Handicapping the Field

Novel Oral Agents in Leukemia Management

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Objectives

1. COMPARE AND CONTRAST THE PHARMACOLOGY OF ASCIMINIB WITH BCR-ABL TARGETING TYROSINE KINASE INHIBITORS IN THE TREATMENT OF CHRONIC MYELOID LEUKEMIA

2. SUMMARIZE KEY FINDINGS FROM STUDIES DEVELOPING THE USE OF NOVEL ORAL DOUBLET THERAPY FOR THE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA

3. REVIEW NOVEL VENETOCLAX BASED COMBINATION THERAPIES FOR THE TREATMENT OF ACUTE MYELOID LEUKEMIA

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DISCLOSURE

No Real or Perceived Conflicts of Interest to Disclose

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NOVEL ORAL AGENT SPOTLIGHT

Chronic Myeloid Leukemia

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Chronic Myeloid Leukemia

Novel Oral Agent Spotlight

BCR-abl TKIs	
2001	Imatinib
2006	Dasatinib
2007	Nilotinib
2012	Bosutinib
2012	Ponatinib

STAMP Inhibitors	
2021	Asciminib

NCCN Clinical Practice Guidelines Version 3.2022 – Chronic Myeloid Leukemia, accessed April 2022.

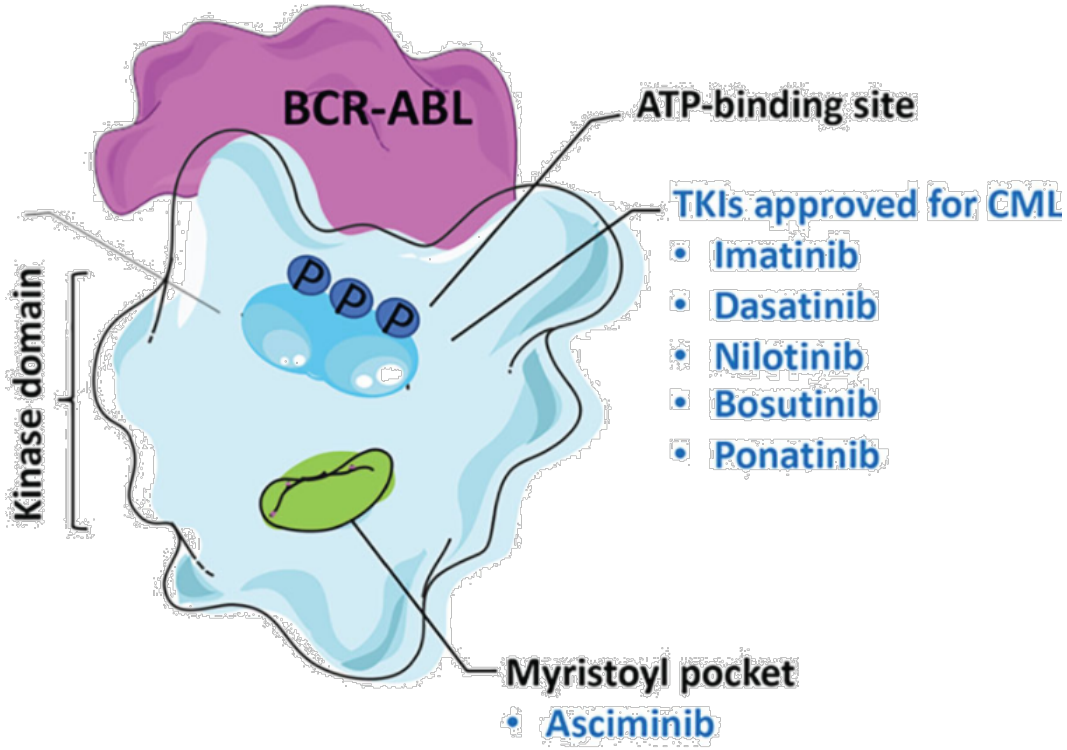
CML

Asciminib

STAMP Inhibitor

***S**electively **T**argeting the **A**BL1 **M**yristoyl **P**ocket*

- Allosteric binding at myristoyl pocket
- Restores inhibition of ABL1 kinase function
- Maintains activity against BCR-ABL1 ATP-site mutations (including T315I)



Andretta E, et al. Potential Approaches Versus Approved or Developing Chronic Myeloid Leukemia Therapy. *Front. Oncol.*, 15 December 2021 | https://doi.org/10.3389/fonc.2021.801779.
Hughes TP, et al. Asciminib in Chronic Myeloid Leukemia after ABL Kinase Inhibitor Failure. *N Engl J Med 2019*;381:2315-26.

