Updates in Therapy
FLASCO 2023

Prostate Cancer Updates

New FDA Approved Indications & Regimens

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HRRm and BRCAm in Prostate Cancer

- Mutations in homologous recombination repair (HRR) genes, including BRCA 1 and BRCA2 genes, are associated with more aggressive prostate cancer
- PROfound and TRITON3 studies have demonstrated a sustained response with the use of monotherapy poly-ADP ribose polymerase (PARP) inhibitor in metastatic prostate cancer.
- PARP Inhibitors
    1. Castration-resistant tumor cells exhibit increased PARP-1 activity
    2. PARP-1 interacts with androgen signaling
    3. Possible synergy by inhibiting PARP and utilizing androgen receptor (AR) therapy concomitantly
    4. New hormonal agents inhibit transcription of several HRR genes, inducing HRR deficiency and increasing sensitivity to PARP inhibition

De Bono J., Mateo J., Fizazi., et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med, 382 (22) (2020), pp. 2091-2102.
Fizazi K., Piulats J.M., Reaume M.N. Rucaparib or physician's choice in metastatic prostate cancer. N Engl J Med. 2023; 388: 719-732.
Kote-Jarai Z, Leongamornlert D, Saunders E, et al. BRCA2 is a moderate penetrance gene contributing to young-onset prostate cancer: implications for genetic testing in prostate cancer patients. Br J Cancer 2011;105:1230-1234.
Polkinghorn. Cancer Discov. 2013;3:1245. Schiewer. Cancer Discov. 2012;2:1134. Schiewer. Cancer Discov. 2012;2:1134.

FDA Approved Indication and Dosing

TALAPRO2 -Talazoparib + Enzalutamide

Talazoparib in combination with enzalutamide for the treatment of adult patients with homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC).

- **Talazoparib 0.5mg** + enzalutamide 160mg by mouth once daily, with or without food until disease progression or unacceptable toxicity .
- In combination with GnRH analog or patients should have had bilateral orchiectomy.
- Dose adjust talazoparib for baseline renal impairment and any drug drug interactions.

TALZENNA [package insert]. New York, NY: Pfizer, Inc. 2023

TALAPRO-2: Study Design

Phase III study assessing clinical benefit, safety and tolerability of talazoparib + enzalutamide in patients with mCRPC in the first-line setting

Patient population
- 1L treatment at mCRPC stage
- ECOG performance status 0-1
- Ongoing androgen deprivation therapy

Stratification
- Prior abiraterone or docetaxel in castration sensitive setting (Y/N)
- HRR gene alteration status
  - Nondeficient or unknown (n=636)
  - **HRRm (n=399)**

R 1:1
n=399

Talazoparib 0.5* mg QD+
Enzalutamide 160mg QD +
N= 200
*(0.35mg QD if moderate renal impairment)

Placebo +
Enzalutamide 160 mg QD
N= 199

Primary endpoint:
- Radiographic progression or death (rPFS) by BICR

Key secondary endpoints:
- Overall survival (alpha protected)

Other secondary endpoints:
- **Time to cytotoxic chemotherapy**
- **PFS2 by investigator assessment**
- **Objective response rate (ORR)**
- **Patient reported outcomes**
- **Safety**

Agarwal N, et al. *Lancet. 2023* Jun 2:S0140-6736(23)01055-3. doi: 10.1016/S0140-6736(23)01055-3.

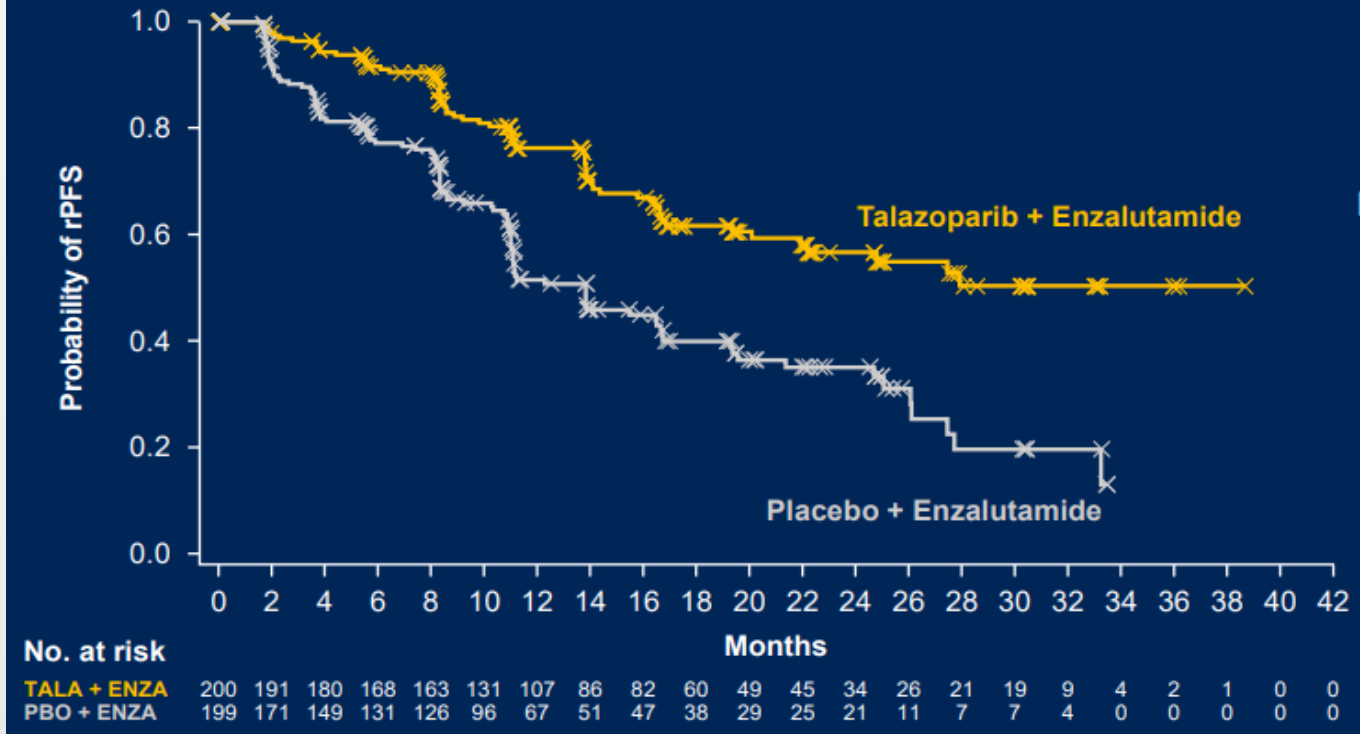
Baseline Characteristics: TALAPRO-2

HRR-Deficient

	Talazoparib + Enzalutamide (n=200)	Placebo + Enzalutamide (n=199)
Median (range) age, years	70 (41-90)	71 (44-90)
Median PSA, ng/mL (range)	19.6 (0.2-3412.0)	18.0 (0.0-1055.0)
Site of metastases, n (%)		
Bone	175 (87.5)	158 (79.4)
Lymph Node	82 (41.0)	94 (47.2)
Visceral (lung/liver)	23 (11.5) / 9 (4.5)	26 (13.1) / 6 (3.0)
Prior Abiraterone or docetaxel, n (%)	75 (37.5)	74 (37.2)
Abiraterone	16 (8.0)	16 (8.0)
Docetaxel	57 (28.5)	60 (30.2)
HRR gene alteration status (for stratification), n (%)		
Deficient	85 (21.1)	84 (20.8)
Non-Deficient or unknown	317 (78.9)	319 (79.2)

Agarwal N, et al. *Lancet. 2023* Jun 2:S0140-6736(23)01055-3. doi: 10.1016/S0140-6736(23)01055-3.

Primary Endpoint: rPFS in TALAPRO-2



	TALA + ENZA (N=200)	PBO + ENZA (N=199)
Events, n	66	104
Median (95% CI), months	Not reached (NR) (21.9–NR)	13.8 (11.0–16.7)
HR (95% CI)	0.45 (0.33–0.61); *P* < 0.0001	

Median follow-up for rPFS was 17.5 and 16.8 months, respectively

Talazoparib + Enzalutamide resulted in a 55% risk reduction of progression or death

A consistent treatment effect was seen for investigator-assessed rPFS: HR 0.48 (95% CI, 0.33–0.67); *P* < 0.0001

Stratified hazard ratios (HRs) and 2-sided *P* values are reported throughout this presentation unless otherwise stated.

rPFS has not yet been reached in the treatment arm compared to 13.8 months in the comparator arm

Agarwal N, et al. *Lancet. 2023* Jun 2:S0140-6736(23)01055-3. doi: 10.1016/S0140-6736(23)01055-3.

