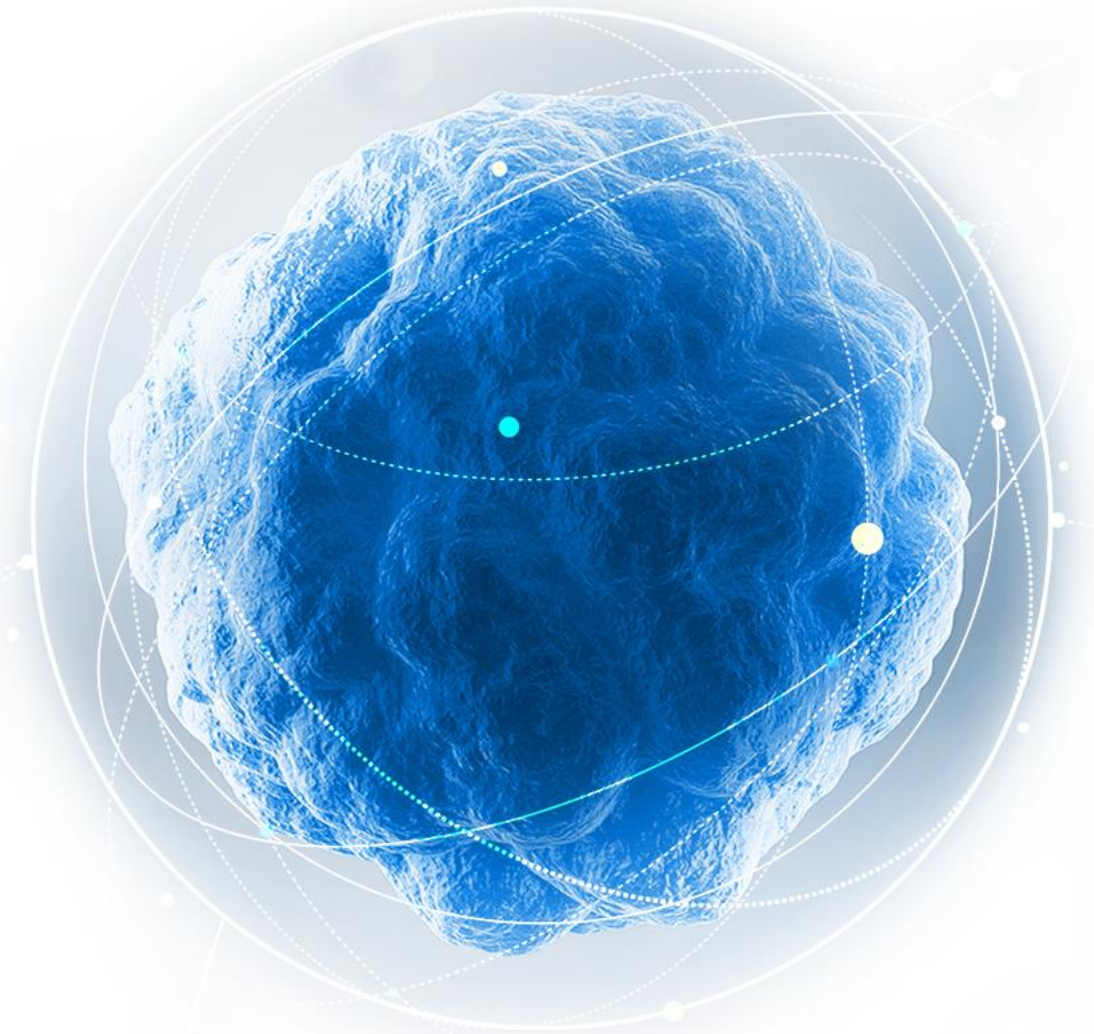
Emavusertib for Acute Myeloid Leukemia



Eric S. Winer, MD
Symposium Co-Chair
Clinical Director, Adult Leukemia
Dana Farber Cancer Institute
Assistant Professor of Medicine
Harvard Medical School

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The State of Acute Myeloid Leukemia

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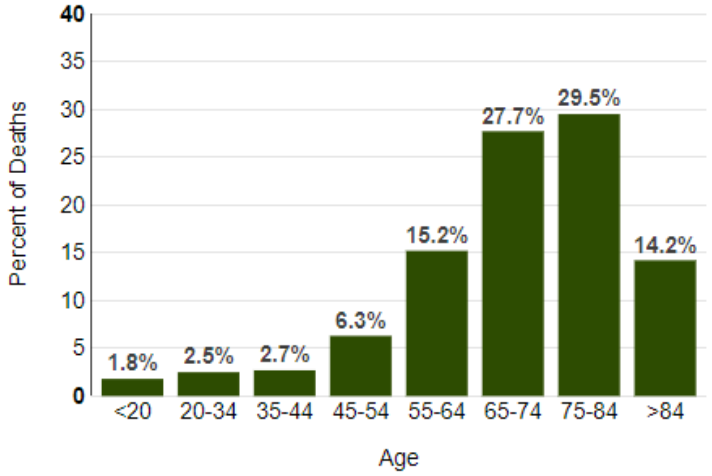
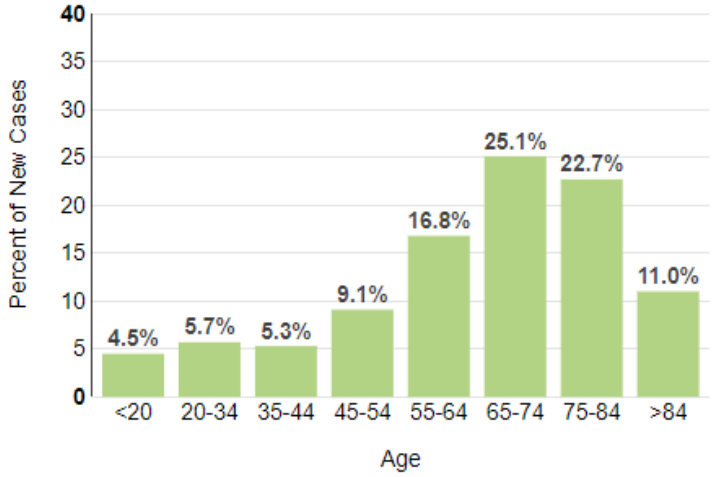
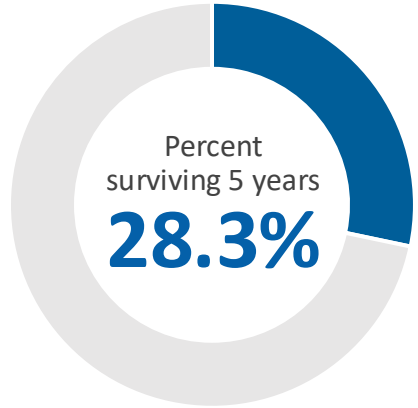
- **Accounts for only 1.2% of all cancer deaths**
  - Estimated new cases 2022: 20,050
  - Estimated Deaths 2022: 11,540
  - 5-year relative survival (2018): 28.3%
- **Median age is 68 years of age**
- **Risk Factors:**
  - Age
  - Prior Chemotherapy
  - Ionizing Radiation
  - Chemicals/Solvents





Median Age at Diagnosis **68**



Median Age at Death **72**

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https://seer.cancer.gov/statfacts/html/amyl.html

The State of AML – novel approved therapies

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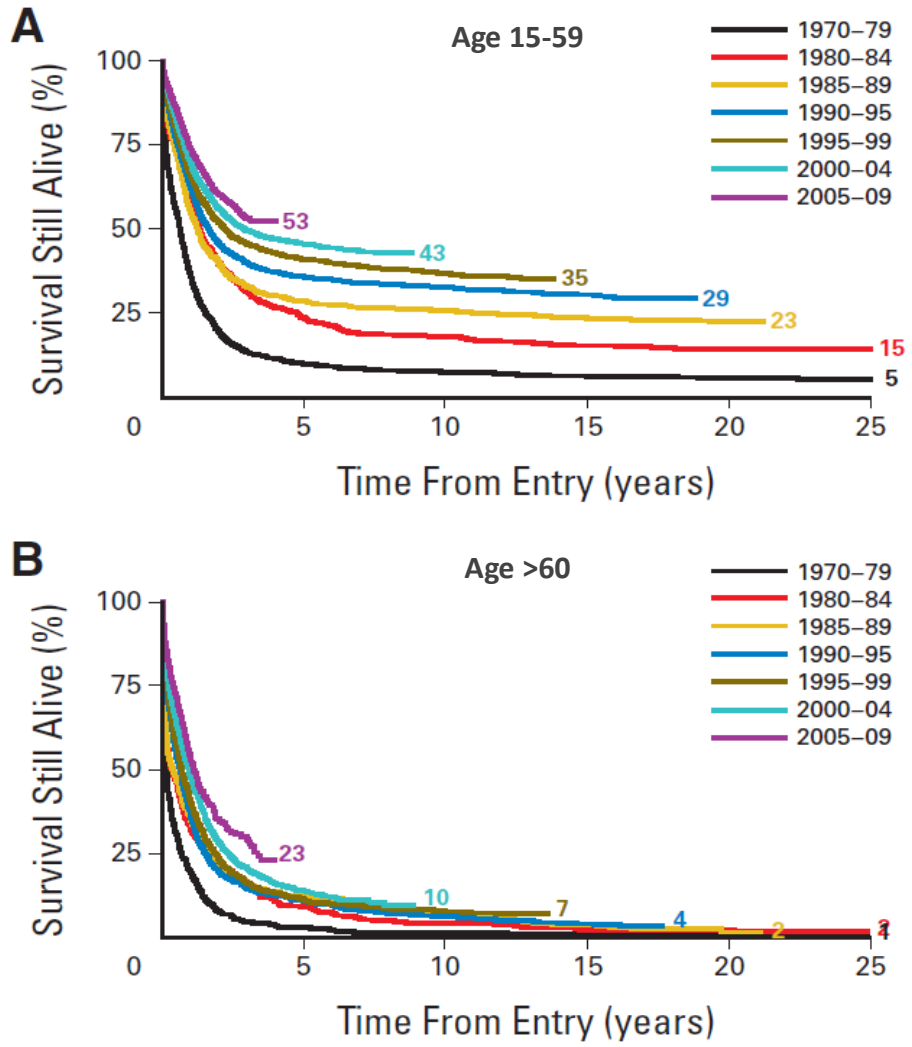
Incremental improvements

- **Midostaurin (induction)**
  - Midostaurin 74.7 months, Placebo 25.6 months
- **Vyxeos (CPX-351) (induction)**
  - Vyxeos 9.6 months, 7+3 5.95 months
- **Venetoclax (with Aza)**
  - Aza/Ven 14.7 months, Aza alone 9.6 months
- **Glasdegib (with Low dose cytarabine)**
  - Glasdegib/LoDAC 8.8 months, LODAC 4.9 months
- **Gilteritinib**
  - Gilteritinib 9.3 months, Salvage 5.6 months
- **Ivosidenib (with aza)**
  - 24 months (Aza/Ivo) v 7.9 months Aza
- **Quizartinib (induction)**
  - Quizartinib 31.9 months v placebo 15.1 months
- **Aza/Ven/Gilt (non-randomized)**
  - 18 mo RFS and OS 71 and 72%



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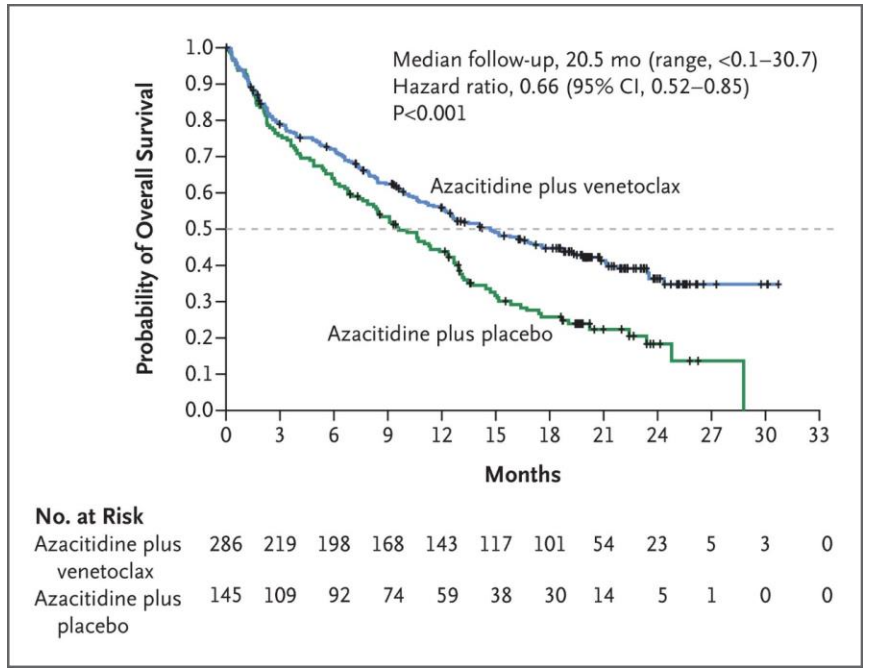
Burnett A et al. *J Clin Oncol 29:487-494*

Venetoclax + Azacitidine AML – VIALE-A

- Randomized trial in patients ineligible for induction
- Median age 76 years old
- Endpoint of Overall Survival
- OS:
  - 14.7 mo Aza/Ven v. 9.6 mo Aza
- CR:
  - 36.7% Aza/Ven v. 17.9% Aza
- CRc:
  - 66.4% Aza/Ven v. 28.3% Aza
- Primary and adaptive resistance seen in activating signaling pathways (i.e. *FLT3*, *RAS*, *TP53*)

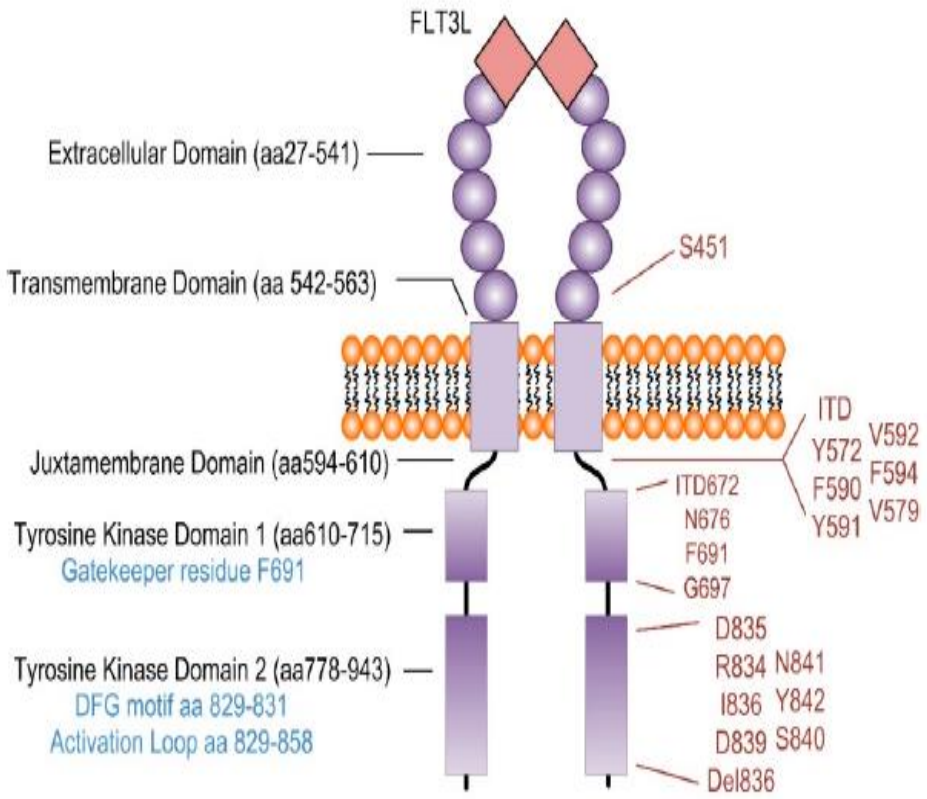


Molecular marker		
FLT3	19/29 (65.5)	19/22 (86.4)
IDH1	15/23 (65.2)	11/11 (100.0)
IDH2	15/40 (37.5)	14/18 (77.8)
IDH1 or *IDH2*	29/61 (47.5)	24/28 (85.7)
TP53	34/38 (89.5)	13/14 (92.9)
NPM1	16/27 (59.3)	14/17 (82.4)

DiNardo et al. *N Engl J Med.*2020;383:617-29. DiNardo et al. *Blood* 2020;135(11):791-803.

FLT and AML

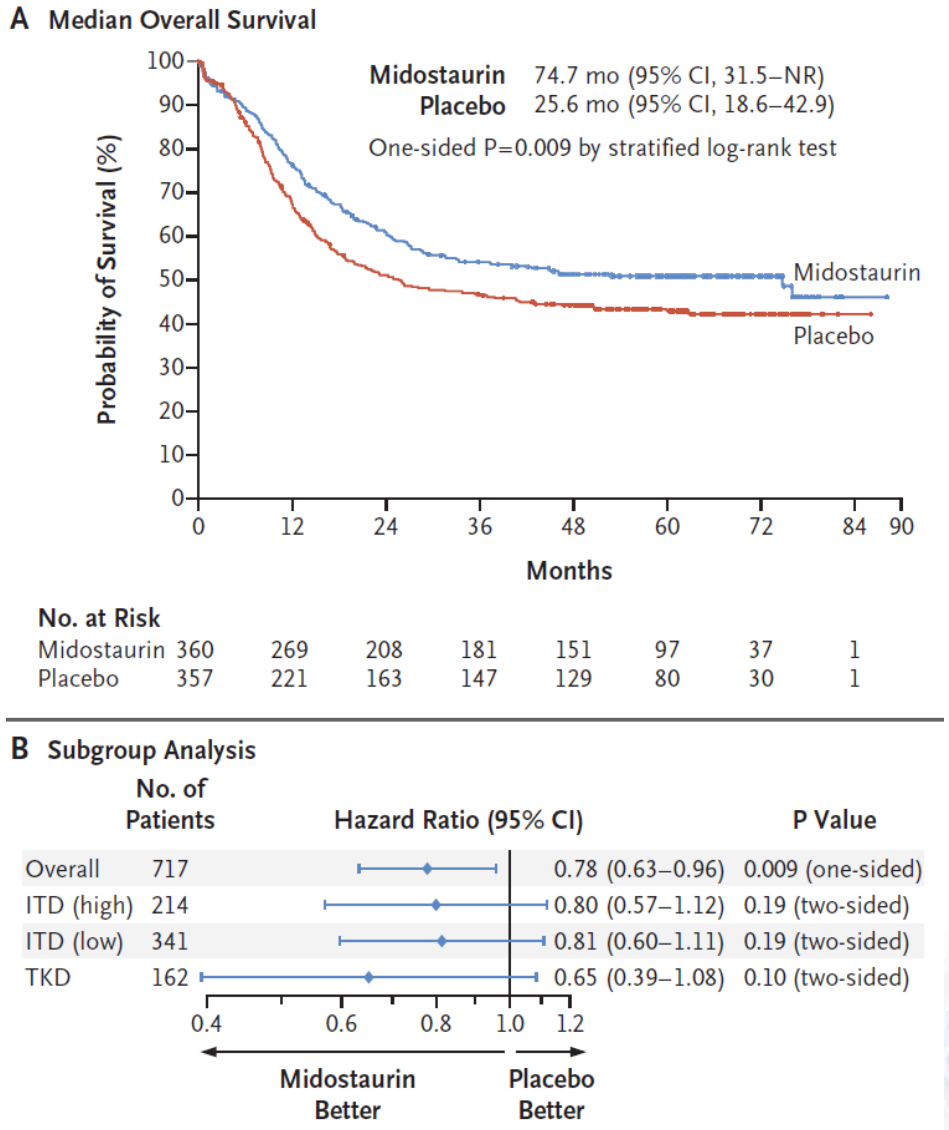
- FLT3 most common mutated gene in AML (30-35%)
- Often associated with normal karyotype
- Different mutations
  - Internal Tandem Duplicates
  - Tyrosine Kinase Domain
- Proliferative phenotype
- Allelic ratio important for pathogenicity/prognosis



Staudt D, et al. *Int J Mol Sci.* 2018;19:3198.

7+3+ Midostaurin for FLT3 positive AML

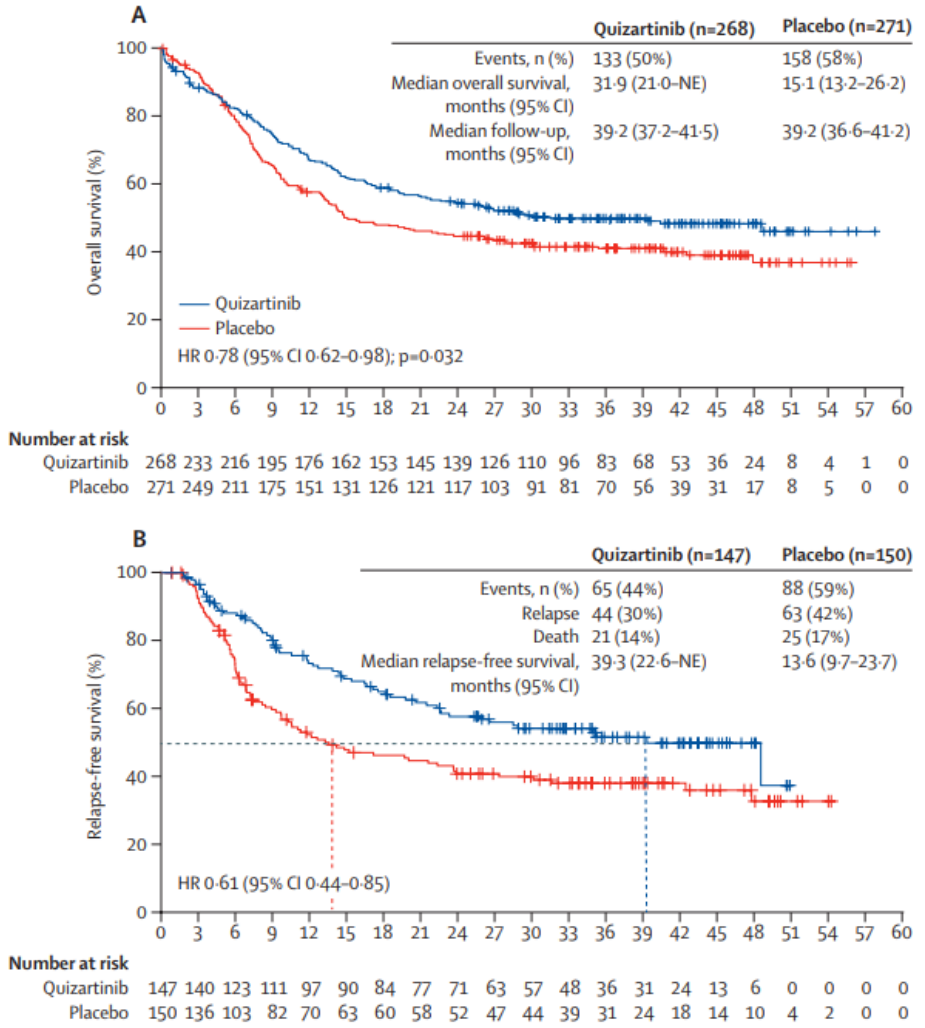
- Patients screened for FLT3 Mutation (ITD or TKD)
  - 3277 screened for 717 participants
- Randomized to either 7+3 or 7+3 + midostaurin (days 8-21)
- Day 21 marrow for aplasia
- Consolidation with HiDAC +/- midostaurin
- Maintenance phase



Stone RM et al. *NEJM* 2017; 377:454-464

7+3+Quizartinib for AML (QuANTUM-First)

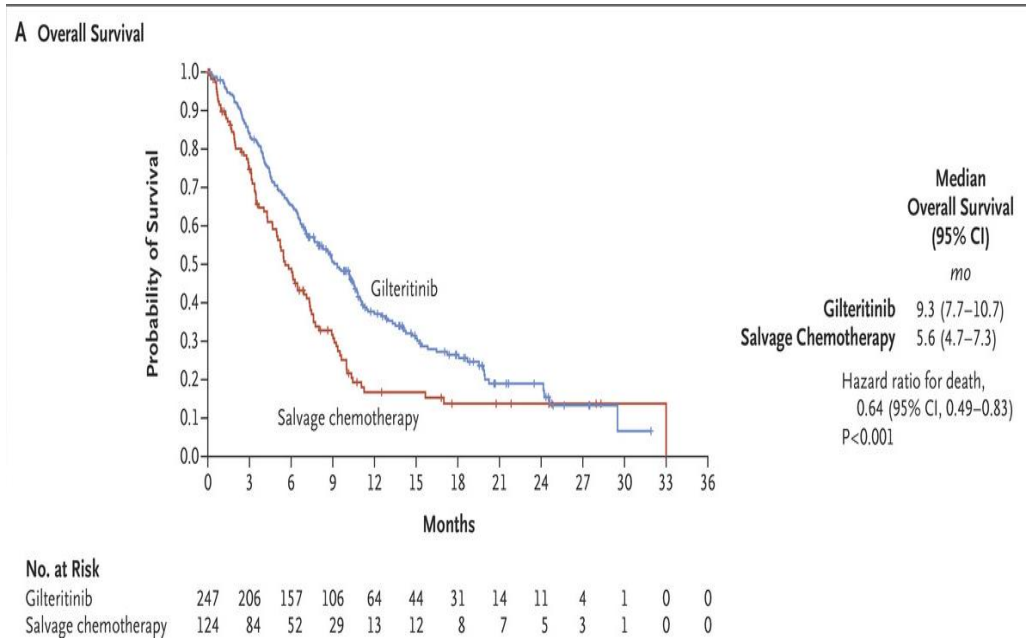
- Enrolled 539 patients with FLT3-ITD positive AML randomized to 7+3+Quizartinib v. 7+3+placebo
- Median age 56 years
- Median overall survival:
  - Quizartinib: 31.9 months (72% CCR)
  - Placebo: 15.1 months (65% CCR)
- MRD (post hoc) $<10^{-4}$
  - Quizartinib: 42%
  - Placebo: 38%



Erba et al. *Lancet.* 2023;401:1571–83

Gilteritinib

- Phase 3 study randomizing 2:1 Gilteritinib v. salvage chemotherapy (MEC, FLAG-IDA, Low dose cytarabine, azacitidine)
- Gilteritinib improved median overall survival of 9.3 months v. 5.6 months
- **EFS 2.8 months v. 0.7 months**
- CR+CRi 34% v. 15.3%
- Hazard ratio for death 0.64 (p<0.001)



Previous therapy for AML — no. (%)			
Anthracycline	311 (83.8)	205 (83.0)	106 (85.5)
FLT3 inhibitor	49 (13.2)	34 (13.8)	15 (12.1)
HSCT	74 (19.9)	48 (19.4)	26 (21.0)

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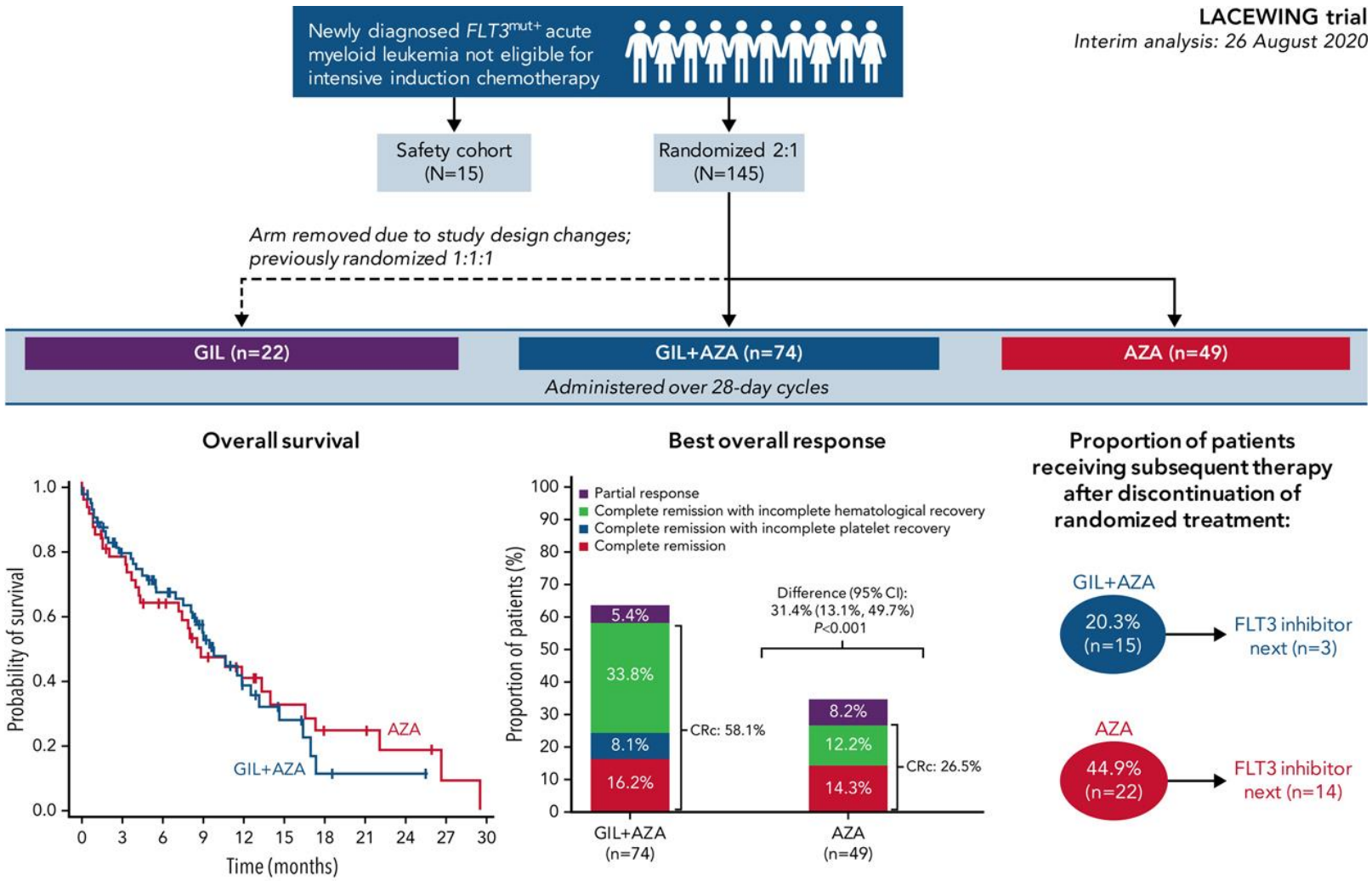
Perl, et al. *N Engl J Med.* 2019;381:1728-1740

Azacitidine + Gilteritinib v. Azacitidine



Abbreviations: AZA, azacitidine 75 mg/m^2 intravenously or subcutaneously daily on days 1–7; CI, confidence interval; CRc, composite complete remission; FLT3, FMS-like tyrosine kinase 3; GIL, gilteritinib 120 mg orally daily on days 1–28; HR, hazard ratio.

Wang ES et al. *Blood.* 2022;140(17):1845–1857

Landscape of response in relapsed FLT-3 AML

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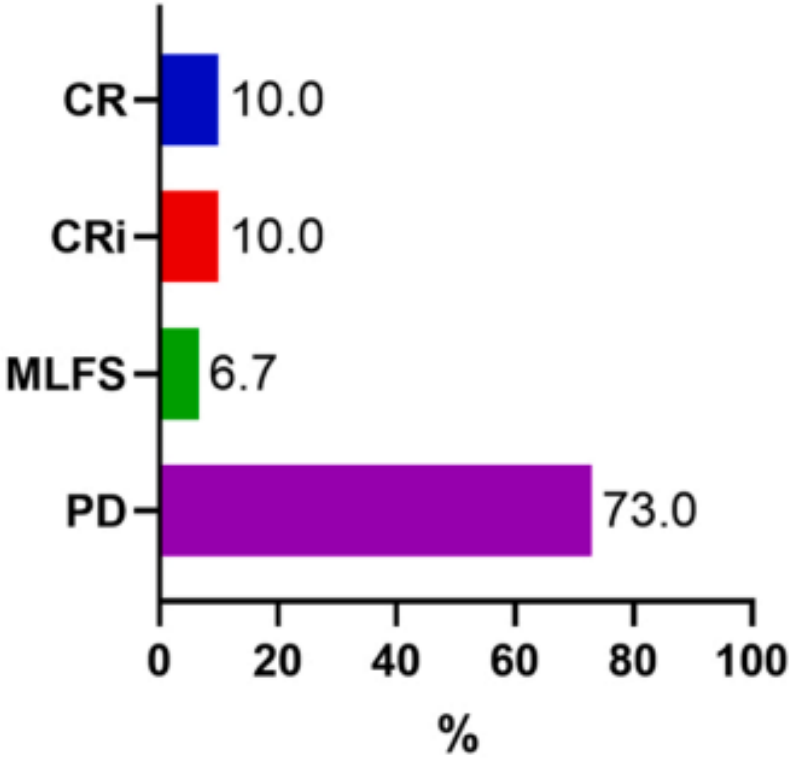
- Retrospective study evaluating response to FLT-3 patients previously treated with venetoclax
- ORR to FLT3 inhibitors was 26.7%
- Median overall survival was 6.7 months among all patients



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Bewerdorf, et al. *Leuk Res*. 2022.

FLT3 Kinome comparisons

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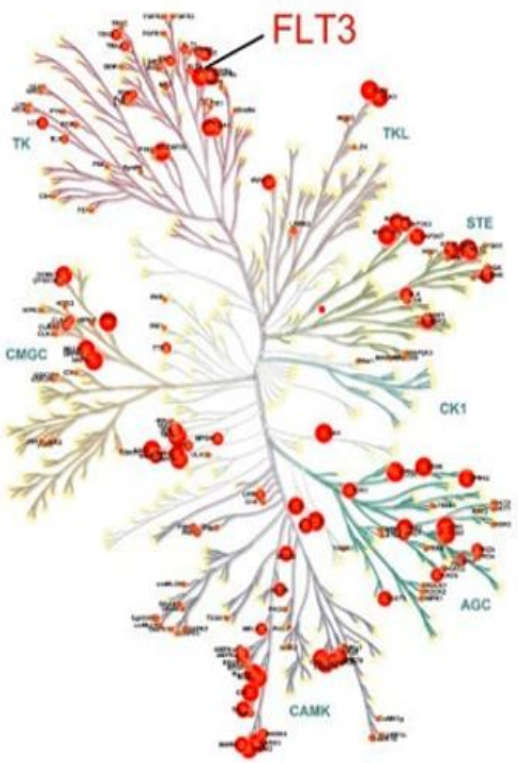
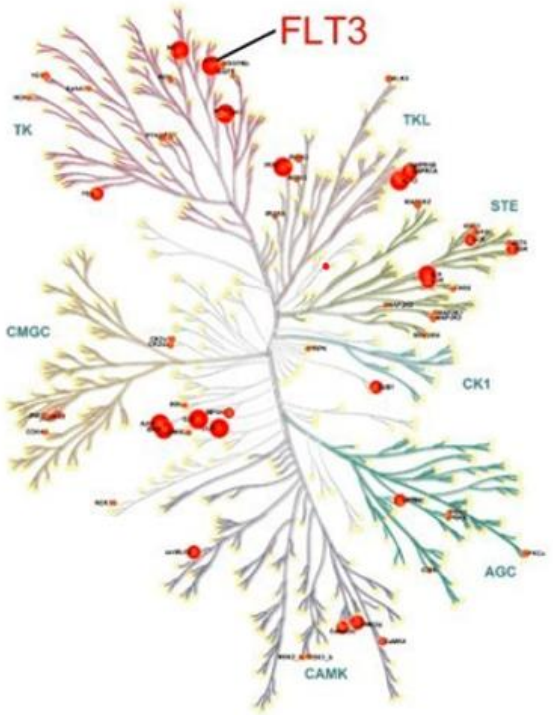
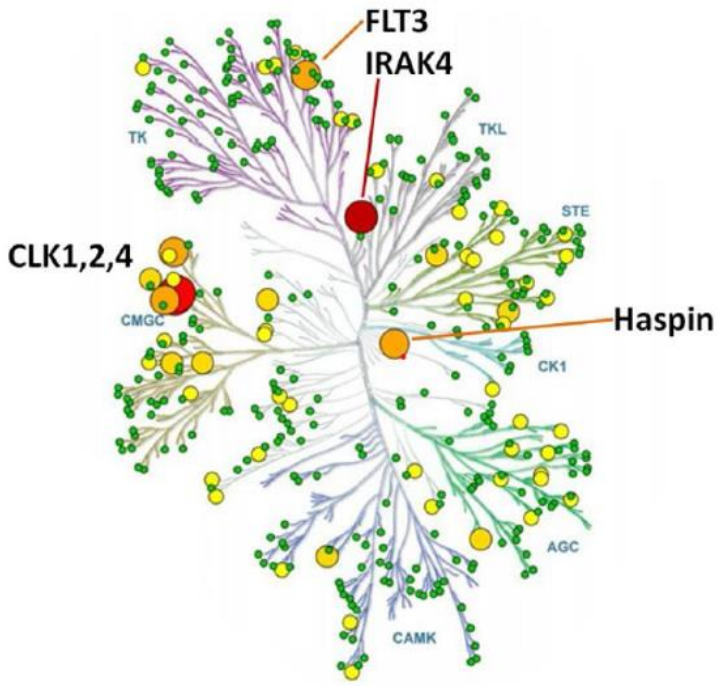


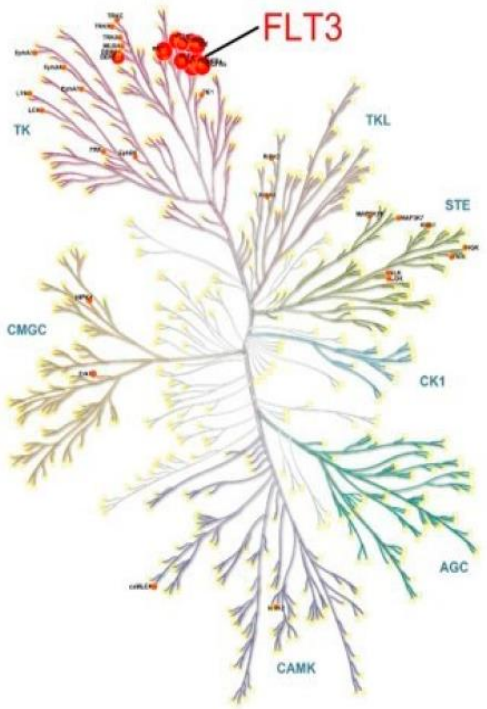
Midostaurin



Gilteritinib



Emavusertib



Quizartinib

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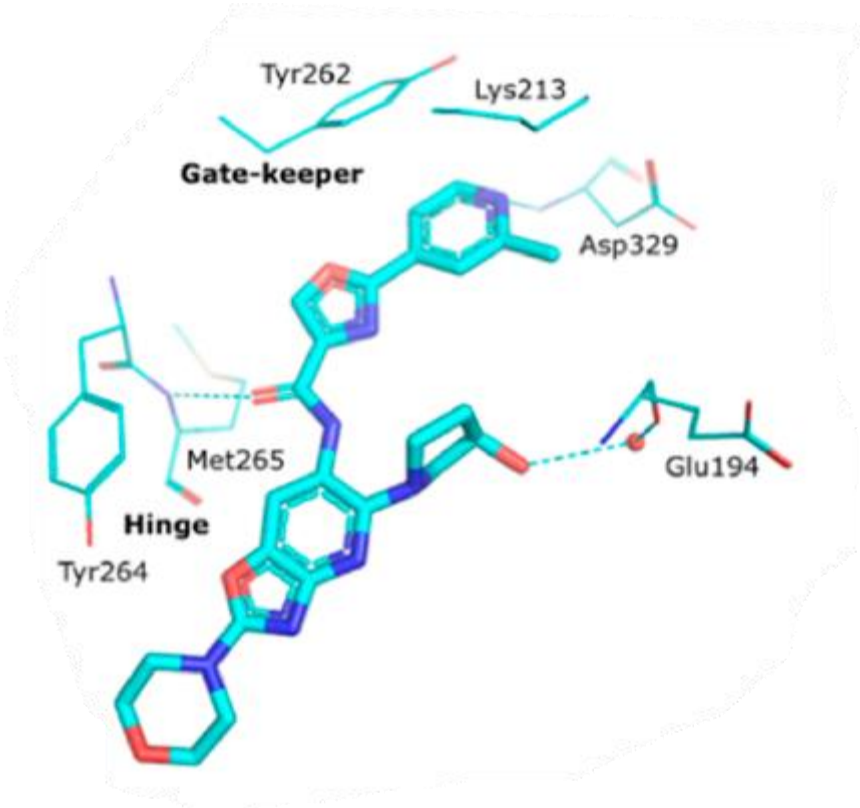
Stoudt, et al. *Int J Mol Sci.* 2018;19:3198.

