LETTER TO THE EDITOR

Investigational venetoclax combination therapy in acute myeloid leukemia – a systematic review and meta-analysis

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- Supplementary File –

Venetoclax combination therapy in acute myeloid leukemia – a systematic review and meta-analysis

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Supplemental Table 1. Investigational venetoclax based regimens

Author (ref.) & Publication year	Venetoclax Combination	Pop.	N	Overall response rate (N, %)	Complete remission (N, %)	MRD negativity (N, %)	Grade 3/4 infection (N, %)	30d mortality (N, %)
Venetoclax + intensive chemotherapy combination								
Chua et al.(1) 2020	"5+2" ara-C+ Ida	ND	51	37, 72%	21, 41%	5/6, 83%	28, 55%	3, 6%
Kadia et al.(2) 2021	Clad+ara-C+ Ida	ND	50	47, 94%	42, 84%	37/45, 82%	42, 84%	1, 2%
Abuasab et al.(3) 2021	Clad+ ara-C+ Ida Gilteritinib	ND	8	7, 87.5%	7, 87.5%	6/7, 85.7%	-	0, 0%
Pullarkat et al.(4) 2021	CPX351	ND	21	10, 50%	8, 40%	-	13, 62%	1, 4.8%
Wang et al.(5) 2021	"7+3" Dauno + ara-C	ND	32	29, 90.6%	29, 90.6%	19/29, 65.5%	26, 81%	0, 0%
Stone et al.(6) 2020	"7+3" Dauno + ara-C	ND	13	10, 100%	9, 90%	6/8, 75%	5, 38.5%	2, 15.4%
Lachowiez et al.(7) 2021	Flu+ ara-C+ Ida + G-CSF	ND	41	40, 97.6%	30, 73.2%	33/36, 91.7%	16, 39%	0, 0%
Marconi et al.(8) 2020	Flu+ ara-C+ Ida	ND	6	5, 100%	3, 60%	-	5, 100%	1, 16.7%
Kim et al.(9) 2021	CPX351	ND + R/R	ND 5 R/R 26	ND 4, 80% R/R 12, 46%	ND 1, 20% R/R 4, 15.4%	ND 3/4 75% R/R 7/9, 78%	19, 61%	ND 0, 0% R/R 3, 11.5%
Dinardo et al.(10) 2021	Flu+ ara-C+ Ida + G-CSF	ND + R/R[a]	ND 29 R/R 39	ND 28, 97% R/R 28, 2%	ND 20, 69% R/R 17, 44%	ND 25, 86% R/R 18/26, 69%	ND 14, 48% R/R 20, 51%	ND 0, 0% R/R 0,0%
Shahswar et al.(11) 2021	Flu+ ara-C+ Ida	R/R	30	22, 73%	-	8/17, 47%	21, 70%	-
Venetoclax + immunotherapy combination								
Roboz et al.(12) 2021	Aza+ Cusatuzumab	ND	44	34, 81%	20, 47%	16/34, 47%	16, 36%	2, 4.5%
Daver et al.(13) 2021	Magrolimab+ Aza	ND + R/R	ND 17 R/R 21	ND 16, 100% R/R 9, 47%	ND 13, 81% R/R 3, 16%	7/13, 55%	12, 32%	ND 0, 0% R/R 0, 0%
Lane et al.(14) 2021	Aza + Tagraxofusp	ND + R/R	ND 9 R/R 3	ND 8, 89% R/R 0, 0%	ND 5, 56% R/R 0, 0%	-	6, 18%[b]	-
Schiller et al.(15) 2021	Lintuzumab Ac225	R/R	10	2, 20%	-	-	1, 10%	-
Short et al.(16) 2020	Ave / GO + Aza	R/R	Ave 9; GO 19	GO 10, 56%	GO 4, 22%	-	-	Ave 0, 0% GO 2, 11%
Daver et al.(17) 2021	IMGN632 + Aza	R/R	35	16, 55%	1,3%,	-	9, 26%	0, 0%
Venetoclax + low dose chemotherapy therapy								
Reville et al.(18) 2021	Clad + LDAC	ND	60	48, 80%	8, 13%	43/51, 84%	10, 16.7%	1, 1.7%
Zucenka et al.(19) 2021	Actinomycin D + LDAC	R/R	50	36, 73%	25, 51%	19/31, 61%	27, 54%	4, 8%
Yu et al.(20) 2020	Hom. + Azacitidine	R/R	22	11, 65%	7, 47%	6/7, 86%	5, 23%	-
Venetoclax + targeted therapy								
Short et al.(21) 2021	Pevonedistat + Aza	ND	28	20, 71%	13, 46%	8/18, 44%	18, 64%	2, 7%
Chua et al.(22) 2021	LDAC+ Midostaurin / Pracinostat	ND	Mido. 18 Prac. 14	Mido. 13, 72% Prac. 8, 57%	Mido. 7, 39% Prac. 4, 28%	-	Mido. 6, 33% Prac. 6, 43%	Mido. 0, 0% Prac. 2, 14%

