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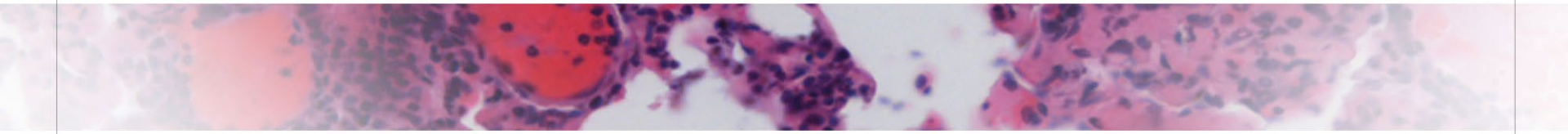

Sonrotoclax (BGB-11417) in Combination With Dexamethasone for the Treatment of Relapsed/Refractory Multiple Myeloma With t(11;14): Safety, Efficacy, and Determination of Recommended Phase 2 Dose

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Background

- Venetoclax, a first-generation BCL2 inhibitor, has demonstrated antimyeloma activity as monotherapy or combination treatment but has no regulatory approvals for MM[1,2]
- Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, has shown more potent and selective BCL2 inhibition and better activity against BCL2-dependent hematological tumors than venetoclax in vitro[3]

	IC_{50}	Relative IC_{50} for various proteins in the BCL2 family				$T_{1/2}$
	BCL2	BCL-XL	BCL-W	MCL1	A1	
Venetoclax	0.20 nM	1:325	1:13,700	1:<50,000	1:<50,000	26 h
Sonrotoclax	0.014 nM	1:2000	1:129,000	1:714,000	1:714,000	4.5 h

- Here, preliminary data from the sonrotoclax + dexamethasone dose-escalation cohorts of an ongoing phase 1b/2 study in patients with R/R MM harboring the t(11;14) translocation are presented

h, hours; IC_{50}, half maximal inhibitory concentration; $t_{1/2}$, half-life.

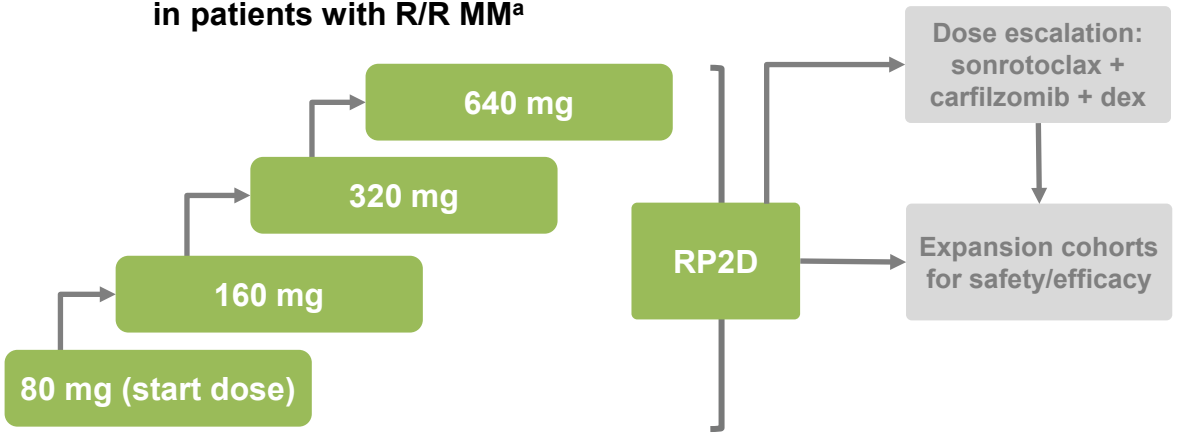
1. Kumar S, et al. *Blood*. 2017;130(22):2401-2409; 2. Mateos MV, et al. IMS 2023. Abstract OA-52; 3. Hu N, et al. AACR 2020. Abstract 3077.