CA-4948: Emavusertib – an IRAK4/FLT3 kinase inhibitor

Emavusertib with interaction points on IRAK4

Potent inhibition of IRAK4 with significant inhibition of pIRAK1 in PK-PD studies

Demonstrates activity in other kinases such as CLK1, CLK2, CLK4, FLT3, DYRK1A, DYRK1B, TrkA, TrkB, Haspin, and NEK11



Emavusertib
Binding Affinity

Target	K_d nM
IRAK1	12,000
IRAK2	>20,000
IRAK3	8,500
IRAK4	**23**
DYRK1A	25
FLT3 wt	**31**
FLT3 (D835H)	**5**
FLT3 (D835V)	**44**
FLT3 (D835Y)	**3**
FLT3 (ITD)	**8**
FLT3 (K663Q)	**47**
FLT3 (N841I)	**16**
Haspin (GSG2)	32
CLK1	10
CLK2	20
CLK3	>20,000
CLK4	14
TrkA	130

DiscoverX Kinase Panel
(378 kinases screened)

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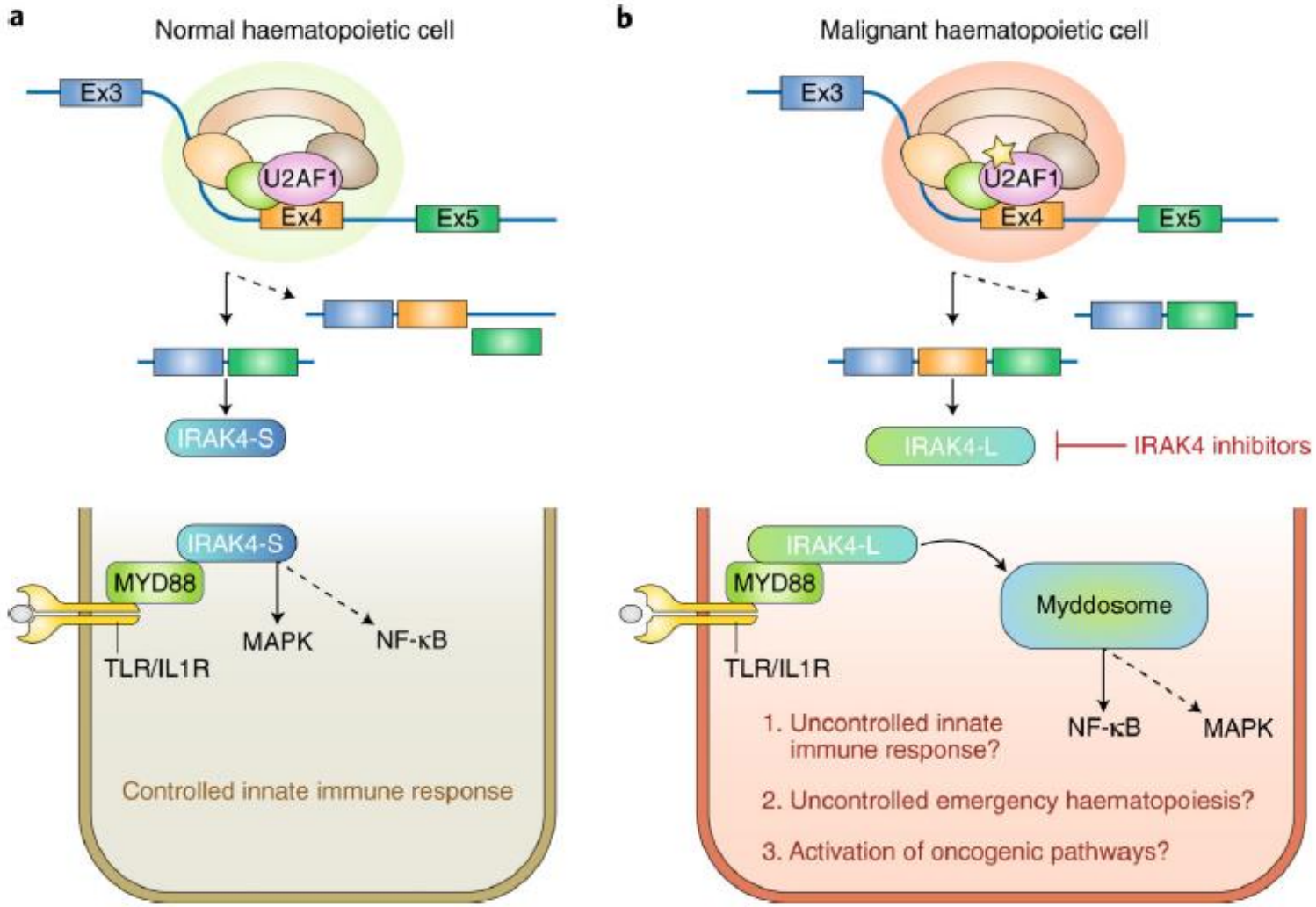
Gummadi, et al. *ACS Med Chem Lett.* 2020(11):2374-2381.

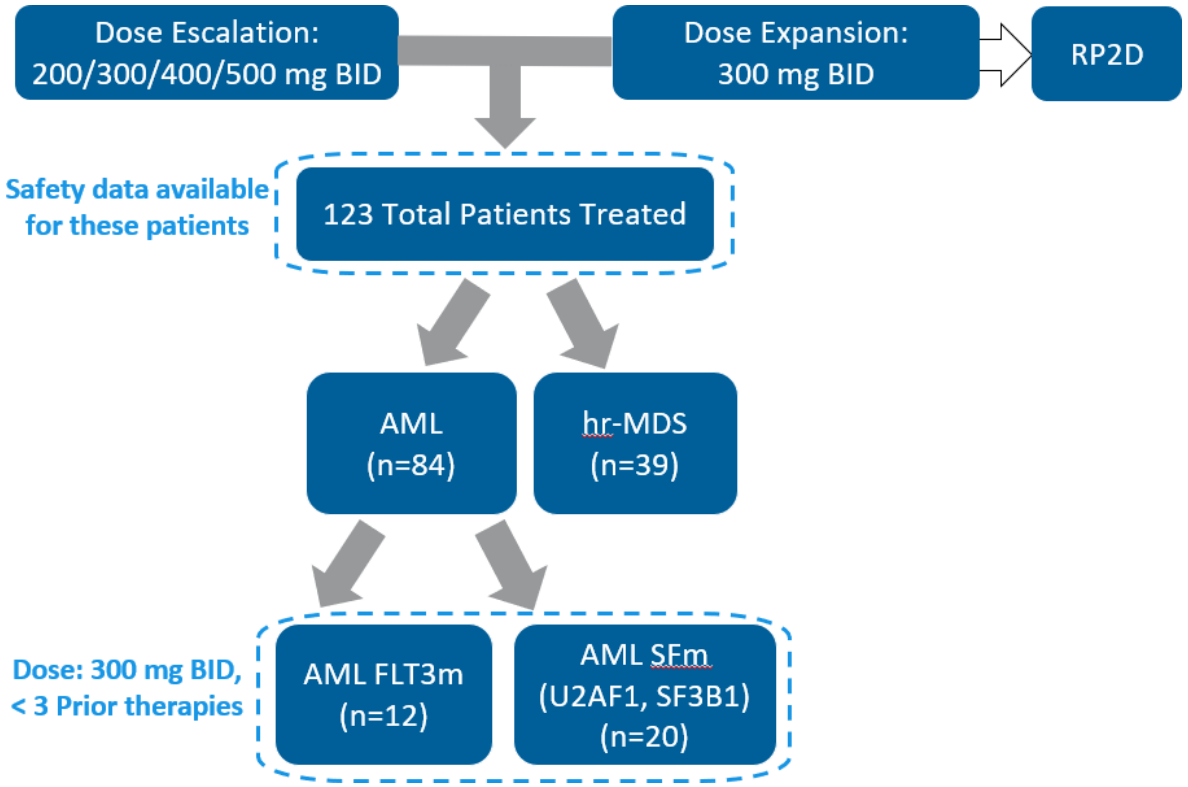
IRAK4: The long and the short

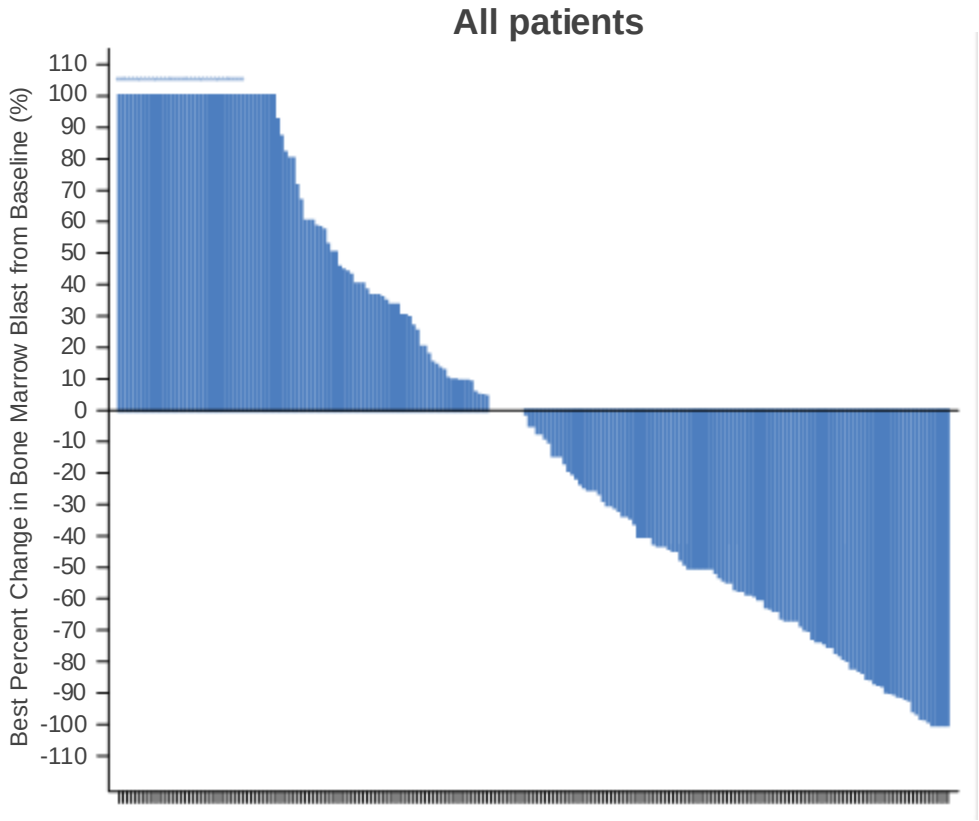


Guillamot and Aifantis. *Nat Cell Biol*. 2019;20(5):536-537.

TakeAim Leukemia study:

Schema





Includes all patients that had baseline and post-treatment bone marrow blast assessments.
*Indicates best percentage change from baseline >100%.

Winer ES, et al. Poster presented at the 2024 ASCO Annual Meeting. May 31–June 4; Chicago, IL. Abstract 6539.

TakeAim Leukemia: Adverse Events

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Treatment-related adverse events (TRAEs) of Grade ≥3 in all TakeAim Leukemia trial patients

Grade 3+ Treatment-Related Adverse Event reported in >1 patients, n (%)	200 mg BID (N = 27)	300 mg BID (N = 78)	400 mg BID (N = 15)	500 mg BID (N = 3)	Total (N=123)
# of patients having grade 3+ TRAEs	4 (14.8)	21 (26.9)	7 (46.7)	2 (66.7)	34 (27.6)
# of patients having non-hematological grade 3+ TRAEs	3 (11.1)	17 (21.8)	6 (40)	2 (66.7)	28 (22.8)
Blood creatine phosphokinase increased	0	6 (7.7)	0	0	6 (4.9)
Platelet count decreased	1 (3.7)	3 (3.8)	2 (13.3)	0	6 (4.9)
Rhabdomyolysis[a,b]	0	2 (2.6)	1 (6.7)	1 (33.3)	4 (3.3)
Anemia	0	3 (3.8)	0	0	3 (2.4)
Aspartate aminotransferase increased	1 (3.7)	2 (2.6)	0	0	3 (2.4)
Alanine aminotransferase increased	2 (7.4)	0	0	0	2 (1.6)
Dizziness	1 (3.7)	1 (1.3)	0	0	2 (1.6)
Febrile neutropenia	0	2 (2.6)	0	0	2 (1.6)
Lipase increased	0	2 (2.6)	0	0	2 (1.6)
Neutropenia	0	1 (1.3)	1 (6.7)	0	2 (1.6)
Neutrophil count decreased	0	1 (1.3)	1 (6.7)	0	2 (1.6)
Syncope	0	1 (1.3)	0	1 (33.3)	2 (1.6)

[a]After discussion with regulatory authorities of investigator-reported AEs, objective laboratory criteria for the determination of rhabdomyolysis were adopted from existing approved drug labels (creatine phosphokinase >10 x upper limit of normal and SCr ≥ 1.5 x upper limit of normal). Previously, reported events of rhabdomyolysis were determined by subjective criteria. **Using the objective criteria, rhabdomyolysis was reported in 1/123 patients.** [b]One patient receiving 300 mg BID emavusertib died with an investigator-reported cause of multi-organ failure and rhabdomyolysis, with the latter assessed by the investigator as likely related to study drug. The Leukemia and Lymphoma Society's independent safety board adjudicated that the fatal outcome in this patient was unrelated to treatment but instead due to multi-organ failure from disease progression.

Winer ES, et al. Poster presented at the 2024 EHA Annual Meeting. June 13-16, 2024; Madrid, Spain. Abstract P554.

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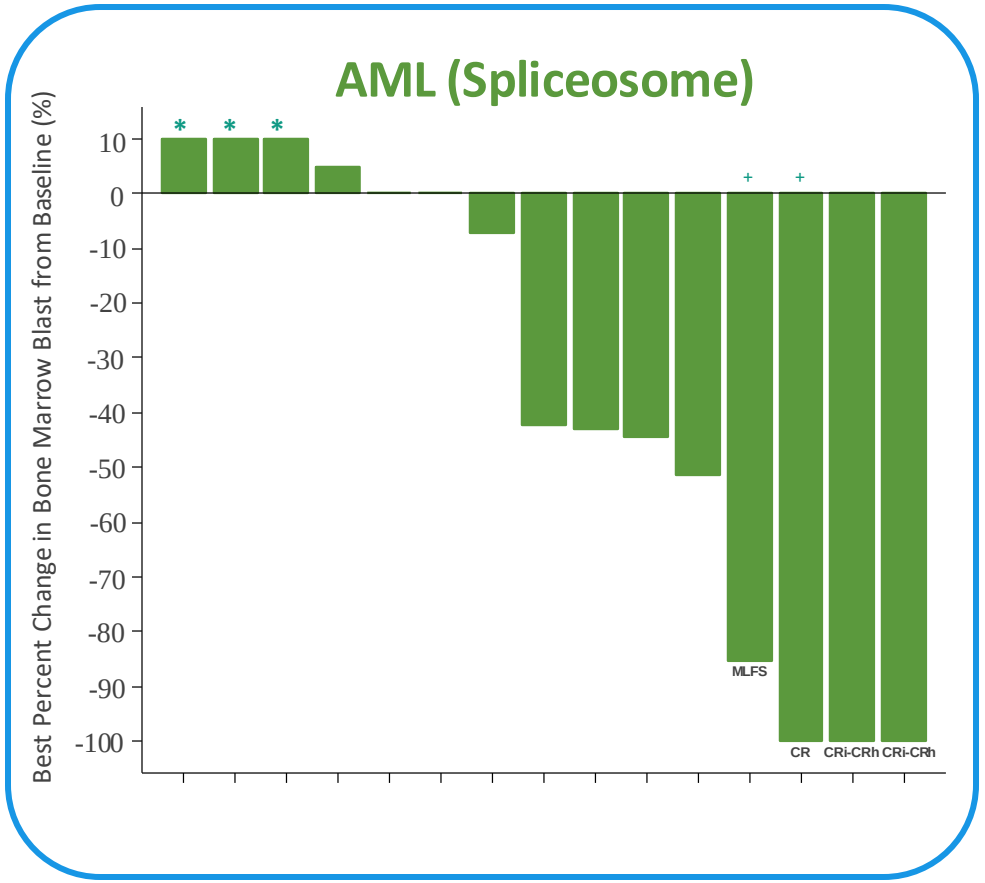
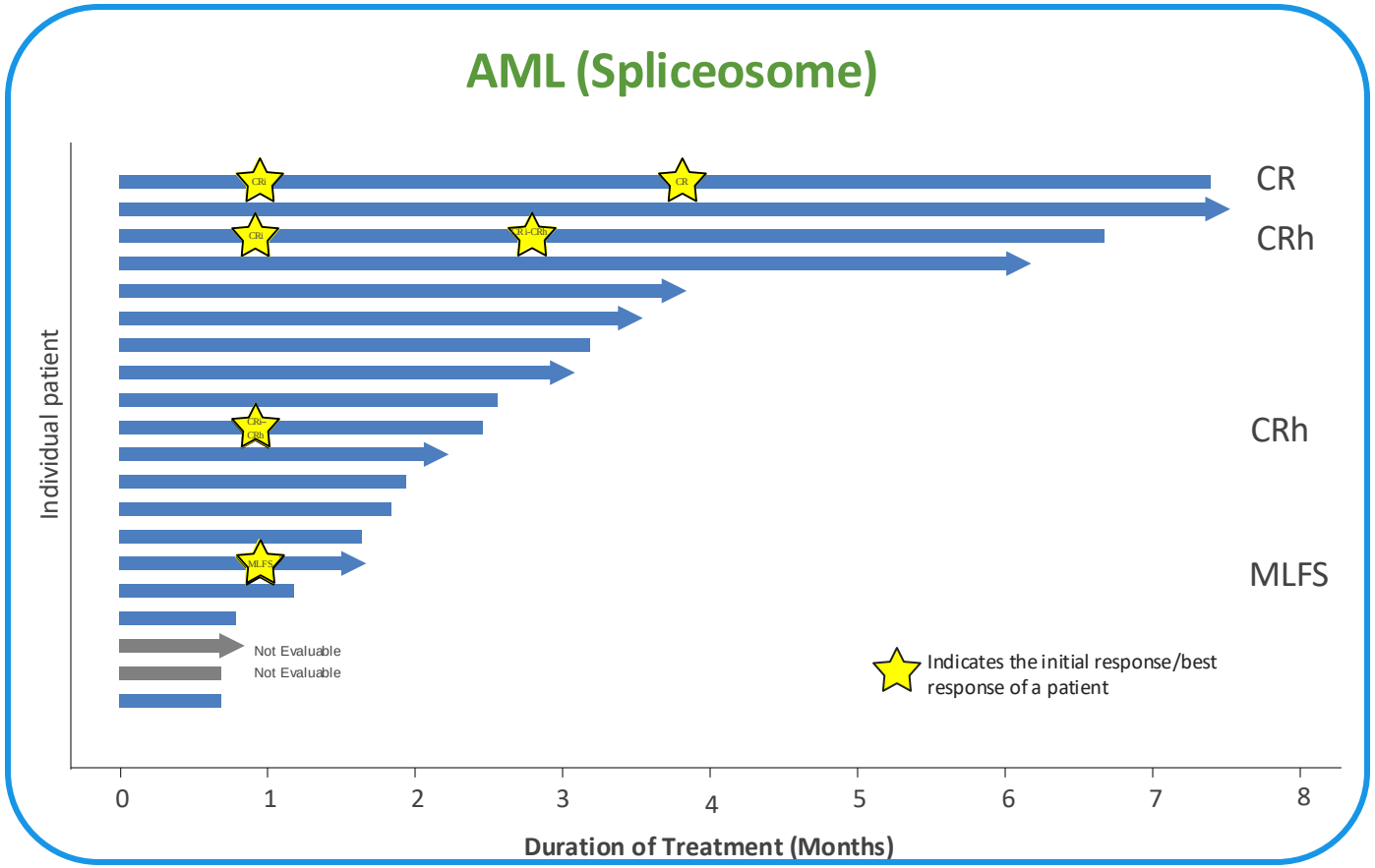
TakeAim Leukemia: Spliceosome mutation (SF3B1 and U2AF1 mutations)

IRAK4 | Symposium





* indicates the best percentage change from baseline >10%

+ indicates concomitant *FLT3* mutation

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TakeAim Leukemia: *FLT3m* Cohort

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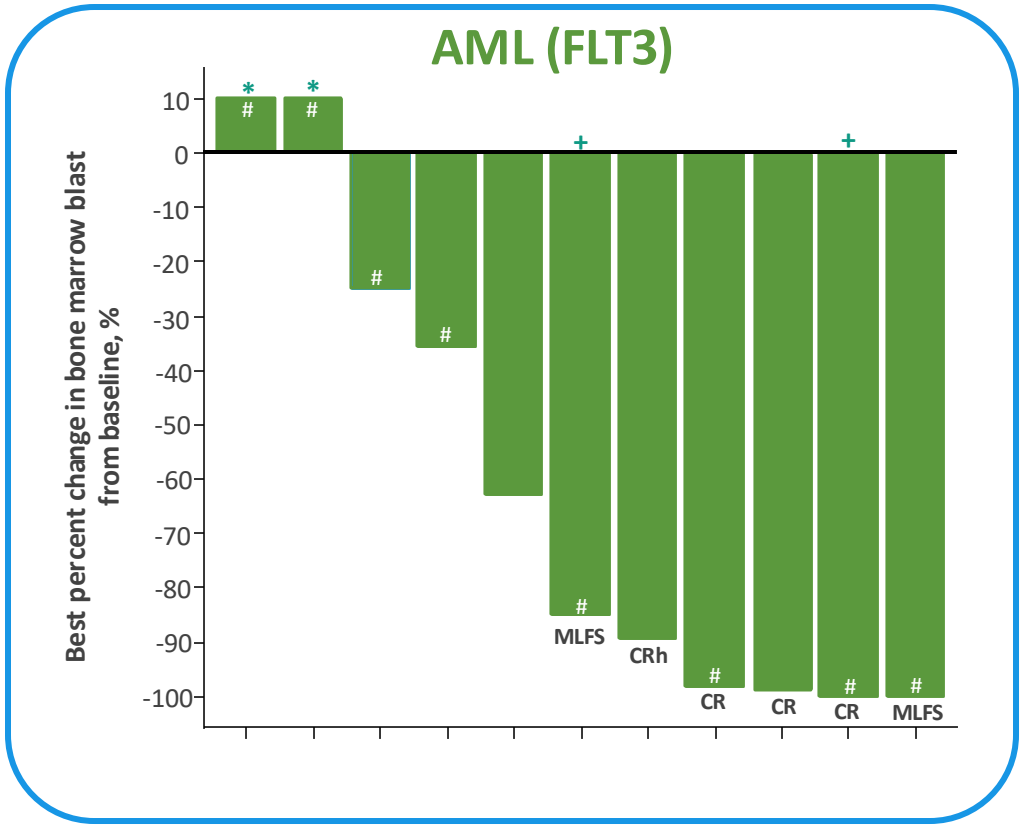

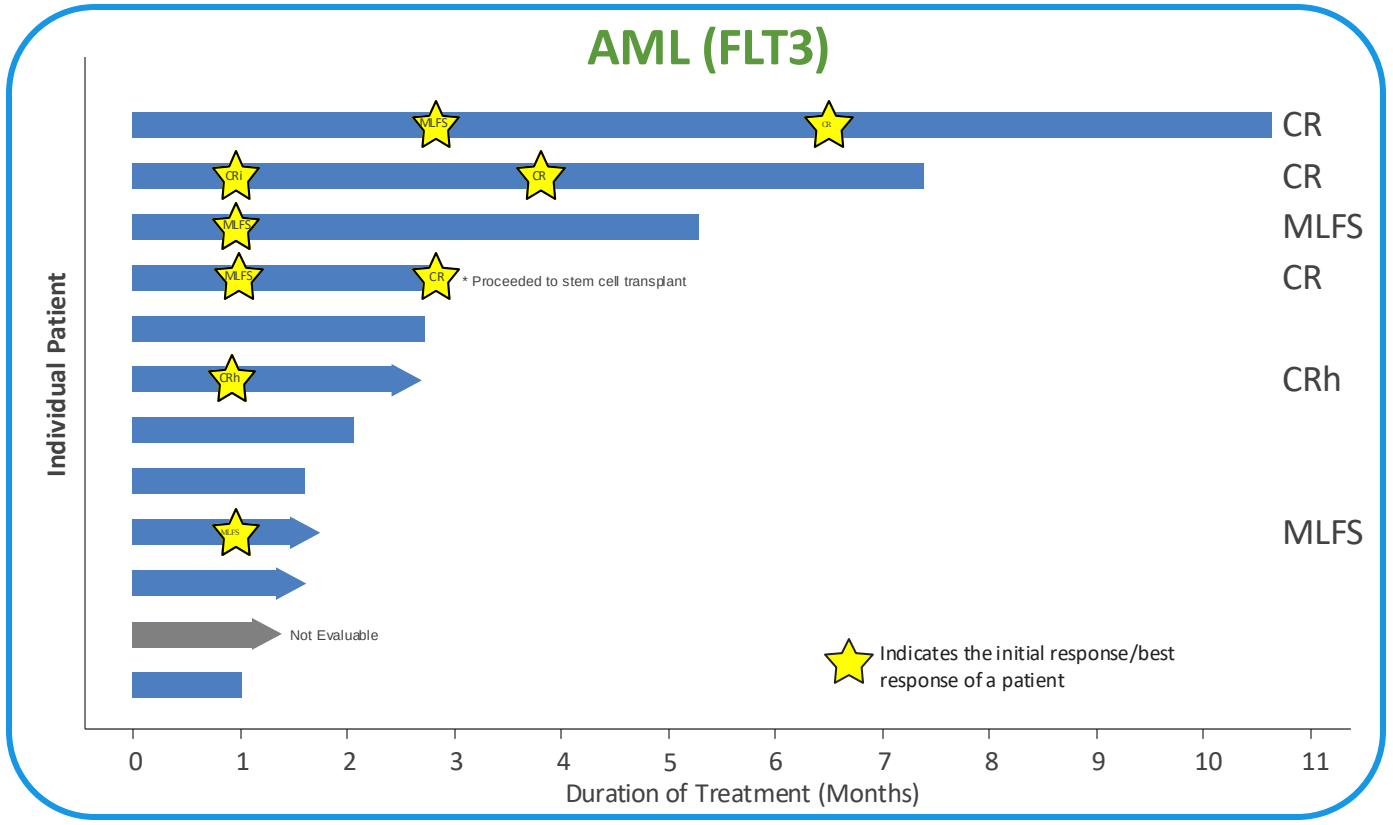

* indicates the best percentage change from baseline >10%

\# demonstrates previous venetoclax exposure

\+ indicates concomitant spliceosome mutation

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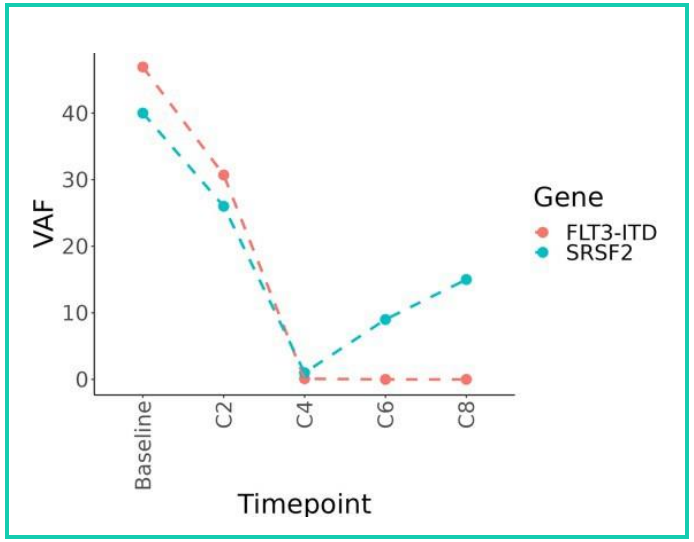
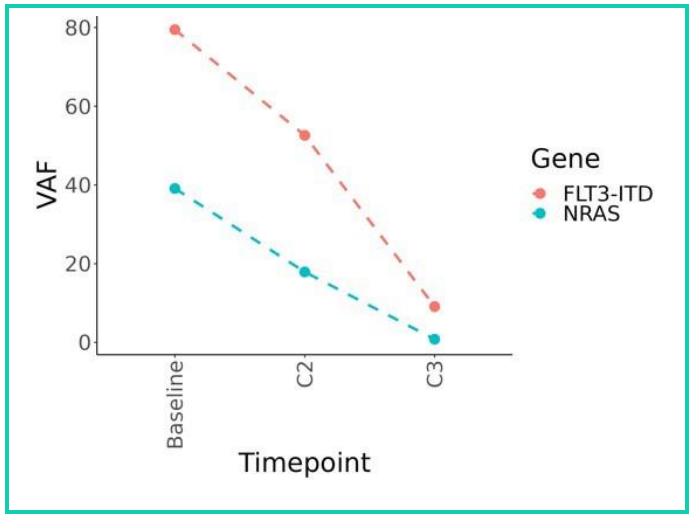
Winer ES, et al. Poster presented at the 2024 EHA Annual Meeting. June 13-16, 2024; Madrid, Spain. Abstract P554.

TakeAim: *FLT3m* responders

Clinical activity in responders with R/R AML - *FLT3m*

#	Age	Sex	ELN risk per 2017	FLT3 mutation	# prior therapy	Prior BCL2i	Prior HMA	Prior FLT3i	Best response	Co-mutations at baseline
1	80	M	Intermediate	ITD	1	Y	Y	N	CR	U2AF1, BCOR, WT1
2	44	M	Adverse	ITD	2	Y	N	Y	CR	NRAS, WT1
3	74	M	Adverse	Not available	2	Y	Y	N	MLFS	SF3B1, GATA2, PHF6, RUNX1, CBLC
4	78	F	Adverse	ITD	2	Y	Y	Y	MLFS	Not available
5	79	F	Intermediate	ITD	2	N	Y	N	CR	DMNT3A, SRSF2
6	74	M	Intermediate	ITD	1	N	Y	Y	CRh	Not available

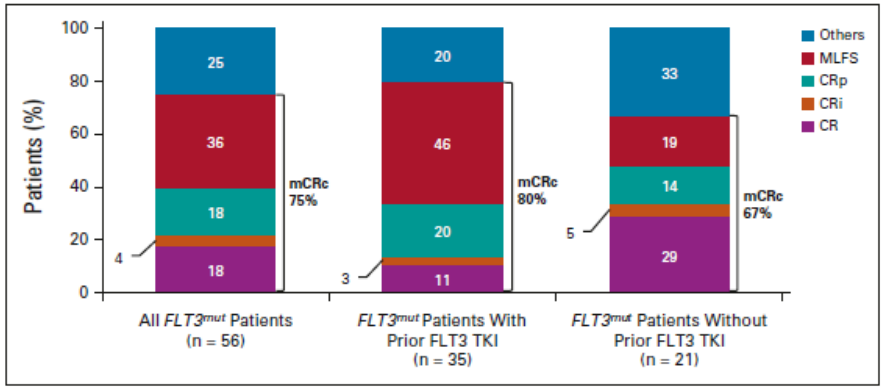


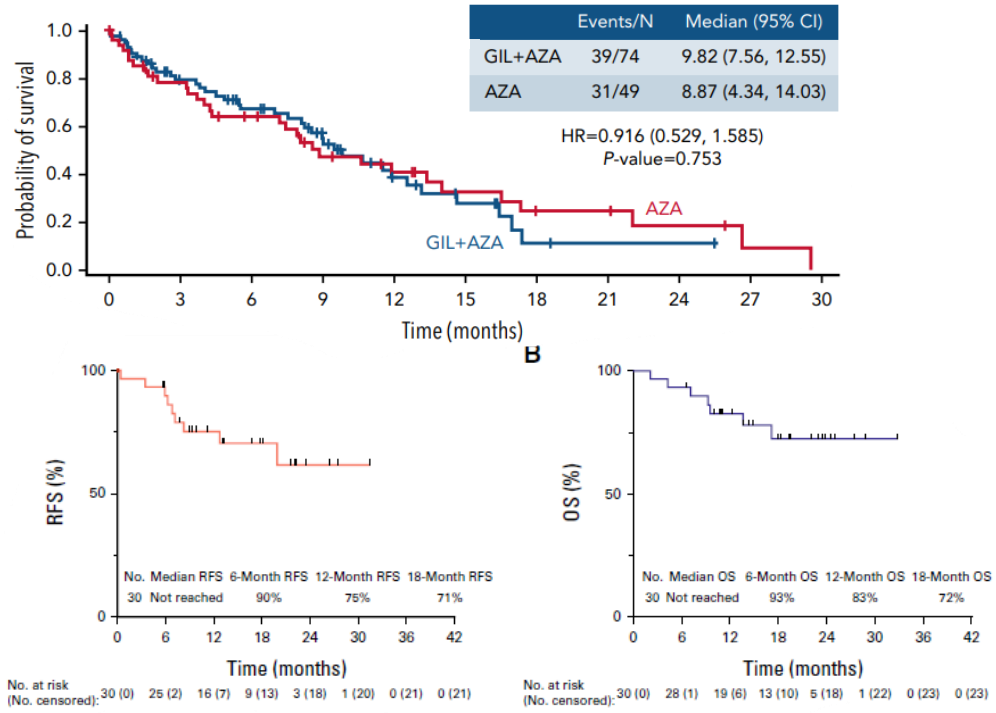


Winer ES, et al. Poster presented at the 2024 EHA Annual Meeting. June 13-16, 2024; Madrid, Spain. Abstract P554.

Doublets and Triplets – More is better?

- Venetoclax + Gilteritinib
  - CR 18%, CRi 4%, CRp 18%, MLFS 36%
  - mDOR 4.9 months
- Azacitidine + Gilteritinib v. Azacitidine
  - No difference in OS (9.82 v 8.87 mo)
- Azacitidine + Venetoclax + Gilteritinib
  - Frontline CR 90%, CRi 6%
  - 97% of patients >60
  - Median number of cycles: 3
  - 43% patients went to alloBMT





Daver N, et al. J Clin Oncol. 2022. Wang E et al. *Blood.* 2022;140(17):1845-57. Short NJ, et al. *J Clin Oncol*. 2024.

Emavusertib with other agents

- Cell line data showed increased cell death in:
  - 2 of 4 cell lines with Venetoclax
  - 3 of 4 cell lines with Azacitidine
  - 1 of 4 cell lines with decitabine
  - 4 of 4 cell lines with Azacitidine and Venetoclax
- Did not seem to have significant activity with daunorubicin and/or cytarabine.

AML cell line	Decitabine + CA-4948	Azacitidine + CA-4948	Venetoclax + CA-4948	Venetoclax + Decitabine + CA-4948	Venetoclax + Azacitidine + CA-4948
THP-1	NS	++	+	NS	+++
F-36P	NS	++	NS	NS	++
OCI-AML2	++	+	++	NS	+++
GDM-1	NS	++	NS	NS	++

AML cell line	Ara-C + CA-4948	Venetoclax + Ara-C + CA-4948	Daunorubicin + CA-4948	Daunorubicin + Ara-C + CA-4948
THP-1	+	++	NS	++
F-36P	++	NS	NS	NS
OCI-AML2	+	NS	NS	NS
GDM-1	NS	NS	NS	NS

+ <50% growth inhibition, P<0.05
++ 50 - <100% growth inhibition p<0.05
+++ 100% growth inhibition and induction of cell death. P<0.05
NS: Not significant

Ugolkov et al. Poster presented at EHA Annual Meeting 2021. June 9–17; virtual. Abstract EP390.

Eligibility:
- Untreated AML
- Adequate organ function

AND
- Age ≥60
  - OR
- sAML
  - OR
- Co-morbidities that preclude intensive chemotherapy.

Level -1: Azacitidine 75mg/m2 IV or SC days 1-7
Venetoclax 400mg PO daily days 1-28*
Emavusertib 50 mg PO daily days 1-28*

Level 1: Azacitidine 75mg/m2 IV or SC days 1-7
Venetoclax 400mg PO daily days 1-28*
Emavusertib 100mg PO daily days 1-28*

Level 2: Azacitidine 75mg/m2 IV or SC days 1-7
Venetoclax 400mg PO daily days 1-28*
Emavusertib 200mg PO daily days 1-28*

Level 3: Azacitidine 75mg/m2 IV or SC days 1-7
Venetoclax 400mg PO daily days 1-28*
Emavusertib 300mg PO daily days 1-28*

*Bone marrow biopsy to be evaluated day 14-18.
If marrow is ablated, then Venetoclax and Emavusertib held until count recovery.

Conclusions: Emavusertib in AML

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- Emavusertib demonstrates an acceptable and manageable safety profile in patients with AML
- The mutational response of emavusertib in AML patients as a single agent demonstrate the on-target efficacy, particularly in FLT3 mutated and spliceosome mutated AML
- Emavusertib monotherapy has shown responses in FLT3 patients who have been refractory to venetoclax and hypomethylating agents and prior FLT3 inhibitors
- A trial will open shortly using emavusertib in combination with azacitidine and venetoclax in untreated AML in patients either >60 years of age, secondary AML, or unfit for intensive induction chemotherapy

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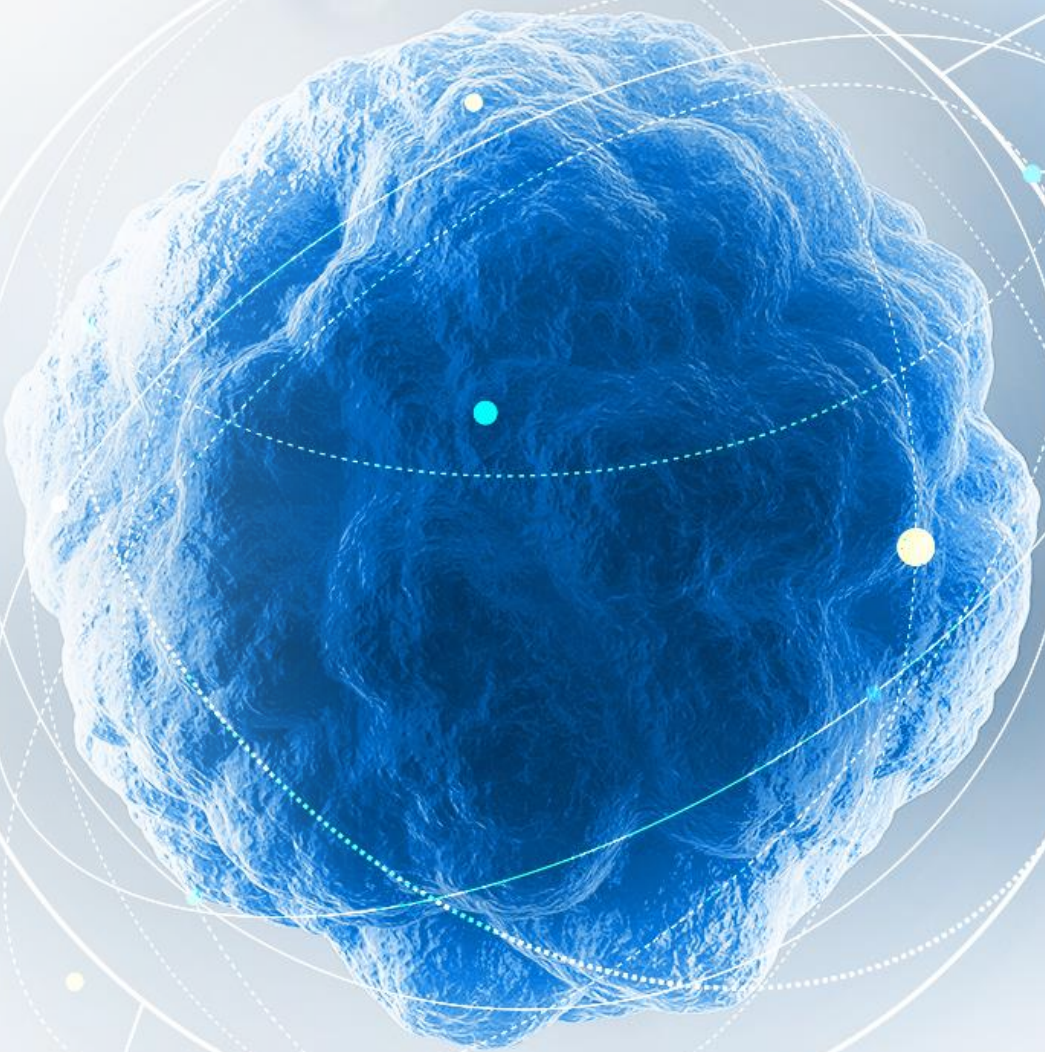
Questions?