TALAPRO-2 Secondary Endpoint: Safety

HRR-Deficient

Adverse events, %	Talazoparib + Enzalutamide (n=198)		Placebo + Enzalutamide (n=199)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Anemia	64.6	40.9	15.6	4.5
Fatigue	33.3	1.5	26.6	4.5
Neutropenia	32.3	18.7	6.5	1
Thrombocytopenia	24.7	7.1	2.5	1
Nausea	20.7	1.5	17.1	0.5
Decreased appetite	20.2	1	14.1	1
Back Pain	19.7	1.5	22.1	1
Arthralgia	12.6	0	22.1	0

- 55.6% had Grade 1-2 anemia at baseline
- Median time to anemia onset: 3.3 months
- 4% discontinued due to anemia
- Median relative dose intensity remained at >80%

In the Talazoparib + Enzalutamide arm, 39% of patients required a blood transfusion and 22% required multiple transfusions.

Agarwal N, et al. *Lancet. 2023* Jun 2:S0140-6736(23)01055-3. doi: 10.1016/S0140-6736(23)01055-3.
TALZENNA [package insert]. New York, NY: Pfizer Inc. 2023

FDA Approved Indication and Dosing

PROpel Study - Olaparib + Abiraterone

In combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC

- Olaparib 300mg twice daily + abiraterone 1000mg once daily + prednisone or prednisolone 5mg by mouth twice daily until disease progression or unacceptable toxicity
- In combination with GnRH analog or patients should have had bilateral orchiectomy
- Dose adjust olaparib for baseline renal impairment

LYNPARZA [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. 2023.

PROpel: Study Design

Phase III study assessing clinical benefit, safety and tolerability of olaparib + abiraterone in patients with mCRPC in the first-line setting.

Patient population
- 1L treatment at mCRPC stage
- Docetaxel allowed mHSPC stage
- No prior abiraterone
- Other NHAs allowed if stopped ≥ 12 months prior to enrollment
- Ongoing ADT
- ECOG performance status 0-1

R 1:1

N=796

Olaparib 300 mg PO BID + abiraterone 1000 mg QD
N= 399

Placebo + abiraterone 1000 mg QD
N= 397

Primary endpoint:
- Radiographic progression or death (rPFS) by investigator assessment

Key secondary endpoints:
- Overall survival (alpha control)

Additional endpoints:
- Time to first subsequent therapy or death
- Time to second progression or death
- Objective response rate
- PSA response
- Time to PSA progression
- HRRm gene mutation status
- Health-related quality of life
- Safety and tolerability

Clarke N, et al. *N Engl J Med Evid*. 2022. doi:https://doi/org/10.1056/EVIDoa22200043.

PROpel Baseline Characteristics

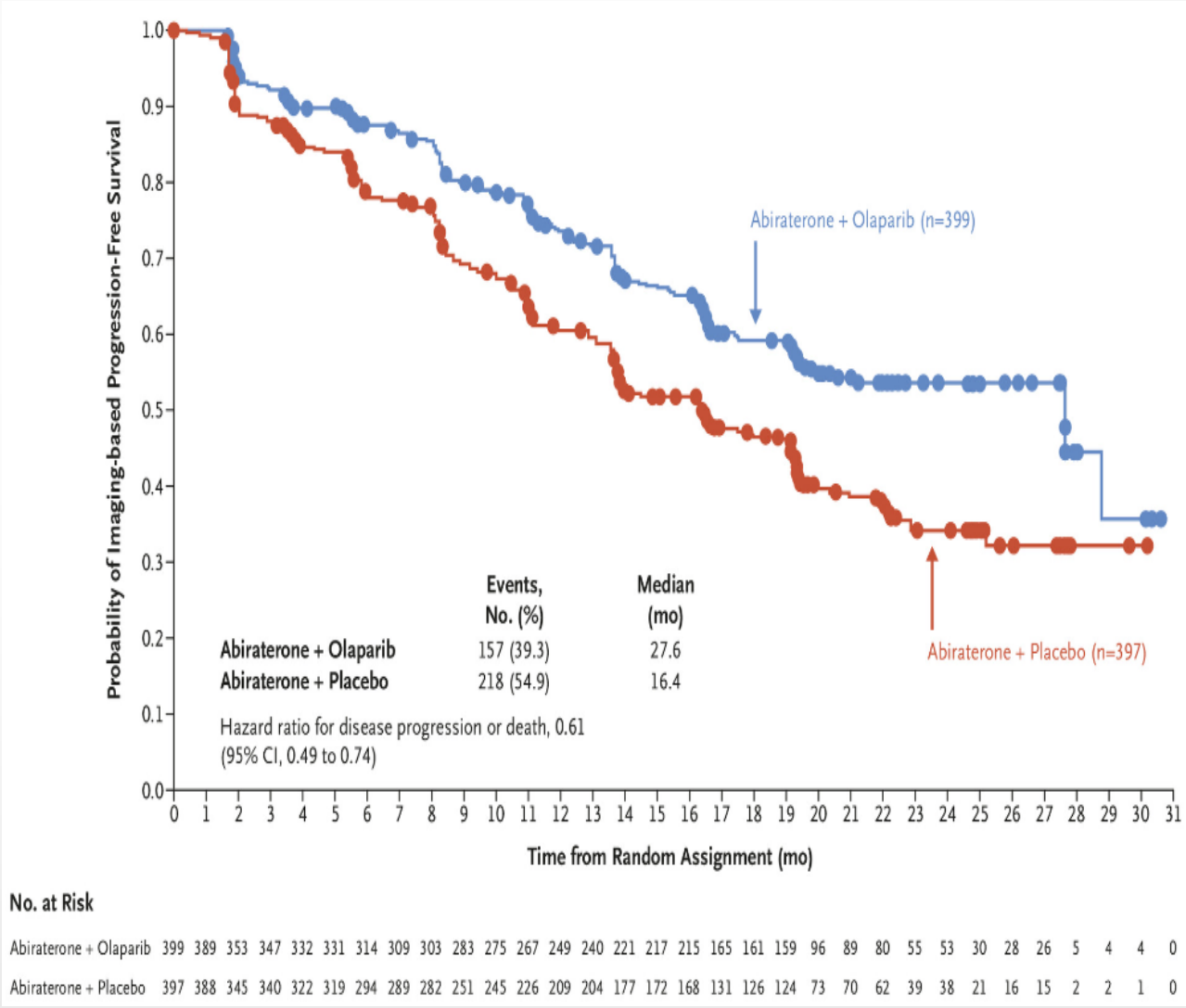
	Olaparib + abiraterone	Placebo + abiraterone
Median (range) age, years	69.0 (43-91)	70.0 (46-88)
ECOG performance status, n (%)		
0	286 (71.7)	272 (68.5)
1	112 (28.1)	124 (31.2)
Site of metastases, n (%)		
Bone	349 (87.5)	339 (85.4)
Distant lymph nodes	133 (33.3)	119 (30.0)
Locoregional lymph nodes	82 (20.6)	89 (22.4)
Prostate and adjacent structures	47 (11.8)	46 (11.6)
Respiratory (including lung)	40 (10.0)	42 (10.6)
Liver	15 (3.8)	18 (4.5)
HRRm status, n (%)		
HRRm	111 (27.8)	115 (29.0)
Non-HRRm	279 (69.9)	273 (68.8)
HRRm unknown	9 (2.3)	9 (2.3)
BRCAm prevalence, n (%)		
BRCA1	9 (2.3)	3 (0.8)
BRCA2	38 (9.5)	35 (8.8)

Clarke N, et al. *N Engl J Med Evid*. 2022. doi:https://doi/org/10.1056/EVIDoa22200043.