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Horse Betting 101

Single Horse Bets

Win = Betting a horse to win the race

Place = Betting a horse will finish first or second

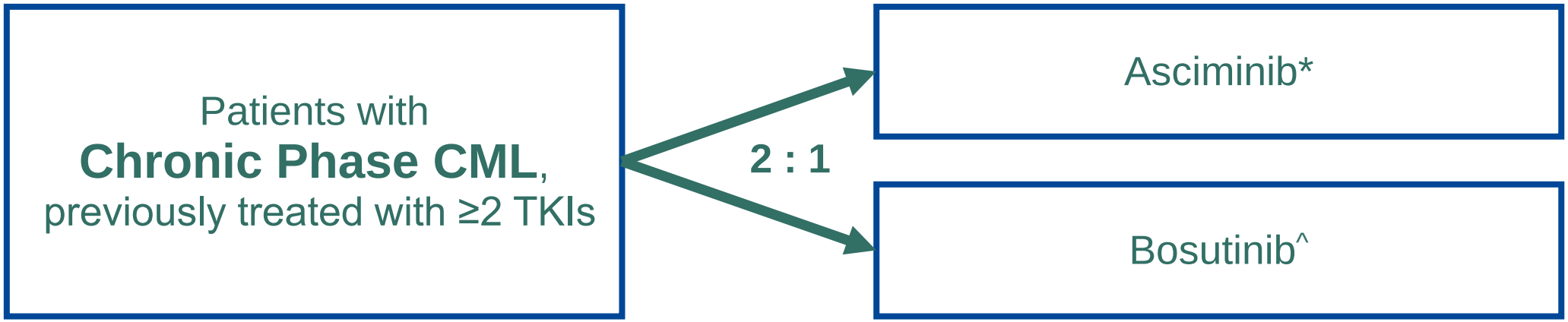
Show = Betting a horse will finish first, second, or third

CML

Asciminib

ASCEMBL Trial

- Phase 3, Randomized, Open Label, Active Controlled Trial



*Asciminib 40 mg PO twice daily

^Bosutinib 500 mg PO daily

Rea D, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. *Blood* 2021;138(21):2031–2041.

CML

Asciminib - ASCEMBL Trial - Baseline Demographics

Characteristic	Asciminib (n=157)	Bosutinib (n=76)
Median Age	52 years	52 years
Sex		
Male	82 (48%)	45 (59%)
Female	75 (52%)	31 (41%)
MCyR at Enrollment	46 (29%)	22 (29%)
Number of prior TKIs		
2	82 (52%)	30 (40%)
3	44 (28%)	29 (38%)
≥4	31 (20%)	17 (22%)
Reason for discontinuation of last TKI		
Lack of efficacy	95 (60%)	54 (71%)
Lack of tolerability	59 (38%)	22 (29%)
Other	3 (2%)	0 (0%)
BCR-ABL1^{IS} at baseline		
>0.1% to ≤1%	15 (9%)	4 (5%)
>1% to ≤10%	45 (29%)	23 (30%)
>10%	97 (62%)	49 (65%)

Rea D, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. *Blood* 2021;138(21):2031–2041.

CML

Asciminib

ASCEMBL Trial

- Efficacy Results

Primary Outcome: MMR Rate at Week 24

- 25.5% vs. 13.2% (p=0.029)

Secondary Outcomes:

- BCR-ABL1^{IS} <10% at week 12: 63.1% vs. 43.4%
- BCR-ABL^{IS} <1% at week 24: 49% vs 23.7%
- CCyR at week 24: 40.8% vs. 24.2%

Rea D, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. *Blood* 2021;138(21):2031–2041.

CML - Asciminib

ASCEMBL Trial – Safety Results

Adverse Event	Asciminib (n=156)		Bosutinib (n=76)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Thrombocytopenia	45 (29%)	34 (22%)	14 (18%)	7 (9%)
Neutropenia	34 (22%)	28 (18%)	16 (21%)	11 (15%)
Diarrhea	18 (11%)	0	54 (71%)	8 (11%)
Nausea	18 (11%)	1 (1%)	35 (46%)	0
Hypertension	18 (11%)	9 (6%)	3 (4%)	3 (4%)
Rash	11 (7%)	0	18 (24%)	3 (4%)
Arthralgia	14 (9%)	0	1 (1%)	0
Increased Amylase	9 (6%)	1 (1%)	4 (5%)	0
Increased Lipase	8 (5%)	6 (4%)	5 (7%)	3 (4%)
Increased ALT	6 (4%)	1 (1%)	21 (28%)	11 (15%)
Increased AST	6 (4%)	1 (1%)	16 (21%)	5 (7%)

Rea D, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. *Blood* 2021;138(21):2031–2041.

CML

ASCEMBL Trial – Safety Results

Treatment Discontinuation due to Adverse Event:

Asciminib 5.8%

Bosutinib 21.1%

Dose Reduction Required due to Adverse Event:

Asciminib 21.2%

Bosutinib 42.1%

Arterial Occlusive Events:

Asciminib 3.2%

Bosutinib 1.3%

Rea D, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. *Blood* 2021;138(21):2031–2041.

CML

Asciminib Pearls

- FDA Approved October 29, 2021
  - Chronic Phase CML:
    - 40 mg PO BID or 80 mg PO daily
  - If T315I Mutation (+):
    - 200 mg PO BID
  - Administer on an empty stomach
    - Food decreases absorption
- Metabolism
  - CYP3A4 Substrate
  - Inhibitor of CYP3A4, CYP2C9, PGP

Asciminib (Scemblix) [package insert]. East Hanover, NJ. Novartis PHarmaceuticals; 2020.

NOVEL ORAL AGENT SPOTLIGHT

Chronic Lymphocytic Leukemia

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Chronic Lymphocytic Leukemia

Novel Oral Agent Spotlight

BTK Inhibitors	
2013	Ibrutinib
2017	Acalabrutinib
2019	Zanubrutinib*
-	Pirtobrutinib^