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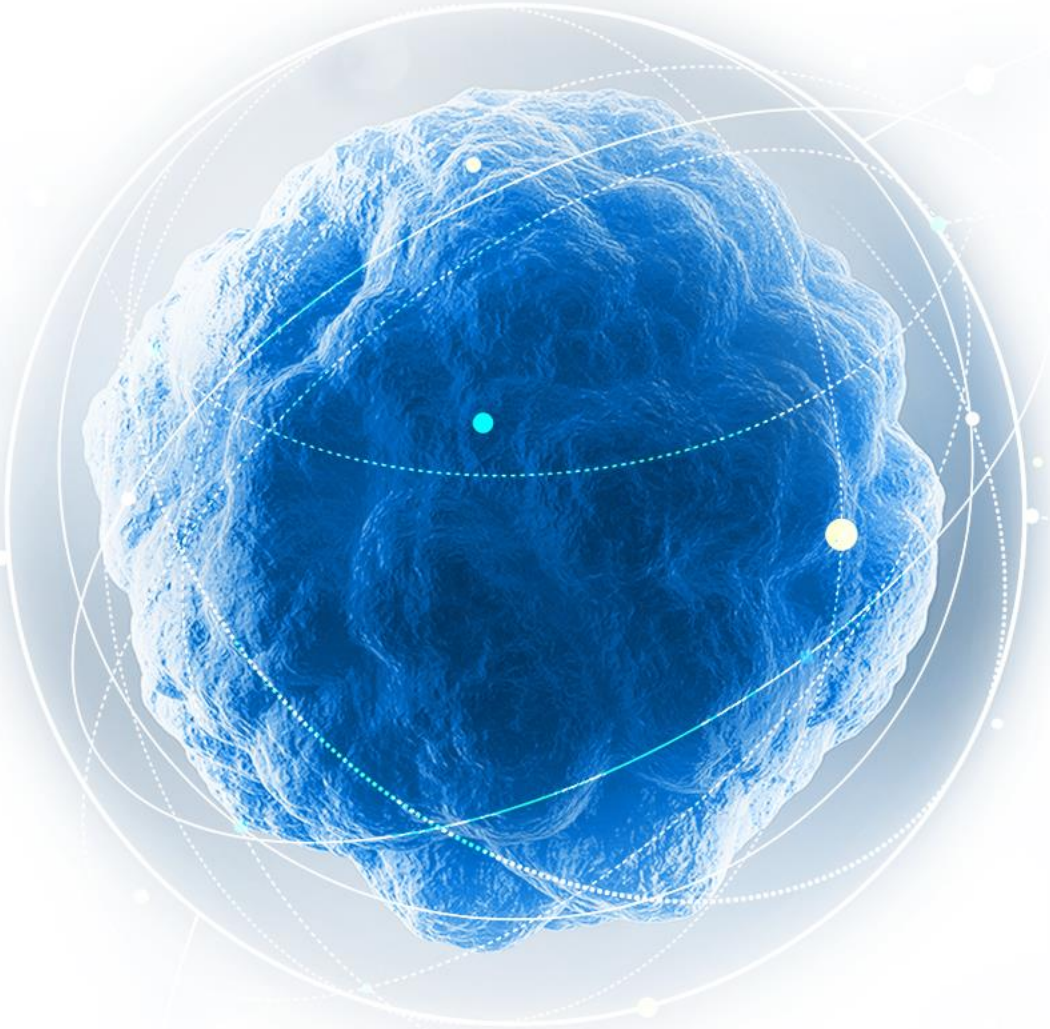
Emavusertib in combination with azacitidine and venetoclax in patients with AML with MRD+ CR



Klaus H Metzeler, MD

Professor of Translational Hematology, University of Leipzig

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Background: AML with MRD+

- AML is a heterogenous disease that exhibits a dynamic mutational landscape as the disease progresses[1,2]
- Achieving MRD− is an important treatment goal in AML[3]
  - In the VIALE-A study, patients with AML with CRc and MRD of $<10^{-3}$ or MRD− had longer DOR, event-free survival, and OS than patients who achieved CRc but with MRD+[3]
- Patients with AML who are older or not suitable for intensive chemotherapy have limited treatment options and resistance to venetoclax-based combinations is common[4-6]
  - In the 1L setting, the current standard of care is azacitidine + venetoclax[5,6]
  - Primary and adaptive resistance to venetoclax-based combinations has been associated with acquisition or expansion of clones with *FLT3-ITD* mutations[4]
  - MCL-1 has also been shown to drive resistance to venetoclax[7]
  - While FLT3-driven relapses are common,[4] there is no established role for a FLT3 inhibitor

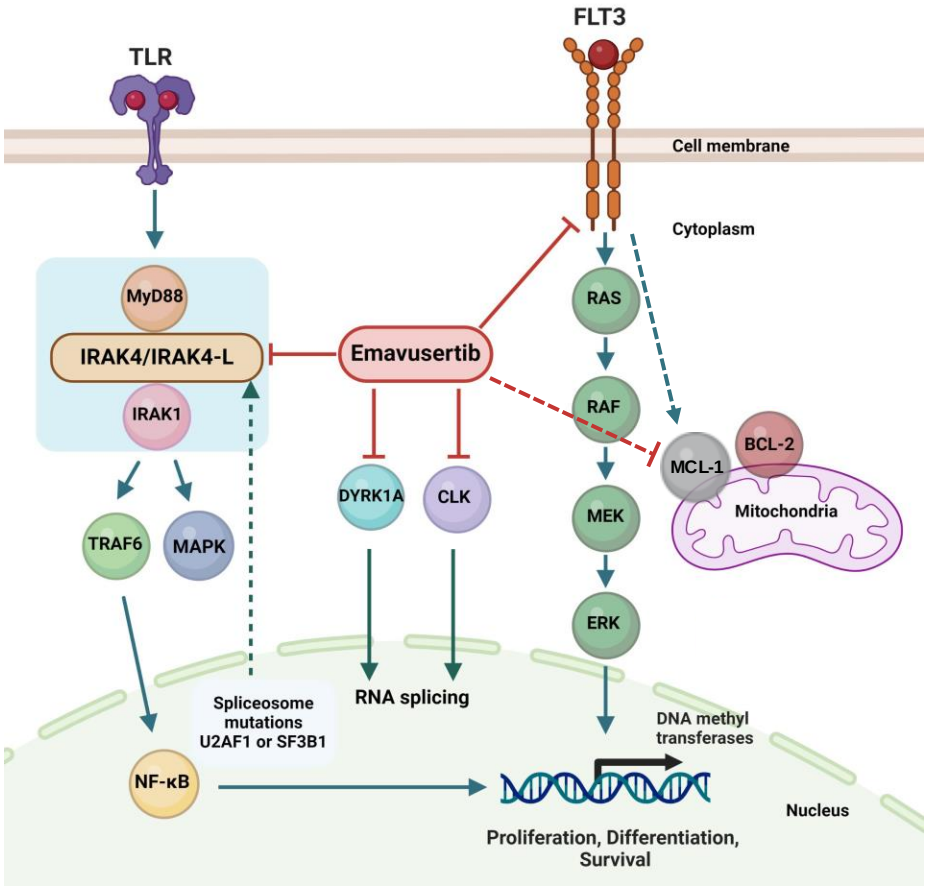
1L, first line; AML, acute myeloid leukemia; CRc, complete remission + complete remission with incomplete hematologic recovery; DOR, duration of response; FLT3, fms related receptor tyrosine kinase 3; ITD, internal tandem duplication; MCL-1, myeloid cell leukemia 1; MRD, measurable residual disease; OS, overall survival; ven, venetoclax

1. Metzeler KH, et al. *Blood.* 2016;128: 686–698. 2. Krönke J, et al, Döhner K. *Blood.* 2013 Jul 4;122(1):100–108. 3. Pratz KW, et al. *J Clin Oncol.* 2022;40:855–865. 4. DiNardo CD, et al. *Blood.* 2020;135(11):791–803. 5. DiNardo CD, et al. *N Engl J Med.* 2020;383:617–629. 6. Short NJ, et al. *J Clin Oncol*; 2024; 42:1499–1508. 7. Thijssen R, et al. Haematologica. 2015;100(8):e302–6.

Emavusertib is a novel inhibitor of IRAK4, FLT3, and CLKs

- IRAK4 is a serine/threonine kinase that mediates signaling downstream of TLRs, resulting in NF-κB and MAPK activation, and is associated with cell survival, proinflammatory cytokine production, and activation of the innate immune system[1-4]
- Emavusertib is a novel potent oral inhibitor of IRAK4 with additional inhibitory activity against FLT3 and CLK1/2/4[5]
- IRAK1/4 inhibition has been shown to result in reduced MCL-1 stability and abundance[6]

Emavusertib mechanism of action[5–7]



CLK, Cdc-like kinase; IRAK1/4, interleukin-1 receptor-associated kinase 1/4; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; TLR, Toll-like receptor.

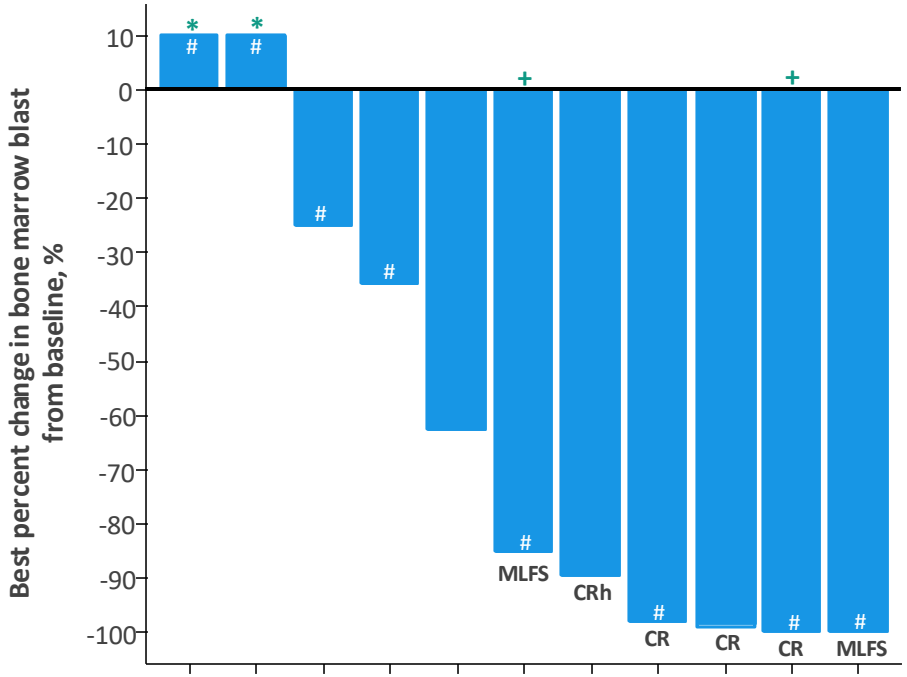
1. Gummadi VR, et al. *ACS Med Chem Lett.* 2020;11:2374-2381. 2. Guillamot M and Aifantis I. *Nat Cell Biol.* 2019;21:536-537. 3. Melgar K, et al. *Sci Transl Med.* 2019;11:eaaw8828. 4. McElroy WT. *Expert Opin Ther Pat.* 2019;29:243-259. 5. de la Fuente A, et al. Poster presented at the 2024 ASCO Annual Meeting. May 31–June 4; Chicago, IL. Abstract TPS6587. 6. Li Z, et al. *J Clin Invest*. 2015;125(3):1081–1097. 7. Ong F, et al. Cancer Drug Resist. 2022 May 6;5(2):380–400.

The efficacy of emavusertib monotherapy has been demonstrated in patients with AML

In the Phase 1 TakeAim Leukemia trial, emavusertib monotherapy has demonstrated both CRs and a significant reduction in blasts in patients with R/R AML with *FLT3*m who received prior therapy with an HMA and/or a FLT3 inhibitor

- Patients with AML with *FLT3*m received 300 mg BID emavusertib; 6 of 11 patients achieved a response of CR, CRh, or MLFS
- Of 6 responders:
  - 4 had prior BCL2 inhibitor therapy
  - 5 had prior HMA therapy
  - 3 had prior FLT3 inhibitor therapy
  - 2/6 had both prior HMA and FLT3 inhibitor therapy

Responses in patients with AML with *FLT3m*



BCL2, B-cell CLL/lymphoma 2; BID, twice daily; CR, complete response; CRh, complete response with partial hematological recovery; HMA, hypomethylating agent; MLFS, morphological leukemia free state; R/R, relapsed/refractory.

*Indicates the best percentage change from baseline >10%. #prior venetoclax exposure. +Indicates 2 AML patients having both a spliceosome and *FLT3* mutation.

Winer ES, et al. Poster presented at the 2024 EHA Annual Meeting. June 13-16, 2024; Madrid, Spain. Abstract P554.

Emavusertib monotherapy had an acceptable and tolerable safety profile

In the Phase 1 TakeAim Leukemia trial, emavusertib monotherapy had an acceptable and tolerable safety profile across the full patient population

Treatment-related adverse events (TRAEs) of Grade ≥3 in all TakeAim Leukemia trial patients

Grade 3+ Treatment-Related Adverse Event reported in > 1 patients, n (%)	200 mg BID (N = 27)	300 mg BID (N = 78)	400 mg BID (N = 15)	500 mg BID (N = 3)	Total (N=123)
# of patients having grade 3+ TRAEs	4 (14.8)	21 (26.9)	7 (46.7)	2 (66.7)	34 (27.6)
# of patients having non-hematological grade 3+ TRAEs	3 (11.1)	17 (21.8)	6 (40)	2 (66.7)	28 (22.8)
Blood creatine phosphokinase increased	0	6 (7.7)	0	0	6 (4.9)
Platelet count decreased	1 (3.7)	3 (3.8)	2 (13.3)	0	6 (4.9)
Rhabdomyolysis[a,b]	0	2 (2.6)	1 (6.7)	1 (33.3)	4 (3.3)
Anemia	0	3 (3.8)	0	0	3 (2.4)
Aspartate aminotransferase increased	1 (3.7)	2 (2.6)	0	0	3 (2.4)
Alanine aminotransferase increased	2 (7.4)	0	0	0	2 (1.6)
Dizziness	1 (3.7)	1 (1.3)	0	0	2 (1.6)
Febrile neutropenia	0	2 (2.6)	0	0	2 (1.6)
Lipase increased	0	2 (2.6)	0	0	2 (1.6)
Neutropenia	0	1 (1.3)	1 (6.7)	0	2 (1.6)
Neutrophil count decreased	0	1 (1.3)	1 (6.7)	0	2 (1.6)
Syncope	0	1 (1.3)	0	1 (33.3)	2 (1.6)

[a]After discussion with regulatory authorities of investigator-reported AEs, objective laboratory criteria for the determination of rhabdomyolysis were adopted from existing approved drug labels (creatine phosphokinase >10 x upper limit of normal and SCr ≥ 1.5 x upper limit of normal). Previously, reported events of rhabdomyolysis were determined by subjective criteria. **Using the objective criteria, rhabdomyolysis was reported in 1/123 patients.** [b]One patient receiving 300 mg BID emavusertib died with an investigator-reported cause of multi-organ failure and rhabdomyolysis, with the latter assessed by the investigator as likely related to study drug. The Leukemia and Lymphoma Society's independent safety board adjudicated that the fatal outcome in this patient was unrelated to treatment but instead due to multi-organ failure from disease progression.

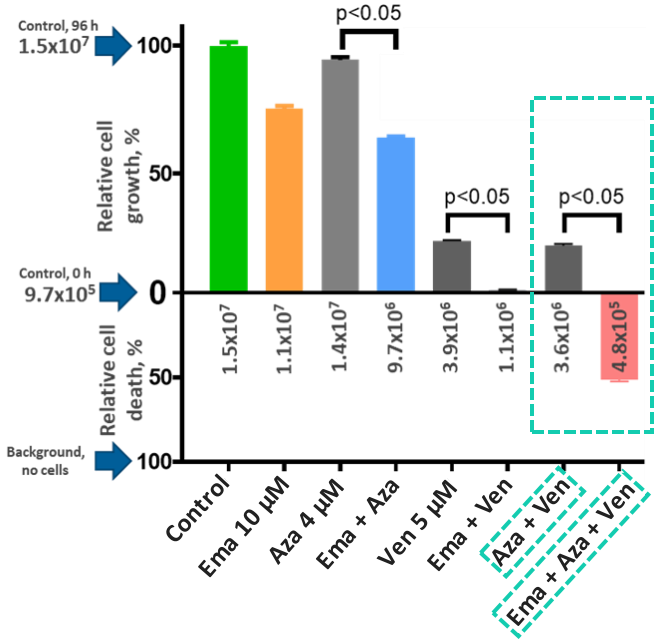
Winer ES, et al. Poster presented at the 2024 EHA Annual Meeting. June 13-16, 2024; Madrid, Spain. Abstract P554.

Addition of emavusertib can restore anti-leukemic activity in resistant AML cell lines

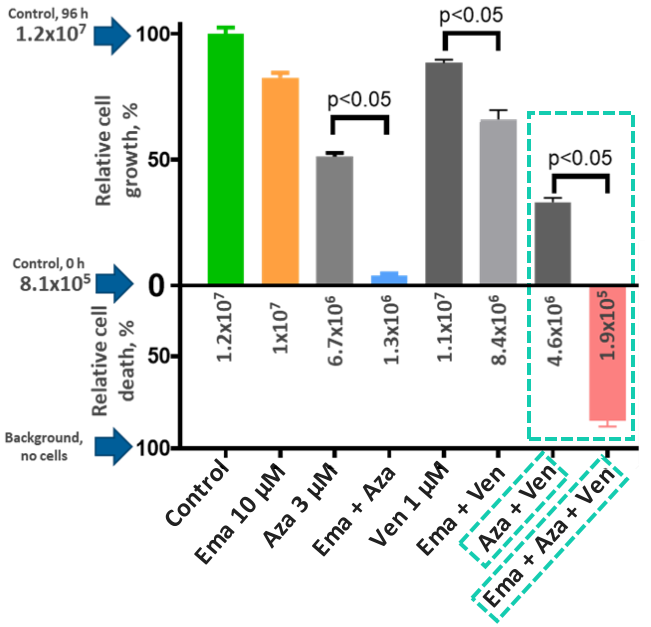
Emavusertib in combination with azacitidine and venetoclax has demonstrated significant anti-leukemic effects in AML cell lines, including azacitidine- or venetoclax-resistant cell lines

- AML cell lines were treated for 96 hours
- Relative cell viability was measured at 0 and 96 hours

OCI-AML2 (Aza resistant)[a]



THP-1 (Ven resistant)[a]



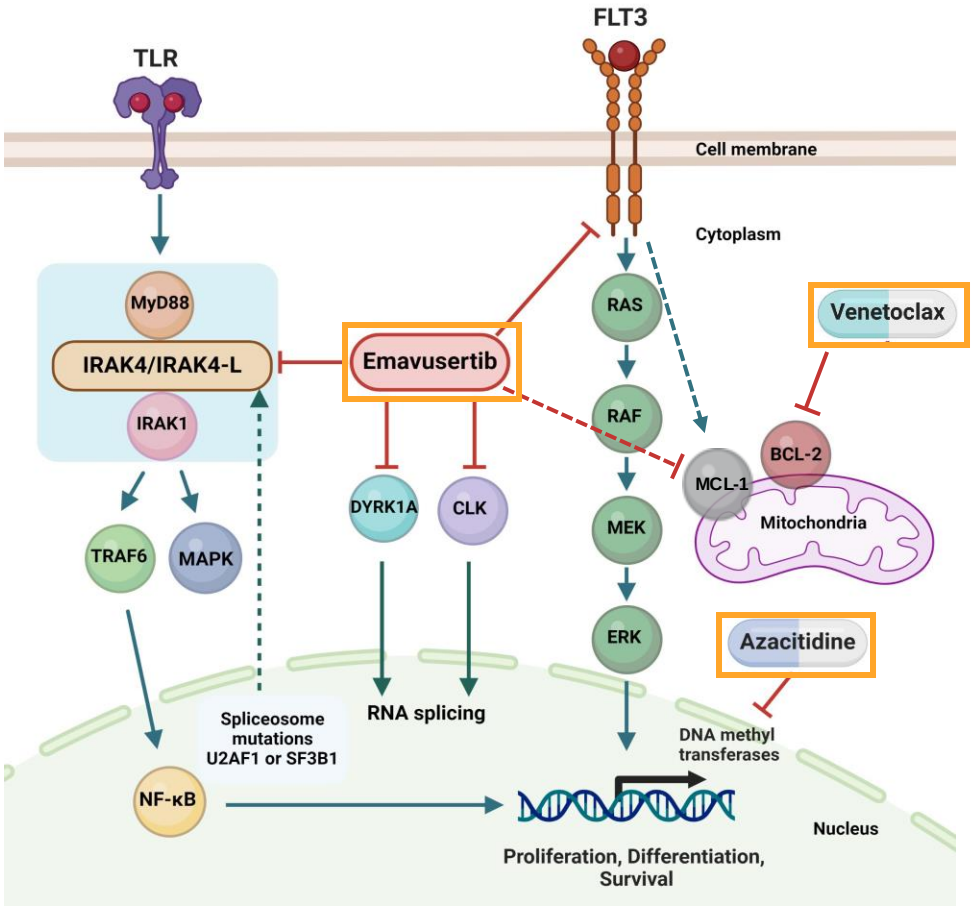
[a]Relative cell viability was measured by CellTiter Glo assay at 0 and at 96 hrs. All values are presented as mean ± standard error. Cell viability assay data were analyzed with one-way ANOVA. P values less than 0.05 were considered significant. Statistical analysis was performed using GraphPad Prism 8.0 software.
ANOVA, analysis of variance; Aza, azacitidine; Ema, emavusertib; Ven, venetoclax.
Ugolkov et al. Poster presented at EHA Annual Meeting 2021. June 9–17; virtual. Abstract EP390.

Preclinical and clinical data of emavusertib support further investigation in patients with AML

IRAK4 | Symposium

- FLT3 mutations and MCL-1 have significant roles in conferring resistance to azacitidine + venetoclax[1,2]
- The activity of emavusertib against FLT3m, preclinical evidence of synergy with azacitidine and venetoclax, and evidence of IRAK4 inhibition resulting in reduced MCL-1 support clinical evaluation of a triplet regimen[3–6]
- Adding emavusertib to the azacitidine/venetoclax doublet in patients in MRD+ CR may enable patients to achieve MRD negativity without significant added toxicity
- The phase 1b CA-4948-104 study was designed to assess the efficacy of emavusertib in combination with venetoclax and azacitidine in AML patients in MRD+ CR (EUCTR#2023-505828-58)[7]

Emavusertib + venetoclax + azacitidine mechanism of action[6–8]



1. DiNardo CD, et al. *Blood*. 2020;135(11):791–803. 2. Thijssen R, et al. Haematologica. 2015;100(8):e302–6. 3. Winer ES, et al. Poster presented at the 2024 EHA Annual Meeting. June 13-16, 2024; Madrid, Spain. Abstract P554. 4. Ugolkov et al., 2021. Poster presented at EHA Annual Meeting 2021. June 9–17; virtual. Abstract EP390. 6. Li Z, et al. *J Clin Invest*. 2015;125(3):1081–1097. 7. de la Fuente A, et al. Poster presented at the 2024 ASCO Annual Meeting. May 31–June 4; Chicago, IL. Abstract TPS6587. 8. Ong F, et al. Cancer Drug Resist. 2022 May 6;5(2):380–400.

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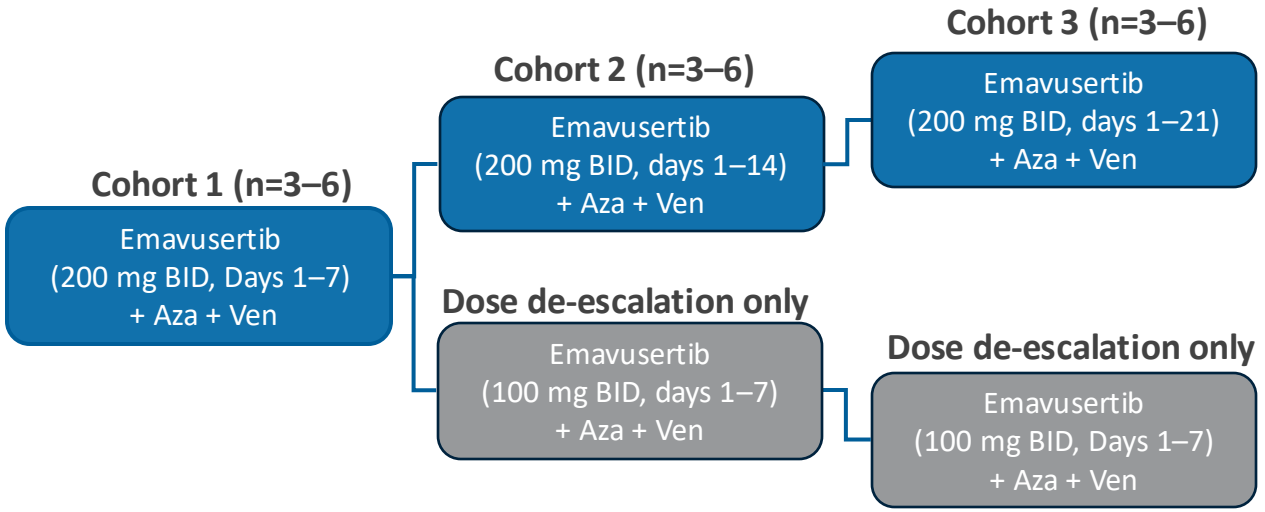
CA-4948-104: Study design

- CA-4948-104 is a Phase 1b, single-arm, open label study assessing emavusertib + venetoclax + azacitidine in patients aged ≥60 years with AML who achieved CR or CRh with MRD+ on venetoclax + azacitidine as 1L therapy (EUCTR#2023-505828-58)[1,2]

Key Eligibility Criteria

- Aged ≥60 years
- Confirmed diagnosis of AML
- Ongoing 1L ven + aza, ≤6 cycles
- Documented CR or CRh within 28 days prior to Cycle 1, Day 1
- Documented bone marrow MRD positivity



Treatment until
- Withdrawal
- Disease progression
- Intolerable toxicity
- Not achieving MRD negative status within 6 cycles

Emavusertib is administered orally 200 mg BID on days 1–7, 1–14, or 1–21 of a 28-day cycle
Aza and ven are administered at the same dose schedule as when patient achieved CR or CRh

1. de la Fuente A, et al. Poster presented at the 2024 ASCO Annual Meeting. May 31–June 4; Chicago, IL. Abstract TPS6587. 2. Curis, Inc. Data on File.

CA-4948-104: Objectives and endpoints

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	Objectives[1]	Endpoints[1,2]
Primary	• Evaluate safety and tolerability of different dose schedules of emavusertib as an add-on agent to the combo of aza + ven (triplet regimen)	Safety, including AEs
Secondary	• Evaluate conversion of MRD+ to MRD− status with triplet regimen • Characterize PK profiles of emavusertib, azacitidine, and venetoclax • Assess effects of triplet regimen on dynamics of MRD status and relationship to outcomes • Evaluate continuous anti-cancer activity of the triplet regimen	• Rate of MRD conversion by flow cytometry • PK parameters • Time to MRD conversion from first dose of triplet regimen • Duration of MRD negativity • OS
Exploratory	• Evaluate the molecular profile of peripheral blood at baseline and following treatment with the triplet regimen	• Changes in expression profiles • Identification of biomarkers

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AE, adverse event; PK, pharmacokinetics.

1. de la Fuente A, et al. Poster presented at the 2024 ASCO Annual Meeting. May 31–June 4; Chicago, IL. Abstract TPS6587. 2. Curis, Inc. Data on File.

CA-4948-104: Patient eligibility

01 Identifying Eligible Patients

- Newly diagnosed patient with AML who is ≥60 years old
- Planned first-line aza + ven or currently receiving aza + ven with ≤6 cycles
- Follow response assessments through cycle 6 for 1st CR/CRh with MRD+

02 Patient tracking

HAS first response of CR/CRh with MRD+ via bone marrow

03 Toxicity

NOT experiencing ≥G2 aza/ven toxicity

04 Stem cell transplant

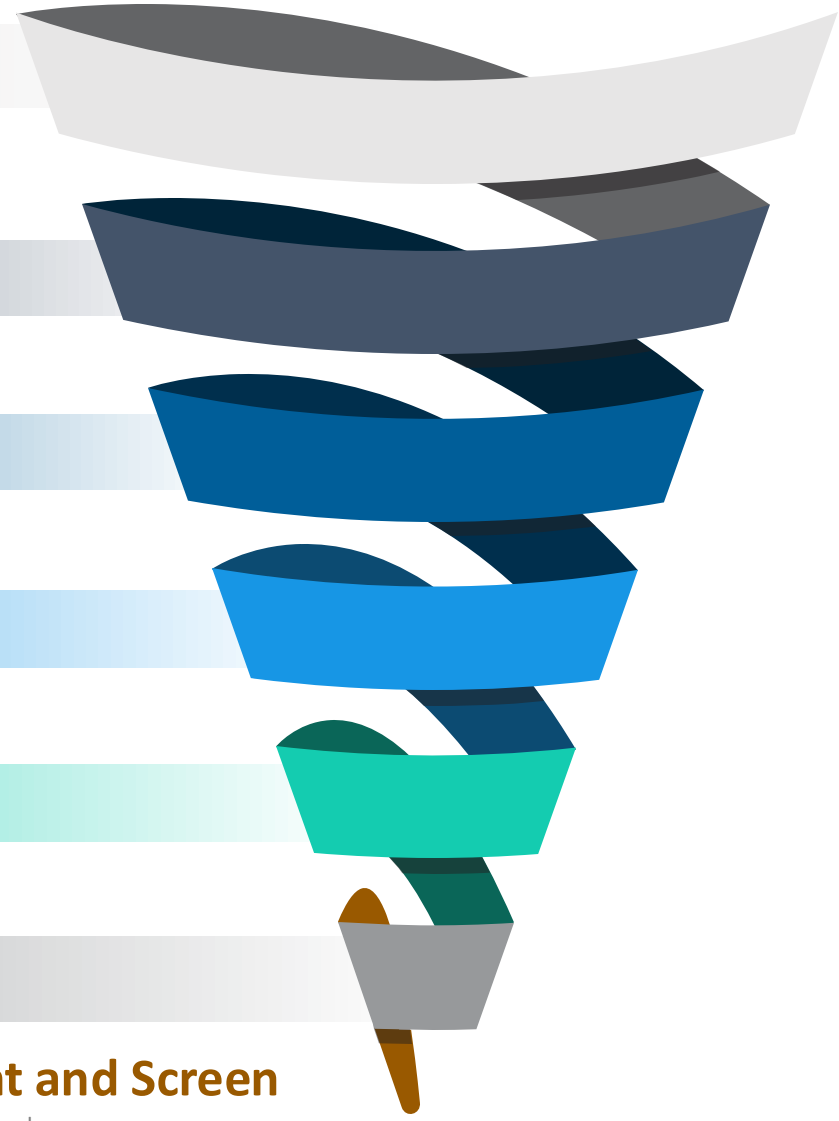
NOT an immediate candidate for allogeneic stem cell transplant

05 ECOG PS, organ function & CPK

WITH ECOG PS ≤2 | **WITH** acceptable organ function and CPK Level (≤2.5 x ULN)

06 Exclusion Criteria

DOES NOT meet exclusion criteria



Consent and Screen

CPK, creatine phosphokinase; ECOG PS, Eastern Cooperative Oncology Group performance status; G, grade; ULN, upper limit of normal.

de la Fuente A, et al. Poster presented at the 2024 ASCO Annual Meeting. May 31–June 4; Chicago, IL. Abstract TPS6587.

Study sites currently enrolling

de la Fuente A, et al. Poster presented at the 2024 ASCO Annual Meeting. May 31–June 4; Chicago, IL. Abstract TPS6587.

Summary

IRAK4 | Symposium

- Emavusertib monotherapy demonstrated promising efficacy and has been well tolerated in patients with R/R AML
- Emavusertib in combination with azacitidine and venetoclax demonstrated synergistic anti-leukemic effects in AML cell lines
- Adding emavusertib to the azacitidine/venetoclax doublet in MRD+ CR may enable patients to achieve MRD negativity without significant toxicity
- This triplet combination has a potential to become a new option in 1L therapy for older/unfit patients with AML, regardless of mutation status
- Exploratory biomarkers will be analyzed to determine predictive biomarkers of response
- The study is currently enrolling patients

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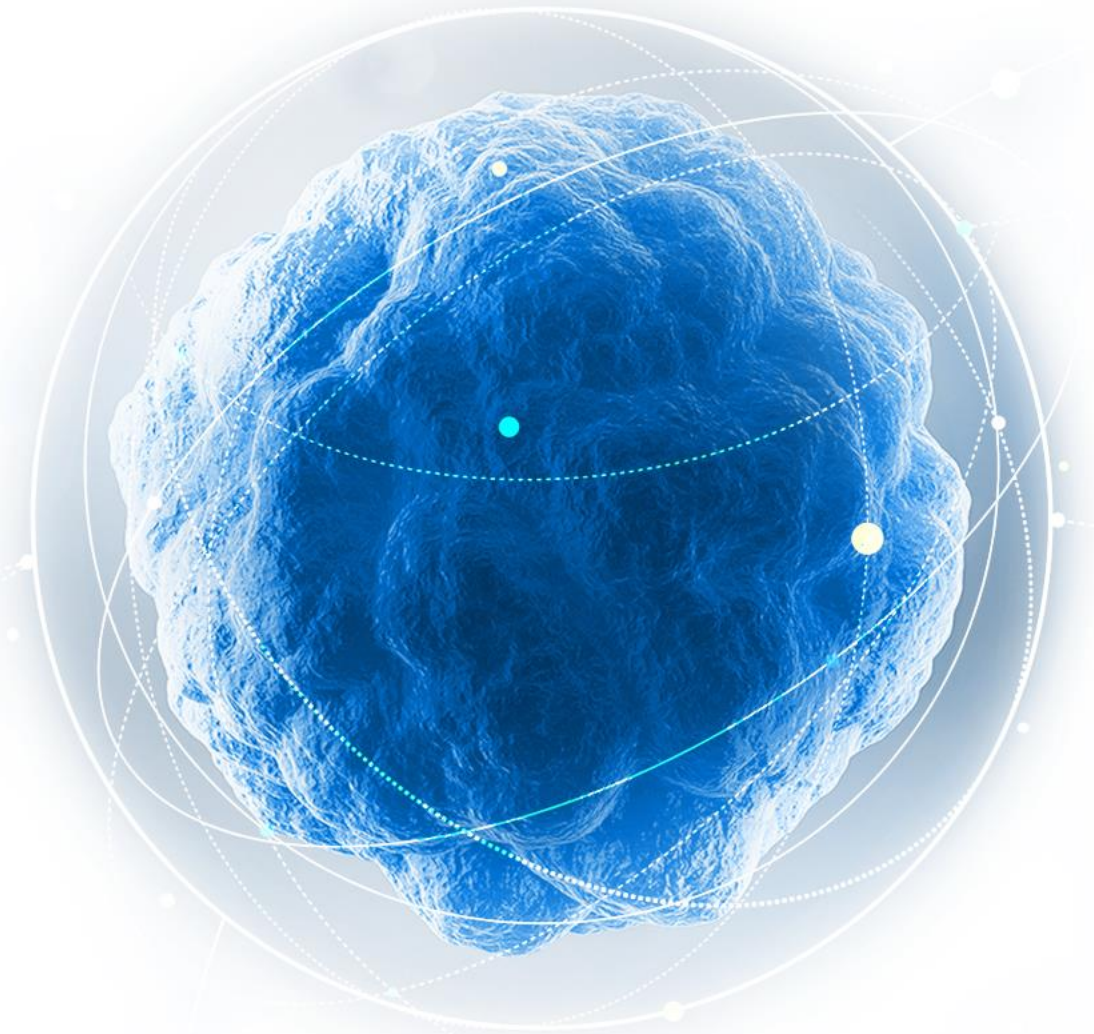
Current and Future Opportunities For IRAK4 Inhibition in Leukemia and MDS Roundtable



Eric S. Winer (moderator)

Guillermo Garcia-Manero

Klaus Metzeler

Marina Konopleva

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Discussion Questions

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- What is your general approach to the older patient with AML/MDS? Do you envision some of the combinations that we are discussing supplanting the “standard” treatment of 7+3 intensive chemotherapy.
- What are key unmet needs in myeloid malignancies*, besides TP53 mutated MDS/AML*?
- What is the optimal combination strategy for IRAK4 inhibition in myeloid malignancies? Do you see a benefit in combining emavusertib with other FLT3 inhibitors? With other agents such as HMA, venetoclax or both?
  - Given current treatment approaches, in which patients and contexts might addition of an IRAK4 inhibitor be an option?
- Which genetic subtypes of myeloid malignancies are likely to be most sensitive to IRAK4 inhibition? Are there biomarkers for response other than mutations?
- What are the expected benefits for reduced dose schedules of emavusertib, such as the 7-day and 14-day dose schedules being tested in MDS? In which patient populations would assessing a modified dose be suitable? Do you see a role for this in AML?
- Is there potential for emavusertib to be a component of treatment either broadly or in specific populations as 1L therapy for MDS or AML? What would need to be demonstrated to support this? What about as monotherapy in 2L, such as following HMA failure?