PROpel Efficacy

- **PROpel demonstrated a median 11.2-month improvement in rPFS and a 39% reduction in the risk of progression or death beyond irrespective of HRRm status.**
- **There was a 77% reduction in the risk of progression or death in the BRCAm group. [HR: 0.23 (0.12-0.43)]**

	Olaparib + Abi (n=399)	Placebo + Abi (n=397)
Events, %	157 (39.3)	218(54.9)
Median rPFS, months	27.6	16.4
HR (95% CI)	0.61 (0.49-0.74); p<0.0001	



Clarke N, et al. *N Engl J Med Evid*. 2022. doi:https://doi/org/10.1056/EVIDoa22200043.

PROpel Safety

Adverse events, %	Olaparib +Abi (n=398)		Placebo + Abi (n=396)	
	Any	Grade ≥3	Any	Grade ≥3
Anemia	46	15	16	3
Nausea	28	0.3	13	0.3
Vomiting	13	1	9	0.3
Fatigue/Asthenia	37	2	28	2
Decreased appetite	15	1	6	0
Hypertension	13	4	16	3
Hypokalemia	7	2	4	0.5
Edema, effusion, fluid overload	15	0	15	0.5
Cardiac Failure	2	1	1	0.3
Arterial embolic and thrombotic event	2	2	3	2

Clarke N, et al. *N Engl J Med Evid*. 2022. doi:https://doi/org/10.1056/EVIDoa22200043.

FDA Approved Indication and Dosing

MAGNITUDE - Niraparib and Abiraterone Dual Action Tablet

In combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC

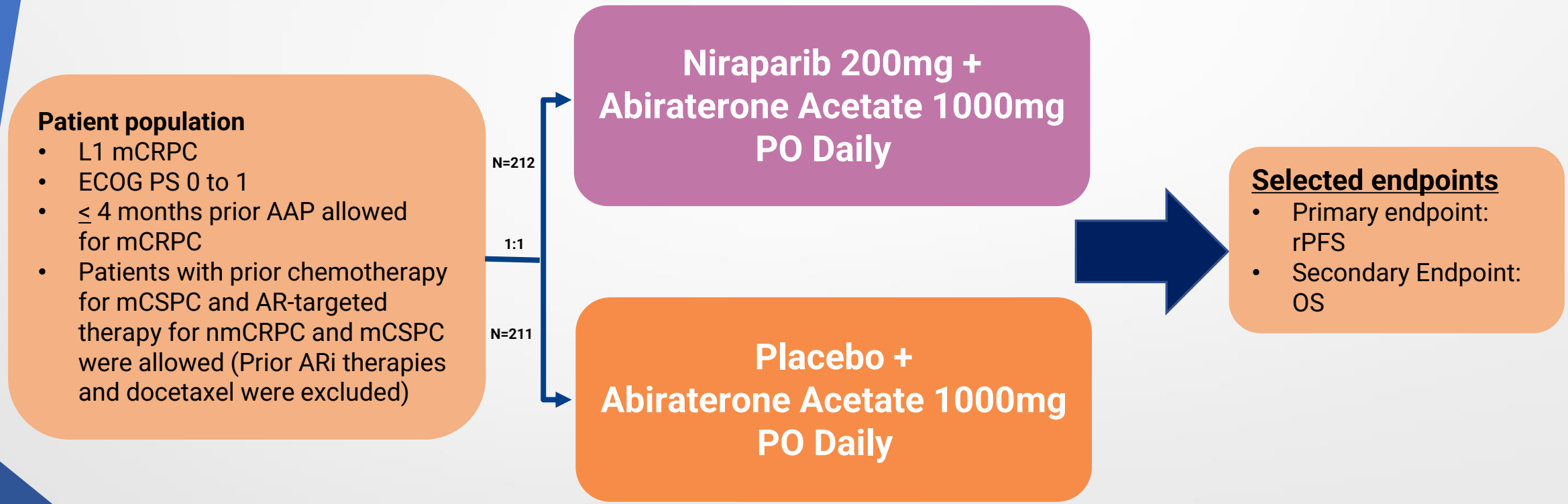
- Niraparib and Abiraterone 200mg/1000mg dual action tablet once daily with prednisone or prednisolone 5mg by mouth twice daily until disease progression or unacceptable toxicity.
- Available as 100 mg niraparib/500 mg abiraterone or 50 mg niraparib/ 500 mg abiraterone dual-action tablets (DAT).
  - **Dose reductions of abiraterone to 250 mg or 750 mg would not be feasible based on the DAT**
- In combination with GnRH analog or patients should have had bilateral orchiectomy

AKEEGA [package insert]. Horsham, PA: Janssen Biotech, Inc. 2023

MAGNITUDE: Study Design

Niraparib and Abiraterone Dual Action Tablet

Phase III assessing rPFS in patients treated with Niraparib and Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer (mCRPC)



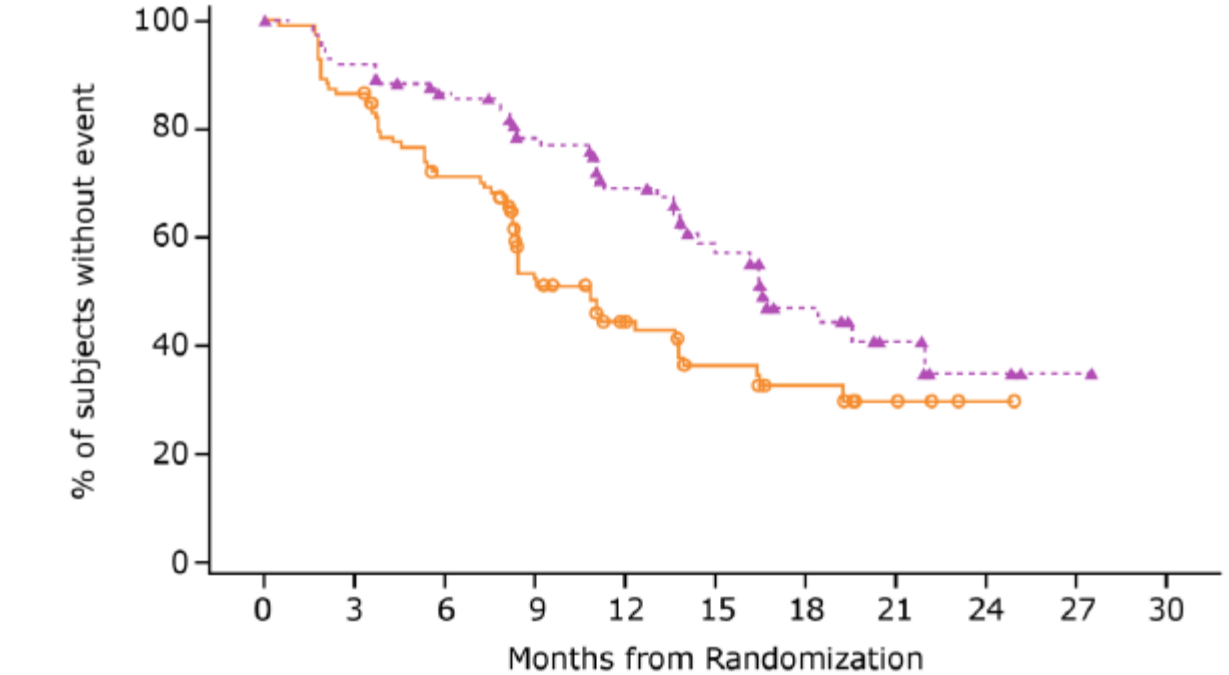
Clarke N, et al. *N Engl J Med Evid*. 2022. doi:https://doi/org/10.1056/EVIDoa22200043.