BCL-2 Inhibitors	
2016	Venetoclax

PI3K Inhibitors	
2014	Idelalisib
2018	Duvelisib

IMIDs	
2005	Lenalidomide*

*Off Label Use in CLL

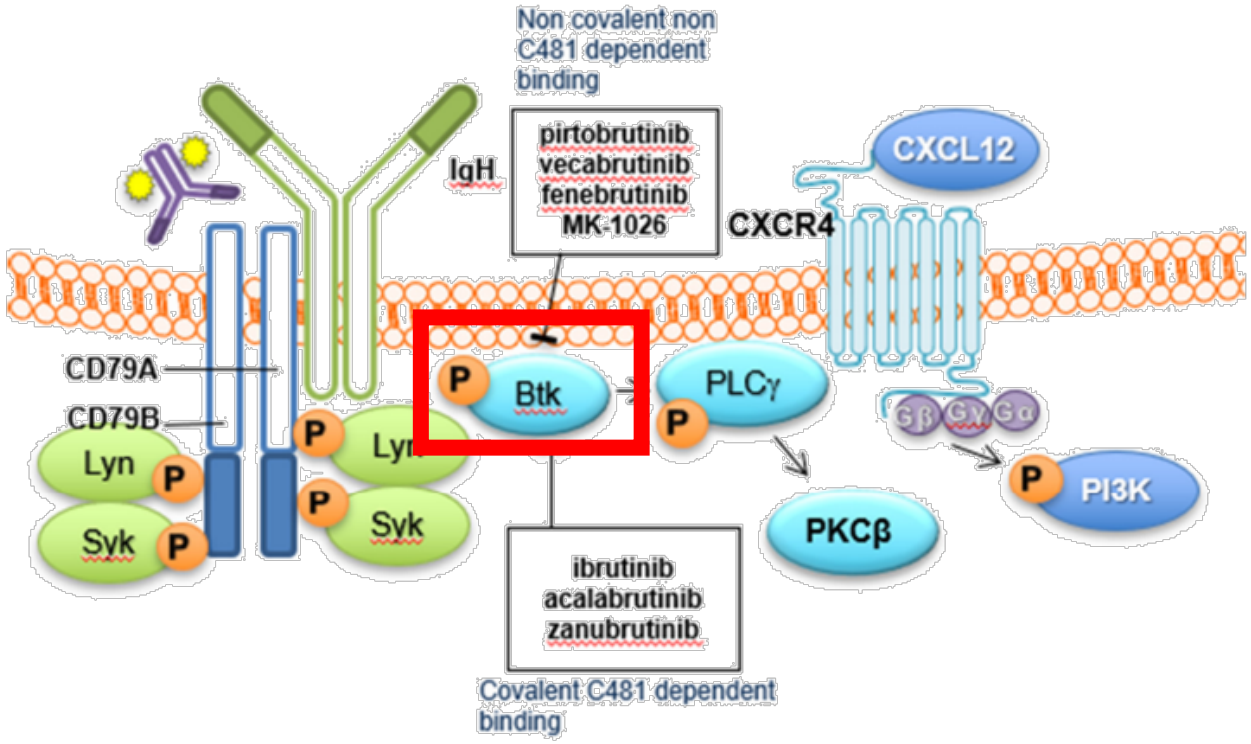
^Not Currently FDA Approved

NCCN Clinical Practice Guidelines Version 2.2022 – Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma, accessed April 2022.

Chronic Lymphocytic Leukemia

Bruton Tyrosine Kinase Inhibitors

- Covalent Inhibitors
  - **Ibrutinib, Acalabrutinib, Zanubrutinib**
  - Irreversibly binds BTK at Cysteine 481
  - Notable Toxicities
    - Atrial Fibrillation
    - Hypertension
    - Bleeding
- Non-Covalent Inhibitor
  - **Pirtobrutinib** (LOXO-305)
  - Selective, Reversible inhibition of BTK

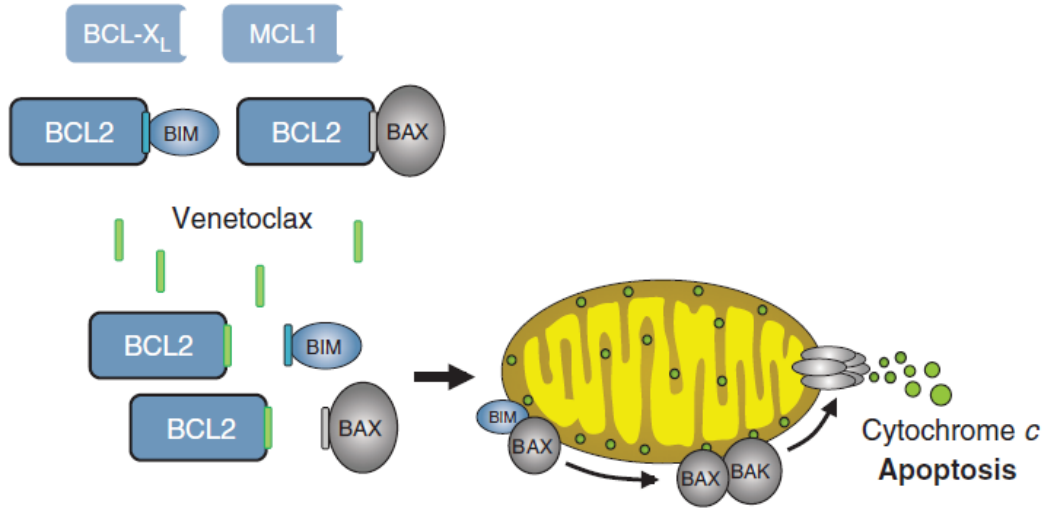


Lewis K, et al. Non-Covalent BTK Inhibitors—The New BTKids on the Block for B-Cell Malignancies. *J. Pers. Med.* 2021, 11, 764. https://doi.org/10.3390/jpm11080764

Chronic Lymphocytic Leukemia

B Cell Lymphoma 2 (BCL-2) Inhibitor

- BCL-2
  - Antiapoptotic Protein
  - Over expressed in variety of hematologic malignancies
- **Venetoclax**
  - BCL-2 Inhibitor
  - Metabolism:
    - CYP3A4, P-glycoprotein substrate
  - Notable Toxicities:
    - Tumor Lysis Syndrome
    - Cytopenias



Konopleva M et al. Efficacy and Biological Correlates of Response in a Phase II Study of Venetoclax Monotherapy in Patients with Acute Myelogenous Leukemia. *Cancer Discov* 2016:6(10);1106–17.