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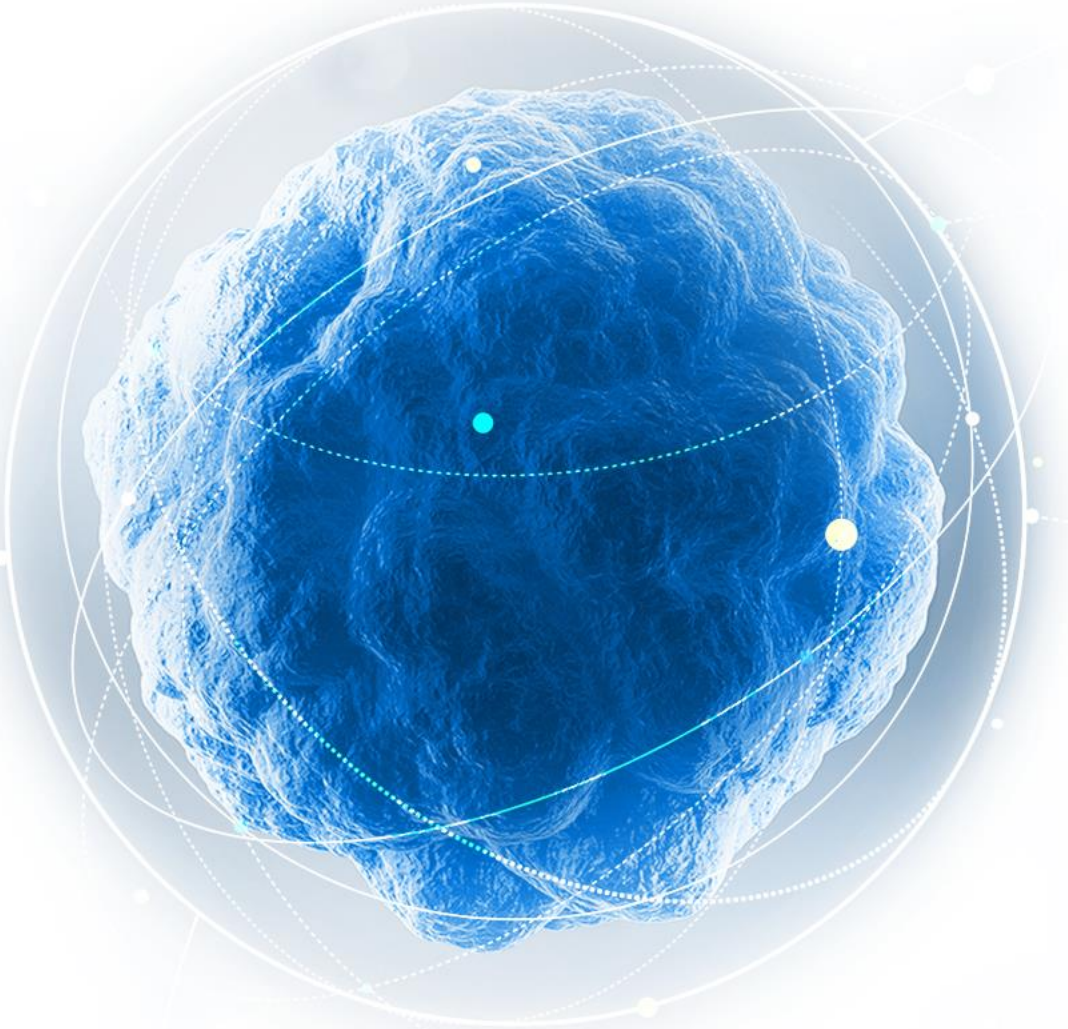
IRAK4 Targeting in PCNSL



Han W. Tun, MD
Professor of Medicine
Department of Hematology/Oncology
Department of Cancer Biology
Mayo Clinic Florida

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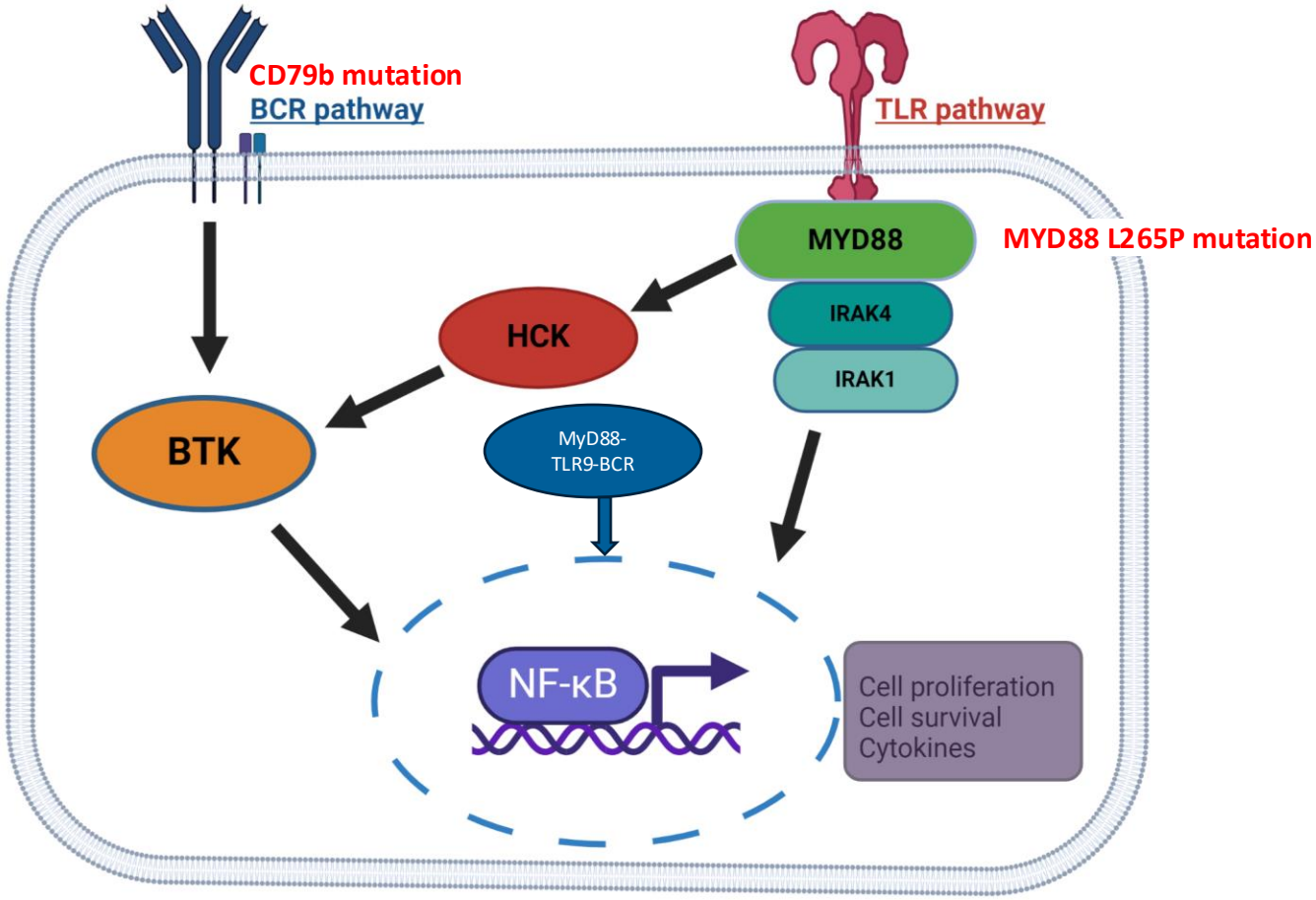
Interleukin-1 Receptor-associated Kinase 4 (IRAK4)

A serine/threonine kinase in the Toll-like receptor and interleukin-1 receptor pathways (Innate immune response)

Recruited to MYD88 upon activation with downstream activation of NFKB and MAPK

Constitutive activation of BCR and TLR pathways in MYD88 mutant B cell lymphomas



MYD88 L265P mutant B-cell non-Hodgkin lymphomas

IRAK4 | Symposium

- Non-germinal center diffuse large B cell lymphoma (33%)
- Primary cutaneous DLBCL, leg type (70%)
- Primary CNS lymphoma (70%)
- Primary testicular lymphoma (70-80%)
- Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma (95-97%)

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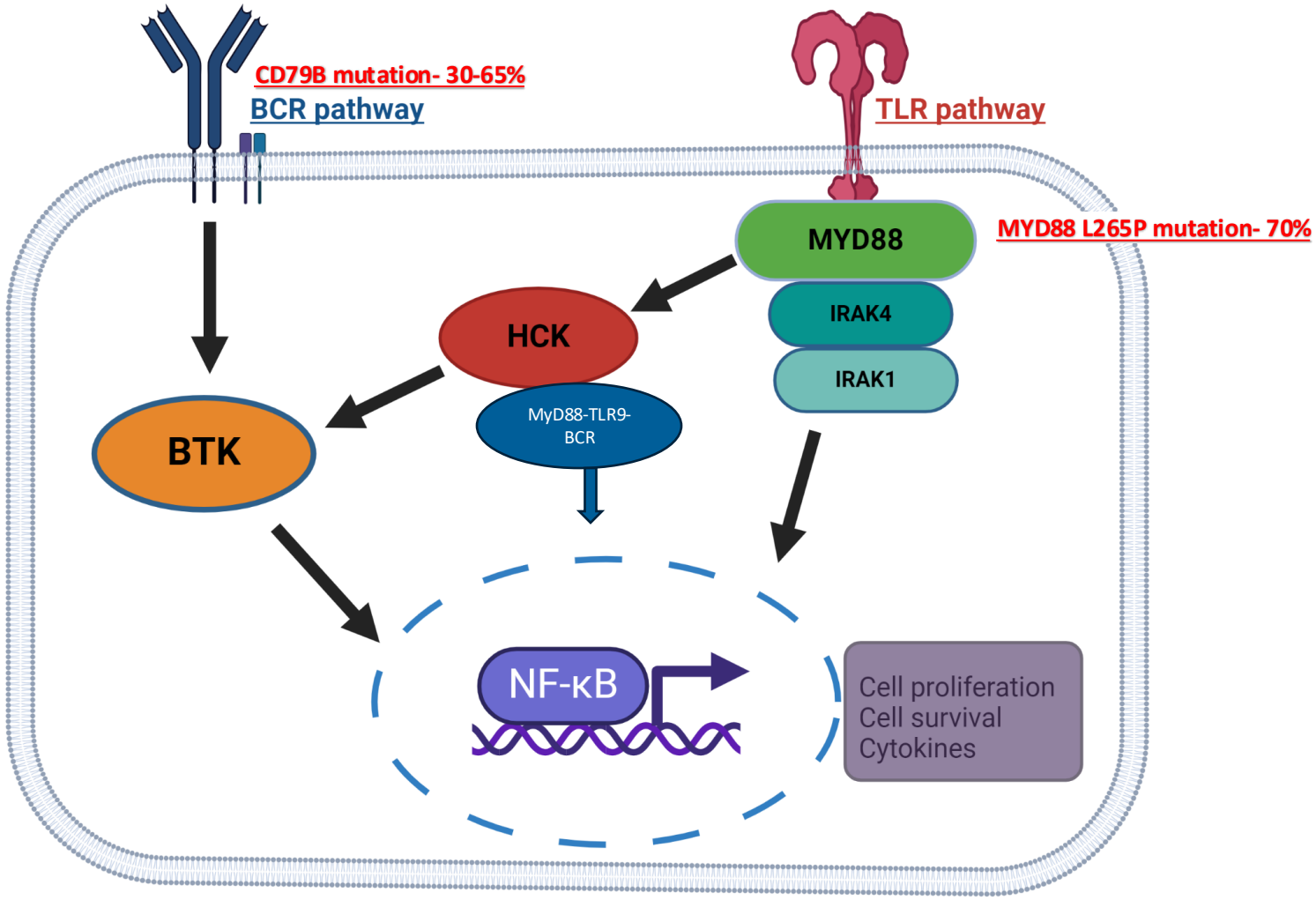
PCNSL



Mutation profile- MCD (MYD88 and CD79B mutations)
Pathway signature- Oncogenic constitutive activation of BCR and TLR pathways
Activated NFKB signaling

Genomic Landscape of PCNSL

- Genomic instability (CDKN2A deletion)
- Oncogenic Toll-like receptor signaling (MYD88 L265P mutation)
- Oncogenic B cell receptor signaling (CD79 mutation)
- Dysregulation of BCL6 (Mutations and translocation involving BCL6)
- Immune evasion (PD-L1/PD-L2 gains and translocation)

Blood 2016;127(7):869-881

Primary CNS lymphoma

Diffuse large B cell lymphoma confined to the central nervous system (brain, leptomeningeal, eyes, spinal cord, cranial nerves)

Incidence ~ 1800 new cases per year in US

Potentially curable with chemoimmunotherapy followed by autologous stem cell transplant

25792 Patients with Non-HIV PCNSL (SEER + CBTRUS- 1973-2013)

Age	Incidence
>50	79%
>60	62%
>70	26%

Age	Median OS
<50 (21%)	83 M
50-69 (53%)	25 M
>70 (26%)	6 M

Median OS for the whole group doubled from 12.5 M in 1970s to 26 M in 2010s

Median OS for age >70 has not changed last 40 years – 6 months

Neuro-Onc 2018;20(5):687-694

Ibrutinib monotherapy in R/R PCNSL/SCNSL

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Clinical Trial	Phase	Treatment	Median F/U	Total accrual	ORR/CR+CRu	mPFS	mOS
Soussain et al.	II	Ibrutinib 560 mg qd	25.7 M	52 with R/R PCNSL or PVRL	52%/19%	3.3 M	14.4 M
Grommes et al.	I	Ibrutinib 560-840 mg qd	15.7 M	13 with R/R PCNSL	77%/38%	4.6 M	15 M
				7 with R/R PCNSL	71%/57%	7.4 M	NR

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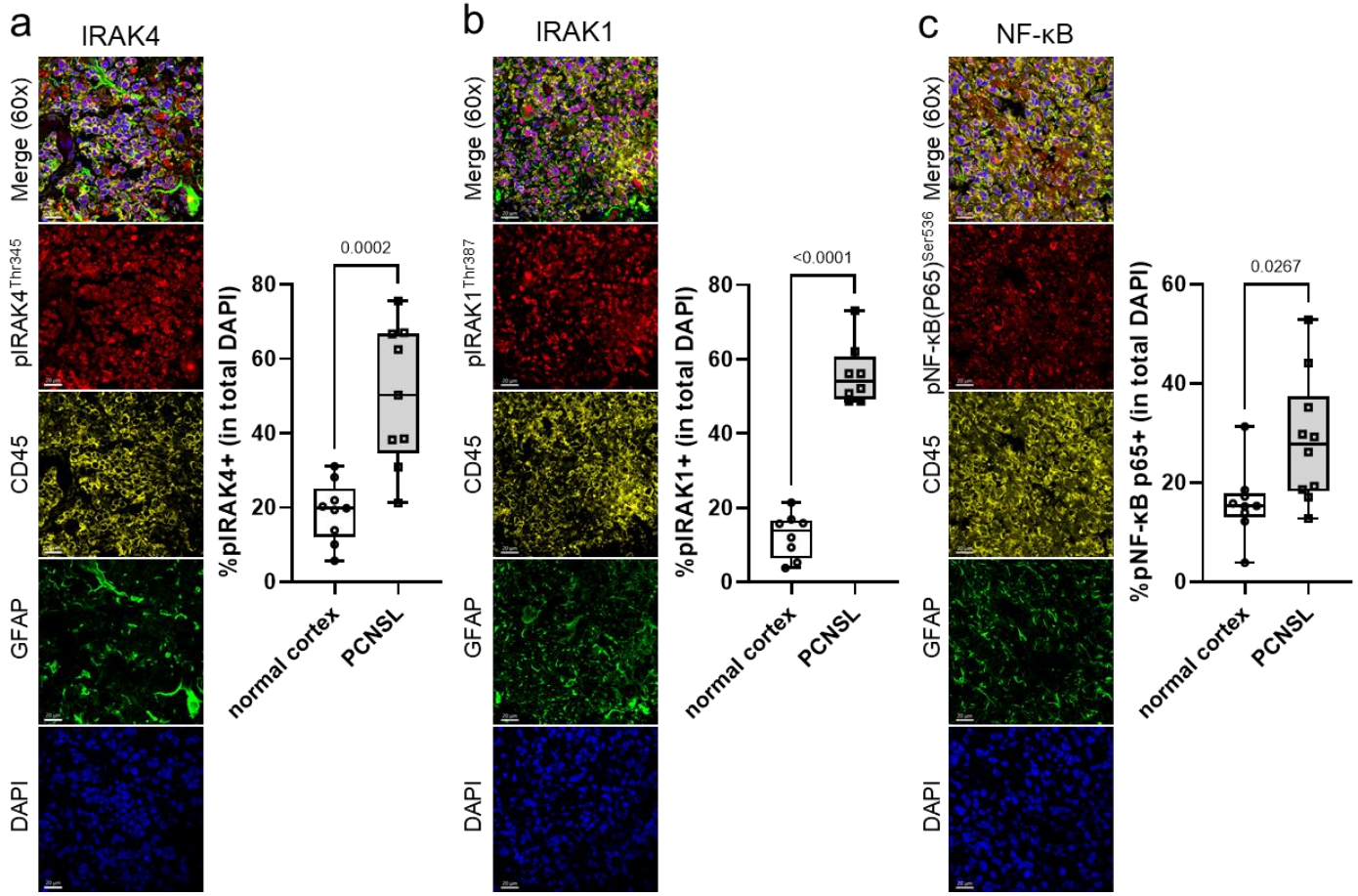
Eur J Cancer 2019;117:121-130
Cancer Discovery 2017;7(9):1018-1029

Pre-clinical evaluation of Emavusertib (IRAK-4 inhibitor)

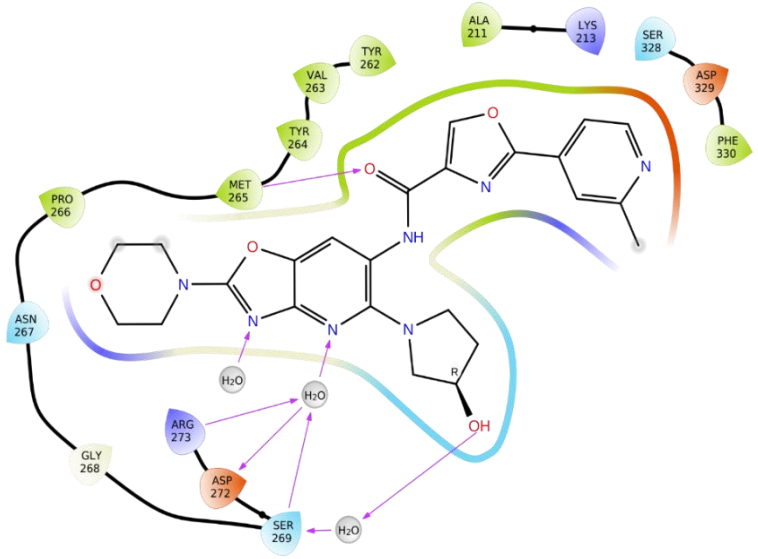
Myddosome expression in human PCNSL



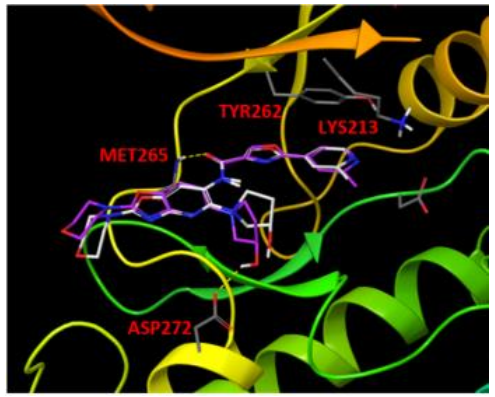
- High levels of p-IRAK4, p-IRAK1, and p-NF-κB
- High CD45 infiltration

Emavusertib (CA-4948)

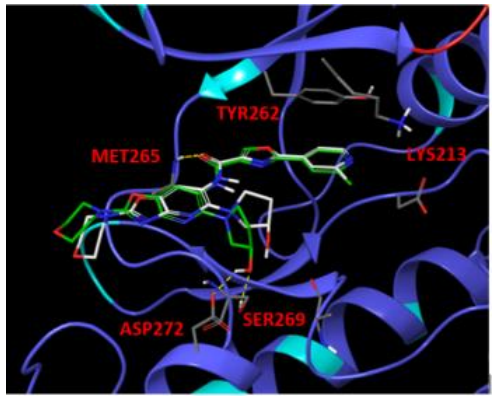
- First-in-class inhibitor
- High binding affinity to human IRAK4 (**23 nM**), high predicted binding affinity to murine IRAK4
- Well tolerated; safety profile allows long-term treatment and combination with other therapies



Human



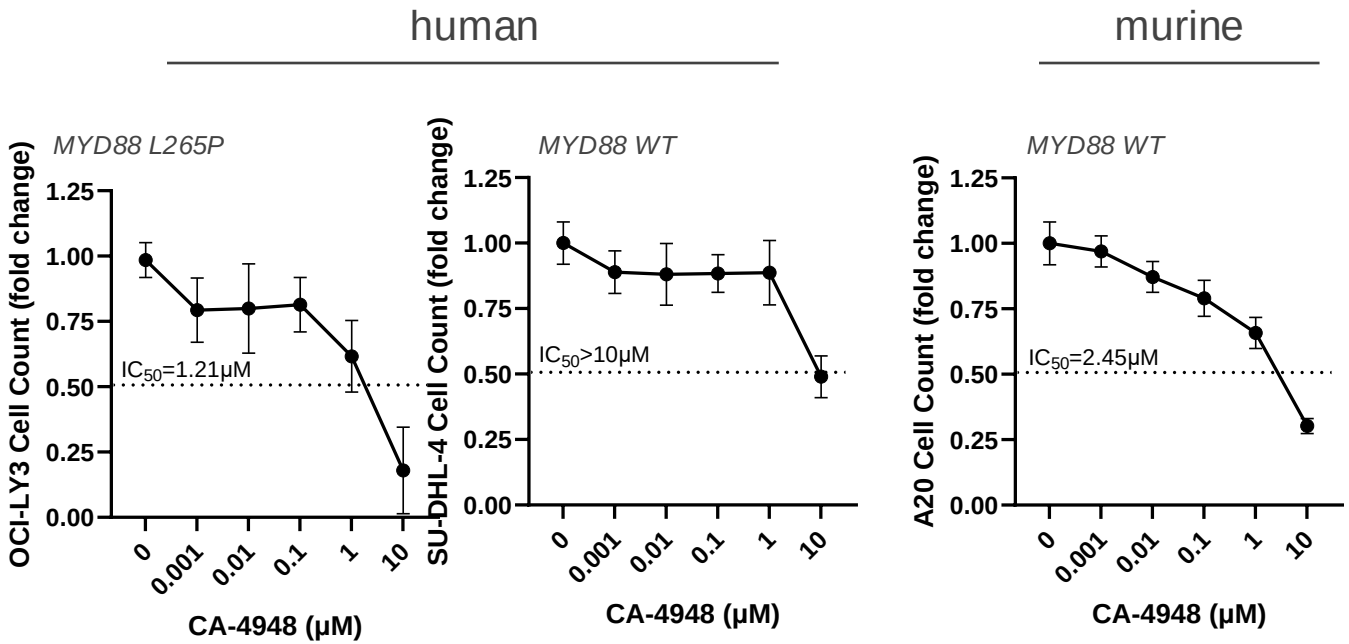
Murine



Clin Can Res. 2023; (29)

Emavusertib anti-lymphoma activity

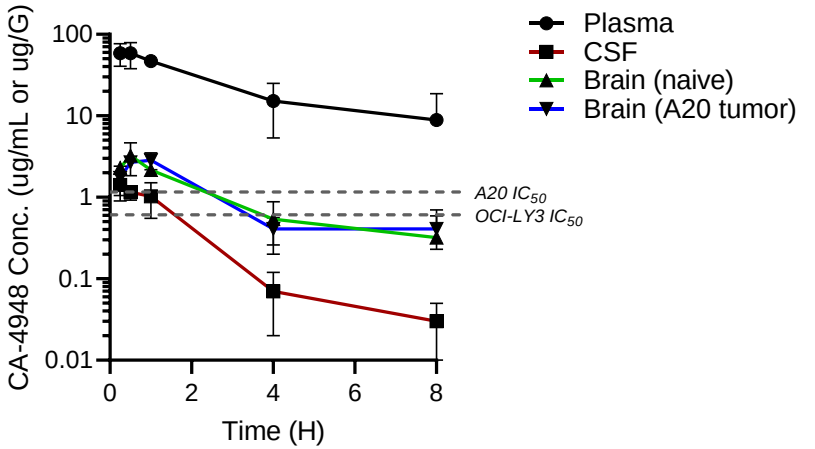
- Dose-dependent decrease in lymphoma proliferation
- MYD88 L265P sensitivity
- Anti-tumor activity in immune-competent *MYD88* WT lymphoma



CNS penetration (preclinical)

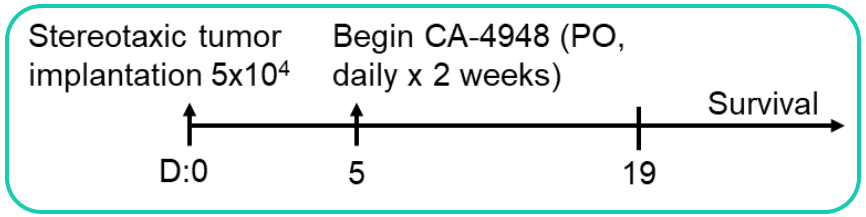
- Emavusertib can cross the BBB
- Relevant therapeutic dose levels detected in naïve parenchyma and CSF
- No notable changes in permeability in tumor-bearing mice

LC-MS/MS detection of CA-4948 in murine CNS

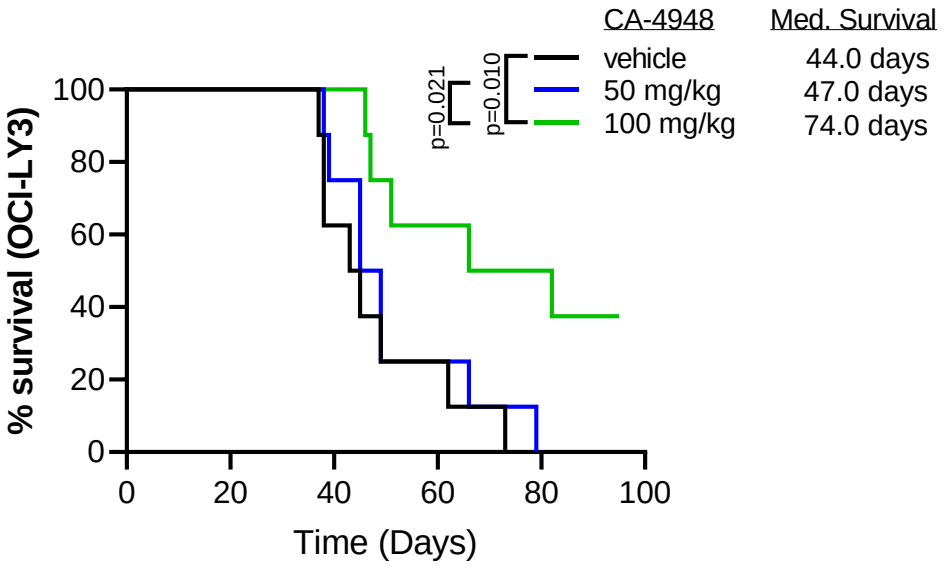


Parameter	Units	Plasma	CSF (Naïve)	Brain (Naïve)	Brain (Tumor)
C_{max}	µg/mL or µg/g	60.3 ± 19.26	1.42±0.52	3.25±1.41	3.22±0.18
T_{max}	h	0.38 ± 0.14	0.25	0.5	0.83±0.29
$T_{1/2}$	h	2.73	1.33	1.39	1.19
$AUC_{0\text{-}8\ h}$	h*µg/mL or h*µg/g	189.51	2.91	8.09	8.68
$AUC_{0\text{-}\infty}$	h*µg/mL or h*µg/g	224.46	2.96	8.72	9.39
Brain to plasma ratio	%		1.53	4.26	4.95

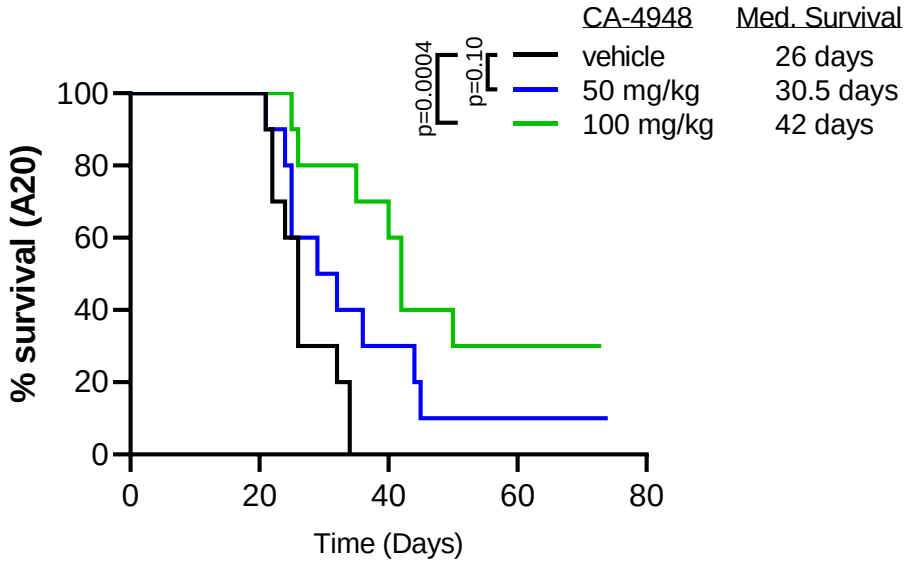
Emavusertib Preclinical PCNSL anti-tumor activity



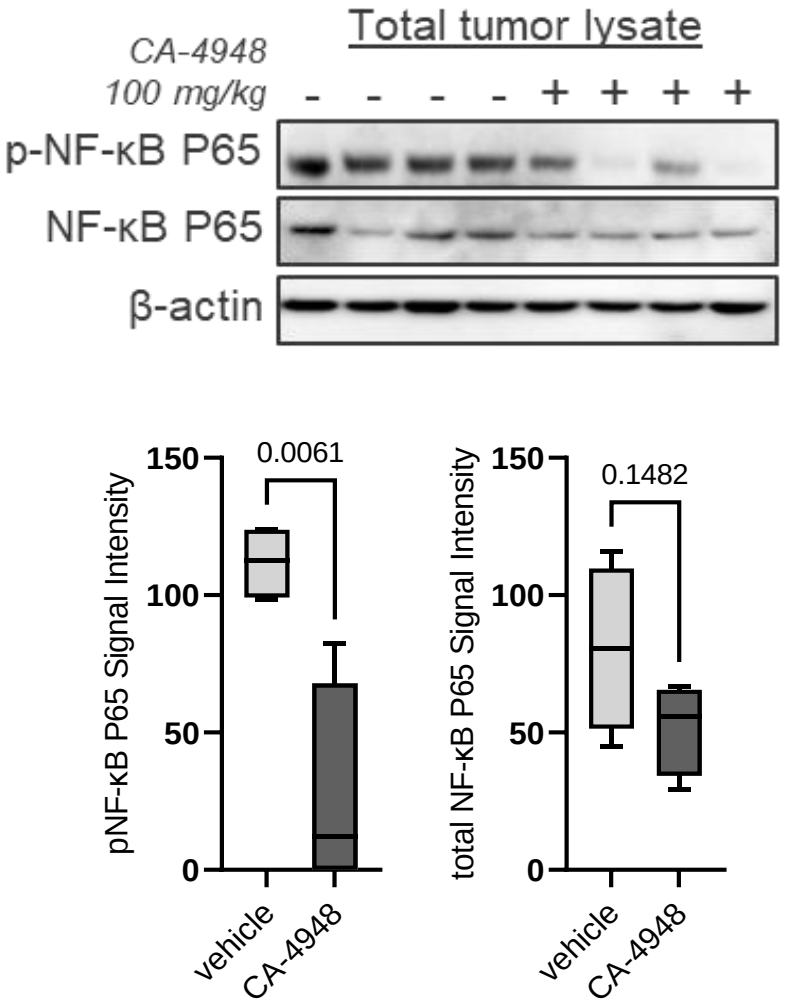
Human MYD88 L265P

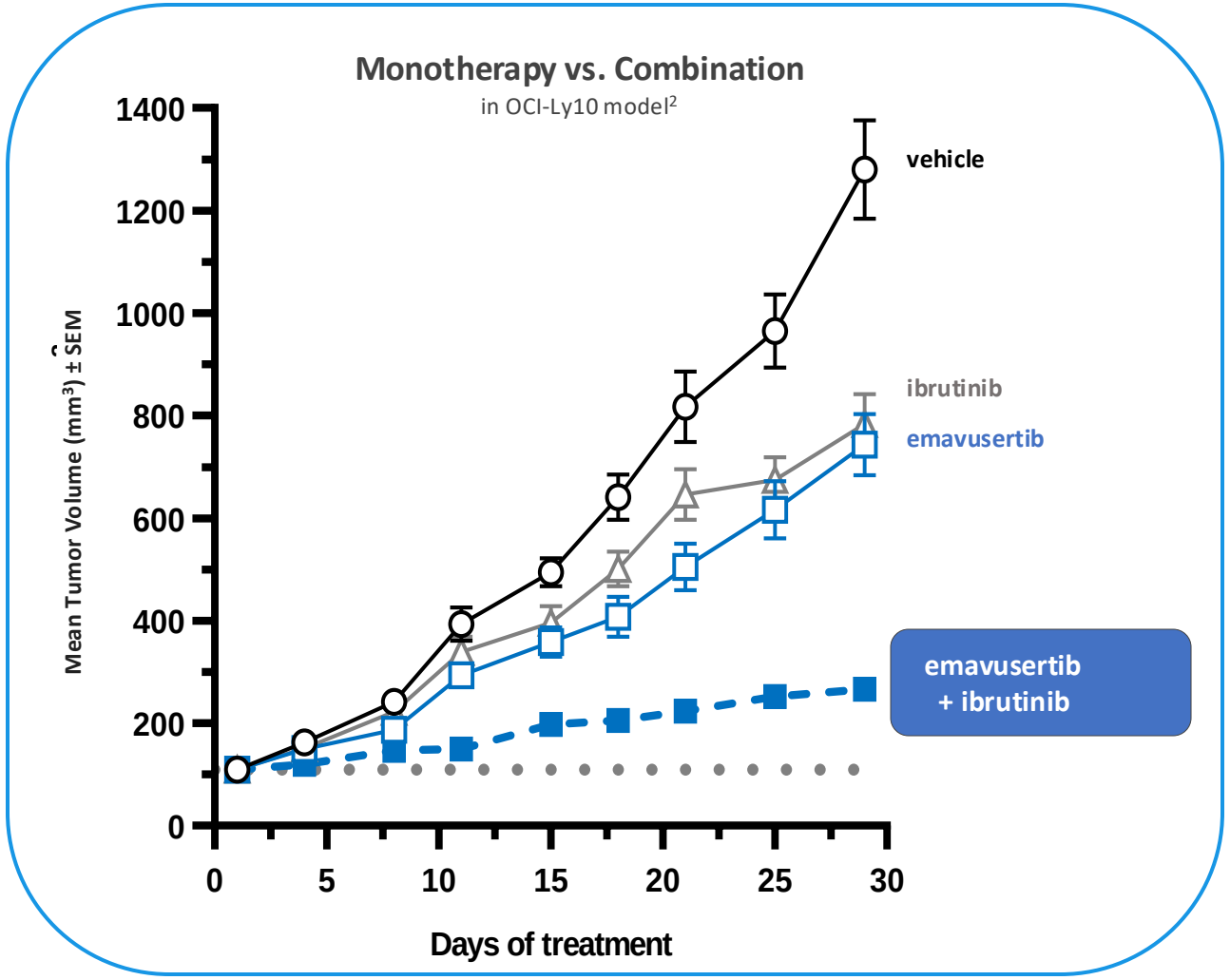


Murine MYD88 WT



NF-κB biomarker downregulation





Booher et al. Waldenström Roadmap Symposium 2019

TakeAim Lymphoma

Open-label expansion trial evaluating the safety, PK/PD, and clinical activity of emavusertib (CA-4948) + ibrutinib in R/R primary CNS lymphoma

NCT03328078

TakeAim Lymphoma

Study Progress – Enrolling into PCNSL Expansion

Complete

Part A1
Monotherapy Dose Escalation (MTD)

First patient enrolled:
January 2018

Complete

Part A2
Combination Dose Escalation

emavusertib (100 - 300 mg BID)
+
ibrutinib (420 - 560 mg QD)

First patient enrolled:
February 2021

Enrolling

Part B
PCNSL Expansion Cohort

emavusertib (100 - 200 mg BID)
+
ibrutinib (560 mg QD)

First patient enrolled:
October 2023

TakeAim Lymphoma PSCNL Expansion Study Design

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Study Objectives

Study Population

Primary CNS Lymphoma

ECOG ≤ 2

Age ≥ 18 years

Dosing

Oral, BID

28-day cycles

emavusertib
(100 - 200 mg BID)
+
ibrutinib (560 mg QD)

Primary

MTD

RP2D

Safety

Secondary

PK profile

Preliminary anti-cancer activity

Study Phases

✓ **Part A1 Monotherapy Dose Escalation**

✓ **Part A2 Combination Dose Escalation**

Part B PCNSL Expansion Cohort [ONGOING]

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TakeAim Lymphoma

Well-tolerated and manageable adverse event profile at multiple dose levels

Treatment-related adverse events (TRAEs) Grade ≥ 3 in all TakeAim Lymphoma trial patients

Grade 3+ Treatment-Related Adverse Event Occurred in >1 Patient	100 mg BID+IBR	200 mg BID+IBR	300 mg BID+IBR	Total
N (%)	**(N=2)**	**(N=10)**	**(N=7)**	**(N=19)**
# patients having grade 3+ TRAEs	1 (50)	7 (70)	6 (86)	14 (74)
Platelet count decreased		2 (20)	1 (14)	3 (16)
Alanine aminotransferase increased		1 (10)	1 (14)	2 (11)
Aspartate aminotransferase increased		1 (10)	1 (14)	2 (11)
Fatigue		1 (10)	1 (14)	2 (11)
Hyponatraemia		2 (20)		2 (11)
Lipase increased	1 (50)	1 (10)		2 (11)

Emavusertib in combination with ibrutinib continues to exhibit a manageable and acceptable safety profile, in heavily pretreated patients, including BTKi-naïve and BTKi-experienced patients.

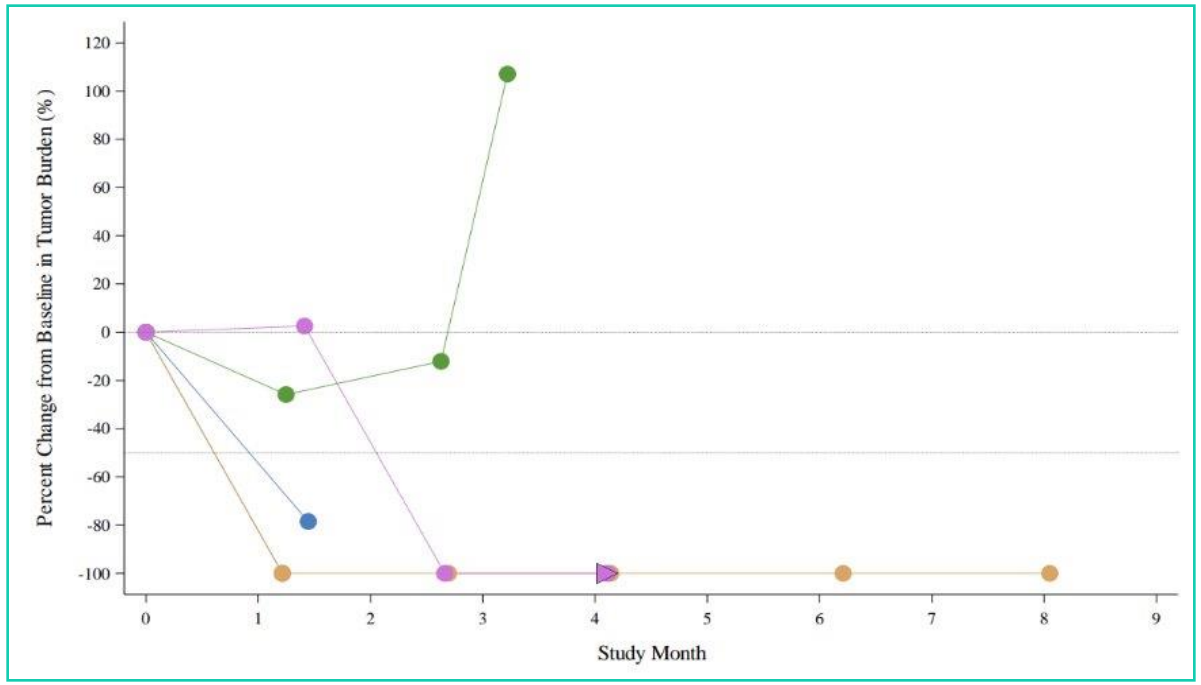
CURIS

Grommes C, et al. Poster presented at the 2023 ASH Annual Meeting.

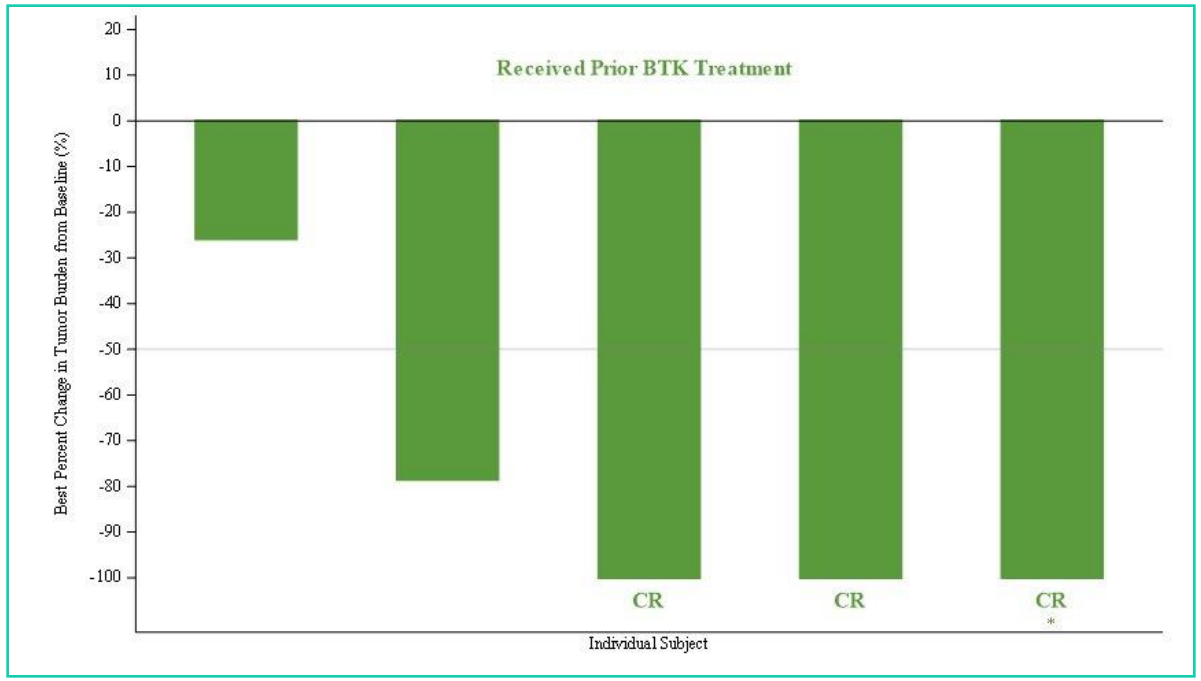
TakeAim Lymphoma: Clinical Outcomes PCNSL

IRAK4 | Symposium

Change in tumor burden over time



Best Percent change in tumor burden



At the October 12, 2023, data cutoff

- **6 patients with PCNSL had received treatment**
- **Of 5 evaluable patients, all previously treated with BTKi, 3 achieved CR (3/5, 60%)**
- **One patient had a durable response for approximately 7 months**

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Grommes C, et al. Poster presented at the 2023 ASH Annual Meeting.