Baseline Characteristics: MAGNITUDE

Patient and Disease Characteristics	Niraparib + AAP (N=212)	Placebo + AAP (N=211)
Age, years, median (range)	69 (45-100)	69 (43-88)
PSA at baseline, µg/L, median (range)	21.4 (0-4, 826.5)	17.4 (0.1-4, 400.0)
Patients with alternations in a single gene, n (%)		
ATM	43 (20.3)	42 (19.9)
BRCA1	12 (5.7)	4 (1.9)
BRCA2	86 (40.6)	88 (41.7)
BRIP1	4 (1.9)	4 (1.9)
CDK12	5 (2.4)	8 (3.8)
CHEK2	18 (8.5)	20 (9.5)
FANCA	5 (2.4)	6 (2.8)
HDAC2	2 (0.9)	3 (1.4)
PALB2	8 (3.8)	4 (1.9)
ECOG performance status, n (%)		
0	130 (61.3)	146 (69.2)
1	82 (38.7)	65 (30.8)
Metastasis stage at diagnosis, n (%)		
M0	76 (35.8)	97 (46.0)
M1	127 (59.9)	106 (50.2)
Unknown	9 (4.2)	8 (3.8)
Prior therapies for prostate cancer, n (%)		
ADT	204 (96.2)	201 (95.3)
Radiotherapy	90 (42.5)	91 (43.1)
Prostatectomy	133 (62.7)	138 (65.4)
AR-targeted therapy for nmCRPC or mCSPC	8 (3.8)	5 (2.4)
Taxane therapy for mCSPC	41 (19.3)	44 (20.9)
AAP (≤ 4 months) for mCRPC	50 (23.6)	48 (22.7)
Others	52 (24.5)	58 (27.5)

Chi KN, et al. MAGNITUDE Principal Investigators. Niraparib and Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer. J Clin Oncol. 2023 Jun 20;41(18):3339-3351. doi: 10.1200/JCO.22.01649. Epub 2023 Mar 23.

Primary Endpoint: rPFS in BRCAm



	Niraparib + AAP	Placebo + AAP
Event of disease progression or death (%)	45 (40)	64 (57)
Median, months (95% CI)	16.6 (13.9, NE)	10.9 (8.3, 13.8)
HR (95% CI)	0.53 (0.36, 0.79)	
***P* value**	0.0014	

Niraparib + AAP led to a 47% risk reduction in progression

Chi KN, et al. MAGNITUDE Principal Investigators. Niraparib and Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer. J Clin Oncol. 2023 Jun 20;41(18):3339-3351. doi: 10.1200/JCO.22.01649. Epub 2023 Mar 23.

Safety

Adverse Reaction	Niraparib + AAP N = 113		Placebo + AAP N = 112	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Musculoskeletal pain	44	4	42	5
Fatigue	43	5	30	4
Constipation	34	1	20	0
Hypertension	33	**14**	27	17
Nausea	33	1	21	0
Hematology Abnormalities				
Hemoglobin decreased	67	**26**	53	7
Lymphocyte decreased	55	22	32	13
WBC decreased	48	6	18	0.9
Platelets decreased	37	8	22	1.8
Neutrophils decreased	32	7	16	2.7

Chi KN, et al. MAGNITUDE Principal Investigators. Niraparib and Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer. J Clin Oncol. 2023 Jun 20;41(18):3339-3351. doi: 10.1200/JCO.22.01649. Epub 2023 Mar 23.

Summary – Take Home

- The **TALAPRO-2** study demonstrated a significantly prolonged rPFS, not yet reached, with enzalutamide combined with talazoparib, compared to 13.8 months with enzalutamide and placebo in first-line treatment for patients harboring HRRm.
  - The combination treatment of talazoparib and enzalutamide significantly reduced the risk of progression or death by 55% in the HRRm subgroup.
  - There was an 80% risk reduction of progression or death in patients with *BRCA1/2* mutations.

- The **PROpel** study demonstrated a rPFS for Olaparib and Abiraterone of 27.6 months compared to 16.4 months in the placebo + Abiraterone arm irrespective of HRRm.
  - In turn, this lead to a 77% risk reduction in progression or death in BRCAm patients.
  - rPFS has not yet been reached in the BRCAm patients compared to 8.4 months with placebo + Abiraterone.

- Based on the **MAGNITUDE** trial, there was a statistically significant improvement in rPFS for niraparib and AAP of 16.6 months compared to placebo of 10.9 months was observed in BRCAm patients.
  - The Niraparib and AAP arm demonstrated a 47% risk reduction in progression or death.

Agarwal N, et al. *Lancet. 2023* Jun 2:S0140-6736(23)01055-3. doi: 10.1016/S0140-6736(23)01055-3.
Clarke NW, et al. *Journal of Clinical Oncology.* 2023 Feb 21:41:6_suppl, LBA16-LBA16. doi:10.1200/JCO.2023.41.6_suppl.LBA16
Chi KN, et al. *Journal of Clinical Oncology* . 2023 Jun 20;41(18):3339-3351. doi: 10.1200/JCO.22.01649. Epub 2023 Mar 23

Highlights

rPFS benefit across TALAPRO-2, PROpel, and MAGNITUDE

	TALAPRO-2	PROpel	MAGNITUDE
	Talazoparib + Enzalutamide	**Olaparib + Abiraterone**	**Niraparib and Abiraterone (DAT)**
Prior Abiraterone/Docetaxel	Prior abiraterone and/or docetaxel was allowed	Only prior docetaxel was allowed.	Prior abiraterone (≤ 4 months)
All Comers	NR vs 21.9m HR 0.63 (0.5-0.78); p<0.001	24.8 vs 16.6m HR 0.66 (0.54-0.81); p<0.001	N/A
BRCA1/2	N/A	NR vs 8.4m HR 0.23 (0.12-0.43)	16.6 vs 10.9m HR 0.53 (0.36-0.79); p<0.0014
HRRm	27.9 vs 16.4m HR 0.46 (0.3-0.7); p<0.001	NR vs 13.9m HR 0.50 (0.34-0.73); p=0.0014	16.5 vs 13.7m HR 0.73 (0.56-0.96); p=0.022
Non-HRRm/unknown	NR vs 22.5m HR 0.70 (0.54-0.89); p<0.001	24.1 vs 19m HR 0.76 (0.60-0.97)	N/A
HRR gene alterations	ATM, BRCA1/2, PALB2, CHEK2, CDK12, FANCA, RAD51C, NBN, MLH1, ATR, MRE11A	ATM, BRCA1/2, CHEK2, BARD1, BRIP1, CDK12, CHEK1, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L	ATM, BRCA1/2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2
FDA Approval	HRR gene-mutated mCRPC	Germline or Somatic BRCAm mCRPC	Germline or Somatic BRCAm mCRPC

Agarwal N, et al. *Lancet. 2023* Jun 2:S0140-6736(23)01055-3. doi: 10.1016/S0140-6736(23)01055-3.
Clarke NW, et al. *Journal of Clinical Oncology.* 2023 Feb 21:41:6_suppl, LBA16-LBA16. doi:10.1200/JCO.2023.41.6_suppl.LBA16
Chi KN, et al. *Journal of Clinical Oncology* . 2023 Jun 20;41(18):3339-3351. doi: 10.1200/JCO.22.01649. Epub 2023 Mar 23

Luspatercept-aamt

New FDA Approved Indication

Jeanine Ewing, PharmD, BCOP
Clinical Oncology Pharmacist
Florida Cancer Specialists & Research Institute

FDA Approval & Dosing

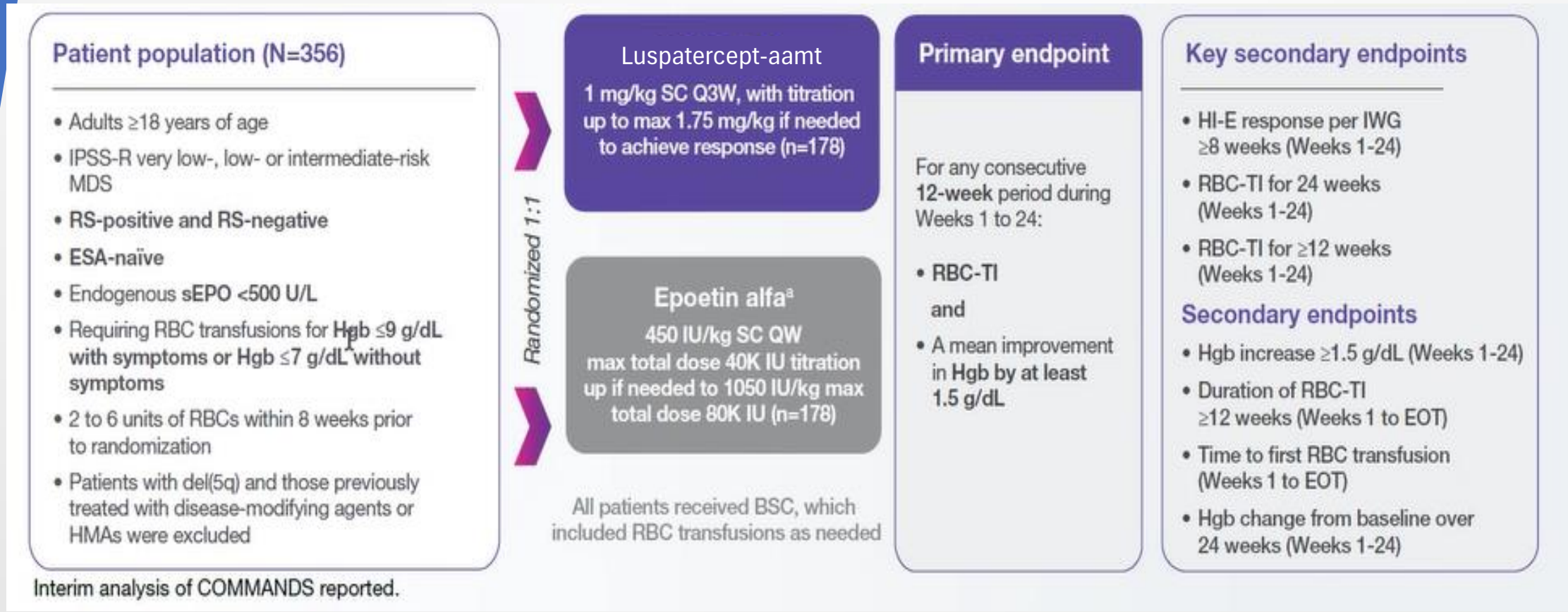
- First-Line treatment of anemia with low- to intermediate-risk MDS who have not previously received ESA and may require regular RBC transfusions