Garcia-Manero et al.(23) 2021	Eprenetapopt +/- Aza	ND	47	16, 53%	11, 37%	-	52%	4, 9%
Lachowiez et al.(24) 2021	Ivosidenib +/- Aza	ND + R/R	ND 13 R/R 8	ND 12, 92%[e] R/R 5, 62%[e]	ND 8, 62% R/R 1, 12%	ND 6, 60% R/R 3, 50%	7, 28%	-
Maiti et al.(25) 2021	Decitabine + Sorafenib / Gilteritinib / Midostaurin	ND + R/R	ND 12 R/R 13	ND 11, 91.7% R/R 8, 61.5%	ND 9, 75% R/R 3, 23%	ND 5/9, 55.6% R/R 5/8, 62.5%	10, 40%	ND 0, 0% -
Short et al.(26) 2021	Gilteritinib + Aza	ND + R/R	ND 11 R/R 15	ND 11, 100% R/R 10, 67%	ND 8, 73% R/R 1, 7%	ND 1/11, 9%	ND 0, 0% R/R 0, 0%	ND 0, 0% R/R 2, 13%
Yilmaz et al.(27) 2021	Decitabine + Quizartinib	ND + R/R	ND 6 R/R 25	ND 5, 100% R/R 15, 65%,	ND 2, 40% R/R 3, 13%	ND 4/5 80% R/R 5/14, 36%	32%	ND 0, 0% RR 1, 4%
Ohanian et al.(28) 2021	Decitabine + Prexigebersen	ND + R/R	ND 2 R/R 4	ND 2, 100% R/R 3, 75%,	ND 0, 0% R/R 1, 25%	-	3, 50%	-
Chan et al.(29) 2021	Enasidenib	R/R	11	5, 55%	2, 22%	-	4, 36%	-
Daver et al.(30) 2021	Gilteritinib	R/R	54	38, 74.5%	-	17/30, 56%	-	-
Daver et al.(31) 2019	Idasantulin	R/R	49	20, 41%	3, 6%	5/11, 45%	22, 45%	3, 6%
Daver et al.(32) 2017	Cobimetinib/ Idasanutlin[i]	R/R	Cobi. 22 Idas. 20	Cobi. 4, 18% Idas. 4, 20%	Cobi. 2, 9% Idas. 1, 5%	-	Cobi. 5, 23% Idas. 6, 30%	-
Borthakur et al.(33) 2021	Mivebresib	R/R	25	3, 12%	1, 4%	-	13, 52%	-
Borate et al.(34) 2021	Ruxolitinib	R/R	20	5, 25%	-	-	8, 40%	-
Murthy et al.(35) 2021	Pevonedistat + Aza	R/R	13	6, 50%	-	3/5, 60%	3, 23%	-
Desikan et al.(36) 2021	Trametinib + Aza	R/R	16	4, 26.7%	1, 6.7%	-	-	-