BGB-11417-105 (NCT04973605) Study Design: Sonrotoclax + Dex Only

Eligible patients

- Relapsed or refractory to most recent therapy line
- t(11;14) positive by FISH
- Failed ≥3 prior lines of therapy including a proteasome inhibitor, IMiD, and an anti-CD38 monoclonal antibody

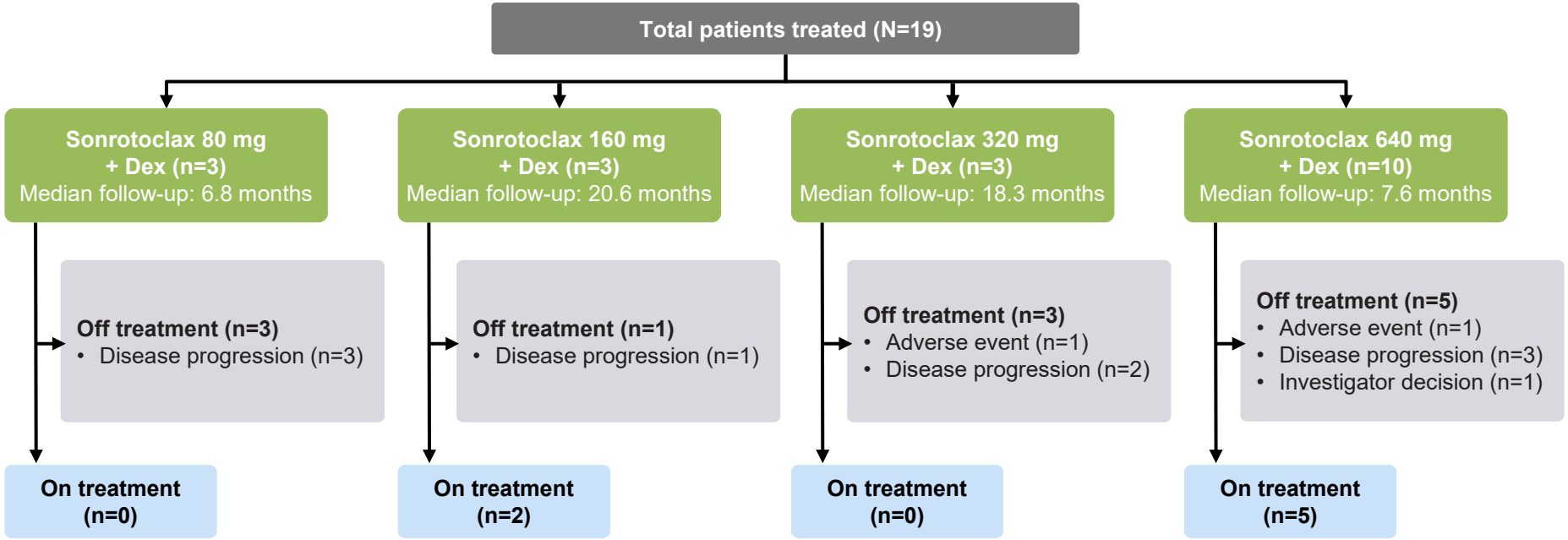
Dose escalation for sonrotoclax + dex in patients with R/R MM[a]



Primary endpoints: Safety and tolerability, MTD/MAD, RP2D
Key secondary/exploratory endpoints: PK, biomarkers, disease response per IMWG 2016 criteria

[a]Daily doses administered orally in 21-day cycles.

Patient Disposition



Data cutoff date: September 18, 2023.

Baseline Demographics and Disease Characteristics

Characteristics	Sonrotoclax 640 mg + Dex (n=10)	All (N=19)
Age, median (range), years	68.5 (56-74)	68.0 (52-81)
Sex, n (%)		
Female	6 (60)	12 (63)
Male	4 (40)	7 (37)
Race, n (%)		
White	9 (90)	18 (95)
Black	1 (10)	1 (5)
ECOG PS, n (%)		
0	4 (40)	10 (53)
1	6 (60)	9 (47)
R-ISS stage at initial diagnosis, n (%)		
Stage I	2 (20)	4 (21)
Stage II	5 (50)	9 (47)
Stage III	1 (10)	4 (21)
Unknown	2 (20)	2 (11)

Characteristics	Sonrotoclax 640 mg + Dex (n=10)	All (N=19)
Time from most recent R/R episode to first dose, median (range), months	2.86 (0.4-17.9)	2.43 (0.4-17.9)
Cytogenic risk, n (%)		
High[a]	2 (20)	3 (16)
Not high risk	8 (80)	12 (63)
Unknown	0	4 (21)
Number of prior lines, median (range)	**4 (3-12)**	**4 (1-12)**
Anti-CD38 antibody	9 (90)[b]	13 (68)[c]
Immunomodulatory agent	10 (100)	19 (100)
Proteasome inhibitor	10 (100)	19 (100)

[a]High-risk group consisted of patients with genetic subtype t(4;14), 1p deletion, del(17p13), and 1q21 amplification. [b]One patient in 640 mg group was incorrectly enrolled by study investigator and did not have prior anti-CD38 exposure. [c]Some patients in 160 mg (n=3) and 320 mg (n=2) group enrolled prior to protocol amendment requiring prior anti-CD38 treatment.