	Dose Recommendation*
Starting Dose	• 1 mg/kg every 3 weeks
Dose increases for insufficient response at initiation of treatment	
Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at 1mg/kg starting dose	• Increase dose to 1.33 mg/kg every 3 weeks
Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at 1.33 mg/kg	• Increase dose to 1.75 mg/kg every 3 weeks
No reduction in RBC transfusion burden including no increase from baseline hemoglobin after at least 3 consecutive doses (9 weeks) at 1.75 mg/kg	• Discontinue treatment

*Review hemoglobin (Hgb) results prior to each administration

REBLOZYL [package insert]. Summit, NJ: Celgene Corporation, a Bristol-Myers Squibb Company; 2023.

COMMANDS Trial Design



With <5% blasts in bone marrow

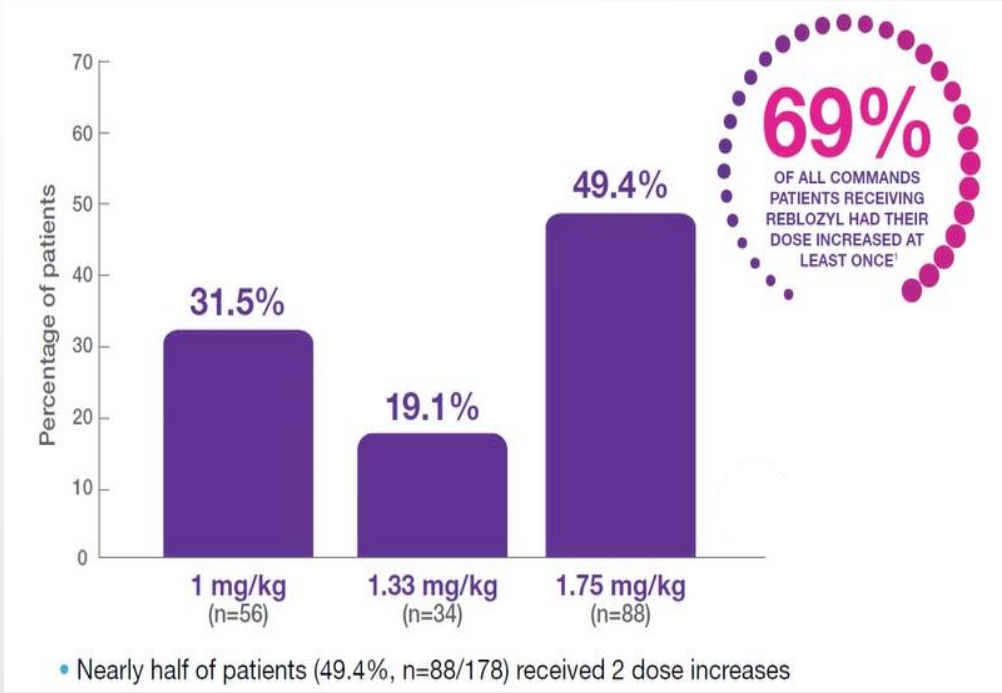
a. >90% of study participants were outside of the U.S. and used a non-US-licensed epoetin alfa product. Direct comparisons between REBLOZYL and US-licensed epoetin alfa product have not been established.

Platzbecker, U. et.al. Efficacy and safety of luspatercept verus epoetin alfa in ESA-naive, transfusion-dependent, lower-risk MDS (COMMANDS). Lancet 402: 373-85; 2023.
https://www.reblozylpro.com/

Dosing in COMMANDS Trial

Dose Escalation Considerations: Meet ALL criteria	Exceptions
Patient Hgb less than target Hgb: 10-12 g/dL	If Hgb 10-12 g/dL due to transfusion
Hgb increase <1 g/dL from previous administration	If >1 g/dL due to transfusion
No protocol dose delays and/or protocol reduction criteria in 2 most recent administrations	Unless dose delay due to transfusion
At least 2 consecutive luspatercept doses at the same level	

- Dosing escalation: 1 mg/kg → 1.33 mg/kg → 1.75 mg/kg
- Median time to first dose escalation was 45 days (min: 43 / max: 125)



(Dosing in Appendix Page 11-12): Platzbecker, et al. COMMANDS interim analysis of Phase 3 open label trial. Lancet, June 10 2023.

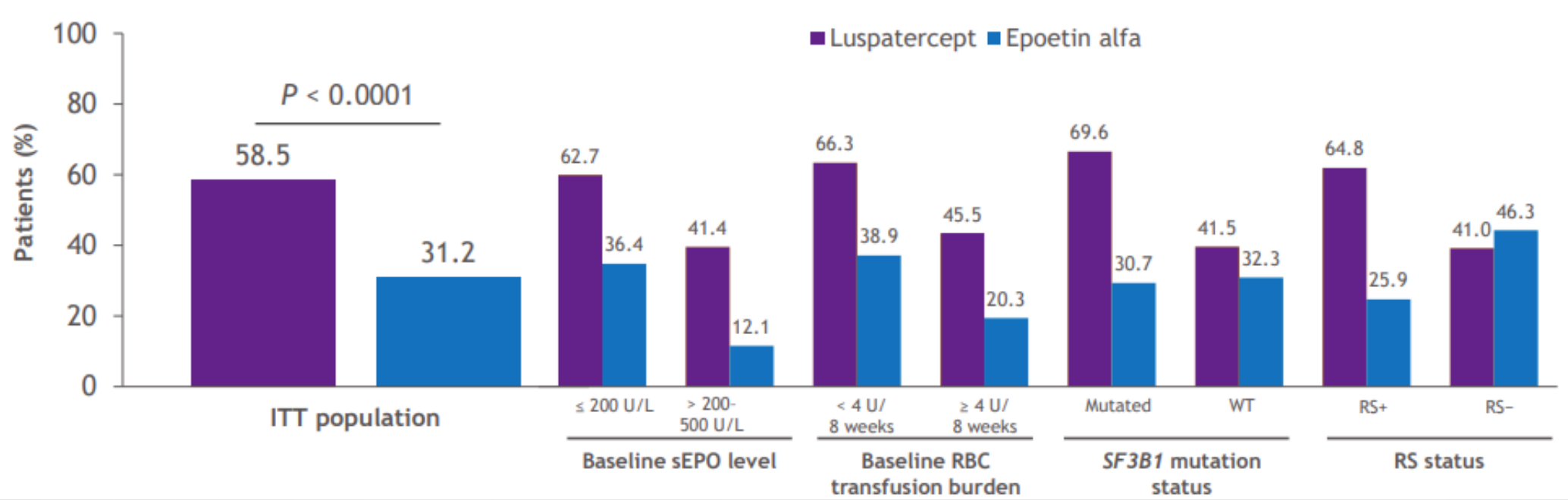
COMMANDS Trial Baseline Demographics

Disease Characteristic	Luspatercept-aamt (n=178)	Epoetin Alfa (n=178)
Age, years	74 (46-93)	75 (33-91)
Hemoglobin (g/dL)	7.8 (4.7 - 9.2)	7.8 (4.5 - 10.2)
Serum EPO (U/L)	78.7 (7.8 - 495.8)	85.9 (4.6 - 462.5)
Baseline Transfusion Burden		
pRBC units, median	3 (1-10)	3 (0-14)
< 4 pRBC units	114 (64%)	109 (61.2%)
≥ 4 pRBC units	64 (36%)	69 (38.8%)
IPSS-R risk classification at baseline – n (%)		
Very Low	16 (9)	17 (9.6)
Low	126 (70.8)	131 (73.6)
Intermediate	34 (19.1)	28 (15.7)
High	1 (0.6)	0 (0)
Missing	1 (0.6)	2 (1.1)
Ring sideroblasts status (WHO criteria) – n (%)		
RS-positive	130 (73)	128 (71.9)
RS-negative	48 (27)	49 (27.5)
Missing	0 (0)	1 (0.6)
SF3B1 mutation status – n (%)		
Mutated	111 (62.4)	99 (55.6)
Non-mutated	65 (36.5)	72 (40.4)
Missing	2 (1.1)	7 (3.9)