Table 1. Pop – Population; MRD – measurable residual disease; ara-C – cytarabine; Ida- idarubicine; ND – newly diagnosed; Clad – cladribine; Dauno – Daunorubicin; G-CSF – granulocyte colony stimulating factor; Flu – fludarabine; R/R – relapsed or refractory; Aza – azacitidine; Ave – avelumab; GO - gemtuzumab ozogamicin; LDAC – low dose cytarabine; Hom – Homoargitonine; Mido – midostaurin; Prac- pracinostat; Cobi – cobimetinib; Idas – Idasanutlin.

a- Only R/R data was analyzed.

b- Toxicity was assessed in all 33 pts. (18pts. treated with Azacitidine + Tagraxofusp and 15pts. treated with Azacitidine + Tagraxofusp + Venetoclax).

Trials included:1. Chua CC, Roberts AW, Reynolds J, et al. Chemotherapy and Venetoclax in Elderly Acute Myeloid Leukemia Trial (CAVEAT): A Phase Ib Dose-Escalation Study of Venetoclax Combined With Modified Intensive Chemotherapy. J Clin Oncol. 2020 Oct 20;38(30):3506-3517. 2. Kadia TM, Reville PK, Borthakur G, et al. Venetoclax plus intensive chemotherapy with cladribine, idarubicin, and cytarabine in patients with newly diagnosed acute myeloid leukaemia or high-risk myelodysplastic syndrome: a cohort from a single-centre, single-arm, phase 2 trial. The Lancet Haematology. 2021;8(8):e552-e561. 3. Abuasab T, Kantarjian H, Garcia-Manero G, et al. Phase II Study of Cladribine, Idarubicin, Cytarabine (CLIA) Plus Gilteritinib in Patients with FLT3 Mutated Acute Myeloid Leukemia (AML). Blood. 2021;138(Supplement 1):2330-2330.4. Pullarkat VA, Levis M, Mannis GN, et al. Preliminary Results By Age Group of Treatment with CPX-351 Plus Venetoclax in Adults with Newly Diagnosed AML: Subgroup Analysis of the V-FAST Phase 1b Master Trial. Blood. 2021;138(Supplement 1):1268-1268.5. Wang H, Mao L, Xie W, et al. Venetoclax Combined with Daunorubicin and Cytarabine (DAV) As Induction Therapy in De Novo Young Adult Acute Myeloid Leukemia. Blood. 2021;138(Supplement 1):2334-2334.6. Stone RM, DeAngelo DJ, Letai AG, et al. Maximal Tolerated Dose of the BCL-2 Inhibitor Venetoclax in Combination with Daunorubicin/Cytarabine Induction in Previously Untreated Adults with Acute Myeloid Leukemia (AML). Blood. 2020;136(Supplement 1):40-41.