Horse Betting 101

Two Horse Bets

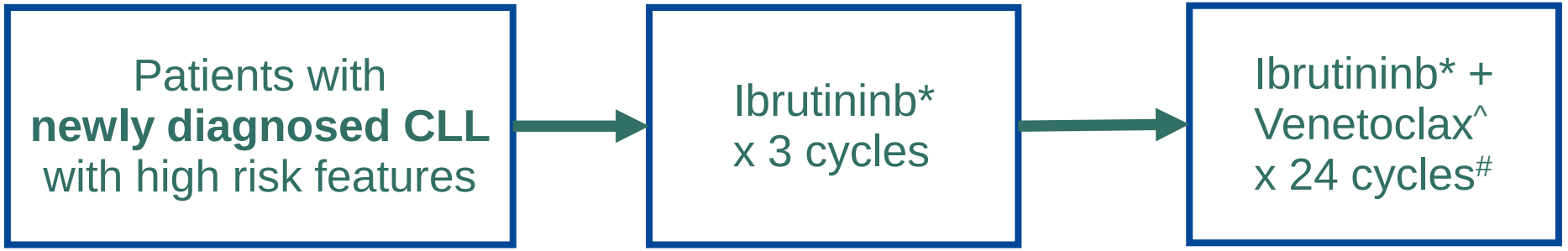
Exacta = Betting on two horses to finish first and second in exact order

CLL Exacta

Ibrutinib + Venetoclax

Jain et al. *JAMA Oncol* 2021

- Phase 2, Single Center, Non Randomized Trial



*Ibrutinib 420 mg PO daily

^Venetoclax standard 5 week ramp up to 400 mg PO daily

#Therapy could be continued x 12 additional cycles if MRD detectable in BM at end of therapy

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Jain N, et al. Ibrutinib Plus Venetoclax for First-line Treatment of Chronic Lymphocytic Leukemia A Nonrandomized Phase 2 Trial. *JAMA Oncol*. 2021;7(8):1213-1219.

CLL Exacta

Ibrutinib + Venetoclax

Jain et al. *JAMA Oncol* 2021

- Baseline Demographics

Characteristic	Enrolled patients (n=80)
Median Age	65 years (26-83)
Sex	
Male	57 (71%)
Female	23 (29%)
Rai Stage III-IV	41 (51%)
Baseline ALC	75.6 x 10^9/L (1.1-338)
CLL Risk Factors	
del(17p)	14 (18%)
dell(11p)	20 (25%)
TP53 Mutated	11 (14%)
IGHV Unmutated	63 (83%)
Complex Karyotype	12 (15%)

Jain N, et al. Ibrutinib Plus Venetoclax for First-line Treatment of Chronic Lymphocytic Leukemia A Nonrandomized Phase 2 Trial. *JAMA Oncol*. 2021;7(8):1213-1219.

CLL Exacta

Ibrutinib + Venetoclax

Jain et al. *JAMA Oncol* 2021

- Efficacy Results

Primary Outcome: CR or CR_i as best response at any time

- 62 Patients (78%)

Secondary Outcomes:

- Overall Response Rate: 86% at 12 months; 82% at 24 months
- Undetectable MRD in Bone Marrow: 56% at 12 months, 66% at 24 months
- Progression Free Survival at 3 years: 93%
- Overall Survival at 3 years: 96%

Jain N, et al. Ibrutinib Plus Venetoclax for First-line Treatment of Chronic Lymphocytic Leukemia A Nonrandomized Phase 2 Trial. *JAMA Oncol*. 2021;7(8):1213-1219.

CLL Exacta

Ibrutinib + Venetoclax

Jain et al. *JAMA Oncol* 2021 - Safety Results

Non-Heme Adverse Event	All Grades	Grade ≥3
Easy Bruising	61 (76%)	0
Arthralgia	46 (58%)	2 (2%)
Diarrhea	42 (53%)	0
Nausea/Vomiting	33 (41%)	0
Myalgia	28 (35%)	1 (1%)
Rash	19 (24%)	0
Fatigue	15 (19%)	1 (1%)
Hypertension	13 (16%)	8 (10%)
Atrial Fibrillation/Flutter	12 (15%)	8 (10%)
Mucositis	12 (15%)	0
Increased ALT	5 (6%)	1 (1%)

Hematologic Toxicity:

Grade 3/4 Neutropenia: 51%

Grade 3 Thrombocytopenia: 2%

Infectious Toxicity:

Febrile Neutropenia: 5%

Infection Requiring Hospitalization: 18%

Jain N, et al. Ibrutinib Plus Venetoclax for First-line Treatment of Chronic Lymphocytic Leukemia A Nonrandomized Phase 2 Trial. *JAMA Oncol*. 2021;7(8):1213-1219.