Platzbecker, U. et.al. Efficacy and safety of luspatercept verus epoetin alfa in ESA-naive, transfusion-dependent, lower-risk MDS (COMMANDS). Lancet 402: 373-85; 2023.

Primary Endpoint:

RBC-Transfusion Independence & mean Hgb Improvement by at least 1.5 mg/dL for any 12 consecutive weeks during Weeks 1-24

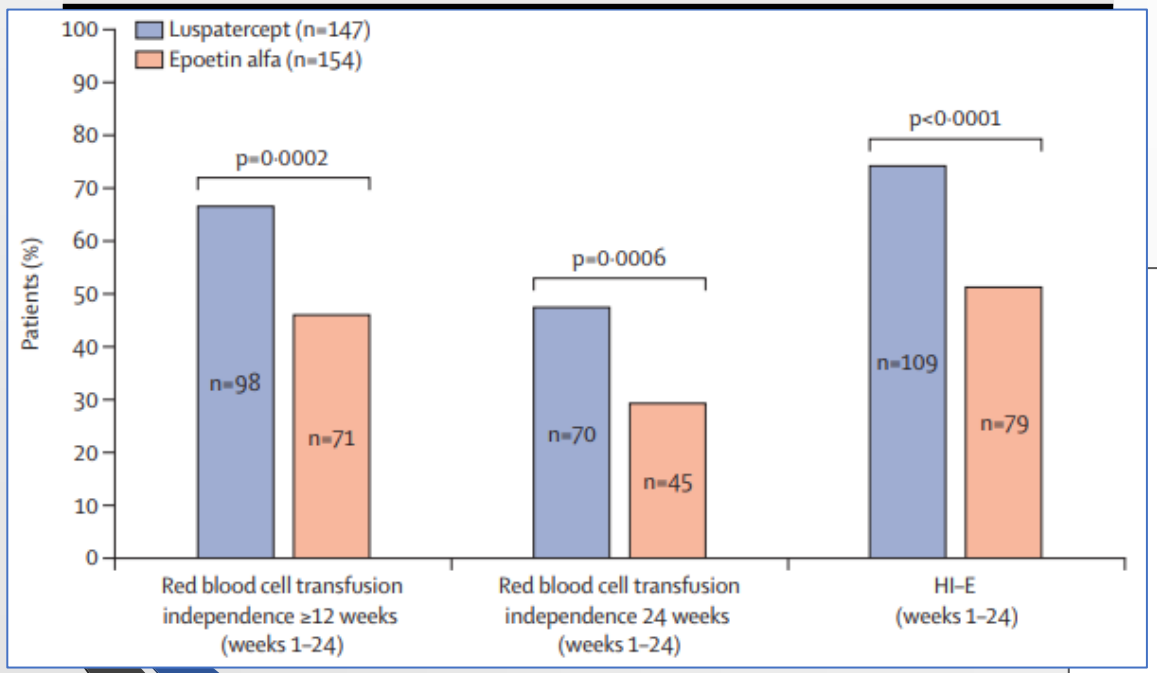


Platzbecker, U. et.al. Efficacy and safety of luspatercept verus epoetin alfa in ESA-naive, transfusion-dependent, lower-risk MDS (COMMANDS). Lancet 402: 373-85; 2023.

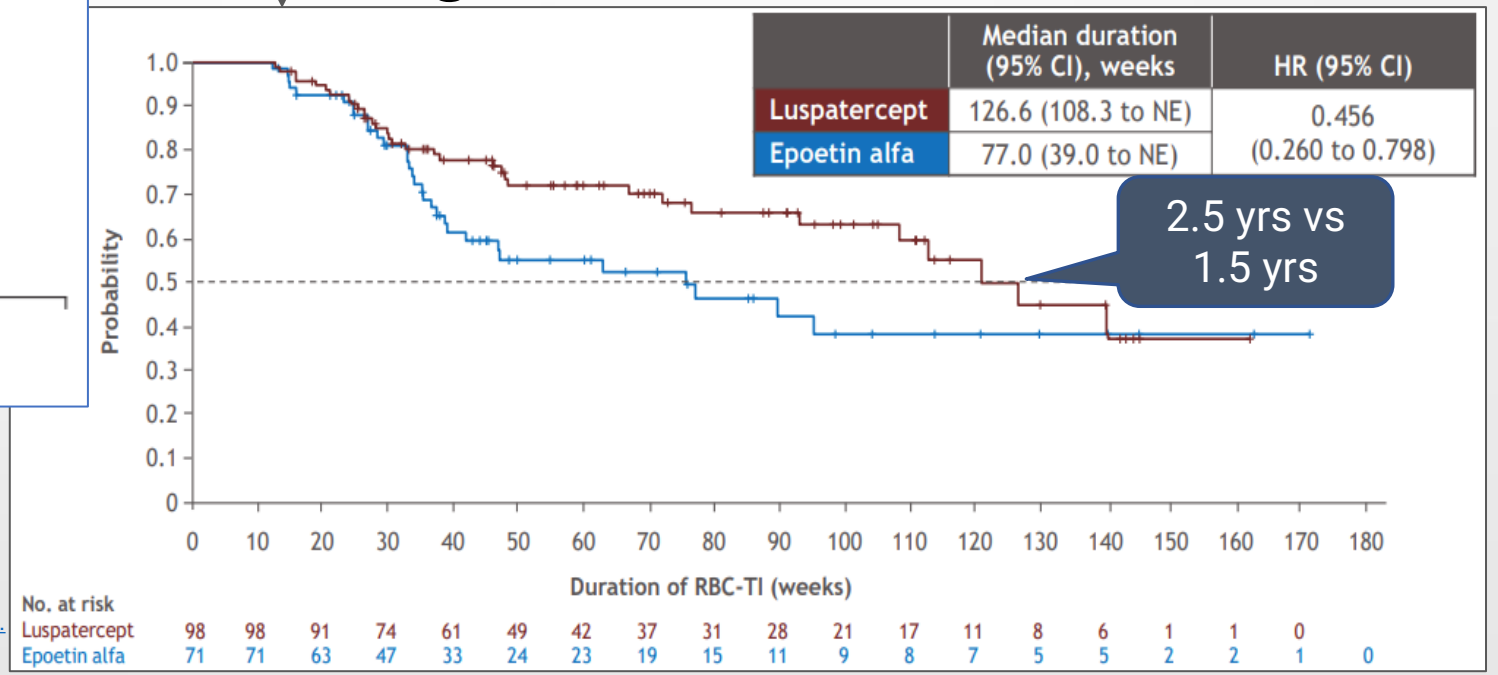
Secondary Endpoint:
RBC Transfusion Independence

	Luspatercept (n=147)	Epoetin alpha (n=154)
Time to first RBC transfusion (week 1-EOT), median (range), days	n=93 168 (64-323)	n=116 42 (22-55)

← Delayed time to first RBC transfusion



↓ Longer duration of RBC-TI



Platzbecker, U. et.al. Efficacy and safety of luspatercept verus epoetin alfa in ESA-naive, transfusion-dependent, lower-risk MDS (COMMANDS). Lancet 402: 373-85; 2023.