PCNSL Patient Case Study

PCNSL Expansion – CA-4948 100 mg BID + Ibrutinib 560 mg QD

Patient Background:
- 53 year old, Male
- Diagnosis: PCNSL diagnosed on 30June2020
- Past Medical History: Unremarkable

Condition:

Baseline: Depression, elevated LFTs, loss of appetite, cerebral edema, mixed IBS, essential hypertension, hiatal hernia, GERD and obstructive sleep apnea

Con Meds: ondansetron, sertraline, tadalafil and OTCs for gastroesophageal reflux and nausea

Prior Tx: (1) MTX, rituximab, Ara-C, thiotepa, high dose BCNU (PR), WBRT & ASCT

(2) ibrutinib (CR then relapse)

Relapsed: 29Nov2022 with 1 target lesion 13 x 12 mm

Treatment Regimen

Date	Intervention
Feb 24, 2023	Started emavusertib 100 mg BID and ibrutinib 560 mg QD
Jun 30 – Jul 9, 2023	Emavusertib was interrupted due to Gr 3 elevated lipase; resumed at same dose level
Feb 6 – Feb 9, 2024	Emavusertib was interrupted due to Gr 1 vomiting; resumed at same dose level

TEAEs:
- Gr 3 amylase increased, and Gr 3 lipase increased: dose interruptions

Outcome:
- Amylase increase recovered to Gr 1 and lipase resolved
- Brain lesion was SD at the end of cycle 2, and disappeared by the end of cycle 4 and onward
- Most recent MRI was performed in Feb '24 and patient is still CR

- Time on the study treatment for > 400 days, well tolerated without major long-term safety concerns
- Duration of CR exceeded ~8 months

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Grommes C, et al. Poster presented at the 2024 ASCO Annual Meeting.

PCNSL patient who achieved CR on ibrutinib + emavusertib

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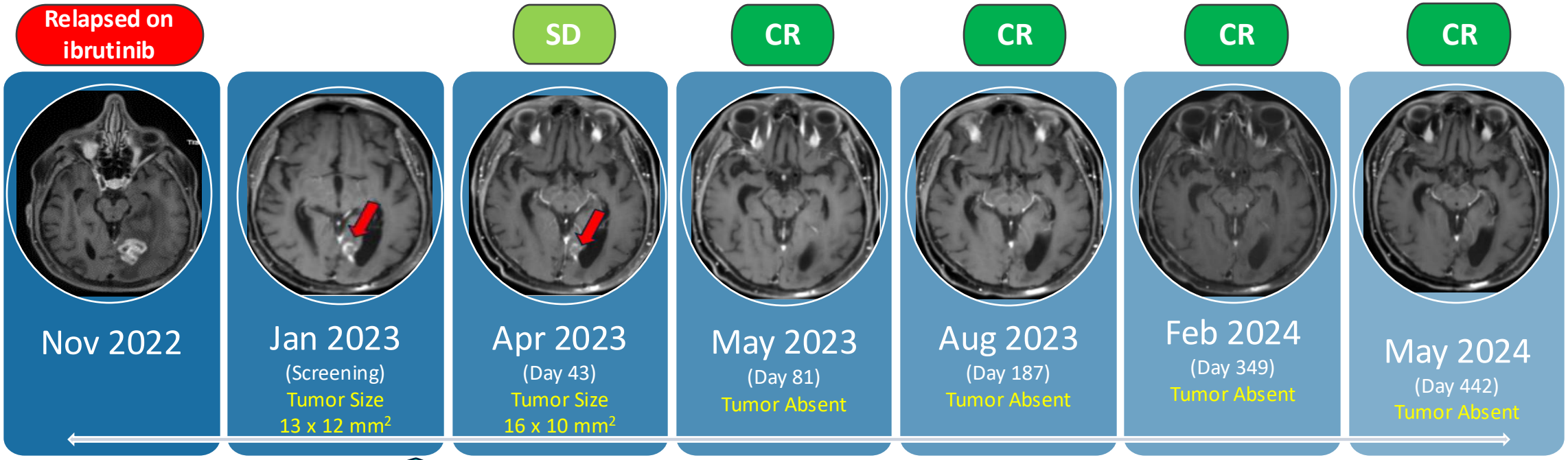
Previous treatments: MATRIX, HD BCNU/Thiotepa-ASCT, whole brain radiation, ibrutinib



Axial Magnetic Resonance images (MRI) showing pre-treatment and post-treatment PCNSL brain images from one R/R PCNSL patient. After two cycles of emavusertib + ibrutinib, the patient showed stable disease (SD). Complete responses (CR) with absent lesions have been seen after cycle 4.

Consistent with our previous findings, these data support the hypothesis that emavusertib can re-sensitize patients to BTKi therapy, marking a significant advancement in R/R PCNSL treatment.

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Grommes C, et al. Poster presented at the 2024 ASCO Annual Meeting.

Genomic profile (GTC Hematology Plus)

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Detected Genomic Alterations				
CD79B	ETV6 (2 mutations)	MYD88	KMT2D	PBRM1
TBL1XR1	IDH1	Chromosomal structural analysis shows: 3p-, 8q-, +9 with bi-allelic deletion of CDKN2A/B), +12, +13, +16, 18q+, and +21.	Expression profiling suggests ABC cell of origin, more aggressive subtype.	

Results Summary

- **-Mutations in CD79B, ETV6 (2 mutations), MYD88, KMT2D, PBRM1, TBL1XR1, and IDH1 genes**
  -Chromosomal structural analysis shows: 3p-, 8q-, +9 with bi-allelic deletion of CDKN2A/B), +12, +13, +16, 18q+, and +21.
  -Increased B-cell markers
  -No significant increase in BCL1, BCL2, or MYC mRNA.
  -Expression profiling suggests ABC cell of origin, more aggressive subtype.

  -These findings are consistent with diffuse large B-cell lymphoma, ABC cell of origin, more aggressive subtype.

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Future directions for BTKi + IRAK4i in PCNSL

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- Concurrent therapy in relapsed/refractory PCNSL
- Concurrent therapy in newly diagnosed PCNSL
- Maintenance therapy in high-risk patients post-induction, ASCT, CAR-T
- Combination with other therapeutic agents- IMiDs and chemotherapy

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Ibrutinib monotherapy in newly diagnosed PCNSL

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Patients	Continuous CR
#1	76 M
#2	61 M
#3	18 M
#4	7 M

Tun HW; Personal communication

Genomic Profile of Patient #1 with CCR for 76 months (GTC Hematology Plus)

IRAK4 | Symposium

Detected Genomic Alterations				
PIM1 (10 mutations)	RET	SOCS1	CD79B	TET2
GNAS	ETV6	MYD88	Chromosomal structural analysis shows: 1q+, 2q-, +3, -5, -6, 8q-, 11q+, 12q +, 17p-(TP53 bi-allelic deletion), 19p-, 19q+, and 22q-.	Expression profiling is consistent with ABC cell of origin, aggressive subtype (ABC2).

Heterogeneity
There is a dominant abnormal clone with PIM1 (p.Lys186Asn) mutation. The PIM1 (9 mutations), RET, SOCS1, CD79B, TET2, GNAS, ETV6, and MYD88 mutations are detected in subclones.

Expression	
Increased B-cell markers	Marked increase in Ki67 mRNA
No significant increase in BCL1, BCL2 or MYC mRNA	No increase in ALK mRNA

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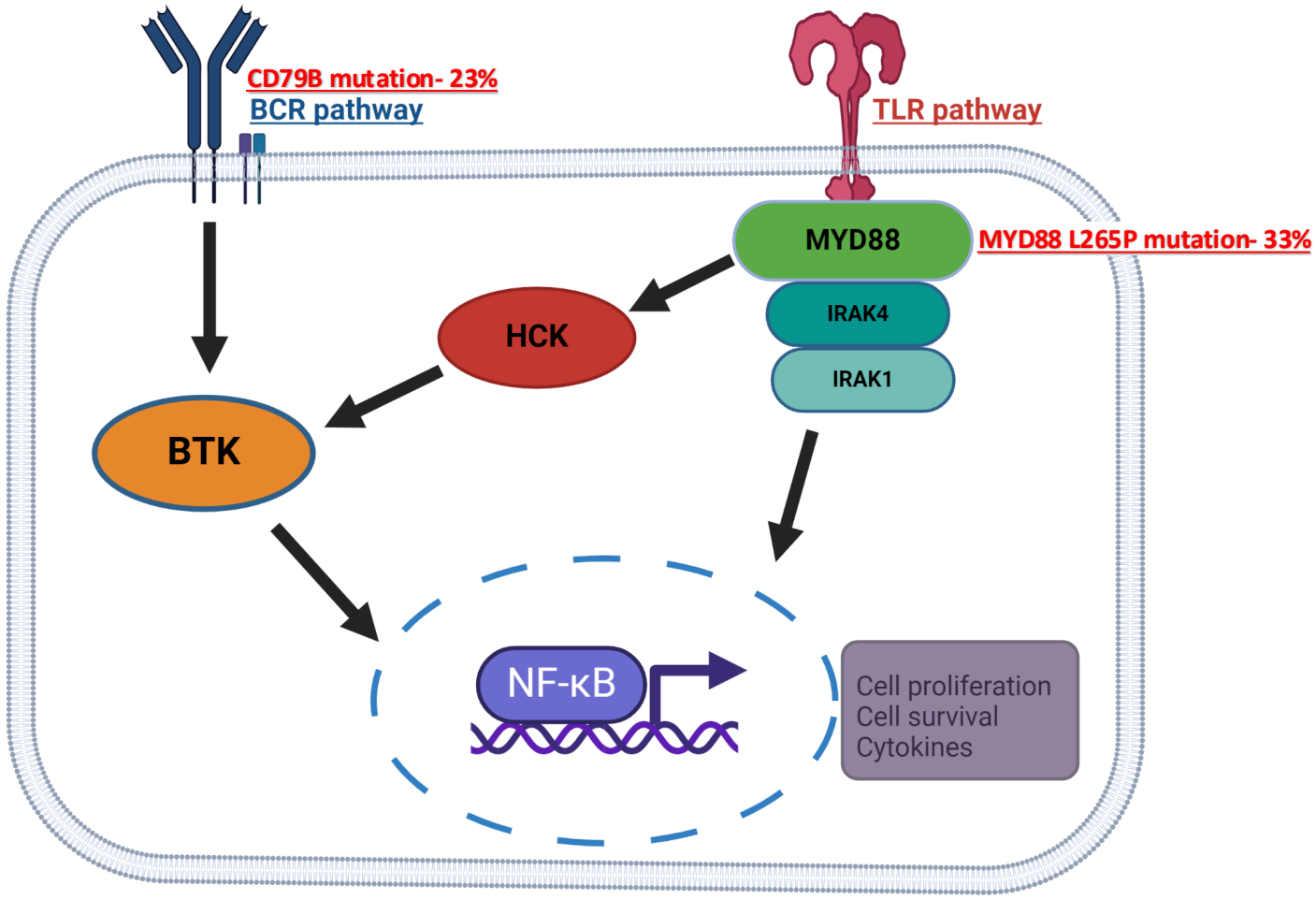
ABC-DLBCL



MCD and N1 subtypes of DLBCL highly sensitive to ibrutinib

CARD11 and TNFAIP3 mutations in BCR pathway associated with resistance to ibrutinib

Ibrutinib monotherapy in R/R ABC-DLBCL

	N=38
ORR	37%
CR	16%
DOR	4.83 M
mPFS	1.64 M
mOS	6.41 M

4/6 complete responders in remission longer than 1 Y

Nature 2015;21:922

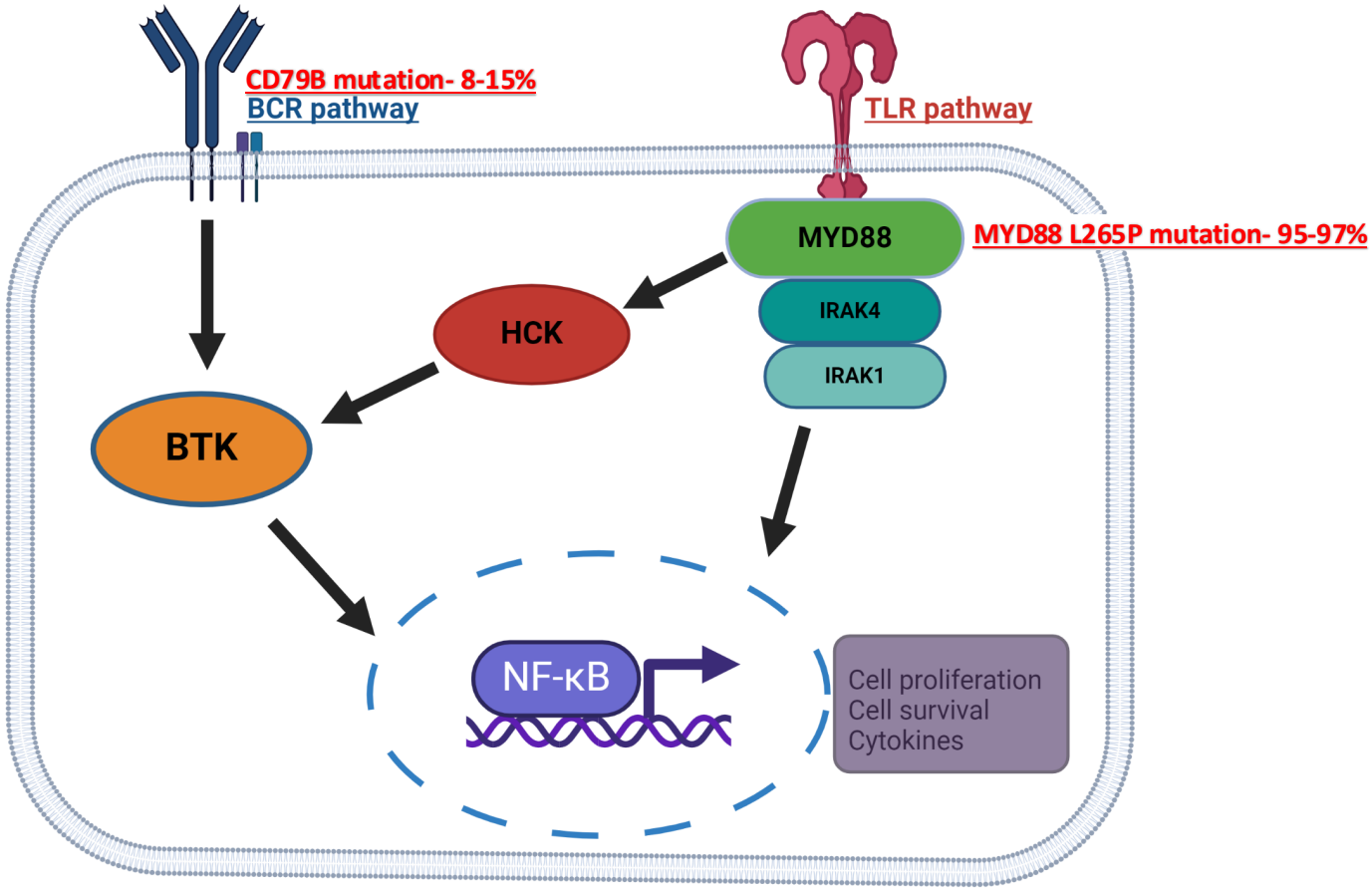
Young patients (age ≤60 years) with non-GCB DLBCL (Phoenix trial)

Young patients with MCD or N1 subtypes of DLBCL-

Genetic subtype	3Y Event-free survival
MCD	IRCHOP- 100% RCHOP- 42.9% (p- 0.0105)
N1	IRCHOP- 100% RCHOP- 50% (p-0.0161)

Cancer Cell 2021;39:1643-1653

Waldenstrom Macroglobulinemia

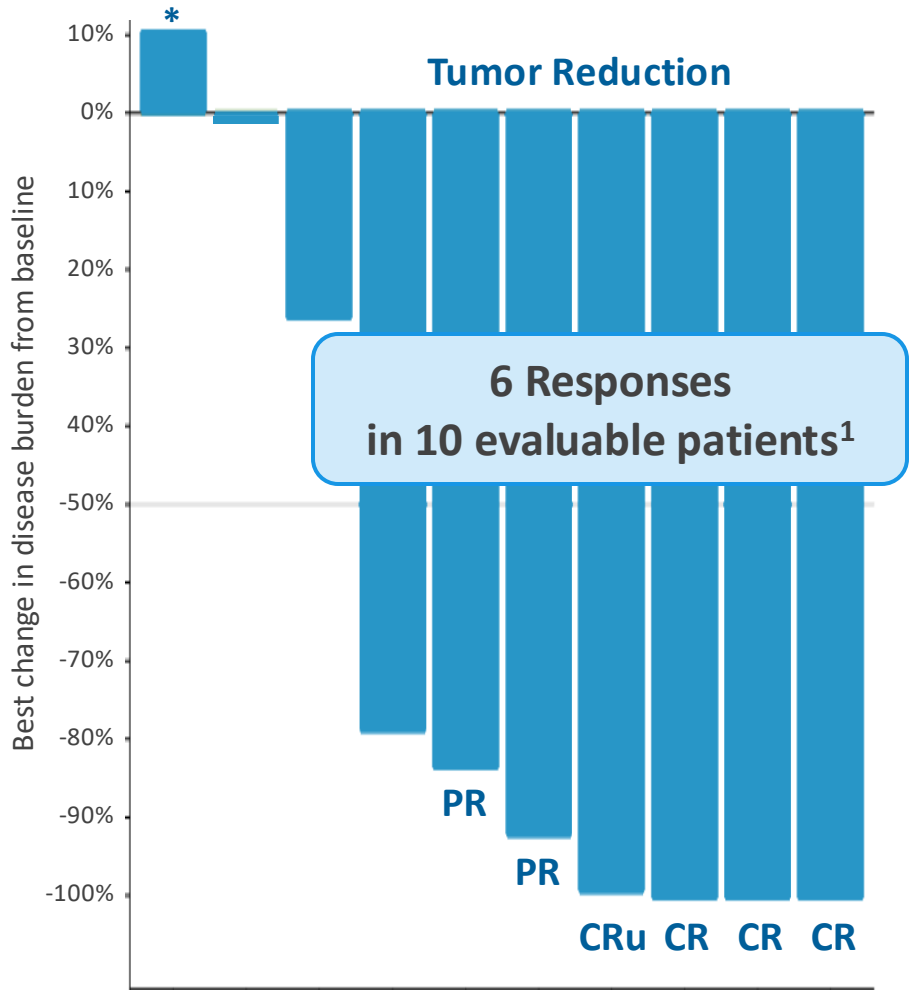


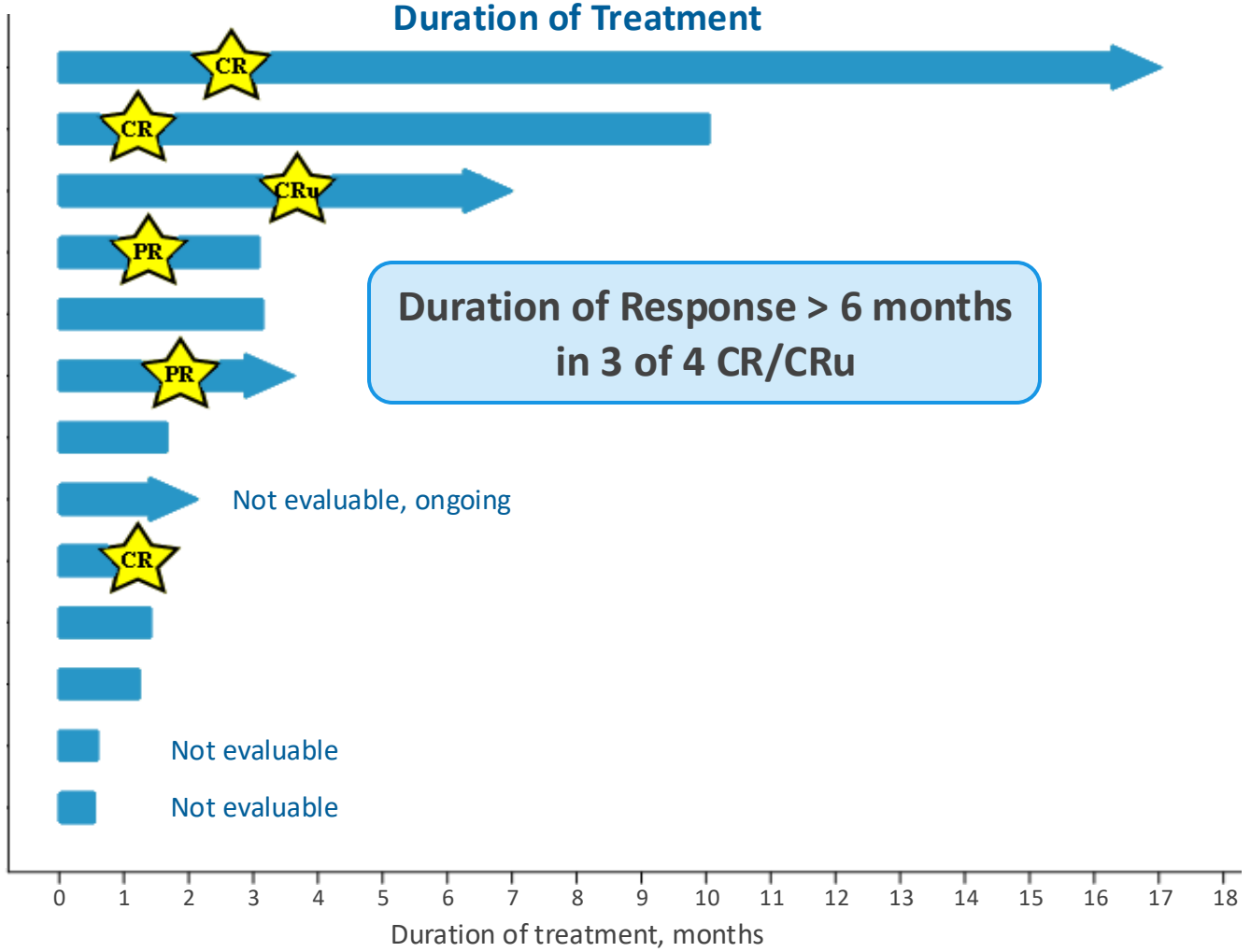
CXCR4 mutation (30-40%) promotes resistance to ibrutinib.
Pathway signature- Oncogenic constitutive activation of BCR and TLR pathways
Activated NFKB signaling

TakeAim Lymphoma

IRAK4 | Symposium

Results in 10 evaluable patients[1] with R/R PCNSL (BTKi-experienced) treated with emavusertib + ibrutinib





[1]Evaluable patients are those who have completed at least one cycle of treatment and received at least one post-treatment assessment. *Indicates best percent change > 10%.

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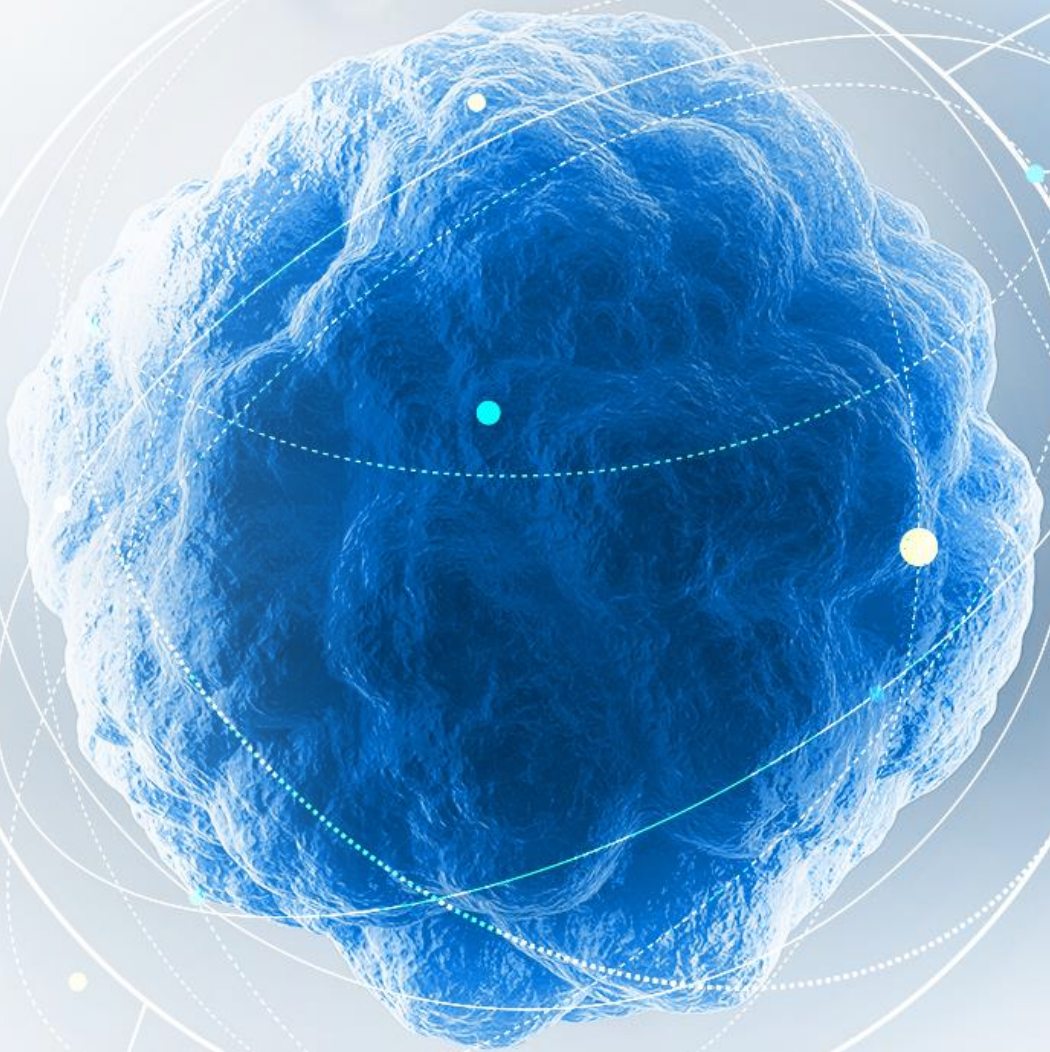
Questions?



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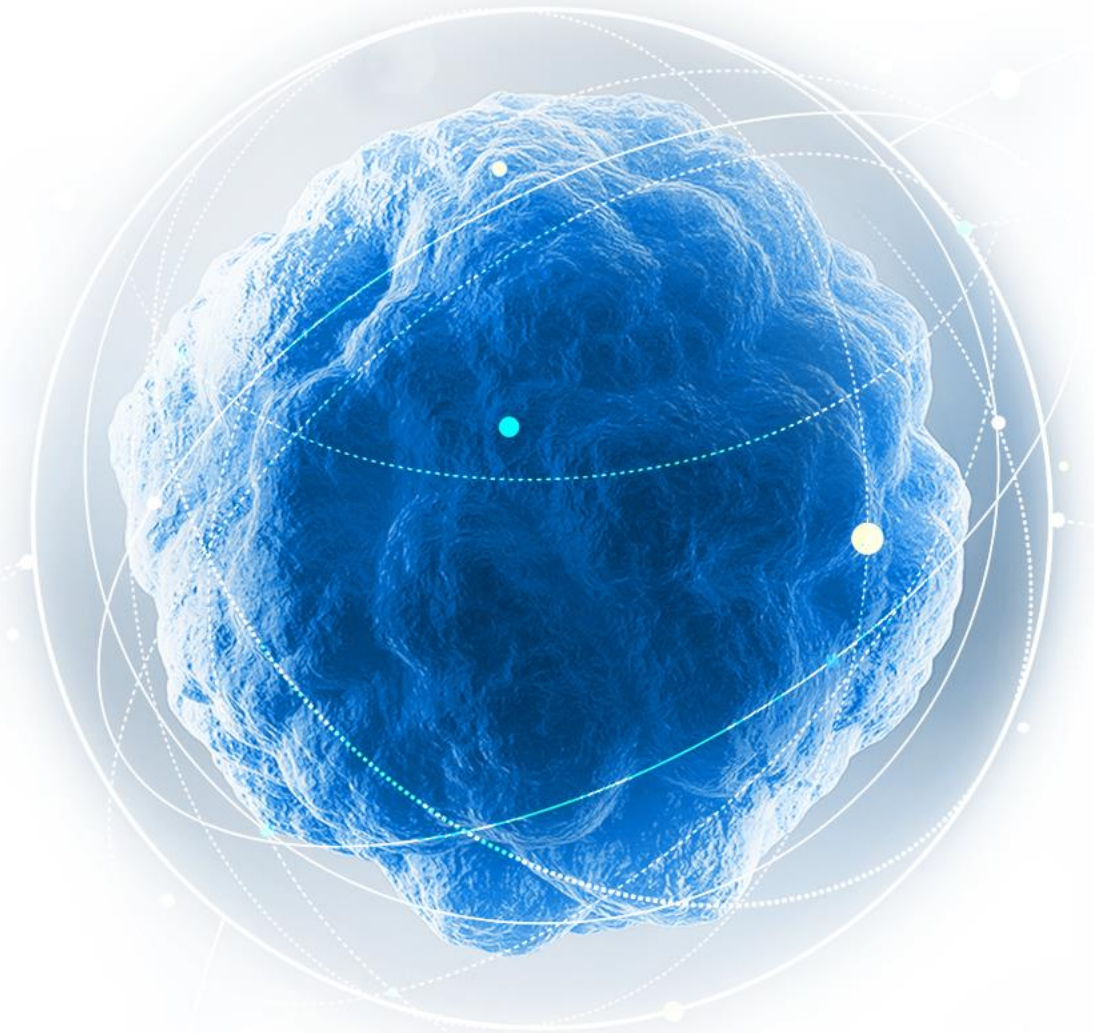
We will now take a short break

Please return in 10 minutes



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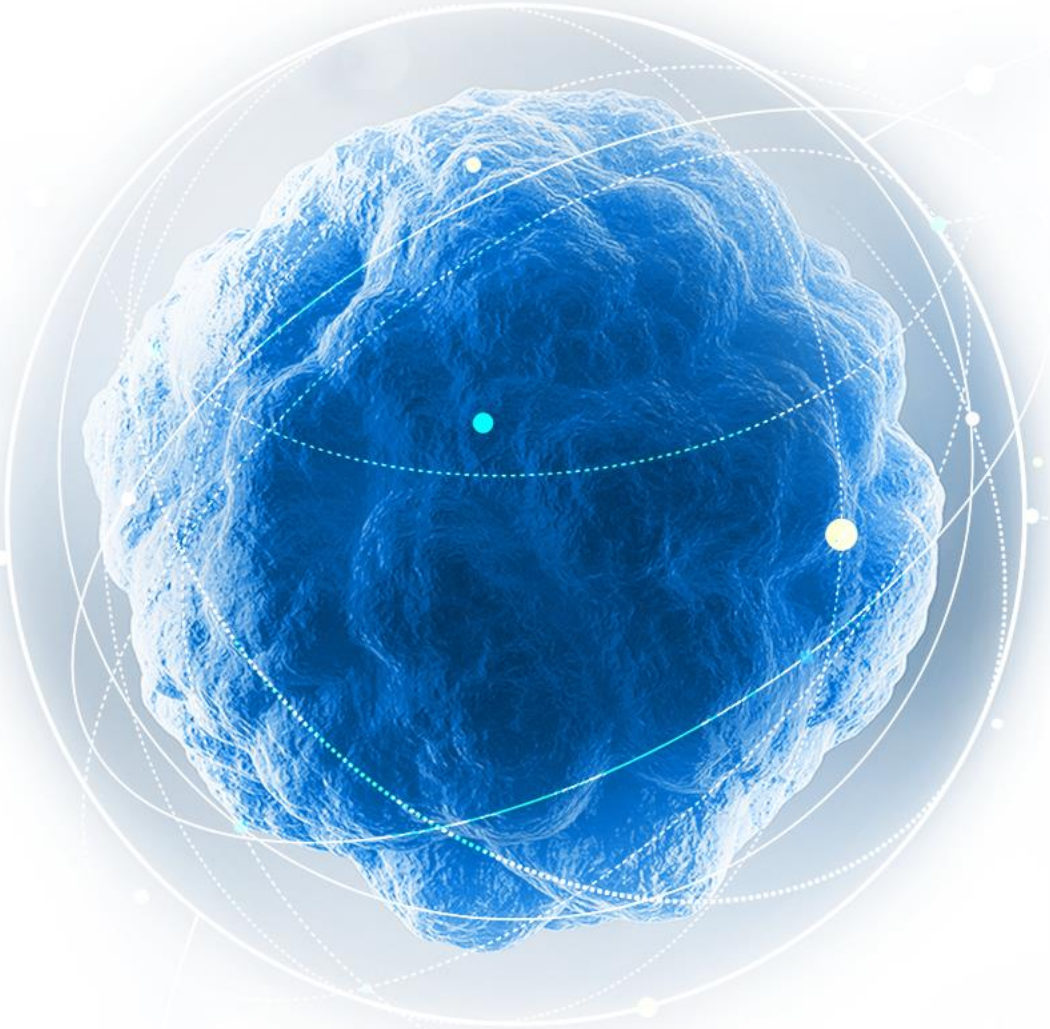
Current and Future Opportunities For IRAK4 Inhibition in Lymphoma Roundtable



Lakshmi Nayak (moderator)

Andrés Ferreri

Han Tun

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Discussion Questions

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- What are unmet needs for patients with NHLs, especially PCNSL?
- By what mechanism does the BTK inhibitor and IRAK4 inhibitor combination potentiate NF-κB blockade?
- How does blocking the TLR-IRAK4 pathway affect BTKi resistance?
- What are current treatment approaches in lymphomas driven by activated MYD88? What are their limitations?
- Do you see potential for emavusertib to overcome BTK resistance in non-MYD88 lymphomas such as mantle cell lymphoma?
- In what specific populations (line of therapy, prior treatment) is emavusertib + ibrutinib being tested in for PCNSL, and why? What are next steps if the expected signal is seen?
- How would a positive result in the PCSNL expansion trial impact 1L therapies, therapy options for elderly patients, or therapy options for the first-relapse population?
  - Would you expect emavusertib to be combined directly with ibrutinib or only after ibrutinib failure?
- Beyond PCNSL, in which other NHLs do you see potential for emavusertib therapy? Are there particular patient populations you would prioritize for this investigation?

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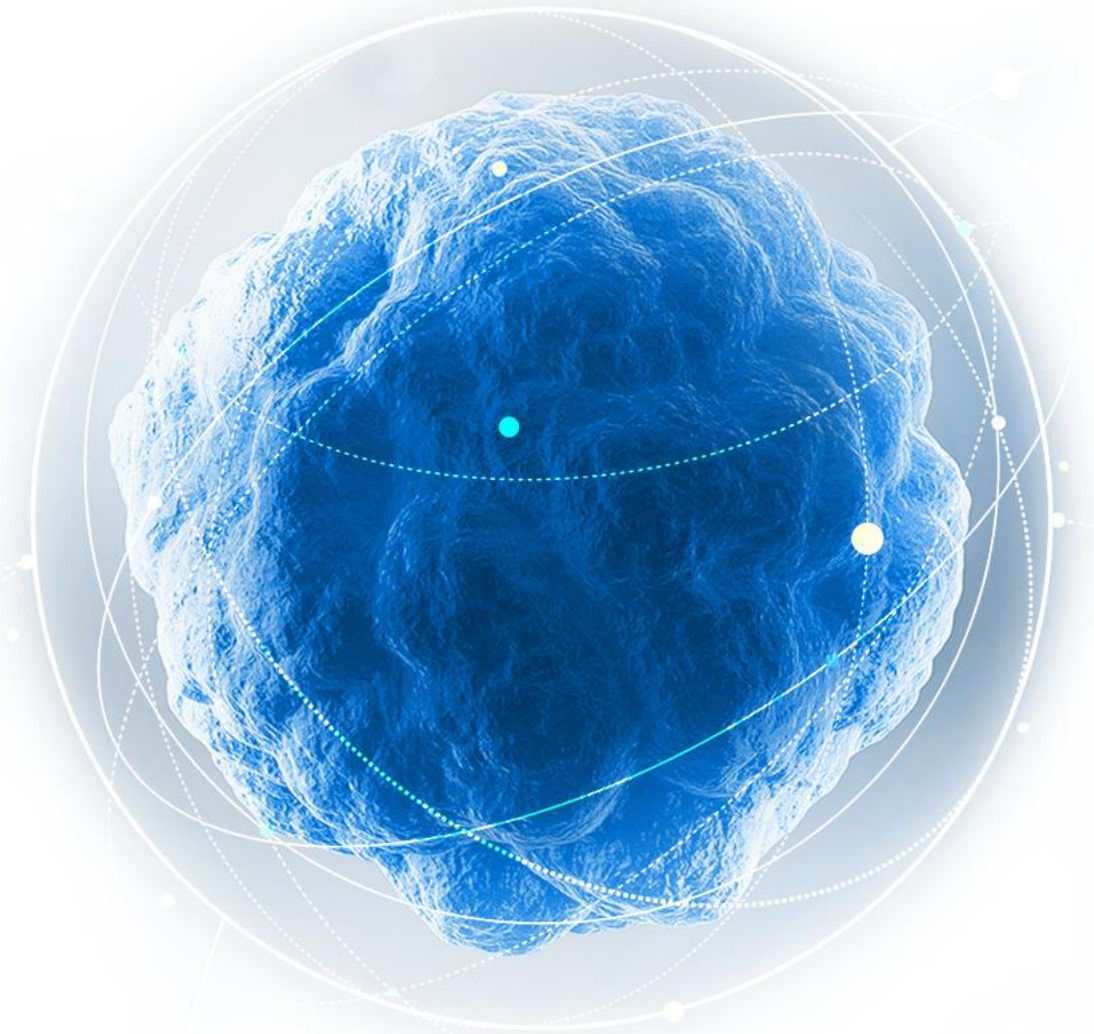
IRAK4 as a therapeutic target in GI cancers



Kian Lim, MD PhD
Professor
Director of GI Oncology
Division of Oncology, Department of Internal Medicine
Washington University School of Medicine in St. Louis

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Disclaimer

IRAK4 | Symposium

- Clinical trials: Merck, BMS, Verastem, Takeda, Biomed Valley, Ipsen, Celgene, AstraZeneca, CURIS, PanCan.
- Advisory: Jacobio, Genentech

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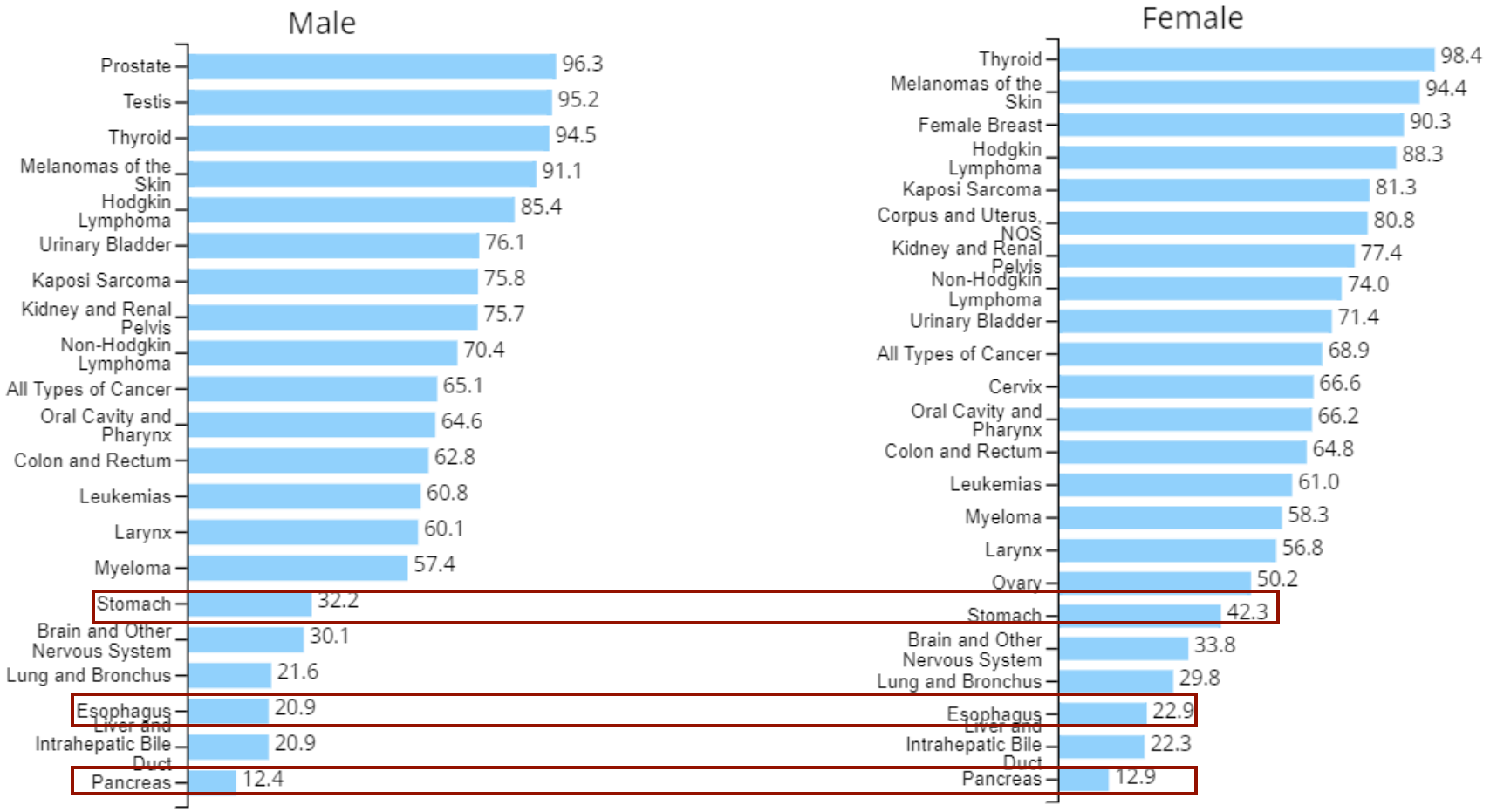
Outline

- **Introduction**
- **Role of IRAK4 in GI cancers**
  - **Pancreatic ductal adenocarcinoma (PDAC)**
  - **Colorectal cancer (CRC)**
  - **Gastric cancer**

5-year Relative Survival (%) by Cancer Type, United States



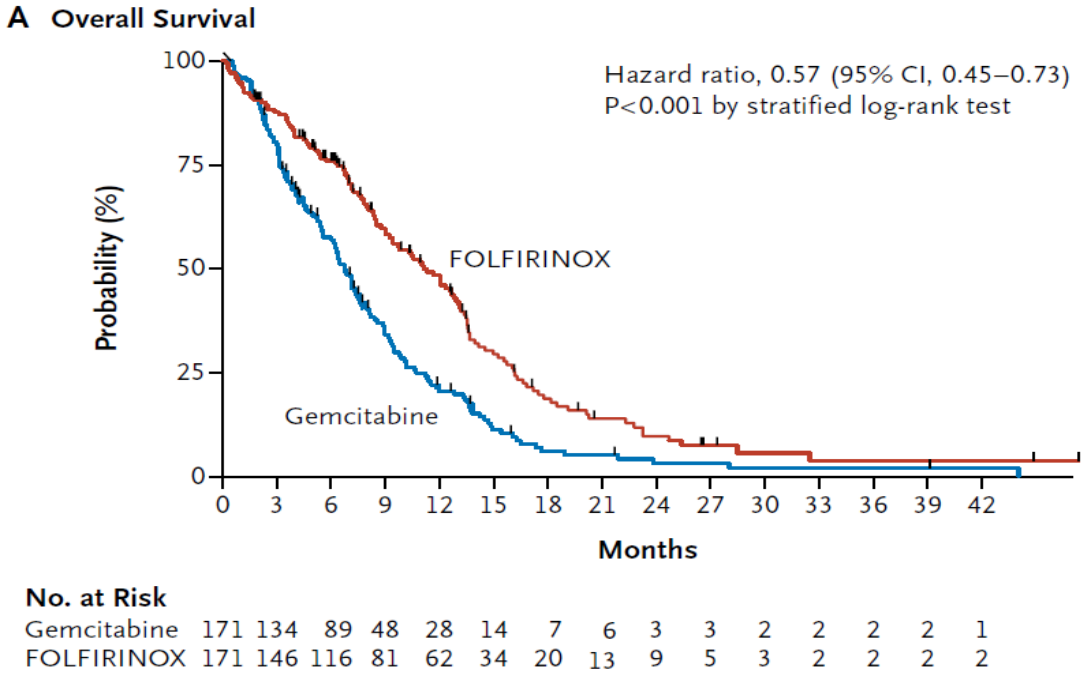
Source - U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2022 submission data (1999-2020): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; https://www.cdc.gov/cancer/dataviz, released in November 2023.