CLL Exacta

Ibrutinib + Venetoclax

- Conclusions
  - Impressive PFS
  - High rates of Undetectable MRD facilitates fixed duration strategies
- Future Directions
  - CAPTIVATE Trial
    - MRD directed duration and fixed duration approaches to Ibrutinib + Venetoclax therapy
  - GLOW Trial
    - Fixed duration Ibrutinib + Venetoclax vs. Chlorambucil + Obinituzumab in older or unfit new CLL
  - CLL13 Trial
    - Fixed duration Ibrutinib + Venetoclax + Obinituzumab vs. Fixed duration Venetoclax + Obinituzumab vs. Fixed duration Venetoclax + Rituximab vs. Chemoimmunotherapy in fit patients with new CLL

NOVEL ORAL AGENT SPOTLIGHT

Acute Myeloid Leukemia

Froedtert & Medical College of Wisconsin

Acute Myeloid Leukemia

Novel Oral Agent Spotlight

FLT-3 Inhibitors

2005	Sorafenib*
2017	Midostaurin
2018	Gilteritinib
-	Quizartinib^

BCL-2 Inhibitors

2018	Venetoclax

Hedgehog Inhibitors

2018	Glasdegib

IDH Inhibitors

2017	Enasidenib
2018	Ivosidenib

Hypomethylating Agents

2020	Decitabine/ Cedazurine*
2020	Azacitidine

*Off Label Use in AML

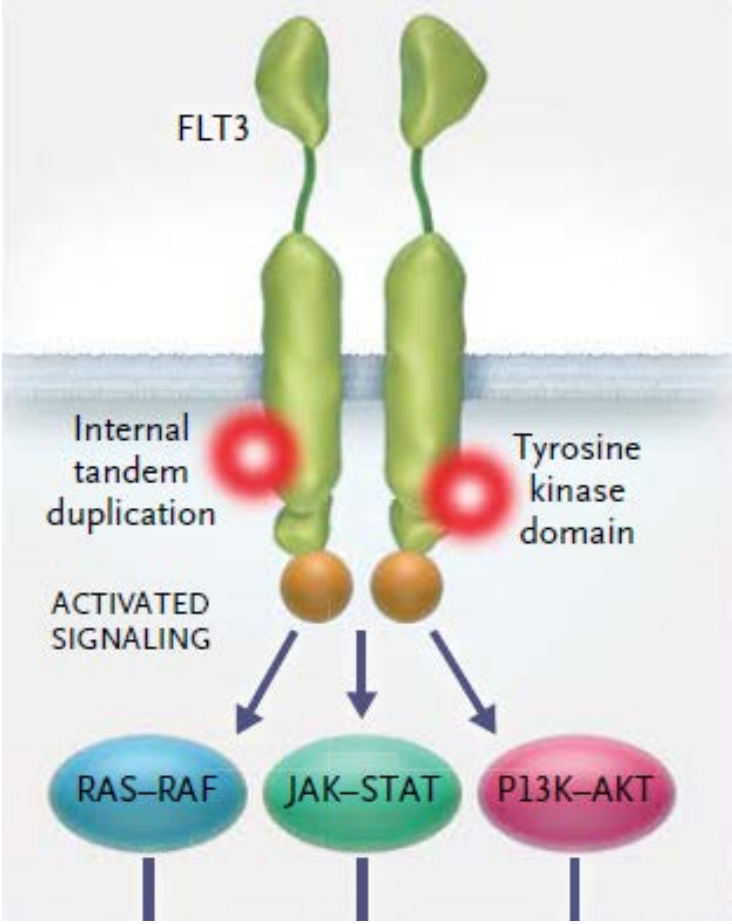
^Not Currently FDA Approved

NCCN Clinical Practice Guidelines Version 1.2022 – Acute Myeloid Leukemia, accessed April 2022.

Acute Myeloid Leukemia

FMS Like Tyrosine Kinase 3 (FLT-3) Inhibitors

- FLT-3 Mutations Present in ~20-30% of AML
  - ITD = Internal Tandem Duplication
  - TKD = Tyrosine Kinase Domain
- Type 1 FLT-3 Inhibitors
  - Inhibit both FLT-3 ITD and FLT-3 TKD
  - Midostaurin
  - Gilteritinib
- Type 2 FLT-3 Inhibitors
  - Active against FLT-3 ITD, no activity against FLT-3 TKD
  - Sorafenib
  - Quizartinib