Safety

Patients, n (%)	Luspatercept (n=178)		Epoetin alfa (n=176)	
ANY TEAEs	164/178 (92%)		150/176 (85%)	
Treatment Duration, weeks	42 (20, 73)		27 (19, 55)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Heme-related TEAEs				
Anemia	17 (9.6%)	13 (7.3%)	17 (9.7%)	12 (6.8%)
Thrombocytopenia	11 (6.2%)	7 (3.9%)	3 (1.7%)	1 (0.6%)
Neutropenia	9 (5.1%)	7 (3.9%)	13 (7.4%)	10 (5.7%)
Leukocytopenia	2 (1.1%)	0	3 (1.7%)	0
TEAEs of interest				
Fatigue	26 (14.6%)	1 (0.6%)	12 (6.8%)	1 (0.6%)
Diarrhea	26 (14.6%)	2 (1.1%)	20 (11.4%)	1 (0.6%)
Peripheral Edema	23 (12.9%)	0	12 (6.8%)	0
Asthenia	22 (12.4%)	0	25 (14.2%)	1 (0.6%)
Nausea	21 (11.8%)	0	13 (7.4%)	0
Dyspnea	21 (11.8%)	7 (3.9%)	13 (7.4%)	2 (1.1%)
Thromboembolic event	8 (4.5%)	5 (2.8%)	5 (2.8%)	1 (0.6%)

Platzbecker, U. et.al. Efficacy and safety of luspatercept verus epoetin alfa in ESA-naive, transfusion-dependent, lower-risk MDS (COMMANDS). Lancet 402: 373-85; 2023.
REBLOZYL [package insert]. Summit, NJ: Celgene Corporation, a Bristol-Myers Squibb Company; 2023.

Warnings & Precautions

- Thrombosis / Thromboembolism
- Hypertension
- Embryo-Fetal Toxicity

REBLOZYL [package insert]. Summit, NJ: Celgene Corporation, a Bristol-Myers Squibb Company; 2023.

Momelotinib

New FDA Approved Therapy

Jeanine Ewing, PharmD, BCOP
Clinical Oncology Pharmacist
Florida Cancer Specialists & Research Institute

FDA Approved Indications & Dosing

- Treatment of intermediate- or high-risk myelofibrosis, including primary myelofibrosis and secondary myelofibrosis (post-polycythemia vera and post-essential thrombocytopenia), in adults **with anemia**

Dosing: momelotinib 200mg by mouth once daily, with or without food

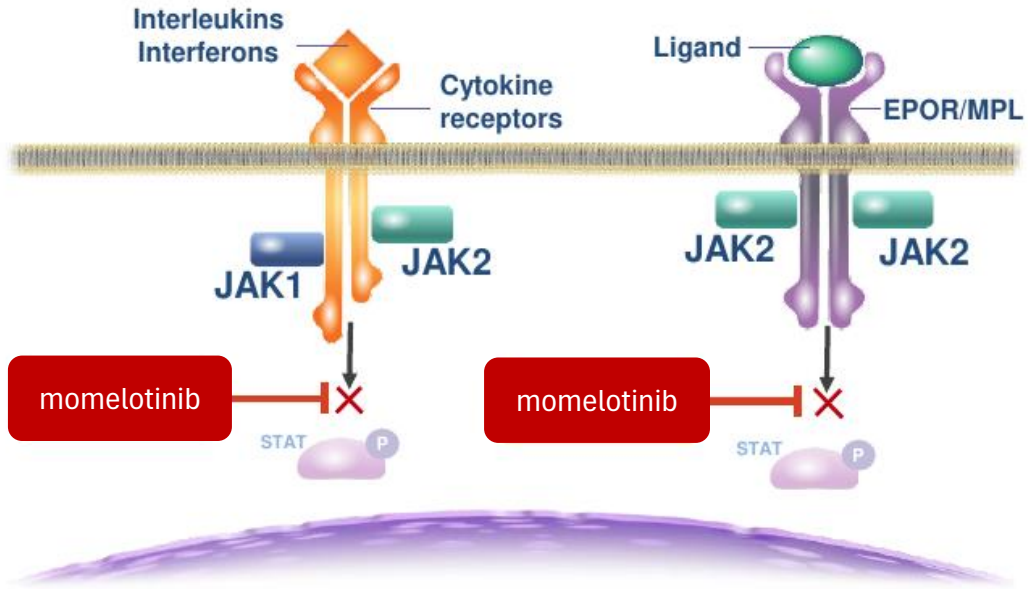
Decrease starting dose to 150mg once daily in severe hepatic impairment (Child-Pugh Class C)

Swallow tablets whole. Do not cut, crush, or chew tablets

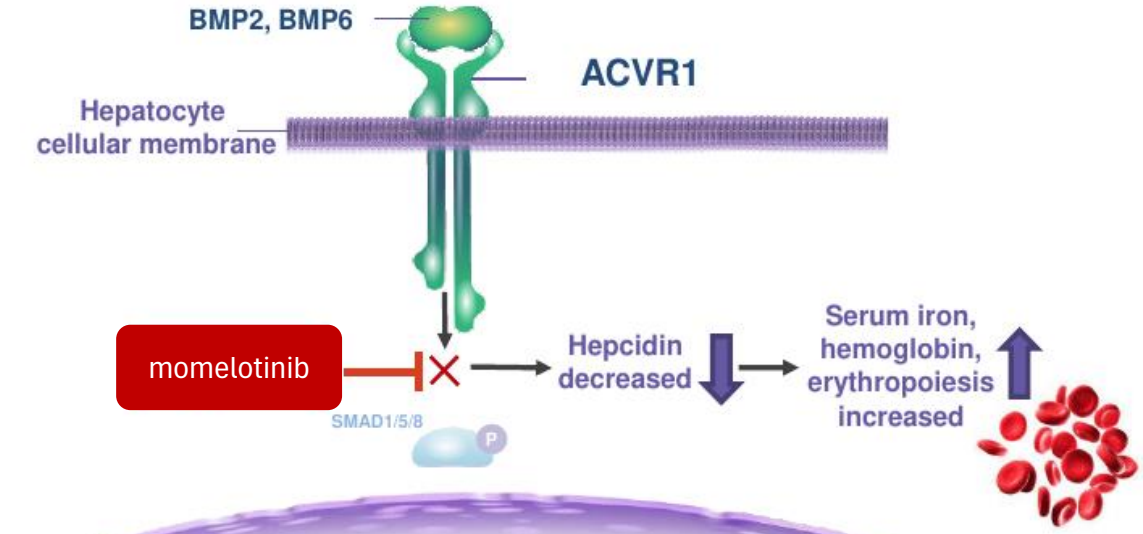
OJJAARA [package insert]. Durham, NC: GlaxoSmithKline; 2023.

Mechanism of Action

- Inhibits JAK1, JAK2, and ACVR1



Dysregulated JAK-STAT signaling in MF drives overproduction of inflammatory cytokines, bone marrow fibrosis, constitutional symptoms, and clonal proliferation, resulting in extramedullary hematopoiesis and splenomegaly.



Chronic inflammation also drives hyperactivation of ACVR1, elevated hepcidin levels, and dysregulated iron metabolism, leading to anemia of MF.

OJJAARA [package insert]. Durham, NC: GlaxoSmithKline; 2023.
Mesa RA, et al. J Clin Oncol. 2017; 35(34):3844-3850.
GSK Data on file (Clinical Study Report. GS-US-352-0101; 2021).

Clinical Trials

	SIMPLIFY-1	MOMENTUM
Trial Status	Completed	Active, Not Recruiting
Trial Phase	Phase 3	Phase 3
Patient Population	JAK inhibitor-naïve (n=432) Anemia (Hgb<10 g/dL: n=181)	Previously treated with JAK inhibitor (n=195)
Comparator	Ruxolitinib	Danazol
Efficacy	Splenic Reduction >35% (SVR35) at week 24 in anemic patients at baseline	Difference in TSS response rate at week 24
Additional trial design considerations	Cross over allowed after week 24 without tapering	Prior to randomization: 21-day taper/washout Cross over allowed after week 24

Mesa RA, et al. J Clin Oncol. 2017; 35(34):3844-3850.
GSK Data on file (Clinical Study Report. GS-US-352-0101; 2021).