PDAC: We still use chemotherapy for all patients

IRAK4 | Symposium

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

N ENGL J MED 364;19 NEJM.ORG MAY 12, 2011



No. at Risk

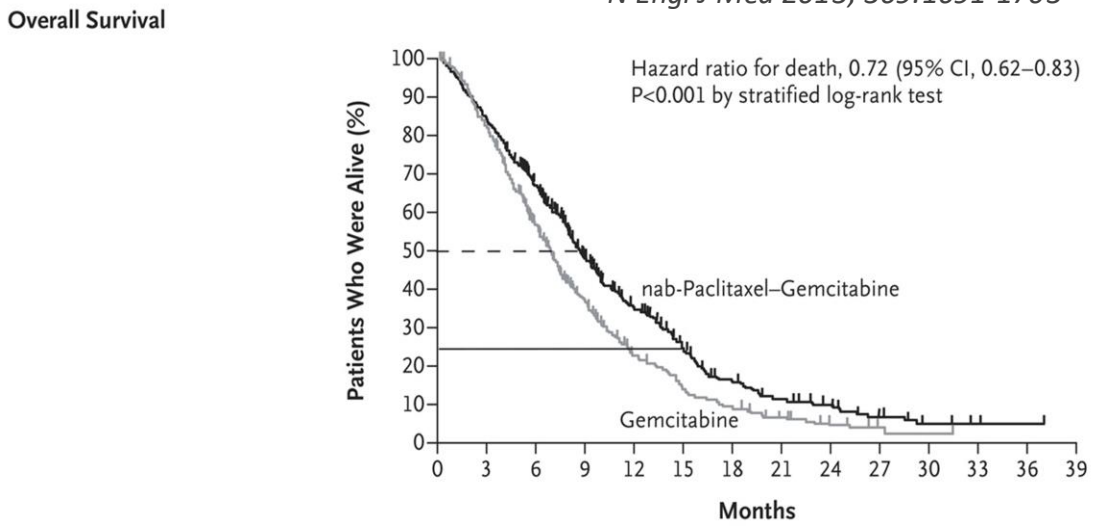
Gemcitabine	171	134	89	48	28	14	7	6	3	3	2	2	2	2	1
FOLFIRINOX	171	146	116	81	62	34	20	13	9	5	3	2	2	2	2

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine

N Engl J Med 2013; 369:1691-1703



No. at Risk

nab-Paclitaxel–Gemcitabine	431	357	269	169	108	67	40	27	16	9	4	1	1	0
Gemcitabine	430	340	220	124	69	40	26	15	7	3	1	0	0	0

Combination chemotherapies are not curative and have significant side effects

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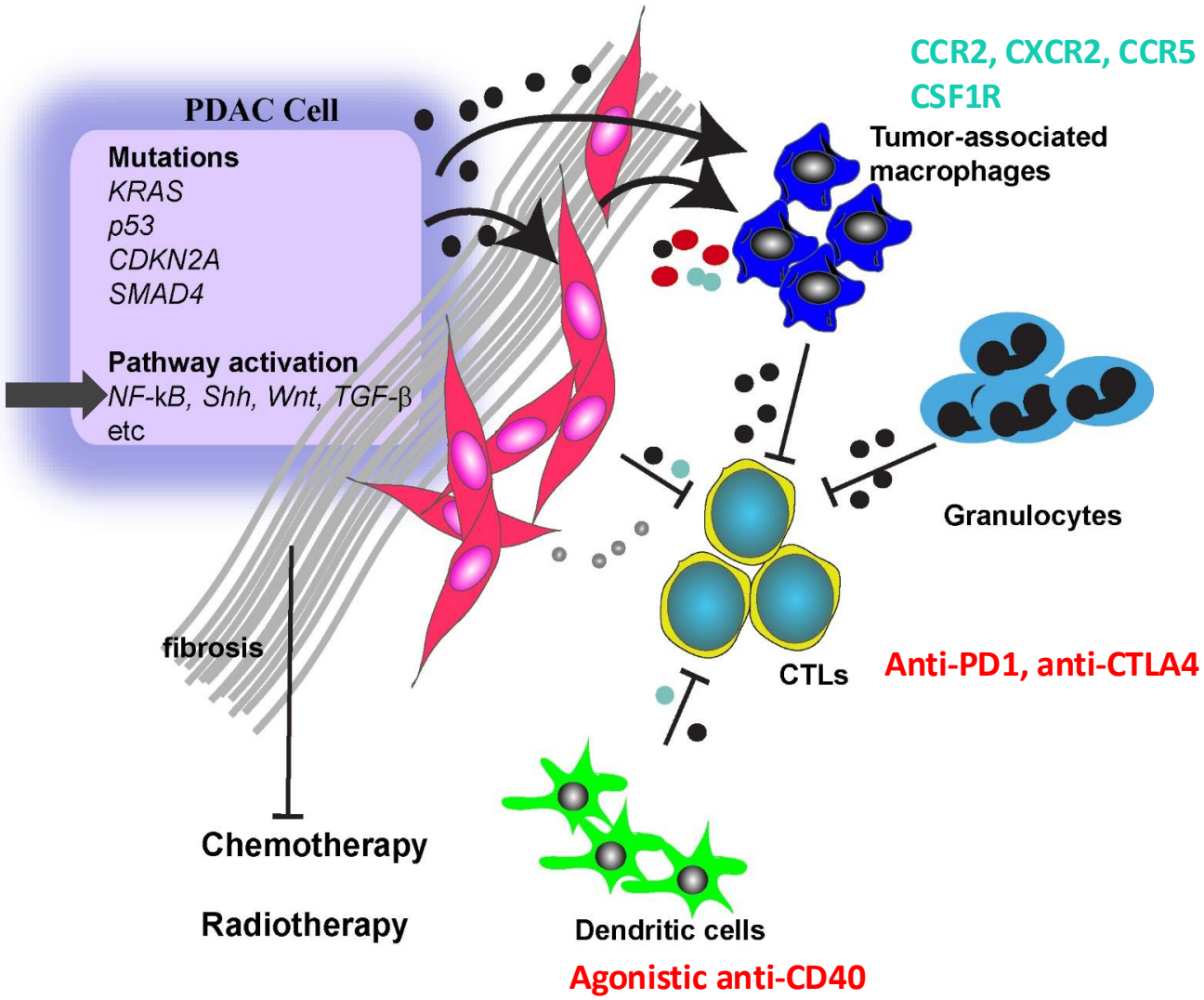
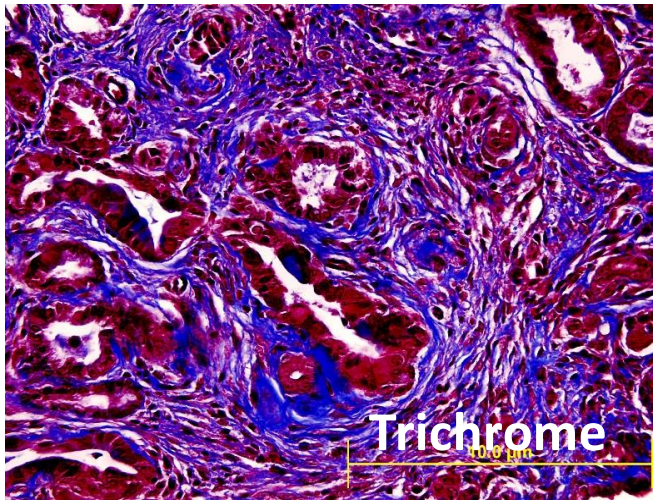
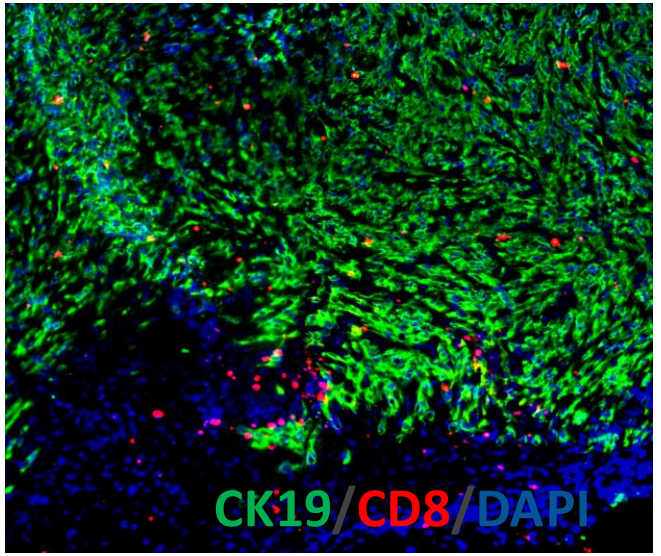
PDAC cells are driven by powerful oncogenes and shielded by a fibrotic stroma



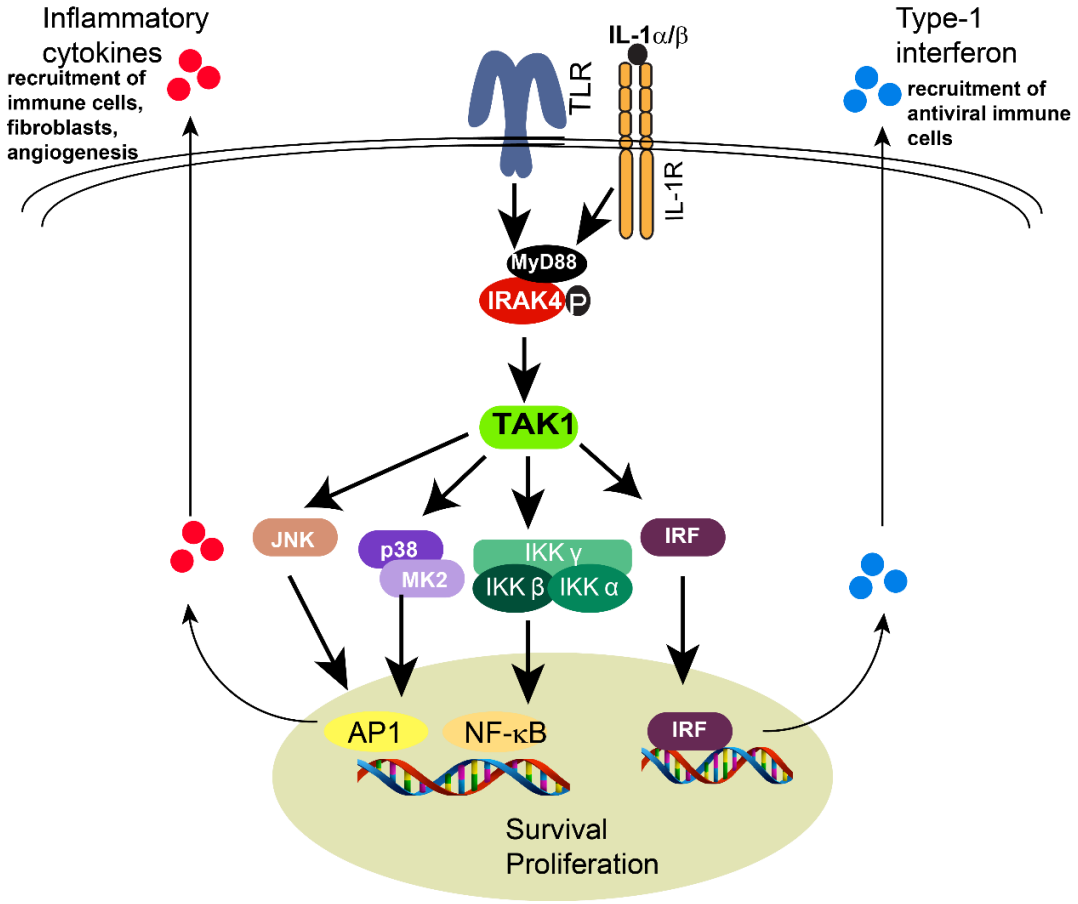




The NF-κB pathway is a therapeutic target in PDAC

- RELA, the p65 subunit of NF-κB, was constitutively nuclear (activated) in **67%** of PDAC and associated with poor prognosis
- Associated with treatment resistance, invasion, metastasis and immune evasion
- Targeted deletion of *IKKβ* abrogates PDAC development in *KRAS/Ink4A* genetic mouse model
- IKK inhibitors are toxic in clinical trials.
- Interleukin-1 Receptor-Associated Kinase 4 (IRAK4) is potentially the new target

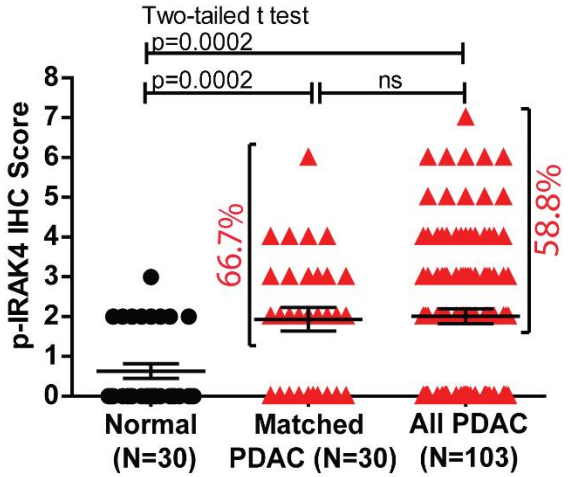
The innate inflammation pathway

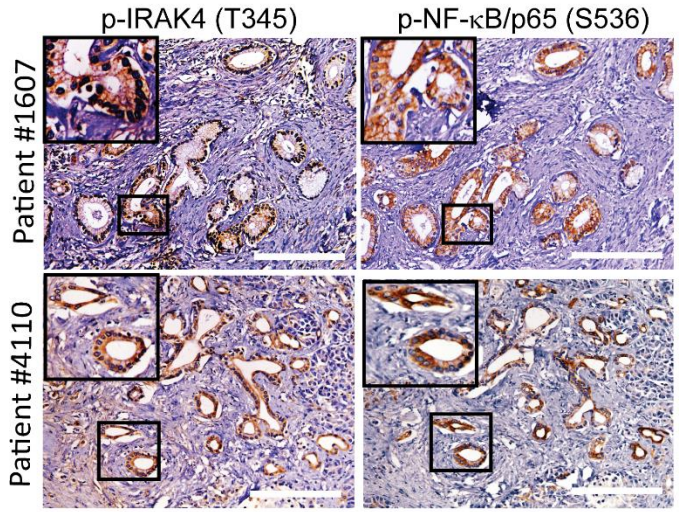


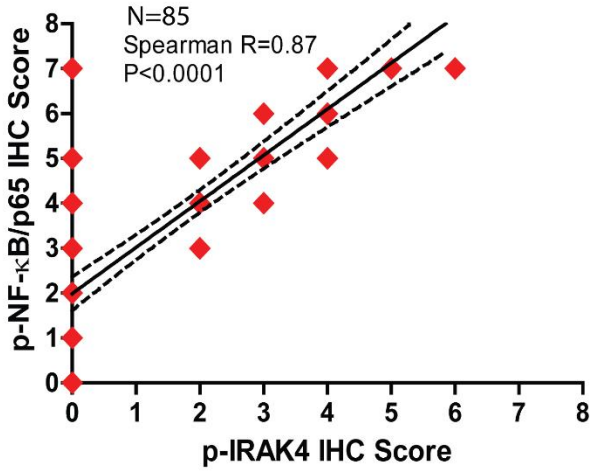
Lim, et al. *Cold Spring Harb Perspect Biol.* 2013;5(1):a011247.

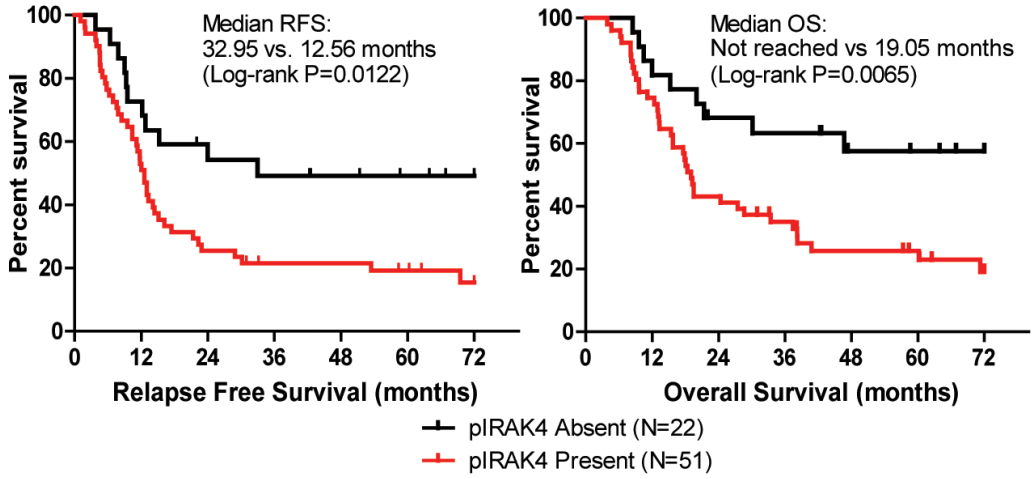
1. *Clin Cancer Res. 1999;5(1):119-27.* 2. *Br J Cancer*. 2007;97(4):523-30. 3. *J Natl Cancer Inst.* 2011;103(15):1190-204. 4. *J Clin Invest.* 2012;122(4):1519-28. 5. *Cancer Cell.* 2012;21(1):105-20. 6. *Cell Rep.* 2014;9(1):90-103.

Activated IRAK4 positively correlates with phospho-RELA/NF-κB1 and poor prognosis in PDAC



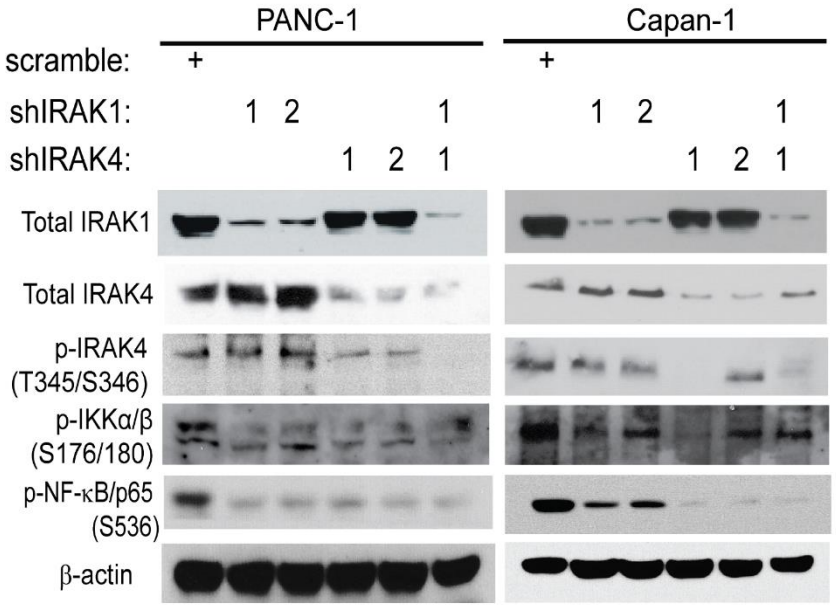






Zhang, et al. *Clin Cancer Res.* 2017;23(7):1748-1759.

IRAK4 kinase activity is required to activate RELA and NF-κB pathway in PDAC

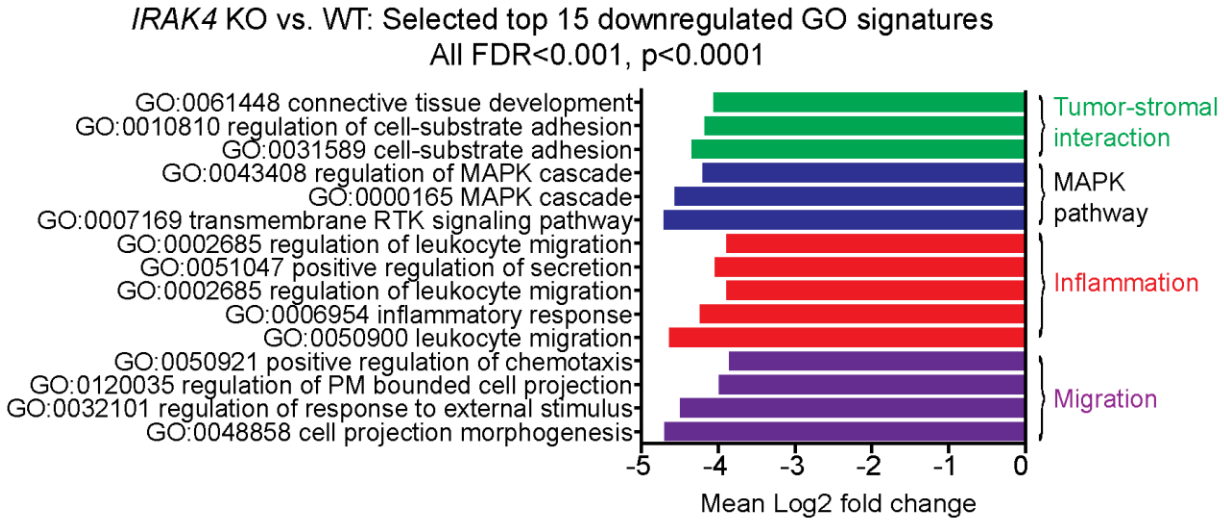


Zhang, et al. *Clin Cancer Res.* 2017;23(7):1748-1759.

IRAK4 controls several suppressive chemokines and checkpoint ligands

IRAK4 | Symposium

KP2 cells (from a *KPC* mouse)



Downregulated in *IRAK4* KO cells, all FDR<0.05
Independently confirmed by *IRAK4* rescue and IRAK4 inhibitor

Gene	log_2FC	adj.P.Val	Reported function in PDAC
CCL2	-0.5411205	1.12E-03	Recruits monocytes, granulocytes
CCL20	-1.1869978	6.63E-03	Recruits Treg, DC
CXCL1	-2.0180684	2.24E-08	Recruits monocytes, DC
CXCL16	-0.7801257	6.98E-05	Directs activated stellate cells
CXCL3	-4.3381343	5.91E-05	Promotes metastasis
CXCL5	-3.1309933	4.93E-07	Promotes angiogenesis
IL-33	-4.1958493	6.11E-10	Promotes M2 TAM polarization
CD274	-0.6596101	2.28E-02	T cell checkpoint
Nectin2	-1.5205052	9.58E-08	T and NK cell checkpoint
TIGIT	-2.3387297	5.74E-04	T and NK cell checkpoint

Q: Does tumor *IRAK4* affect T cell response?

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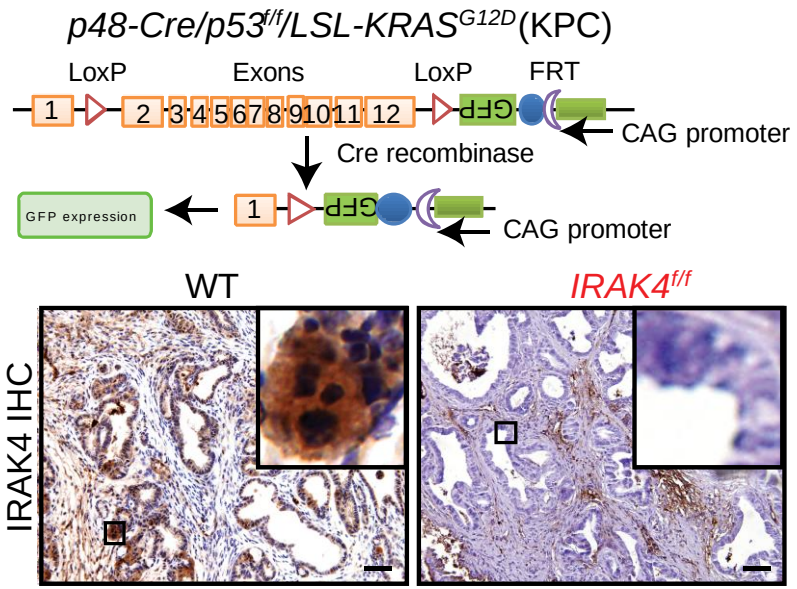
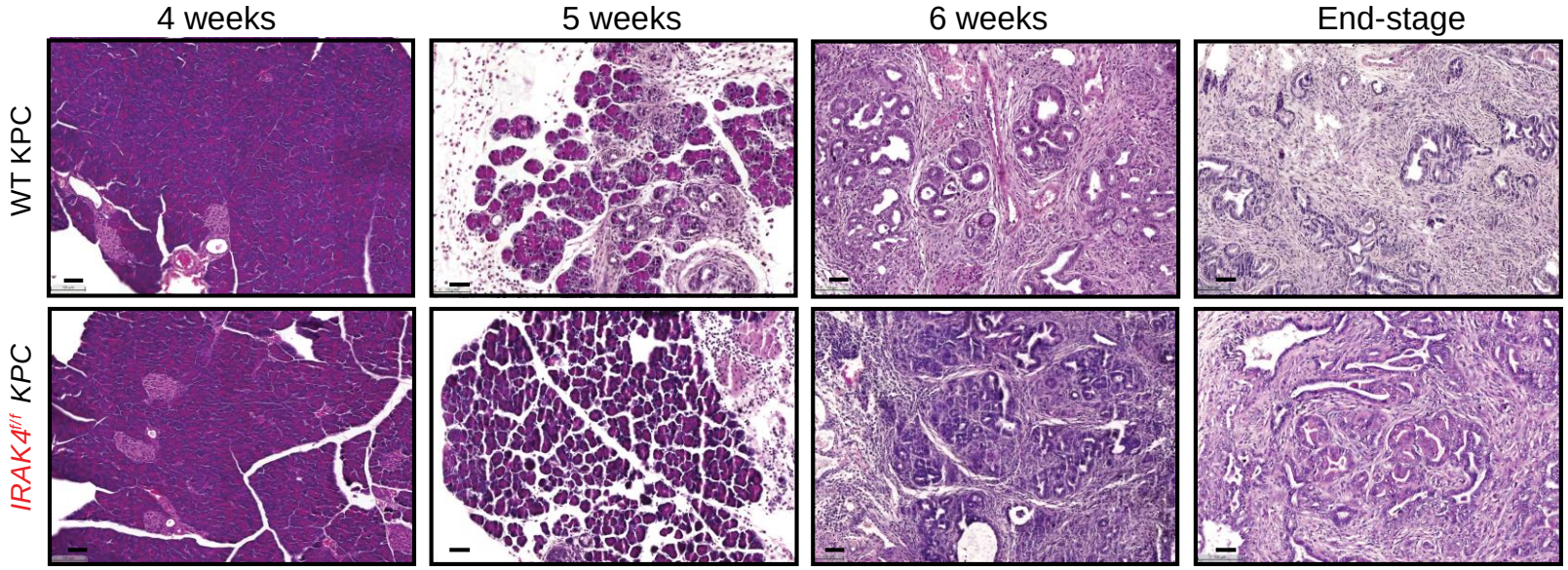
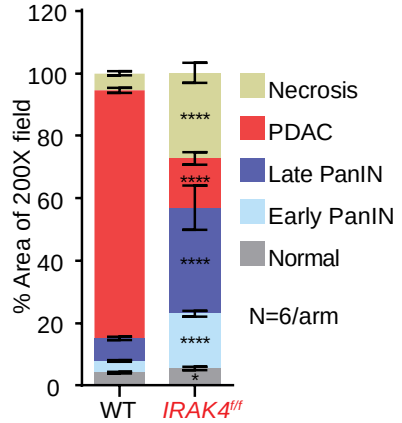
Somani, et al. *Gastroenterology.* 2022;162(7):2047-2062.

Conditional *IRAK4*$^{flox/flox}$ KPC

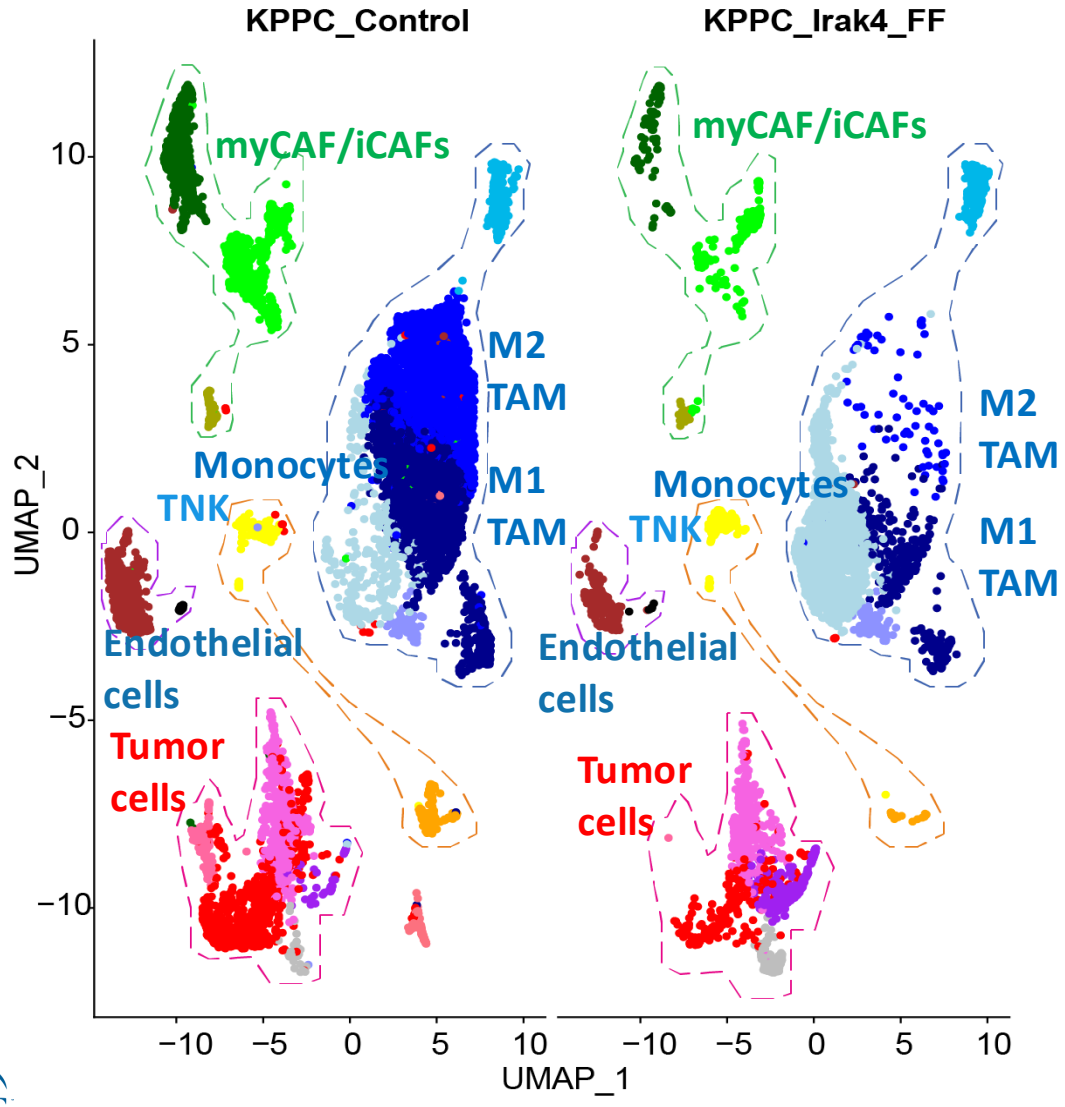


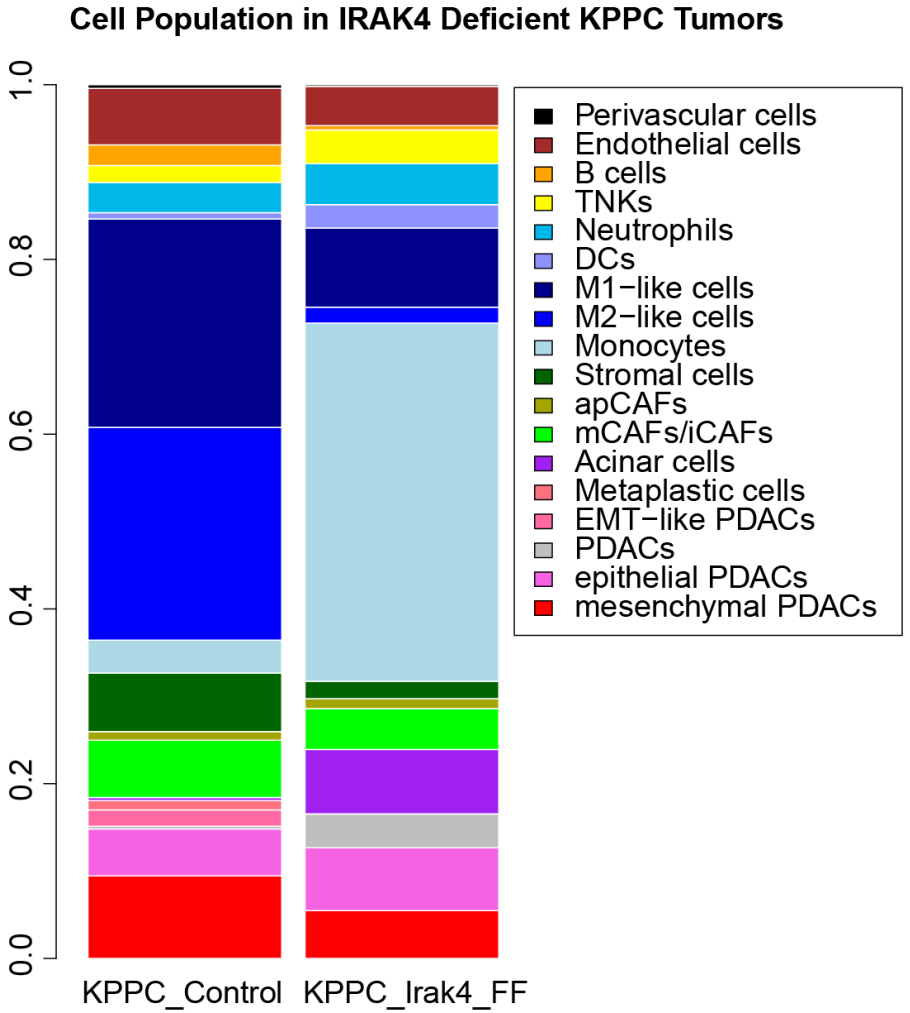




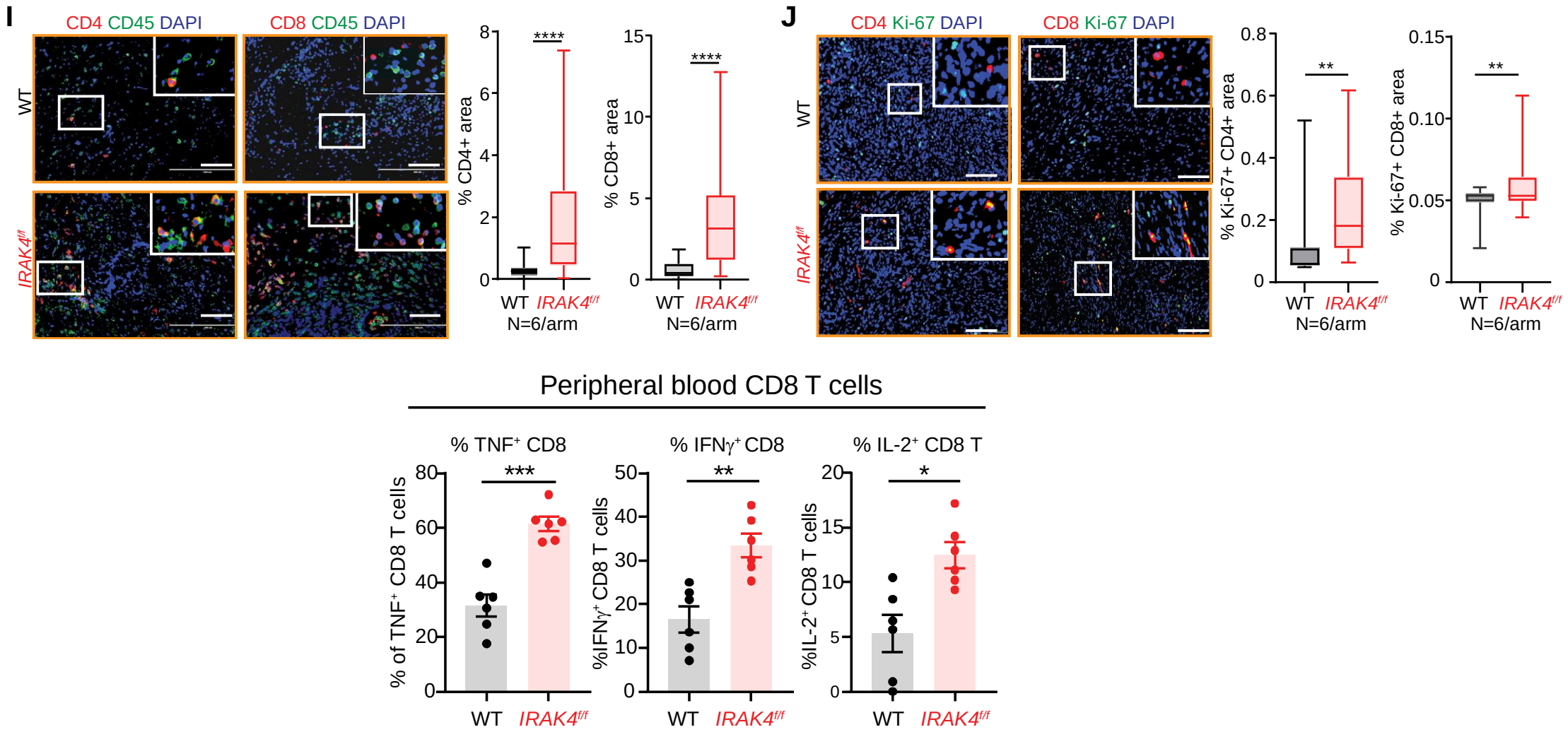
Somani, et al. *Gastroenterology.* 2022;162(7):2047-2062.