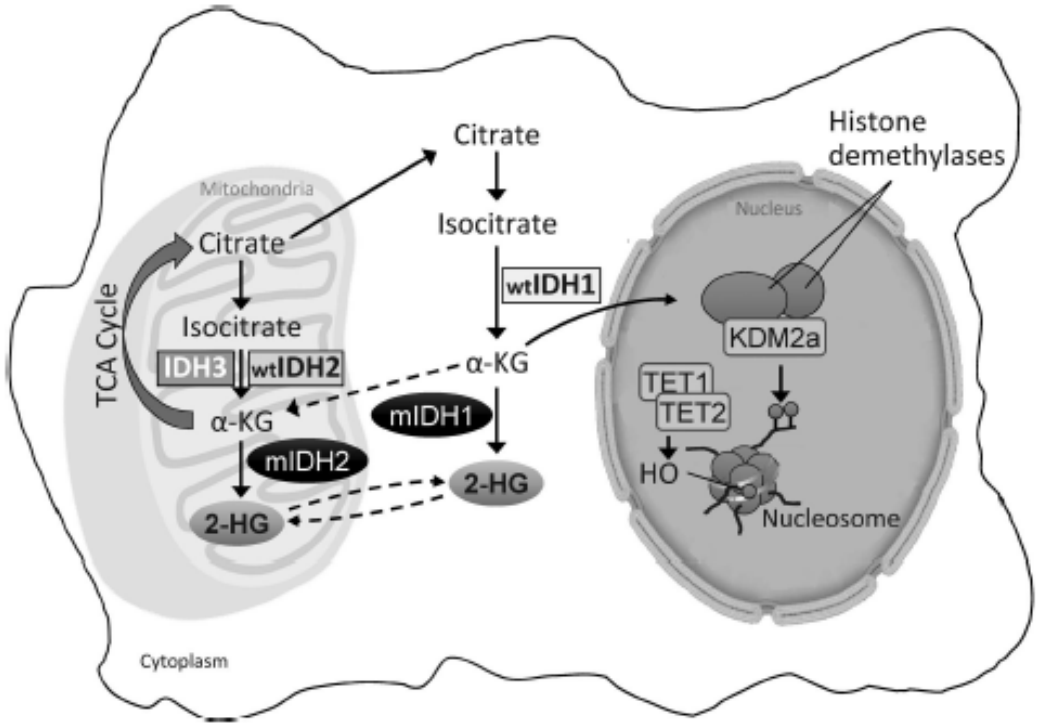


Dohner H, et al. Acute Myeloid Leukemia. *N Engl J Med* 2015;373:1136-52.

Acute Myeloid Leukemia

Isocitrate Dehydrogenase 1 and 2 Inhibitors

- IDH1 Mutations Present in 5-10% of AML
- IDH1 Inhibitor:
  - **Ivosidenib**
- IDH2 Mutations Present in 10-15% of AML
- IDH2 Inhibitor:
  - **Enasidenib**
- Mechanism:
  - Inhibition of mIDH production of oncometabolite 2-HG
- Toxicities:
  - Differentiation Syndrome
  - Leukocytosis



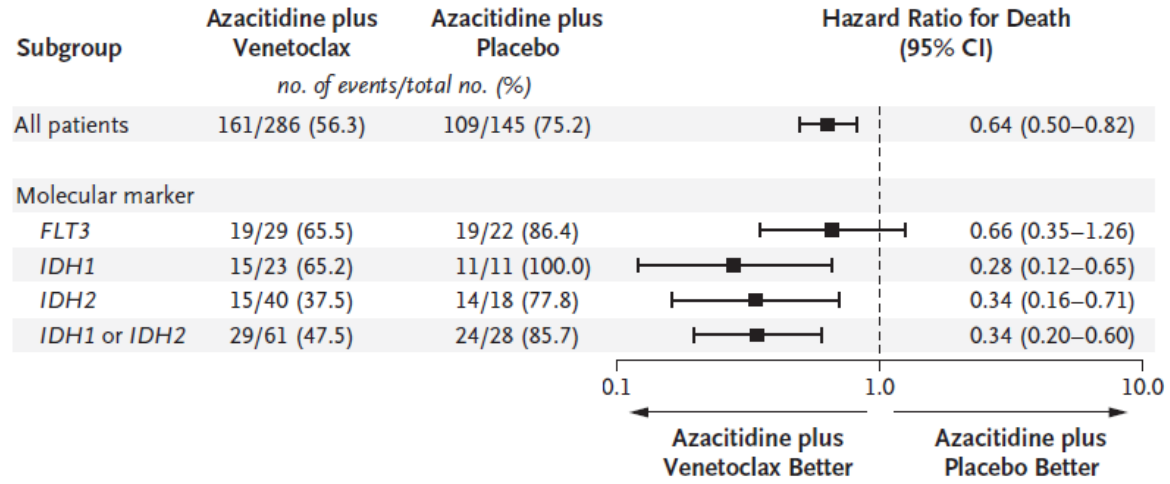
Medeiros BC, et al. Isocitrate dehydrogenase mutations in myeloid malignancies. *Leukemia* 2017:31;272–281.

AML Exacta

Azacitidine + Venetoclax

- **VIALE-A Trial**
  - Azacitidine + Venetoclax vs. Azacitidine + Placebo for newly diagnosed AML
- **Overall Survival**
  - 14.7 months vs. 9.6 months (p<0.001)
- **Complete Remission**
  - 36.7% vs. 17.9% (p<0.001)
- **Composite Complete Remission** (CR + CR_i)
  - 66.4% vs. 28.3% (p<0.001)

Figure 3. Subgroup Analysis of Overall Survival.



DiNardo C, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. *N Engl J Med* 2020;383:617-29.

AML Exactas

Azacitidine + Targeted Oral Agents

- **AGILE Trial**
  - **Azacitidine*** + **Ivosidenib** 500 mg PO daily vs. Azacitdine* + Placebo
  - Newly diagnosed IDH1 AML
  - Overall Survival
    - 24 months vs. 7.9 months (p=0.001)
  - Complete Remission
    - 47% vs. 15% (p<0.001)
  - Composite Complete Remission (CR + CR_h)
    - 53% vs. 18% (p<0.001)

- **AG221-AML-005 Trial**
  - **Azacitidine*** + **Enasidenib** 100 mg PO daily vs. Azacitdine* + Placebo
  - Newly diagnosed IDH2 AML
  - Overall Survival
    - 22 months vs. 22.3 months (p=0.93)
  - Complete Remission
    - 54% vs. 12% (p<0.0001)
  - Composite Complete Remission (CR + CRi + CR_p) 63% vs. 30% (p=0.0019)

- **LACEWING Trial**
  - **Azacitidine*** + **Gilteritinib** 120 mg PO daily vs. Azacitdine* + Placebo
  - Newly diagnosed FLT3 AML
  - Overall Survival
    - 9.8 months vs. 8.9 months (p=0.753)
  - Complete Remission
    - 16.2% vs. 14.3% (p=not reported)
  - Composite Complete Remission (CR + CRi + CR_p)
    - 58.1% vs. 26.5% (p<0.001)