Overall Safety Summary and DLTs

	Sonrotoclax 80 mg + Dex (n=3)	Sonrotoclax 160 mg + Dex (n=3)	Sonrotoclax 320 mg + Dex (n=3)	Sonrotoclax 640 mg + Dex (n=10)	All (N=19)
Treatment cycles, median (range), n	3.0 (2-4)	28.0 (11-30)	6.0 (4-6)	8.0 (4-22)	7.0 (2-30)
Serious TEAE, n (%)	0	0	1 (33)	1 (10)	2 (11)
TEAE leading to death, n (%)	0	0	1 (33)	0	1 (5)
TEAE leading to discontinuation, n (%)					
Sonrotoclax	0	0	1 (33)	2 (20)[a]	3 (16)
Dexamethasone	0	0	1 (33)	2 (20)	3 (16)
TEAE leading to dose interruption, n (%)					
Sonrotoclax	0	2 (67)	1 (33)	2 (20)	5 (26)
Dexamethasone	0	2 (67)	0	1 (10)	3 (16)
TEAE leading to dose reduction, n (%)					
Sonrotoclax	0	0	0	0	0
Dexamethasone	2 (67)	2 (67)	1 (33)	4 (40)	9 (47)

- Serious TEAEs were COVID-19 and cancer pain (n=1 each)
- Three patients[a] discontinued sonrotoclax due to TEAEs (COVID-19, hematuria, cancer pain; n=1 each)
- No DLTs occurred
- Four patients (21%) died on study; no deaths were related to study treatment
  - One patient died while receiving study therapy (COVID-19)
  - Three patients died ≥50 days after treatment discontinuation (COVID-19, PD, unknown, n=1 each)[b]

[a]One patient originally reporting a TEAE (cancer pain) leading to discontinuation was subsequently found to have PD. [b]All AEs and serious AEs, regardless of relationship to the study drug(s), were reported until 30 days after the last dose of study drug or until initiation of new anticancer therapy; 3 of 4 patients got subsequent treatment.

Most Common TEAEs (≥10% of All Patients)

Patients, n (%)	Sonrotoclax 640 mg + Dex (n=10)		All (N=19)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
≥1 TEAE	10 (100)	3 (30)	19 (100)	5 (26)
Insomnia	4 (40)	0	10 (53)	0
Fatigue	3 (30)	1 (10)	7 (37)	1 (5)
Nausea	4 (40)	0	7 (37)	0
Arthralgia	2 (20)	0	5 (26)	0
COVID-19	2 (20)	0	4 (21)	1 (5)[a]
Alopecia	2 (20)	0	3 (16)	0
Diarrhea	2 (20)	0	3 (16)	1 (5)
Dyspnea	1 (10)	0	3 (16)	0
Rash	1 (10)	0	3 (16)	0
Vomiting	1 (10)	0	3 (16)	0
Back pain	0	0	2 (11)	0
GERD	1 (10)	0	2 (11)	0
Headache	2 (20)	0	2 (11)	0
Toothache	1 (10)	0	2 (11)	0
UTI	0	0	2 (11)	0

- Only 1 Grade ≥3 TEAE (diarrhea) was assessed as sonrotoclax-related

[a]One fatal case of COVID-19 in the 320 mg group.

Hematologic and Infection TEAEs

Patients, n (%)	Sonrotoclax 640 mg + Dex (n=10)	All (N=19)
Hematologic toxicities	3 (30)	4 (21)
Anemia	1 (10)	1 (5)
Decreased lymphocyte count	1 (10)	1 (5)
Neutropenia/decreased neutrophil count	1 (10)	2 (11)[a]
Decreased platelet count	1 (10)	1 (5)