Conditional *IRAK4*$^{flox/flox}$ KPC mice have lower intratumoral TAMs and CAFs



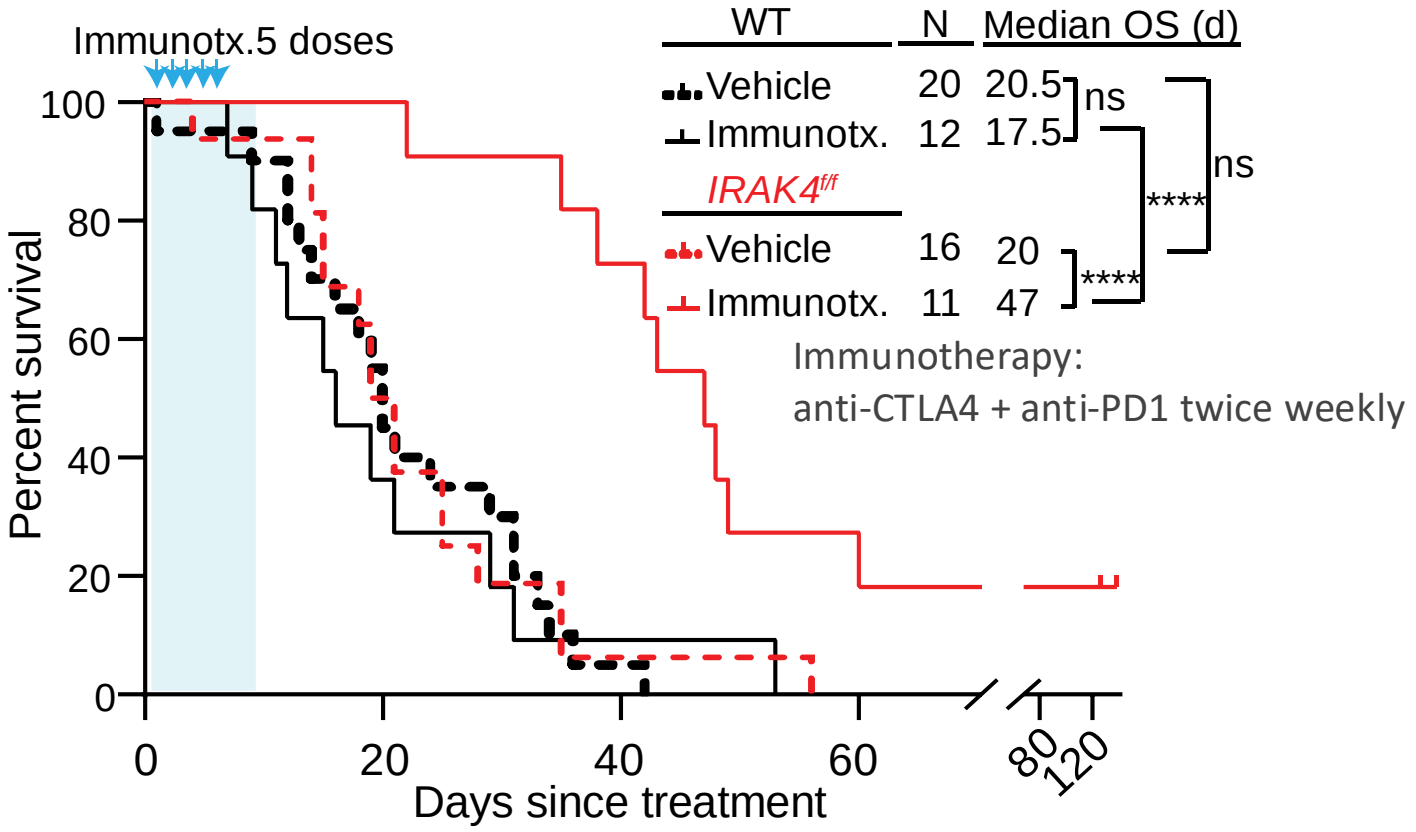


Conditional *IRAK4*$^{flox/flox}$ KPC mice have higher intratumoral and systemic activated T cells



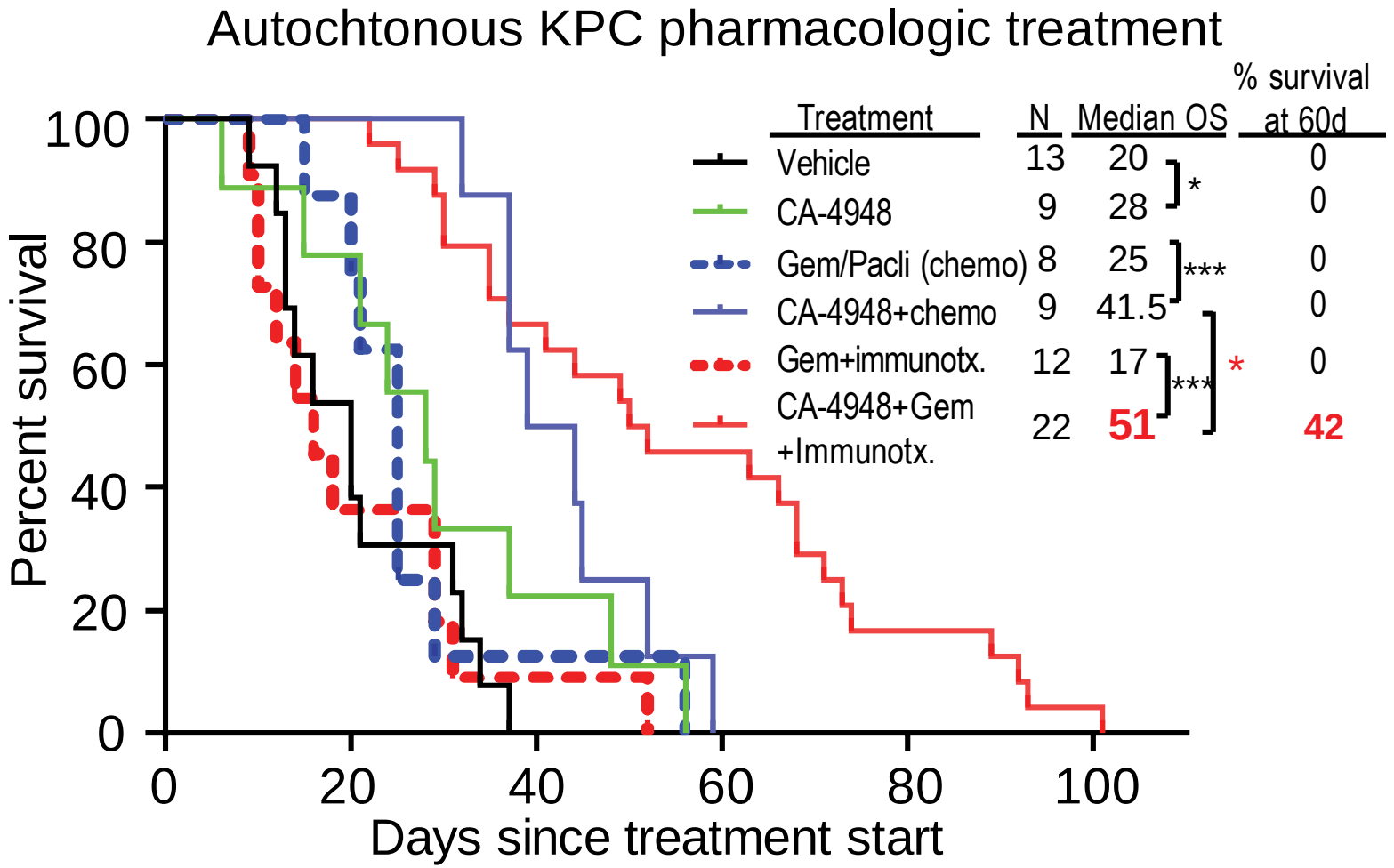
Somani, et al. *Gastroenterology.* 2022;162(7):2047-2062.

Conditional *IRAK4*$^{flox/flox}$ KPC mice respond to checkpoint immunotherapy



Somani, et al. *Gastroenterology.* 2022;162(7):2047-2062.

CA-4948 plus chemo-immunotherapy is an effective combination



Somani, et al. *Gastroenterology.* 2022;162(7):2047-2062.

Single patient compassionate use

Single patient compassionate use of Gemcitabine/Abraxane plus CA-4948 and pembrolizumab
(FDA approved IND#161391, Wash U IRB approved)

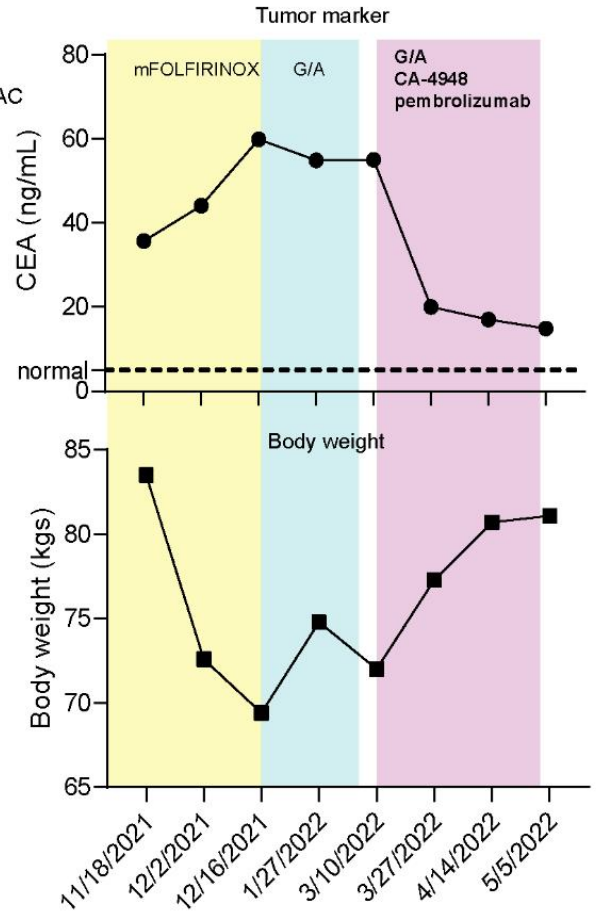
A

47 year-old man
diagnosed with metastatic PDAC

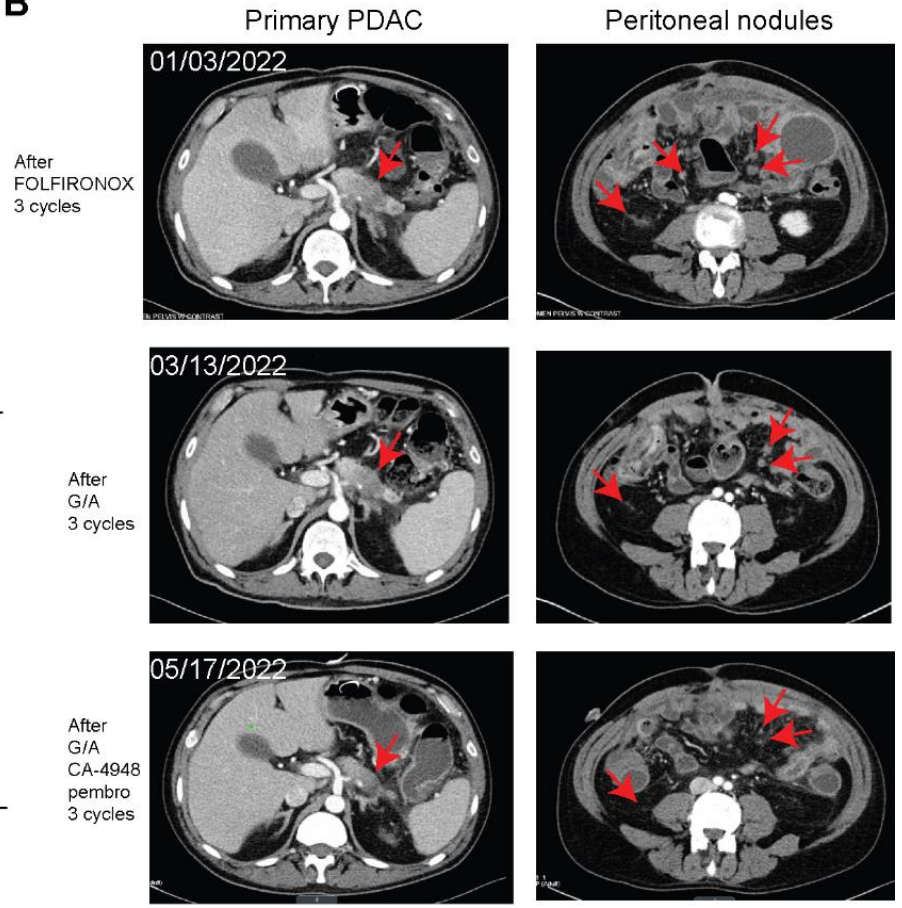
Tumor genetics:
KRAS(G12D)
TP53(R282W)

Tumor mutational burden
1.2m/MB

Microsatellite stable



B



NCI ETCTN 10522: A Phase 1 Clinical Trial of CA-4948 in Combination with Gemcitabine and Nab-Paclitaxel in Metastatic or Unresectable Pancreatic Ductal Carcinoma (original proposal was to include anti-PD1)

PI (Lead Organization): Patrick Grierson, MD PhD (Wash U)
Translational PI: Kian-Huat Lim, MD PhD. (Wash U)
Sites: Columbia, UF, Yale, Vanderbilt, Wash U, UCI….

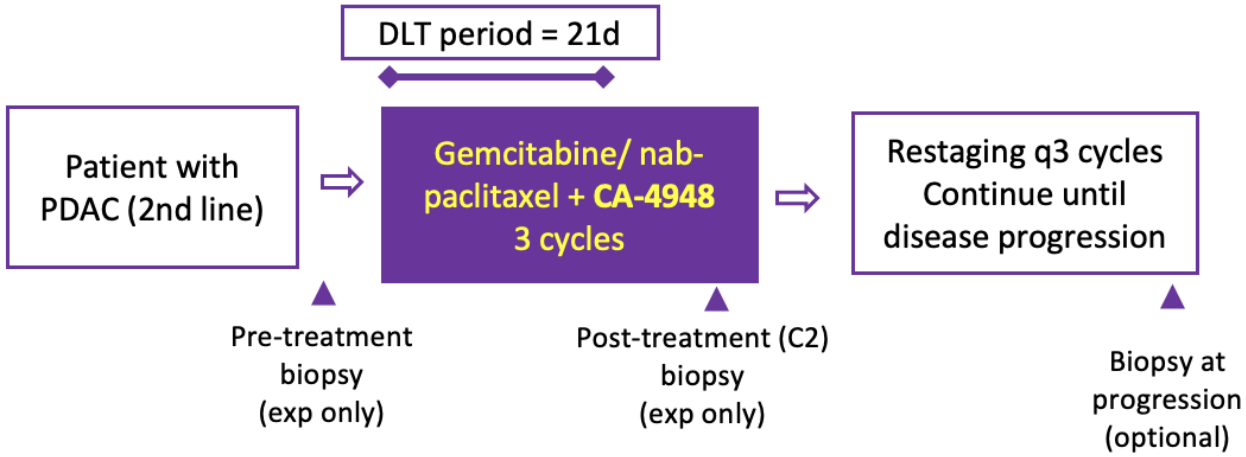
Part A. Dose Escalation (N=up to 18)

CA4948 + gemcitabine/nab-paclitaxel (D1, 8 q21d)

Dose level	CA-4948 (PO BID)
-1	100mg
0 (starting)	150mg
1	200mg
2	250mg
3	MTD (-)1 level
4	MTD

*For Dose Levels 3 and 4, gem/nab-paclitaxel will be given D1, 8, 15 q28d

Part B. Dose Confirmation/Expansion (N= up to 18)

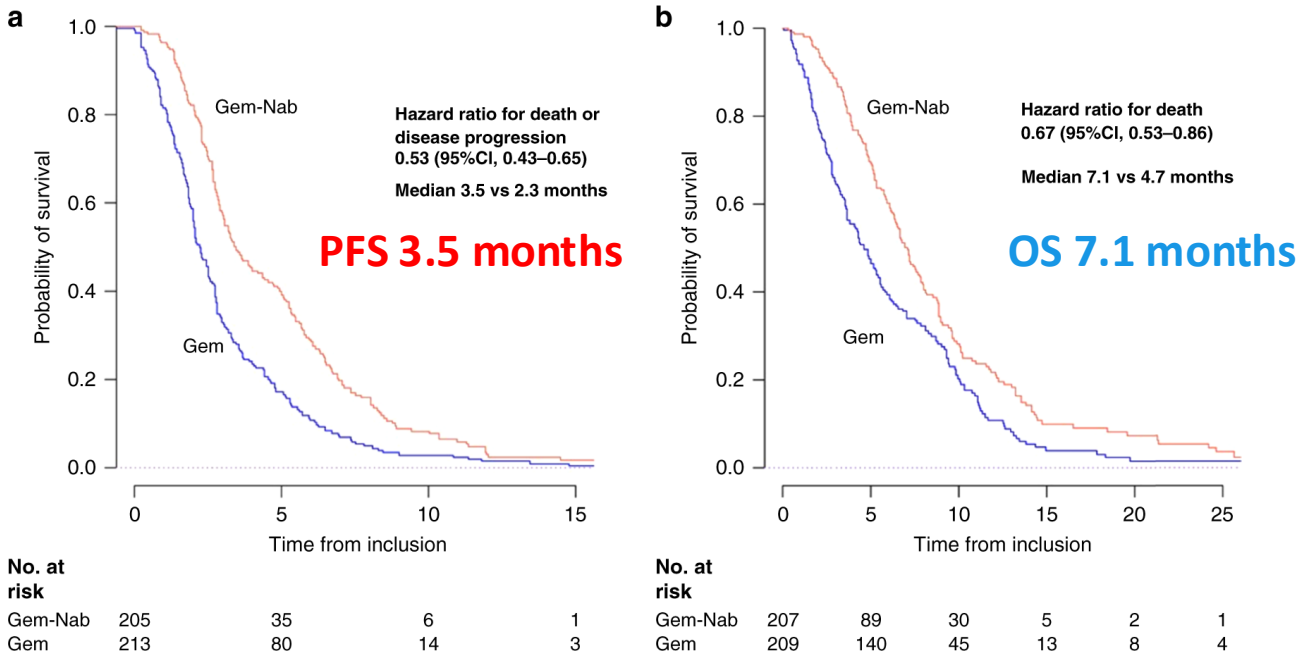


Gemcitabine + Nab-paclitaxel or Gemcitabine alone after FOLFIRINOX failure in patients with metastatic pancreatic adenocarcinoma: a real-world AGEO study

Sonia Zaibet[1], Vincent Hautefeuille[2], Edouard Auclin[3,4], Astrid Lièvre[5], David Tougeron[6], Mathieu Sarabi[7], Marine Gilabert[8], Julie Wasselin[2], Julien Edeline[9], Pascal Artru[10], Dominique Bechade[11], Clémence Morin[7], Agnes Ducoulombier[12], Julien Taieb[1] and Simon Pernot[11]✉

18 French centers

Best response	Gem-Nab (*N* = 219)	Gem (*N* = 208)	
Partial response—*N* (%)	22 (11.28%)	13 (8.28%)	*P* < 0.001
Stable disease—*N* (%)	87 (44.62%)	38 (24.2%)	
Progressive disease—*N* (%)	86 (44.1%)	106 (67.52%)	
NA	24	51	



Gemcitabine plus nab-paclitaxel for advanced pancreatic cancer after first-line FOLFIRINOX: single institution retrospective review of efficacy and toxicity

Yue Zhang[1*], Howard Hochster[2], Stacey Stein[2] and Jill Lacy[2]

Table 1 Patient characteristics at initiation of gemcitabine and nab-paclitaxel

Age, years	61 (50–74)
Sex, no (%)	
Male	11 (39.3 %)
Female	17 (60.7 %)
Disease, no (%)	
Metastatic	23 (82.1 %)
Locally advanced	5 (17.9 %)
ECOG performance status, no (%)	
≤1	27 (96.4 %)
≥2	1 (3.6 %)
Median no of FOLFIRINOX cycles (range)	12 (5–46)
Median interval from last FOLFRINOX to initiation of G + Nab-P, weeks (range)	5.4 (1.7–40.3)
N = 28	

Table 3 Efficacy of second line gemcitabine and nab-paclitaxel

PFS 3 months

Median time to treatment failure, weeks	12.0 (2.0–36.0)
Median overall survival, weeks	23.0 (2.1–85.4)
Response by RECIST, n (%)	**OS 5.7 months**
Partial response	5 (17.9)
Stable disease	8 (28.6)
Progressive disease	12 (42.8)
Inevaluable	3 (10.7)
Serologic response, n (%)[a]	
CA 19-9	13 (46.4)
CEA	11 (39.3)

[a] >30 % decrease from pre-treatment baseline

Summary and next steps for PDAC

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1. Adding CA-4948 to G/A is tolerable without added toxicities beyond chemo
   - Dose escalation is ongoing to achieve DLT→ dose expansion

2. Pre- and post-treatment tumor samples will be obtained from dose expansion to study immunological changes→ justification of adding anti-PD1

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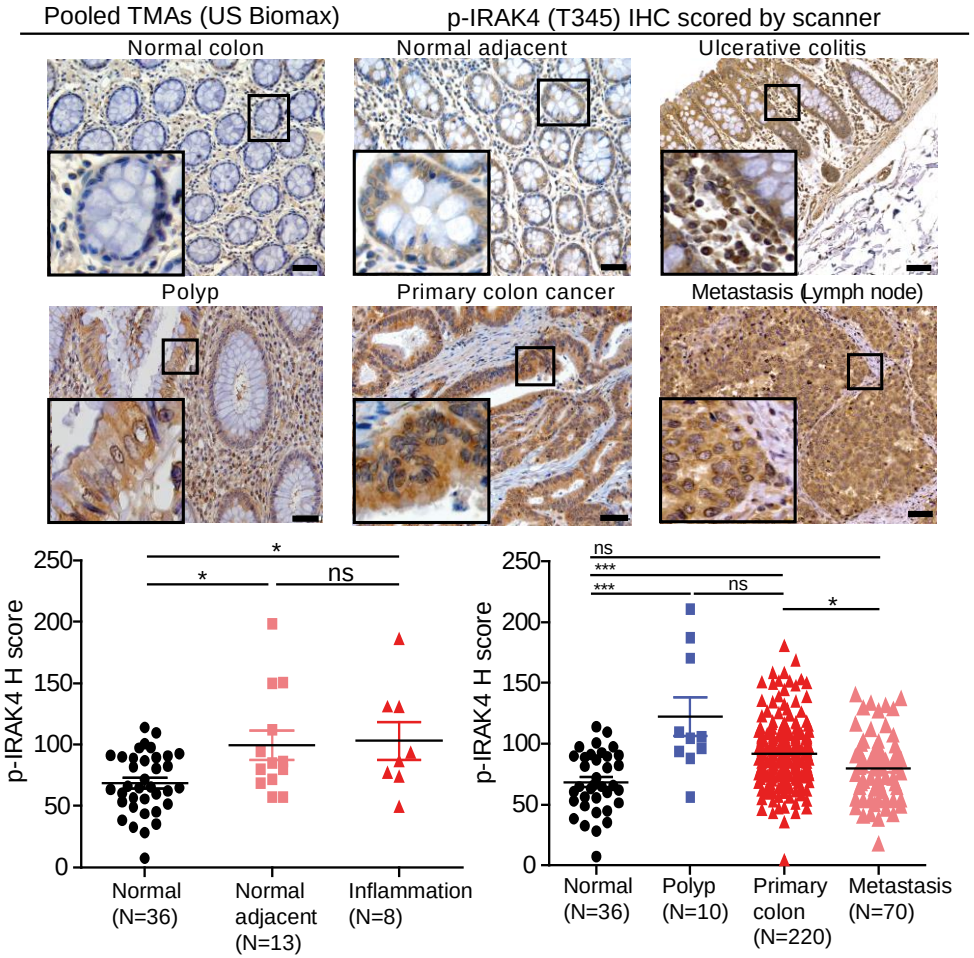
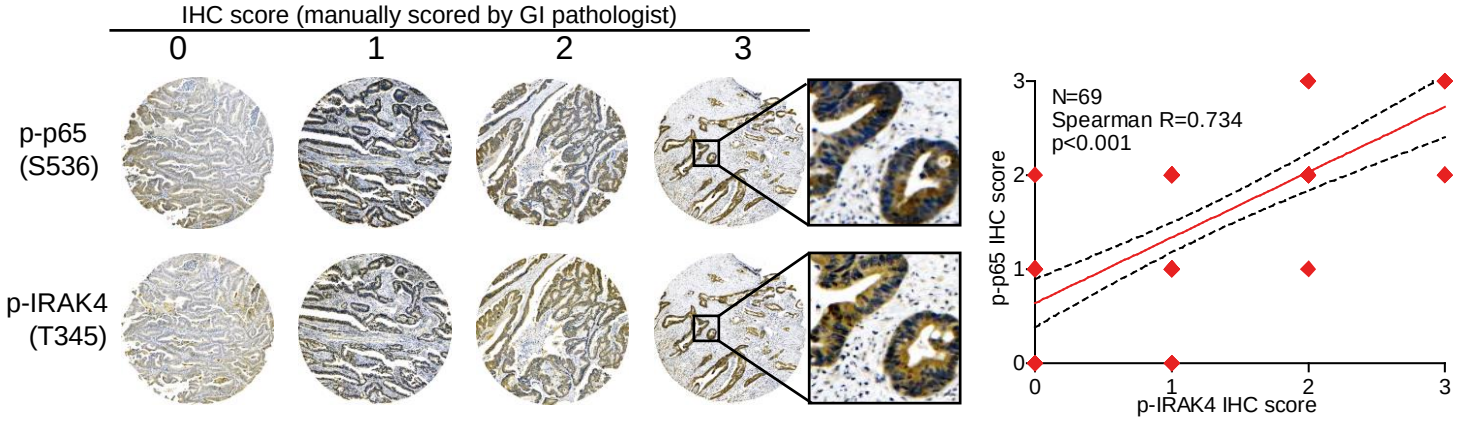
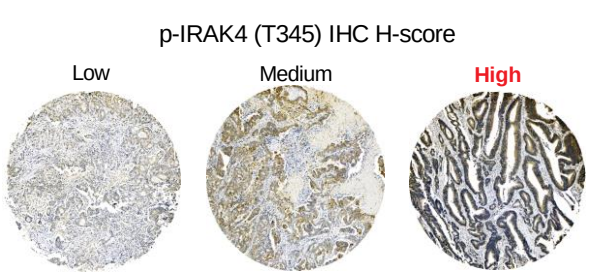
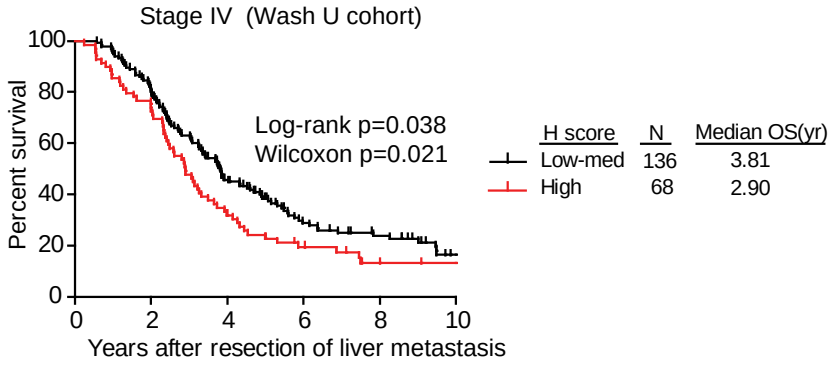
Activated IRAK4 positively correlates with phospho-RELA and poor prognosis in colon cancer



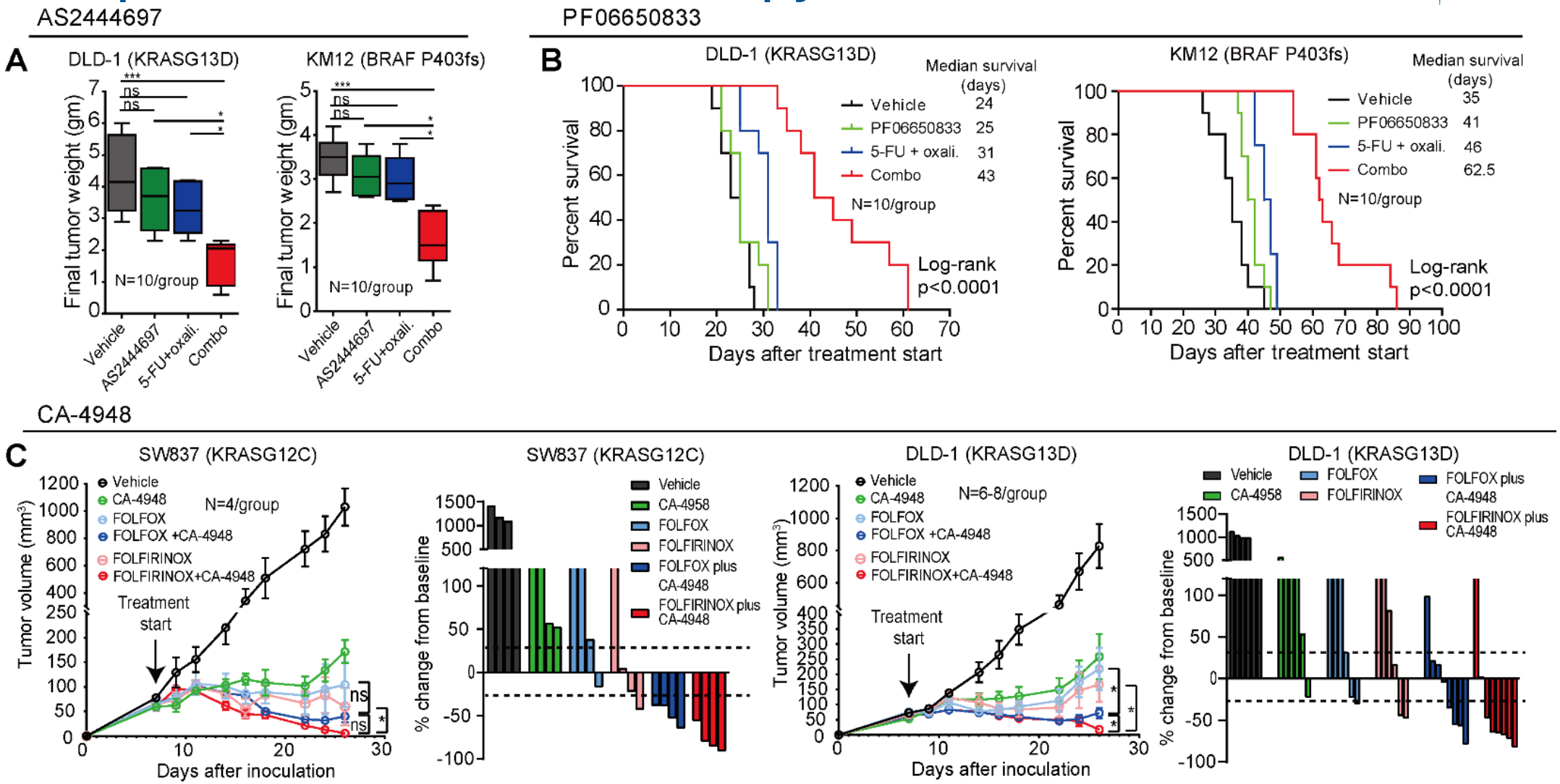






Li, et al. *JCI Insight.* 2019;4(19):e130867.

IRAK4i potentiates chemotherapy



Li et al. *JCI Insight*. 2019;4(19):e130867.
J Clin Invest. 2020;130(9):4771-4790.

Study Rationale/Hypothesis

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- Activated IRAK4 is a driver of NF-kB activity, leading to chemo-resistance and poor prognosis
- Our preclinical data strongly support combining CA-4948 with chemotherapy and ICB in gastrointestinal cancer
- Standard first-line therapy includes FOLFOX-based chemotherapy in several GI cancer, including colorectal cancer and gastroesophageal cancer
- Improving efficacy of first-line therapy by adding a novel agent with no overlapping toxicities may improve long-term survival in this population

➢ ***We hypothesize that combining CA-4948 with FOLFOX and bevacizumab or nivolumab will be well-tolerated while improving anti-tumor efficacy***

NCI ETCTN 10655: Phase 1 Clinical Trial of CA-4948 in Combination with FOLFOX + Bevacizumab as Frontline Treatment in Patients with Metastatic Colorectal Cancer

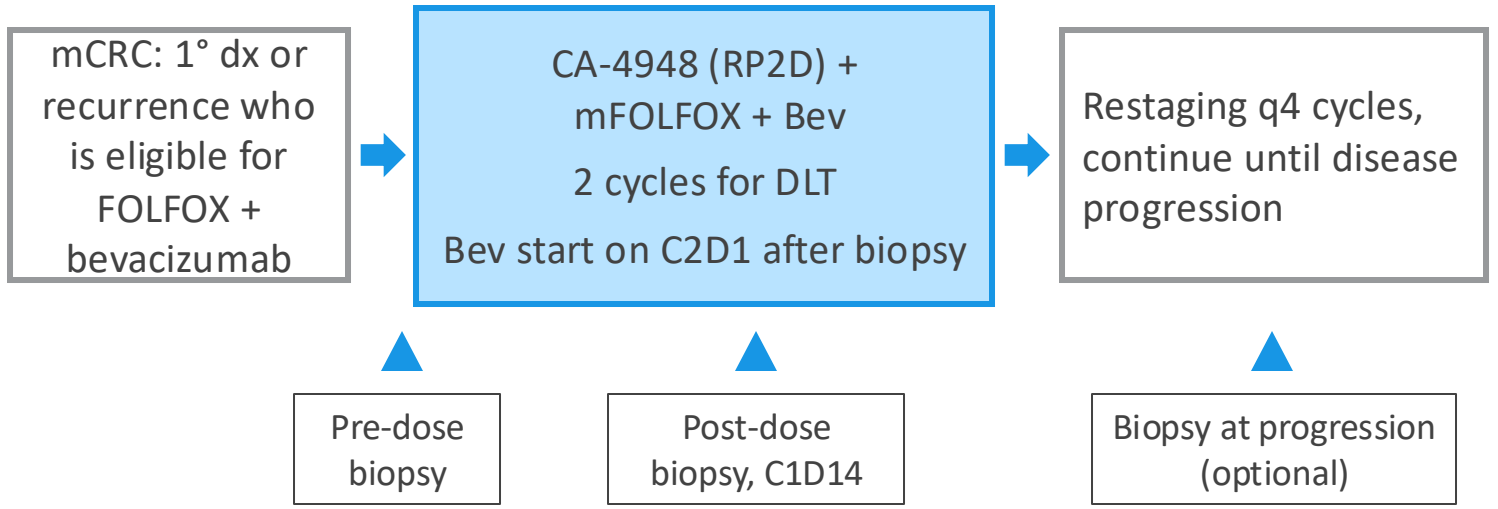
PI: Susanna Ulahannan, M.D., Stephenson Cancer Center at Oklahoma University
CrD Mentor: Thomas George, M.D., University of Florida in Gainesville
Translational PI: Kian-Huat Lim, M.D., Ph.D., Washington University in St. Louis
Status: Trial protocol writing in final stage
Target population: Newly diagnosed metastatic CRC patients

Part A. Dose Finding Phase (N=up to 18)

CA-4948 (PO, BID, D1-14) + mFOLFOX6+Bev, D1, q2w, DLT period: 28 days

Dose level	CA-4948 Dose (PO, BID)
-1	100 mg
1 (starting)	150 mg
2	200 mg
3	250 mg

Part B. Dose Expansion (N=up to 12)



Wash U IIT: Phase I trial of CA-4948 in combination with FOLFOX/PD-1 inhibitor +/- trastuzumab for untreated unresectable gastric and esophageal cancer

Dose Escalation
(N=up to 18)

CA-4948 + mFOLFOX7 + nivolumab q14d

Dose level	CA-4948 (PO BID)
-1	100mg
0 (starting)	150mg
1	200mg

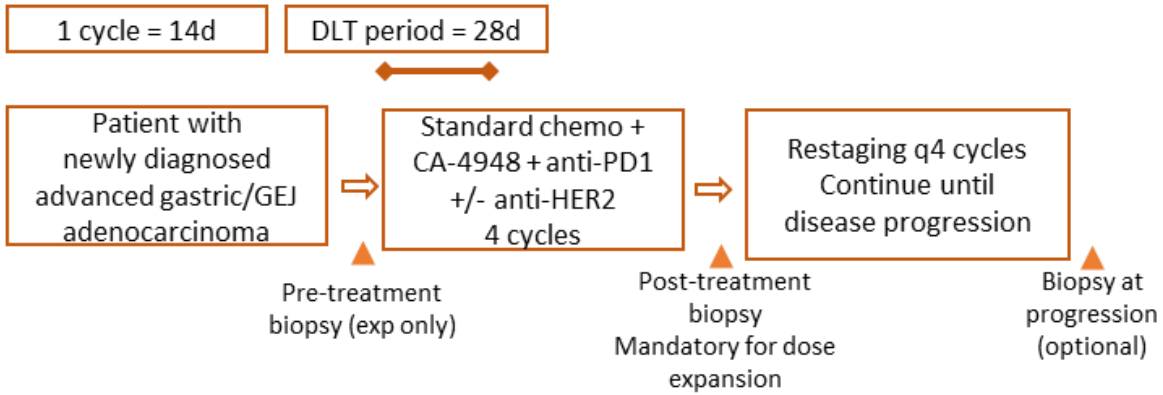
Dose escalation per BOIN

Dose Expansion
Cohort A (HER2 negative)
(N=up to 12 evaluable)

CA-4948 (RP2D) + mFOLFOX7 + nivolumab q14d

Cohort B (HER2 positive)
(N=up to 12 evaluable)

CA-4948 (RP2D) + (mFOLFOX7 + trastuzumab) q14d + pembrolizumab q42d



First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial

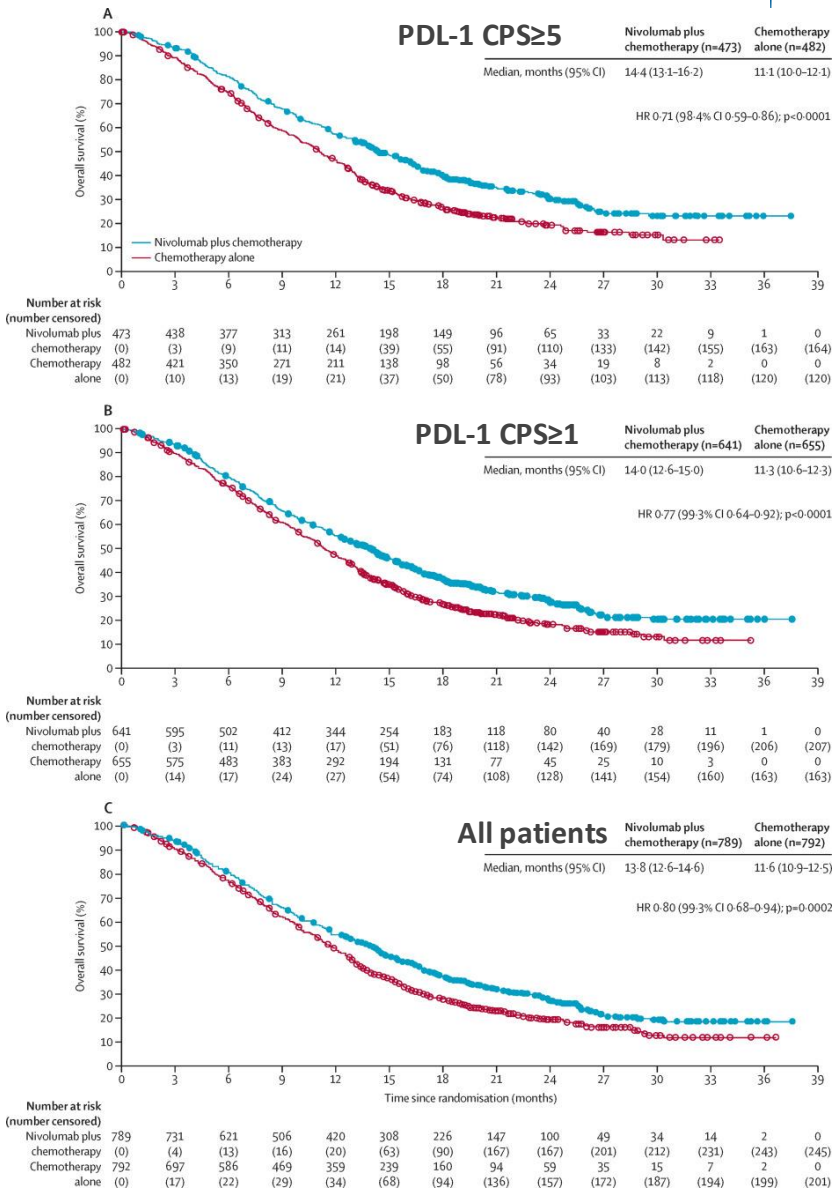
Yelena Y Janjigian, Kohei Shitara*, Markus Moehler, Marcelo Garrido, Pamela Salman, Lin Shen, Lucjan Wyrwicz, Kensei Yamaguchi, Tomasz Skoczylas, Arinilda Campos Bragagnoli, Tianshu Liu, Michael Schenker, Patricio Yanez, Mustapha Tehfe, Ruben Kowalyszyn, Michalis V Karamouzis, Ricardo Bruges, Thomas Zander, Roberto Pazo-Cid, Erika Hitre, Kynan Feeney, James M Cleary, Valerie Poulart, Dana Cullen, Ming Lei, Hong Xiao, Kaoru Kondo, Mingshun Li, Jaffer A Ajani*

CheckMate 649

1581 patients, non-HER2 positive
Chemo (N=792)
FOLFOX q2weeks or CAPOX q3weeks

Chemo + anti-PD1 (N=789)
Nivolumab 240mg q2weeks or 360mg q3weeks

ORR 58%
Median PFS 7.7 months
Median OS 13.8 months



Lancet. 2021;398(10294):27.