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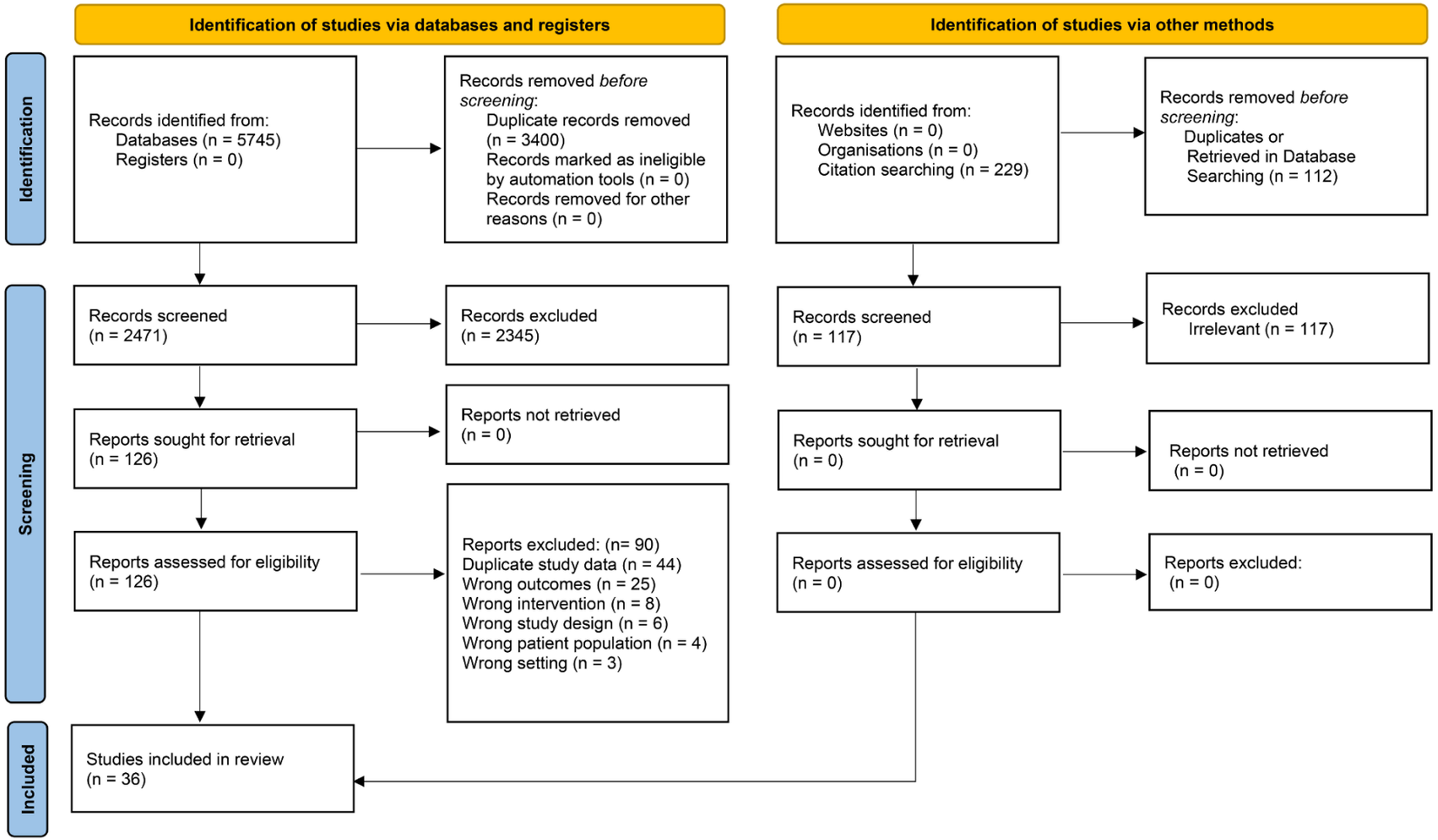
Supplemental Figure 1 – PRISMA diagram



Adapted from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372: n71. doi: 10.1136/bmj. n71. For more information, visit: http://www.prisma-statement.org/

Supplementary table 2: Quality assessment of included studies using Downs and Black checklist