*Azacitidine 75 mg/m2 IV or SQ Days 1-7 of 28 day cycles

Montesinos P, et al. Ivosidenib and Azacitidine in IDH1-Mutated Acute Myeloid Leukemia. *N Engl J Med* 2022;386:1519-31.
DiNardo C, et al. Enasidenib plus azacitidine versus azacitidine alone in patients with newly diagnosed, mutant-IDH2 acute myeloid leukaemia (AG221-AML-005): a single-arm, phase 1b and randomised, phase 2 trial. *Lancet Oncol* 2021; 22: 1597–608.
Wang E, et al. Phase 3, Open-Label, Randomized Study of Gilteritinib and Azacitidine Vs Azacitidine for Newly Diagnosed FLT3-Mutated Acute Myeloid Leukemia in Patients Ineligible for Intensive Induction Chemotherapy [abstract]. *Blood* 2021; 138 (Supplement 1): 700.

Horse Betting 101

Three Horse Bets

Trifecta = Betting on three horses to finish first, second, and third in exact order

AML Trifecta

Azacitidine + Venetoclax + FLT3 Inhibitor

- **Short et al – 2021 Phase 1/2 Study**
- **Azacitidine + Venetoclax + Gilteritinib:**
- Cycle 1:
  - Azacitidine 75 mg/m^2 IV or SQ D 1-7 + Venetoclax 400 mg PO daily x 14-28 days + Gilteritinib 80-120 mg PO daily x 14-28 days
- Cycle 2+:
  - Azacitidine 75 mg/m^2 IV or SQ x 5-7 days Venetoclax 400 mg PO daily x 7-14 days + Gilteritinib 80-120 mg PO daily
- Recommended Phase 2 Dose of Gilteritinb = 80 mg

Outcome	ND AML (n= 11)	RR AML (n=15)
Median OS	Not Reached	10.5 months
CR	73%	7%
CR_c	82%	27%

- **Yilmaz et al – 2021 Phase 1/2 Study**
- **Decitabine + Venetoclax + Quizartinib:**
- Cycle 1:
  - Decitabine 20 mg/m^2 IV D 1-10 + Venetoclax 400 mg PO daily x 14-21 days + Quizartinib 30-40 mg PO daily
- Cycle 2+:
  - Decitabine 20 mg/m^2 IV D 1-5 Venetoclax 400 mg PO daily x 14 days+ Quizartinib 30-40 mg PO daily
- Recommended Phase 2 Dose of Quizartinib = 30 mg

Outcome	ND AML (n= 5)	RR AML (n=23)
Median OS	14.5 months	7.5 months
CR	40%	13%
CR_c	100%	65%

Short N, et al. A Triplet Combination of Azacitidine, Venetoclax and Gilteritinib for Patients with FLT3-Mutated Acute Myeloid Leukemia: Results from a Phase I/II Study. *Blood* (2021) 138 (Supplement 1): 696. https://doi.org/10.1182/blood-2021-153571
Yilmaz M, et al. Quizartinib (Quiz) with Decitabine (DAC) and Venetoclax (VEN) Is Highly Active in Patients (pts) with FLT3-ITD Mutated Acute Myeloid Leukemia (AML) - RAS/MAPK Mutations Continue to Drive Primary and Secondary Resistance. *Blood* (2021) 138 (Supplement 1): 370. https://doi.org/10.1182/blood-2021-153426

AML Trifecta

Azacitidine + Venetoclax + IDH Inhibitor

- **Lachowiez et al – 2021 Phase 1/2 Study**
- **Venetoclax + Ivosidenib +/- Azacitidine**
- Dose Level 3 (Triplet Cohort)
  - Azacitidine 75 mg/m^2 IV or SQ D 1-7 + Venetoclax 400 mg PO daily x 14 days + Ivosidenib 500 mg PO daily x D 15-28 in C1, continuous in C2+

Outcome	AZA + VEN + IVO (n=13)
Median OS	Not Reached
CR	54%
CR_c	85%

- **Venugopal et al – 2022 Phase 2, Open Label Study**
- **Azacitidine + Enasidenib +/- Venetoclax**
- Triplet Cohort:
  - Azacitidine 75 mg/m^2 IV or SQ D 1-7 + Enasidenib 100 mg PO daily continuously + Venetoclax addition allowed as indicated

Outcome	AZA + VEN + ENA (n=7)
Median OS	Not Reached
CR	71%
CR_c	86%

Lachowiez C, et al. A phase Ib/II study of ivosidenib with venetoclax +/- azacitidine in IDH1-mutated myeloid malignancies. *Journal of Clinical Oncology* - published online before print May 28, 2021. DOI: 10.1200/JCO.2021.39.15_suppl.7012
Venugoapl S, et al. Efficacy and safety of enasidenib and azacitidine combination in patients with IDH2 mutated acute myeloid leukemia and not eligible for intensive chemotherapy. *Blood Cancer Journal* (2022) 12:10 ; https://doi.org/10.1038/s41408-021-00604-2

Horse Betting 101

Four Horse Bets

Superfecta = Betting on four horses to finish first, second, third, and fourth in exact order

AML Superfecta

FLAG + Ida + Venetoclax

DiNardo et al. *J Clin Oncol* 2021

- Phase 1b/2, Single Arm, Dose Finding and Dose Expansion Trial

Phase 1b Induction:

Patients with **Relapsed or Refractory AML**

→

Fludarabine 30 mg/m^2 IV D2-6

Cytarabine* 1.5-2 g/m^2 IV D2-6

Filgrastim 5 mcg/kg SQ D1-7

Idarubicin 6 mg/m^2 IV D4-5

+

Dose Level -1

Venetoclax^ 200 mg PO D 1-21

Alternate Dose Level -1

Venetoclax^ 200 mg PO D 1-14

Dose Level 0:

Venetoclax^ 400 mg PO D 1-14

*Cytarabine Dosing: Dose Level -1 = 2 g/m^2; Alternate Dose Level -1 and Dose Level 0 = 1.5 g/m^2

^Venetoclax dose was titrated per standard dosing instructions

DiNardo C, et al. Venetoclax Combined With FLAG-IDA Induction and Consolidation in Newly Diagnosed and Relapsed or Refractory Acute Myeloid Leukemia *J Clin Oncol* 2021 *39:2768-2778.*

AML Superfecta

FLAG – Ida – Venetoclax

DiNardo et al. *J Clin Oncol* 2021

- Phase 1b/2, Single Arm, Dose Finding and Dose Expansion Trial

Phase 2a Induction:

Patients with **Newly diagnosed AML or High Risk MDS**

→

Fludarabine 30 mg/m^2 IV D2-6

Cytarabine 1.5 g/m^2 IV D2-6

Filgrastim 5 mcg/kg SQ D1-7

Idarubicin 8 mg/m^2 IV D4-6

+

Dose Level 0:

Venetoclax 400 mg PO D 1-14

^Venetoclax dose was titrated per standard dosing instructions

Consolidation: Fludarabine + Cytarabine D2-4, Filgrastim D1-5, Venetoclax D1-7, Idarubicin (at MD discretion in up to two cycles) D3-4

DiNardo C, et al. Venetoclax Combined With FLAG-IDA Induction and Consolidation in Newly Diagnosed and Relapsed or Refractory Acute Myeloid Leukemia *J Clin Oncol* 2021 *39:2768-2778.*

AML Superfecta

FLAG – Ida – Venetoclax

DiNardo et al. *J Clin Oncol* 2021

- Phase 1b/2, Single Arm, Dose Finding and Dose Expansion Trial

Phase 2b:

Patients with **Relapsed or Refractory AML**

→

Fludarabine 30 mg/m^2 IV D2-6

Cytarabine 1.5 g/m^2 IV D2-6

Filgrastim 5 mcg/kg SQ D1-7

Idarubicin 6 mg/m^2 IV D4-5

+

Dose Level 0:

Venetoclax 400 mg PO D 1-14

^Venetoclax dose was titrated per standard dosing instructions

Consolidation: Fludarabine + Cytarabine D2-4, Filgrastim D1-5, Venetoclax D1-7, Idarubicin (at MD discretion in up to two cycles) D3-4

DiNardo C, et al. Venetoclax Combined With FLAG-IDA Induction and Consolidation in Newly Diagnosed and Relapsed or Refractory Acute Myeloid Leukemia *J Clin Oncol* 2021 *39:2768-2778.*

AML Superfecta

FLAG – Ida – Venetoclax

DiNardo et al. *J Clin Oncol* 2021

- Baseline Demographics

Characteristic	Phase 2a – ND AML (n=29)	Phase 1b – RR AML (n=16)	Phase 2b – RR AML (n=23)
Median Age	45 years	51 years	47 years
Male Sex	13 (45%)	10 (62%)	14 (61%)
ELN Risk Group Favorable Intermediate Adverse	 5 (17%) 13 (45%) 11 (38%)	 6 (38%) 2 (12%) 8 (50%)	 6 (26%) 3 (13%) 14 (61%)
Median Bone Marrow Blast %	41%	63%	46%
Median Lines of Prior Therapies	-	2 (1-6)	1 (1-3)
Prior HSCT	-	7 (44%)	7 (30%)

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- Efficacy Results

CRc Rates

- Phase 2a – ND AML (n=29) – 90%
- Phase 1b – RR AML (n=16) – 75%
- Phase 2b – RR AML (n=23) – 61%

12 Month Overall Survival

- Phase 2a – ND AML (n=29) – 94%
- Phase 1b – RR AML (n=16) – 38%
- Phase 2b – RR AML (n=23) – 68%

38 Patients Progressed to HSCT

- ND AML: 20 patients (69%)
- RR AML: 18 patients (46%)

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- Safety Results

Toxicity	Phase 2a – ND AML (n=29)	Phase 1b – RR AML (n=16)	Phase 2b – RR AML (n=23)
Median Time to ANC > 500 and Platelet > 50,000	31 days	37 days	37 days
Febrile Neutropenia	14 (48%)	8 (50%)	12 (52%)
Bacteremia	6 (21%)	8 (50%)	10 (43%)
Pneumonia	8 (28%)	4 (25%)	7 (30%)
Sepsis	3 (10%)	4 (25%)	1 (4%)

30 Day Mortality = 0%
60 Day Mortality = 4.4%

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AML

Novel Oral Agent Combination Regimens

- Exactas
  - Azacitidine + Venetoclax Odds on Favorite
  - Azacitidine + Ivosidenib potentially closing the gap
- Trifectas
  - Azacitidine + Venetoclax + FLT-3 Inhibitor potent combination, but limited by toxicity
  - Azacitidine + Venetoclax + IDH inhibitor in early phases of development
- Superfecta
  - FLAG + Ida + Venetoclax effective bridge to transplant strategy in R/R AML

Questions?

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Handicapping the Field

Novel Oral Agents in Leukemia Management

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MAY 7, 2022

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