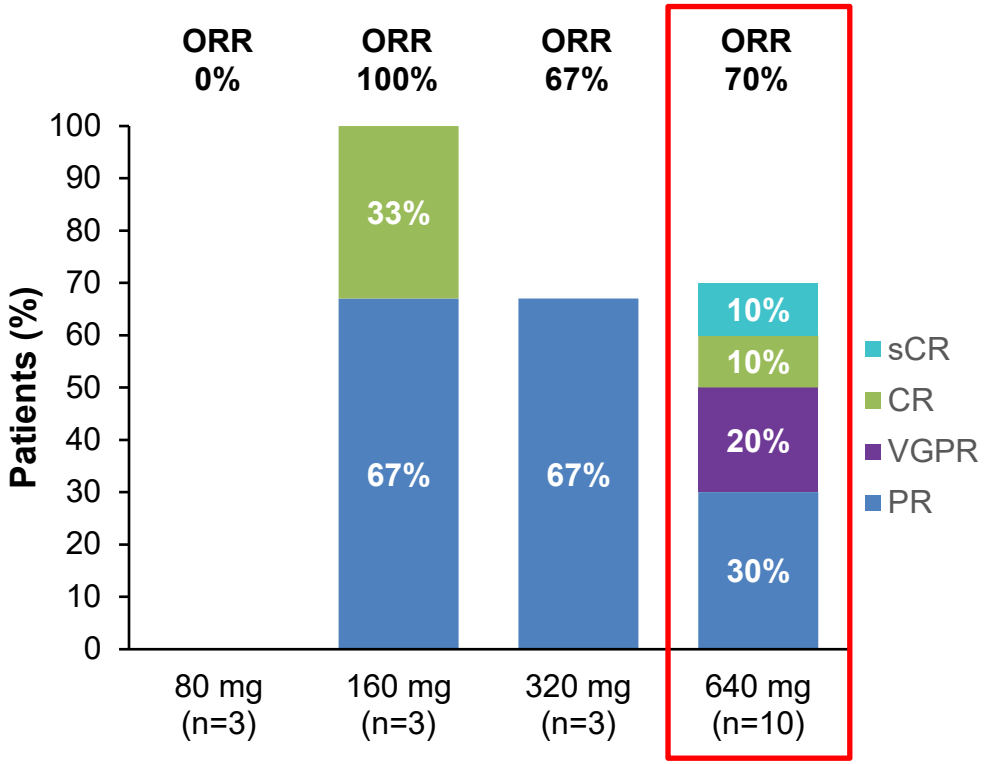
Patients, n (%)	Sonrotoclax 640 mg + Dex (n=10)	All (N=19)
Infections and infestations	2 (20)	6 (32)
COVID-19	2 (20)	4 (21)
UTI	0	2 (11)
Conjunctivitis	0	1 (5)
Respiratory syncytial virus infection	0	1 (5)
Rhinovirus infection	0	1 (5)
URI	1 (10)	1 (5)

- Of the hematologic TEAEs, decreased lymphocyte count and decreased platelet count were Grade 3
- All infections were Grade 1-2 except for 1 case of COVID-19

[a]Neutropenia occurred in 1 patient at a dose <640 mg.

Investigator-Assessed Response Rates

- Median treatment duration:
  All patients: 5.1 months (range, 1.2-21.1 months)
  640 mg: 5.5 months (range, 2.4-15.1 months)
- Rate of VGPR or better was 40% in a heavily pretreated patient population (median of 4 prior lines of therapy)
- The longest DoR was 18.9 months, which was still ongoing at data cutoff
  - This patient is a 70-year-old woman with high cytogenic risk. She received 160 mg sonrotoclax + dex and achieved PR at 1.4 months, VGPR at 4.1 months, and CR at 7.8 months. She was still in CR at her most recent assessment at 20.2 months



Conclusions

- Sonrotoclax + dexamethasone combination treatment was well tolerated in a heavily pretreated population (median of 4 prior lines of therapy), with no DLTs observed at any tested dose level and the majority (74%) of patients only experienced Grade 1 or 2 AEs
  - No significant hematologic toxicity was seen at any dose
  - Diarrhea was low grade and manageable with dose interruption
  - Only 1 infection was Grade ≥3 (COVID-19)
- Sonrotoclax + dexamethasone 640 mg is being evaluated in the expansion cohort based on the totality of safety and efficacy data
  - The majority of patients (70%) receiving 640 mg achieved a clinical response including ≥VGPRs of 40%
- Recruitment is ongoing for the sonrotoclax + dexamethasone expansion cohort and the sonrotoclax + dexamethasone + carfilzomib dose-finding arms
- Later cohorts in this study will investigate other combinations

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