IRAK4 is a novel therapeutic target in GI cancers

IRAK4 | Symposium

- Tumor intrinsic IRAK4 activation drives MAPK and NF-κB activity→ treatment resistance
- Tumor IRAK4 activation drives secretion of suppressive chemokines and checkpoint ligands (PD-L1, Nectin2) that collectively exhaust T cells
- Targeting IRAK4 represents a promising strategy to potentiate chemo- and immunotherapies

Ongoing work

- Role of IRAK4 in other cancer types: Lung, colon
- Cell type specific role: myeloid (*CSF1R-Cre:IRAK4$^{f/f}$*)
- Downstream signaling targets driven by IRAK4

Thanks for your attention!

Acknowledgements

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- Ashenafi Bulle, Sapana Bansod, Timothy Chen
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- Huaping Li, Yutong Geng

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- Salman Chaudhry, MD
- Caron Ridgen, MD
- Kian Lim, MD PhD

Department of Pathology and Immunology

- Marianna Ruzinova

Biostatistics Core

- Esther Lu

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Washington University SPORE In Pancreatic Cancer
Pancreatic Cancer Action Network
The Foundation for Cancer Research
American Cancer Society
Concern Foundation
The Conquer Cancer Now Award
PDXNet
ELSA U. PARDEE FOUNDATION
Siteman Cancer Center
Barnes-Jewish Hospital
Washington University in St. Louis School of Medicine

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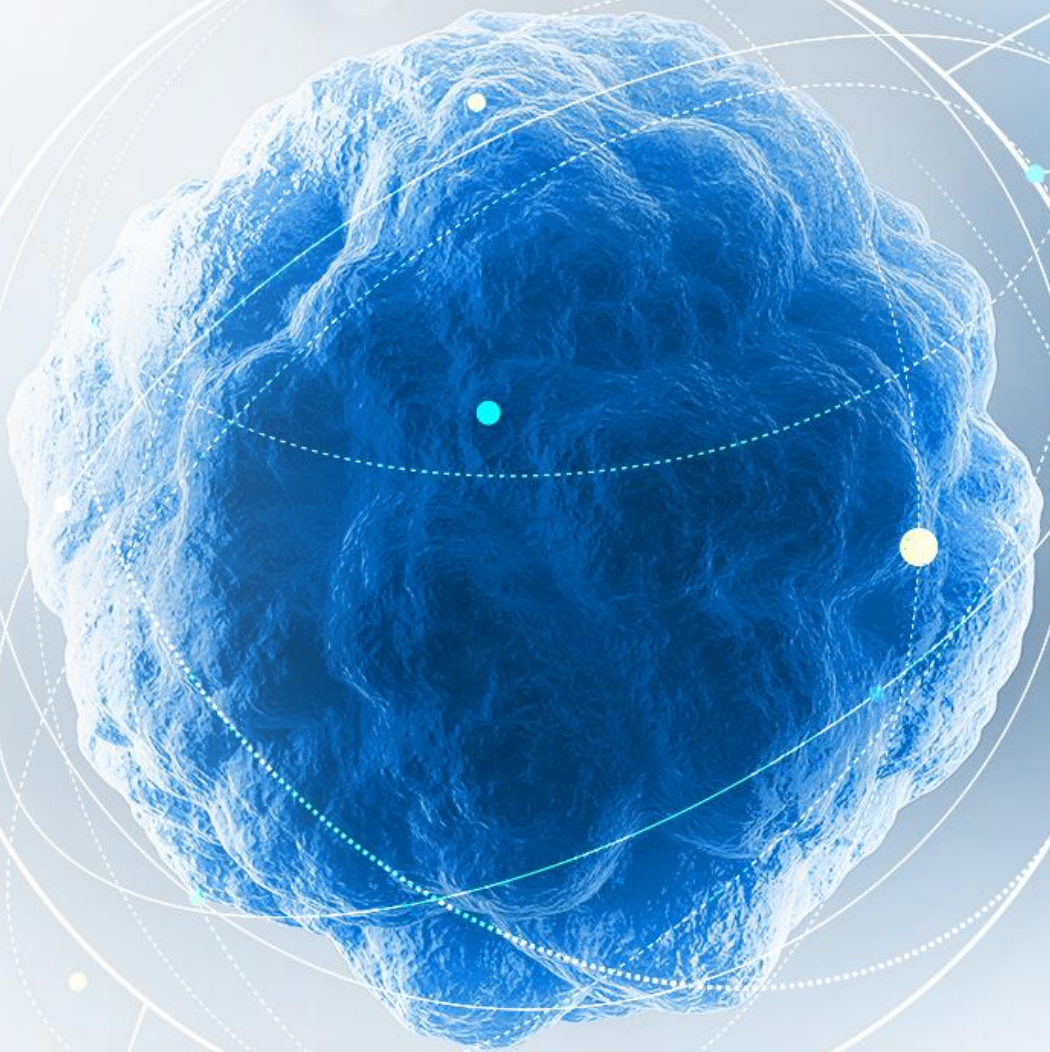
IRAK4 | Symposium

Questions?



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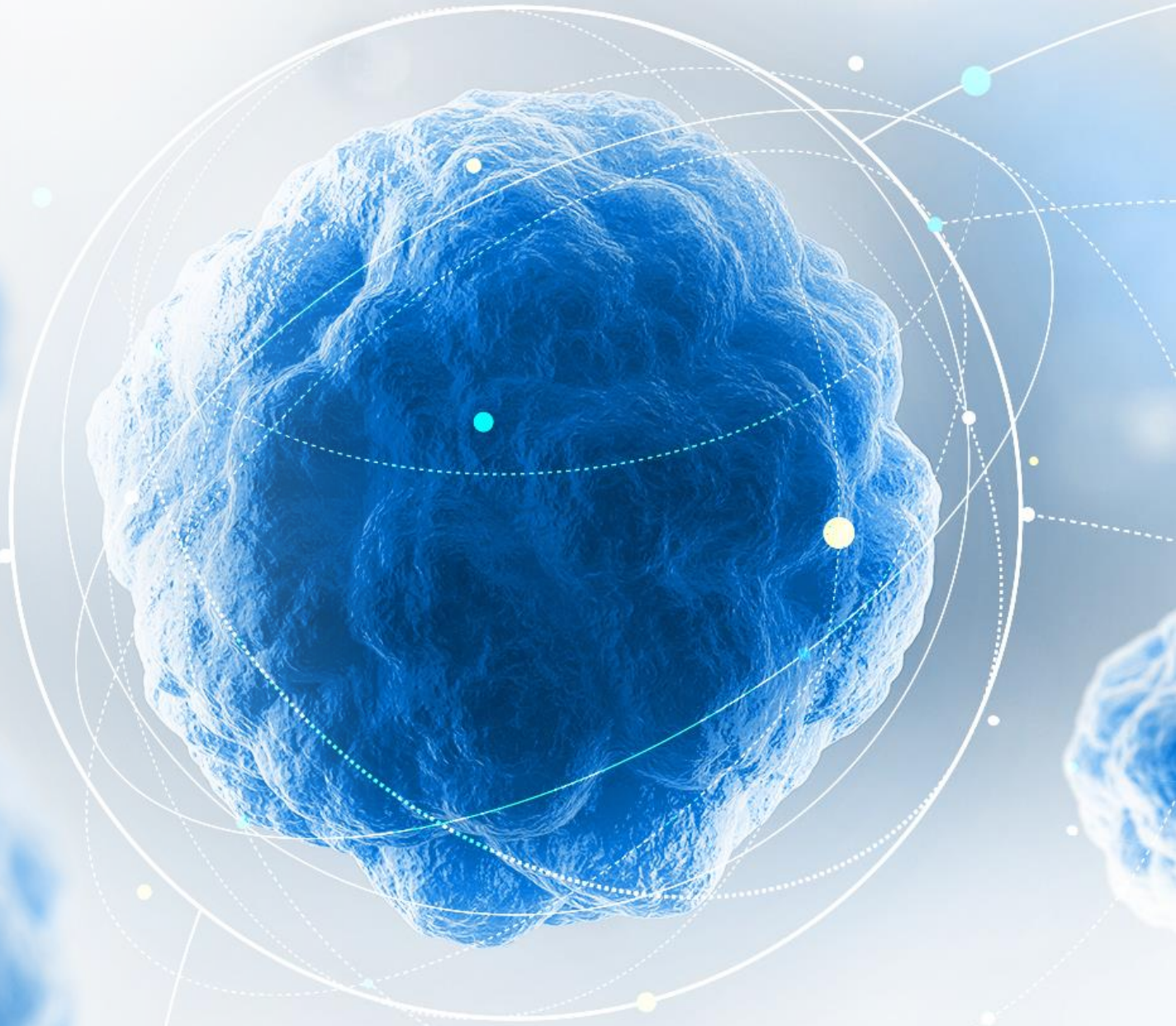
Emavusertib plus Pembrolizumab for Melanoma Brain Metastases



Dr. Bently Doonan, MD, MS

Assistant Professor

University of Florida Health Cancer Center

UF Wells Brain Tumor Immunotherapy Center

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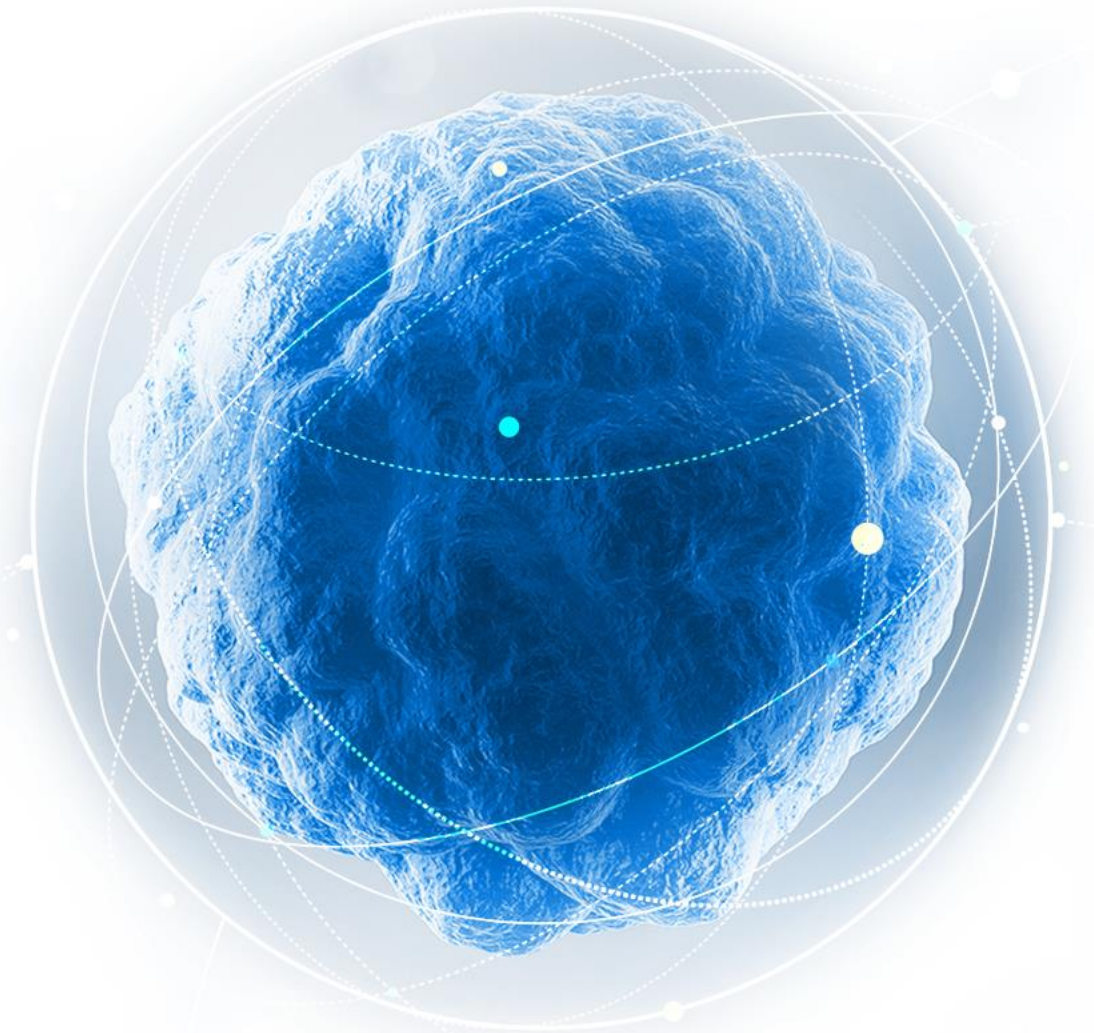
Disclosures

- *Preclinical research support from Curis, Inc*
- *Clinical trial research support from Merck, Inc*
- *Clinical trial drug support from Curis, Inc*
- *Advisory board: Immunocore, Inc; Pfizer, Inc; Replimune*



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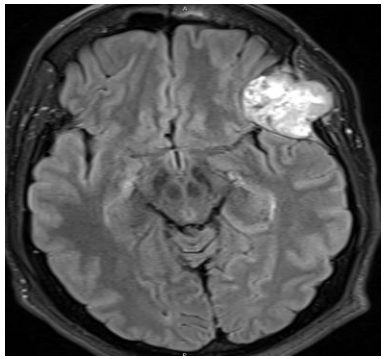
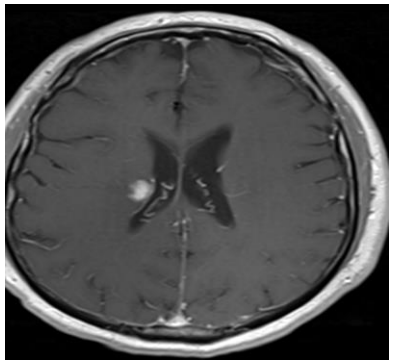
Melanoma Brain Metastases (MBM)

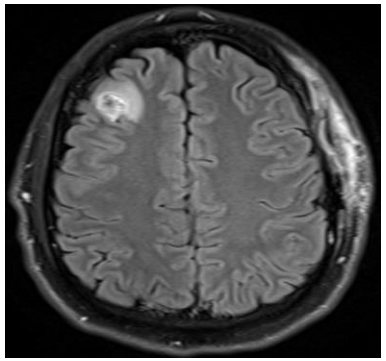
- Melanoma diagnoses are expected to continue to increase over the next 20 years, particularly in men[1, 2]
- Metastatic melanoma caries a 60-75% risk of development of brain metastases during the course of the disease[3, 4]
- Standard of care options include surgical resection, stereotactic radiosurgery, systemic immunotherapy, or targeted therapy in BRAF mutated patients[5-8]
- Even with maximally tolerated therapy, roughly 50% of patients will experience intracranial relapse within the first 3 years[9]
- Resistance to therapy develops at an increased rate intracranially and is often the only site of progression[10]



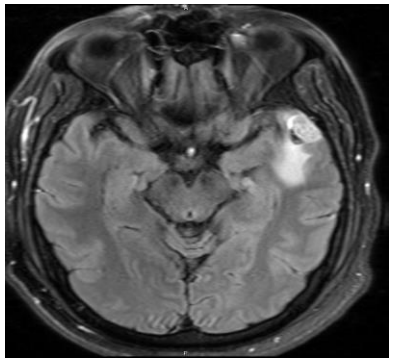
35 yo previously stage IIIC with intracranial recurrence as de novo metastasis



50 yo 10 months after Ipi/Nivo induction, while in CR oral TKI for C-KIT mutation



MBM recurrence following Ipi/Nivo induction + Surgery + SRS

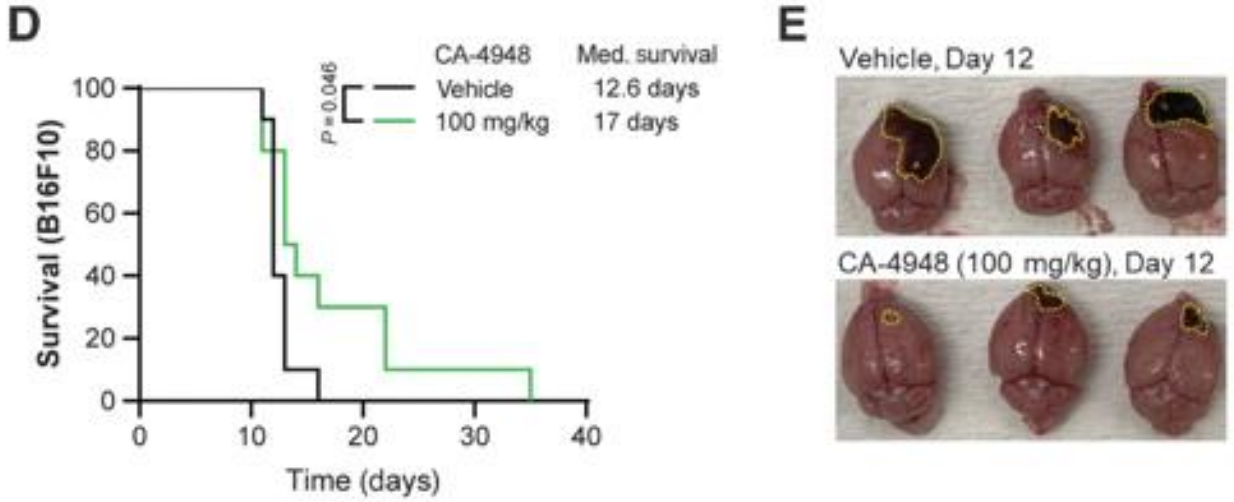


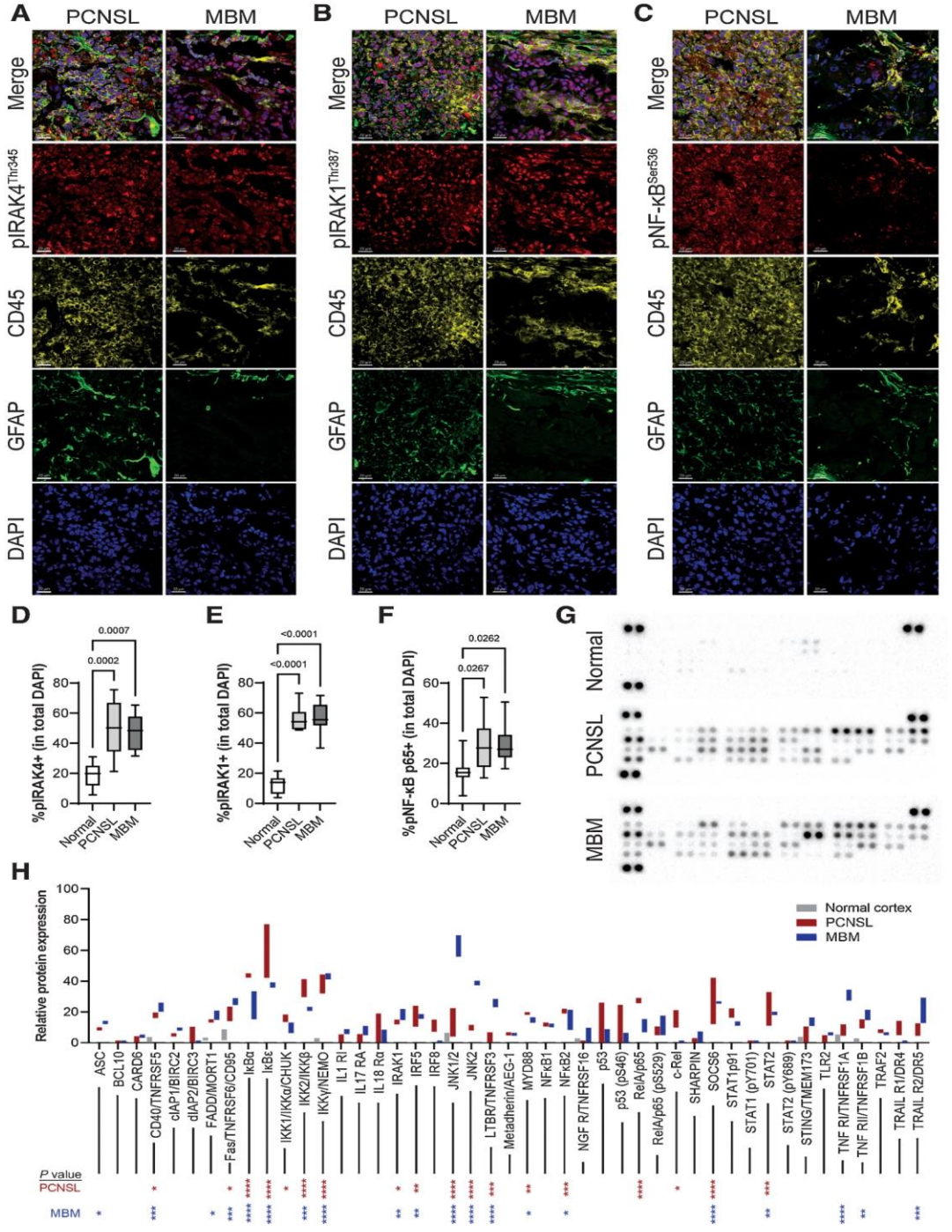
56 yo 6 months after Ipi/Nivo induction, while on second line Opdualag

1. Rahib L, et al. *JAMA Network Open.* 2021;**4**(4):p.e214708. 2. Arnold M, et al. *JAMA Dermatology.* 2022;**158**(5):495. 3. Li C, et al. *Crit Rev Oncol Hematol.* 2024;**194**:104227. 4.Tang HKC, et al. *J Cancer.* 2024;**15**(11):3495-3509. 5. Wilkes JG, et al. *Expert Opin Pharmacother.* 2021;**22**(11):1443-1453. 6. Kreidieh FY and Tawbi HA. *Clin Adv Hematol Oncol.* 2022;**20**(10):619-627. 7. Anvari A, Sasanpour P, Kheradmardi MR. *Hematol Oncol Stem Cell Ther.* 2023;**16**(1):1-20. 8. Nowacka A, et al. *Cancers (Basel).* 2023:**15**(16). 9. Wang J and HA Tawbi. *Neuro-Oncology Advances.* 2021;**3**(Suppl_5):v43-v51. 10. Fernandes GNC. *Discoveries (Craiova).* 2023;**11**(2):e169.

IRAK 4 as Target in MBM

- We have previously shown the upregulation in IRAK4, Myd88 and downstream transcription factors in MBM[11]
- We have also shown the intracranial permissibility and penetrance of Emavusertib through the BBB[11]
- Emavusertib has modest single agent activity in aggressive MBM models[11]

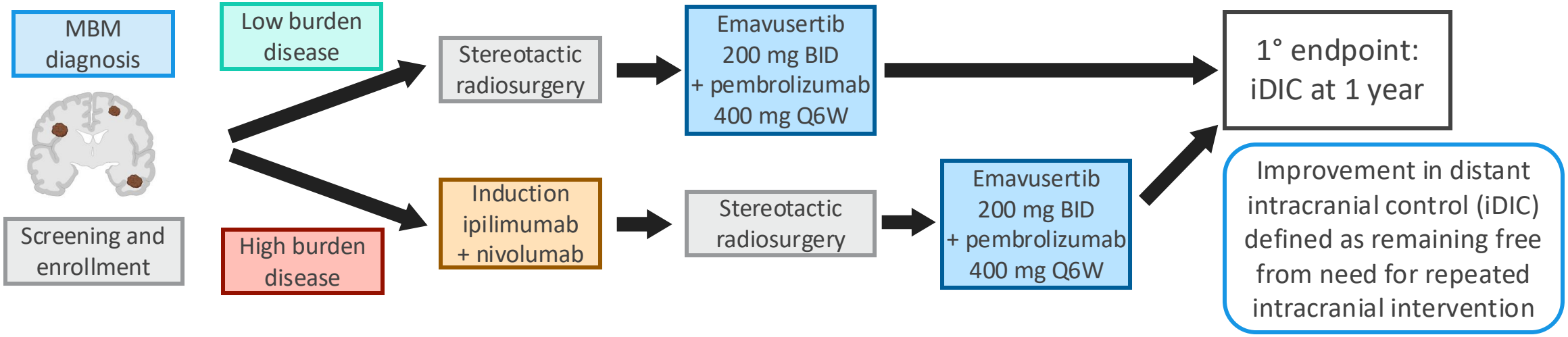




11. Von Roemeling CA, et al. *Clin Cancer Res*. 2023;**29**(9):1751-1762.

Phase 1/2 Study of Emavusertib in combination with pembrolizumab following SRS in patients with melanoma brain metastases

PI: Dr. Bently Doonan. Sponsors: Merck, Inc and Curis, Inc: NCT05669352



- Simon's 2 stage design
- Phase I safety run in (fixed dose emavusertib)
- No max limit of MBM, inclusion characteristic is ability to receive definitive SRS by institutional standard

Brain MRI q3 months for response monitoring RANO-BM

Open and enrolling at the University of Florida, pending activation at Duke University

Questions and Thanks

- Team and Collaborators
  - Dr. Duane Mitchell
  - Dr. Christina Von Roemeling
  - Dr. Changlin Yang
  - Jeet Patel
  - Savannah Carpenter
  - Skye Speakman
  - Dr. Thom George
  - Dr. Ji-Hyun Lee
  - Dr. April Salama (Duke University)
  - Entire UFBTIP

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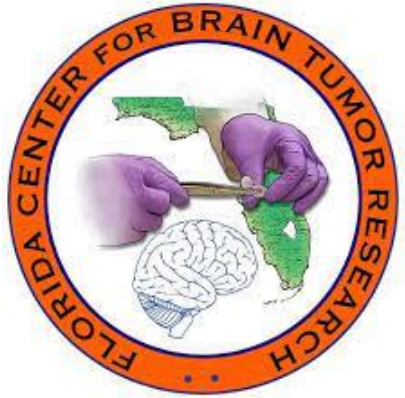
- Adam Rosen Foundation



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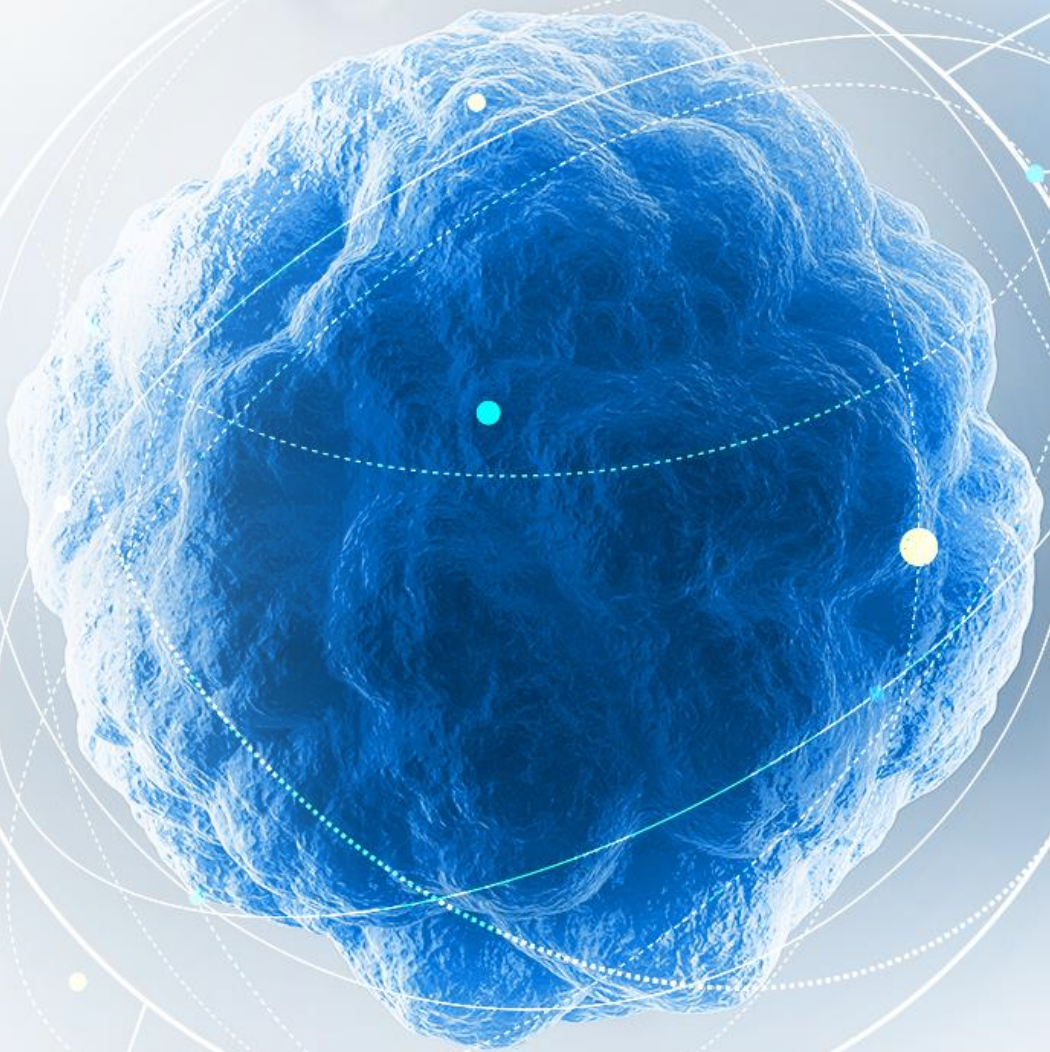
Questions?



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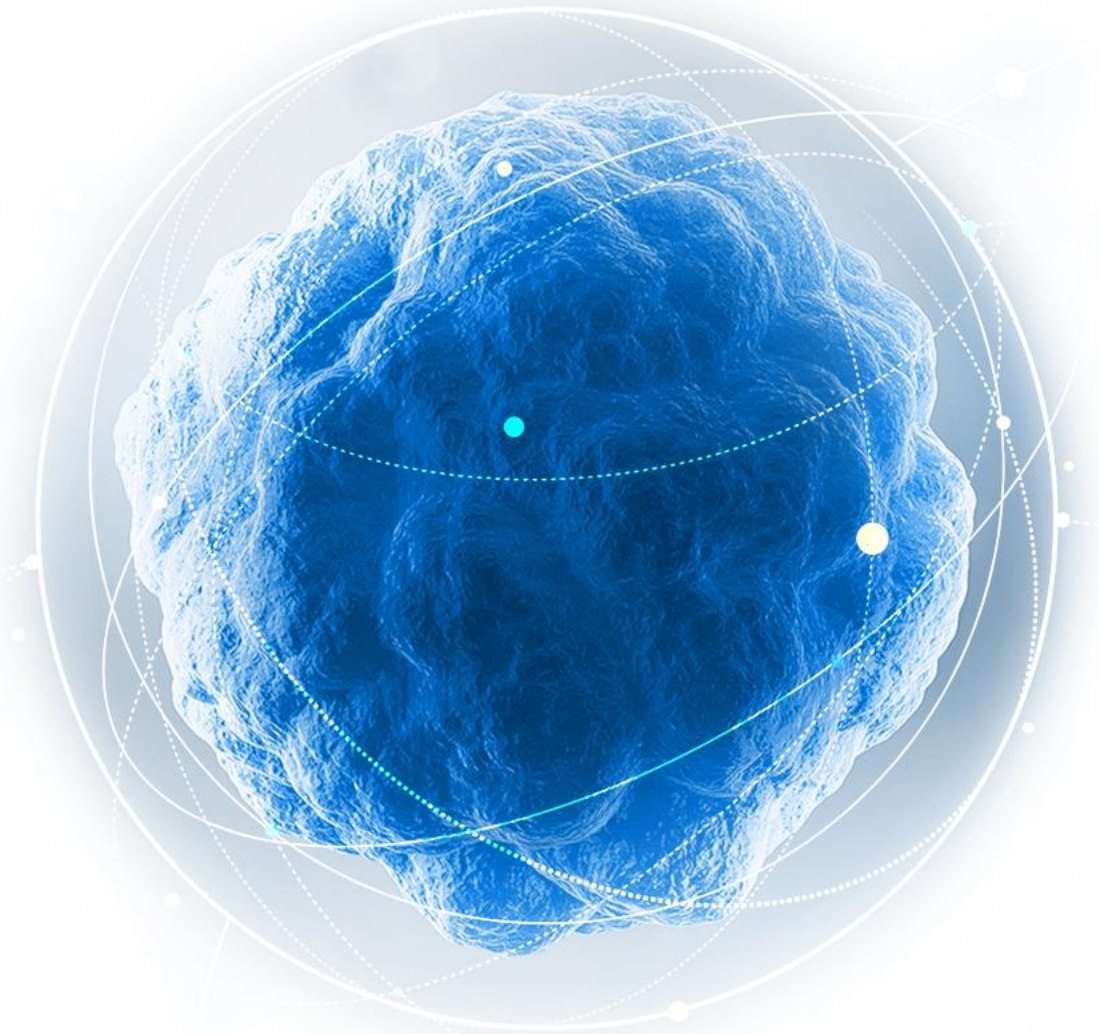

Panel Discussion: Advances and Next Steps

Eric S. Winer (moderator)

All speakers invited to join

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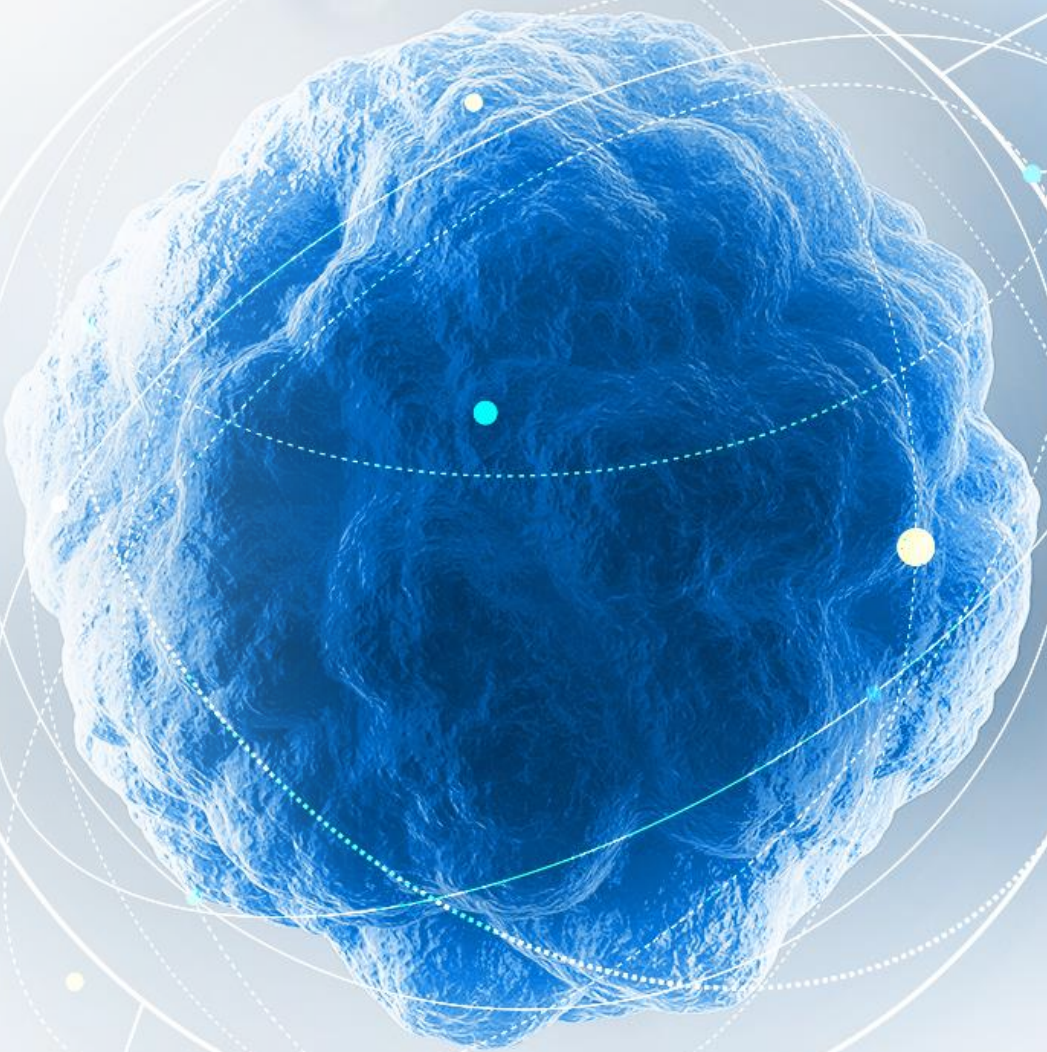
Discussion Questions

- What do you think is the main role of IRAK4 inhibition as an anti-cancer mechanism? A signaling inhibitor, an anti-inflammatory agent, a T-cell exhaustion fixer, or something else?
- Do you see most benefit for emavusertib as a monotherapy or as part of a combination regimen? What combinations?
- What are the most important safety signals to consider in developing emavusertib alone and in combination?
  - Which patients might be considered for a modified dosing approach?
- Are there additional malignancies outside those discussed in this symposium where TLR-IRAK4 pathway activation may play a role in either initial pathogenesis or treatment resistance?
- How do you see the treatment landscape for the malignancies discussed today changing? How would emavusertib fit into this landscape?
- Do you expect specific mutationally defined subtypes to be more likely to respond to emavusertib?
- What advances in treatment do you hope to see in the next 5 years?

IRAK4 | Symposium

Thank you!



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