Author (reference)	Reporting bias (Items 1-10; max. 11 points)	External validity bias (Items 11-13; max. 3 points)	Internal validity bias (Items 14-20; max. 7 points)	Internal validity; confounding bias (Items 21-26; max. 6 points)	Power (Item 27; max. 1 point)	Total
Chua et al. 2020(1)	7	2	3	2	0	14
Stone et al. 2020(2)	7	3	3	1	0	14
Marconi et al. 2020(3)	5	2	3	1	0	11
Kadia et al. 2021(4)	7	3	2	2	0	14
Abuasab et al. 2021(5)	6	2	2	1	0	11
Pullarkat et al. 2021(6)	7	2	2	1	0	12
Kim et al. 2021.(7)	6	2	3	1	0	12
Wang et al. 2021(8)	8	3	2	1	0	14
Lachowiez et al. 2021(9)	6	1	3	1	0	11
Roboz et al. 2021(10)	7	2	3	1	0	13
Garcia-Manero et al. 2021(11)	7	2	3	1	0	13
Lachowiez et al. 2021 (2)(12)	7	3	3	1	0	14
Daver et al. 2021(1)(13)	7	3	3	1	0	14
Reville et al. 2021(14)	7	2	3	1	0	13
Chua et al. 2021(15)	7	2	3	1	0	13
Ohanian et al. 2021(16)	6	2	3	1	0	12
Maiti et al. 2021(17)	7	3	3	1	0	14
Short et al. 2021 (1)(18)	5	2	3	1	0	11
Short et al. 2021 (2)(19)	6	2	3	1	0	12
Yilmaz et al. 2021(20)	6	2	3	1	0	12
Lane et al. 2021(21)	6	3	3	1	0	13
Daver et al. 2019(22)	6	2	3	1	0	12
Yu et al. 2020(23)	5	3	3	1	0	12
Short et al. 2020(24)	6	3	3	1	0	13
Dinardo et al. 2021(25)	7	3	3	1	0	14
Shahswar et al. 2021(26)	7	2	3	1	0	13
Zucenka et al. 2021(27)	7	2	3	1	0	13
Chan et al. 2021(28)	6	3	3	1	0	13
Daver et al. 2021 (2)(29)	5	3	3	1	0	12
Daver et al. 2021 (3)(30)	7	3	3	1	0	14
Daver et al. 2017(31)	6	3	3	1	0	13
Schiller et al. 2021(32)	6	3	3	1	0	13
Borthakur et al. 2021(33)	6	3	3	2	0	14
Borate et al. 2021(34)	6	3	3	1	0	13
Murthy et al. 2021(35)	7	3	3	1	0	14
Desikan et al. 2021(36)	6	3	3	1	0	13

Trials included:1. Chua CC, Roberts AW, Reynolds J, et al. Chemotherapy and Venetoclax in Elderly Acute Myeloid Leukemia Trial (CAVEAT): A Phase Ib Dose-Escalation Study of Venetoclax Combined With Modified Intensive Chemotherapy. J Clin Oncol. 2020 Oct 20;38(30):3506-3517. 2. Kadia TM, Reville PK, Borthakur G, et al. Venetoclax plus intensive chemotherapy with cladribine, idarubicin, and cytarabine in patients with newly diagnosed acute myeloid leukaemia or high-risk myelodysplastic syndrome: a cohort from a single-centre, single-arm, phase 2 trial. The Lancet Haematology. 2021;8(8):e552-e561. 3. Abuasab T, Kantarjian H, Garcia-Manero G, et al. Phase II Study of Cladribine, Idarubicin, Cytarabine (CLIA) Plus Gilteritinib in Patients with FLT3 Mutated Acute Myeloid Leukemia (AML). Blood. 2021;138(Supplement 1):2330-2330.4. Pullarkat VA, Levis M, Mannis GN, et al. Preliminary Results By Age Group of Treatment with CPX-351 Plus Venetoclax in Adults with Newly Diagnosed AML: Subgroup Analysis of the V-FAST Phase 1b Master Trial. Blood. 2021;138(Supplement 1):1268-1268.5. Wang H, Mao L, Xie W, et al. Venetoclax Combined with Daunorubicin and Cytarabine (DAV) As Induction Therapy in De Novo Young Adult Acute Myeloid Leukemia. Blood. 2021;138(Supplement 1):2334-2334.6. Stone RM, DeAngelo DJ, Letai AG, et al. Maximal Tolerated Dose of the BCL-2 Inhibitor Venetoclax in Combination with Daunorubicin/Cytarabine Induction in Previously Untreated Adults with Acute Myeloid Leukemia (AML). Blood. 2020;136(Supplement 1):40-41.
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