SIMPLIFY-1 Trial Design

- Phase 3, randomized
- JAK inhibitor naïve
- Intermediate-1, intermediate-2, & high-risk patients
- PLT ≥ $50x10^9$/L
- n=432

  (1:1 randomized)

Double-blind treatment

Momelotinib
200mg once daily

Ruxolitinib
20mg twice daily

Primary Endpoint assessed at Week 24

Open label → Long-term follow-up

Momelotinib
200mg once daily

Primary Endpoint*:
SVR35 from baseline to week 24 (noninferiority)

Secondary Endpoints*:
- Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) – Total Symptom Score (TSS) response rate from baseline to week 24
- RBC Transfusion Independence (TI) at week 24

*Results based on patients with anemia (Hgb < 10 g/dL): n=180

Mesa RA, et al. J Clin Oncol. 2017; 35(34):3844-3850.
GSK Data on file (Clinical Study Report. GS-US-352-0101; 2021).

SIMPLIFY-1 Baseline Demographics

	Momelotinib (n=86)	Ruxolitinib (n=94)
Median Age, years	70	68
Myelofibrosis subtype, %		
Primary	68.6	57.4
Post-Polycythemia Vera	12.8	12.8
Post-Essential Thrombocythemia	18.6	29.8
IPSS risk category, %		
Intermediate-2	30.2	21.3
High	67.4	74.5
Total Symptom Score, mean	17.6	16.3
Hgb level, mean	8.6	9
Transfusion independent, %	29.1	43.6
Central spleen volume, median, cm3	1788.1	1958.5

Mesa RA, et al. J Clin Oncol. 2017; 35(34):3844-3850.
GSK Data on file (Clinical Study Report. GS-US-352-0101; 2021).

MOMENTUM Trial Design

- Phase 3, global, randomized
- Previously treated with JAK inhibitor (taper ≥21 days)
- Symptomatic (TSS≥10) and anemic (Hgb<10 g/dL)
- PLT ≥ $25x10^9$/L
- n=195

(2:1 randomization)

Momelotinib
200mg once daily
(n=130)

Danazol
300 mg twice daily
(n=65)

Open label /cross over → Long-term F/U

Momelotinib
200mg once daily

Primary & Secondary Endpoints assessed at Week 24

Primary Endpoint:
TSS response rate at week 24

Secondary Endpoints:
- Transfusion Independence (TI) at week 24
- SVR at week 24
- Change from baseline of mean TSS at week 24
- Proportion of patients with o RBC units transfused through week 24

Mesa RA, et al. J Clin Oncol. 2017; 35(34):3844-3850.
GSK Data on file (Clinical Study Report. GS-US-352-0101; 2021).

MOMENTUM Baseline Demographics

Patient and Disease Characteristics	Momelotinib (N=130)	Danazol (N=65)
Age, years, median (range)	71 (65-75)	72 (67-78)
Myelofibrosis subtype, n (%)		
Primary	78 (60%)	46 (71%)
After PV	27 (21%)	11 (17%)
After ET	25 (19%)	8 (12%)
DIPSS risk category, n (%)		
Intermediate-1	7 (5%)	3 (5%)
Intermediate-2	72 (55%)	40 (62%)
High	50 (38%)	19 (29%)
Missing	1 (1%)	3 (5%)
JAK2 Val617Phe mutation, n (%)		
Positive	97 (75%)	51 (78%)
Negative	28 (22%)	12 (18%)
Unknown or missing	5 (4%)	2 (3%)
ECOG performance status, n (%)		
0	16 (12%)	15 (23%)
1	83 (64%)	34 (52%)
2	31 (24%)	16 (25%)
Mean previous JAK inhibitor duration (weeks)	138.5 (123.0)	124.8 (120.0)
Hemoglobin		
Mean (g/dL)	8.1 (1.1)	7.9 (0.8)
Median (g/dL)	8.0 (7.5-8.8)	8.0 (7.3-8.4)
>8 g/dL	67 (52%)	33 (51%)
Transfusion independent, n (%)	17 (13%)	10 (15%)
Transfusion dependent, n (%)	63 (48%)	34 (52%)

Mesa RA, et al. J Clin Oncol. 2017; 35(34):3844-3850.
GSK Data on file (Clinical Study Report. GS-US-352-0101; 2021).

Clinical Trial Efficacy

SIMPLIFY-1			
Anemic subgroup with Hgb< 10g/dL at baseline	Momelotinib (n=86)	Ruxolitinib (n=94)	P-value
SVR ≥ 35%	31%	33%	--
TSS response rate at week 24	25%	36%	

MOMENTUM				
	Momelotinib	Danazol	P-value	Treatment difference (95% CI)
MFSAF TSS response rate (≥ 50%)	25%	9%	<0.01	16% (6-26)
TI rate at week 24	30%	20%	0.023	14% (2-25)
SVR ≥ 25%	39%	6%	<0.0001	33% (23-44)
SVR ≥ 35%	22%	3%	0.001	18% (10-27)
Rate of zero transfusions during 24-week treatment period	35%	17%	0.001	17% (8-26)

Mesa RA, et al. J Clin Oncol. 2017; 35(34):3844-3850.
GSK Data on file (Clinical Study Report. GS-US-352-0101; 2021).

Clinical Trial Safety

SIMPLIFY-1 (anemic subgroup with Hgb <10g/dL at baseline; randomized treatment period), %				
	Momelotinib (n=85)		Ruxolitinib (n=95)	
Serious Adverse Reactions	28		25	
Fatal Adverse Reactions	1		4	
Permanent Discontinuation due to Adverse Reaction	19		6	
Adverse Reactions in ≥20% of pt receiving momelotinib	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**
Dizziness	24	1	15	2
Fatigue	22	0	25	1
Bacterial infection	21	8	12	2
Hemorrhage	21	1	18	2
Thrombocytopenia	21	11	34	6
Nausea	20	0	3	1
Elevated Liver Enzymes	11	4	9	0
Viral Infection	6	0	13	2

Momentum (randomized treatment period), %				
	Momelotinib (n=130)		Danazol (n=65)	
Serious Adverse Reactions	35		40	
Fatal Adverse Reactions	12		17	
Permanent Discontinuation due to Adverse Reaction	18		23	
Adverse Reactions in ≥20% of pt receiving momelotinib	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**
Thrombocytopenia	28	22	17	12
Diarrhea	22	0	9	2
Hemorrhage	22	2	18	8
Fatigue	21	2	20	5
Elevated Liver Enzymes	10	2	9	3
Viral Infection	12	5	3	0

Mesa RA, et al. J Clin Oncol. 2017; 35(34):3844-3850.
GSK Data on file (Clinical Study Report. GS-US-352-0101; 2021).

Warnings & Precautions

Risk of Infections

- Bacterial and viral infections occurred – delay starting therapy until active infections are resolved and monitor patients

Hepatitis B Reactivation

- In patients with HBV infections, check hepatitis B serologies prior to starting & consider consultation with hepatologist if positive

Hepatotoxicity

- Reversible drug-induced liver injury (new or worsening AST, ALT, and Total bilirubin)
- Median time to onset was 2 months, with 75% of cases occurring within 4 months
- Monitor and initiate dose adjustments according to prescribing information

Thrombocytopenia and Neutropenia

- Monitor CBC and interrupt or reduce dosing as indicated

OJJAARA [package insert]. Durham, NC: GlaxoSmithKline; 2023.

Warnings & Precautions (cont.)

Major Adverse Cardiac Events (MACE)

- Consider benefits vs risks, particularly in current or past smokers and patients with other cardiovascular risk factors

Thrombosis

- Evaluate and treat promptly

Malignancies

- Increase risk of lymphoma and other malignancies, excluding nonmelanoma skin cancer
- Current and past smokers are at increased risk

OJJAARA [package insert]. Durham, NC: GlaxoSmithKline; 2023.

Drug Interactions

- Momelotinib is an OATP1B1/B3 substrate
  - Concomitant administration may lead to increased concentrations of momelotinib, which may increase adverse reactions
  - Monitor patients closely and consider dose adjustments based on the package insert
- Momelotinib is a BCRP inhibitor
  - Concomitant administration may increase exposure to BCRP substrates which may lead to increased adverse reactions
  - Dose adjust BCRP substrates if administered concomitantly

OJJAARA [package insert]. Durham, NC: GlaxoSmithKline; 2023.

QUESTIONS???