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The HIV Protease Inhibitor Nelfinavir in Combination with Bortezomib and Dexamethasone (NVd) has Promising Activity in Patients with Proteasome Inhibitor- Refractory Multiple Myeloma

A Multicenter Phase II Trial (SAKK 39/13)

Rationale

- Poor treatment options for patients with advanced, proteasome inhibitor-refractory multiple myeloma (MM)
- ≈ 30% ORR for approved drugs
- Activity of the unfolded protein response (UPR) and high expression of IRE1/XBP1 correlate with bortezomib sensitivity
  (Ling et al.,Haematologica. 2012 Jan;97(1):64-72)
- IRE1/XBP1 downregulation provides proteasome inhibitor resistance and is found in proteasome inhibitor-refractory MM patients
  (Leung-Hagesteijn et al., Cancer Cell. 2013 Sep 9;24(3):289-304)
- Pharmacologic upregulation of IRE1/XBP1 re-sensitizes myeloma cells for proteasome inhibitor treatment
  (Kraus et al., Blood Cancer J. 2013 Mar 1;3)

Nelfinavir

- Inhibitor of HIV protease, no known human homologues
- Approved for oral HIV therapy 2 x 1250 mg, generic drug
- Induces UPR activation and IRE1/XBP1 expression and overcomes proteasome inhibitor resistance in vitro
  (Kraus et al., Blood Cancer J. 2013 Mar 1;3)
- Phase I, SAKK 65/08 trial:
  - Induction of UPR and IRE1/XBP1 in PBMC, no DLT
  - RP2D: 2 x 2500 mg with standard bortezomib/dexamethasone
  - 5/6 BTZ/LEN double-refractory patients clinical benefit (3 PR, 2 MR)

  (Driessen et al., Haematologica. 2016 Mar;101(3):346-55)

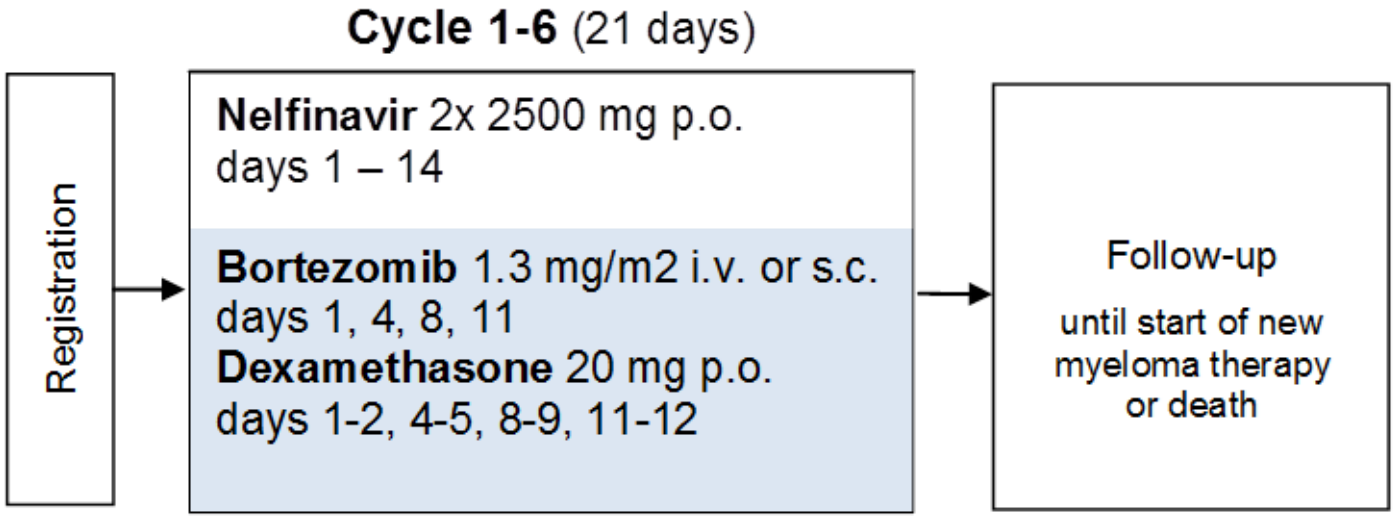
Objective

Establish, whether in proteasome inhibitor-refractory patients with multiple myeloma,

the addition of nelfinavir to approved bortezomib-dexamethasone therapy is sufficiently active to merit further investigation in a randomized trial.

Trial design

- Prospective, single-arm, multi-center, open-label phase II



- Simon's two stage design, n=34
  ≤ 15% response rate uninteresting, ≥ 30% response rate promising
  power=80%, alpha=5%
- Completion after cycle 6 (18 weeks maximum trial therapy)
- Academic trial without industry (finance/drug) support

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Treatment schedule

Cycle	1 – 6																			
Week	1							2							3					
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Nelfinavir 2 x 2500 mg p.o.	• •	• •	• •	• •	• •	• •	• •	• •	• •	• •	• •	• •	• •	• •							
Bortezomib 1.3 mg/m2 i.v. or s.c.	x			x				x			x										
Dexamethasone 20 mg p.o.	x	x		x	x			x	x		x	x									

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Trial endpoints

- Primary
  - Response rate (best response PR or better, IMWG criteria)
- Secondary
  - Adverse events
  - Time to next new anti-myeloma therapy or death
  - PD under trial treatment
  - Duration of response
  - Progression-free survival (PFS)
  - Time to progression (TTP)

Key inclusion criteria

- IMID-exposed or intolerant
- Refractory (IMWG criteria*) to most recent proteasome inhibitor-containing regimen**
- PS ≤ 3, no upper age limit
- Creatinine clearance ≥ 15 ml/min, platelets ≥ 50 x 10^9/l, hemoglobin ≥ 80 g/l (transfusion allowed)

* progressive on or within 60 days after proteasome inhibitor-containing salvage therapy; Rajkumar et al., Blood 2011 117:4691-4695

** bortezomib had to have been dosed ≥ 1.0 mg/m^2 with
≥ 4 doses/28 days, when given as monotherapy/steroid combination
or ≥ 2 doses/28 days, when given with alkylator, anthracycline or IMID

Key exclusion criteria

- Uncontrolled, clinical significant, active concurrent disease
- Concomitant additional systemic cancer treatment
- Concomitant radiotherapy, except for local pain control
- Significant neuropathy (grades 3-4 or grade 2 with pain)

Patient population

	Total - 34 patients **Median (min-max) or n (%)**
Age (years)	67 (42-82)
Male	21 (62%)
Performance status 0, 1, 2	20 (59%), 11 (32%), 3 (9%)
Number of prior systemic therapy lines	5 (2-10)
Prior ASCT	26 (76%)
Time from last dose of prior therapy to enrollment (days)	27 (3-402)
Known poor risk cytogenetics	13 (38%)

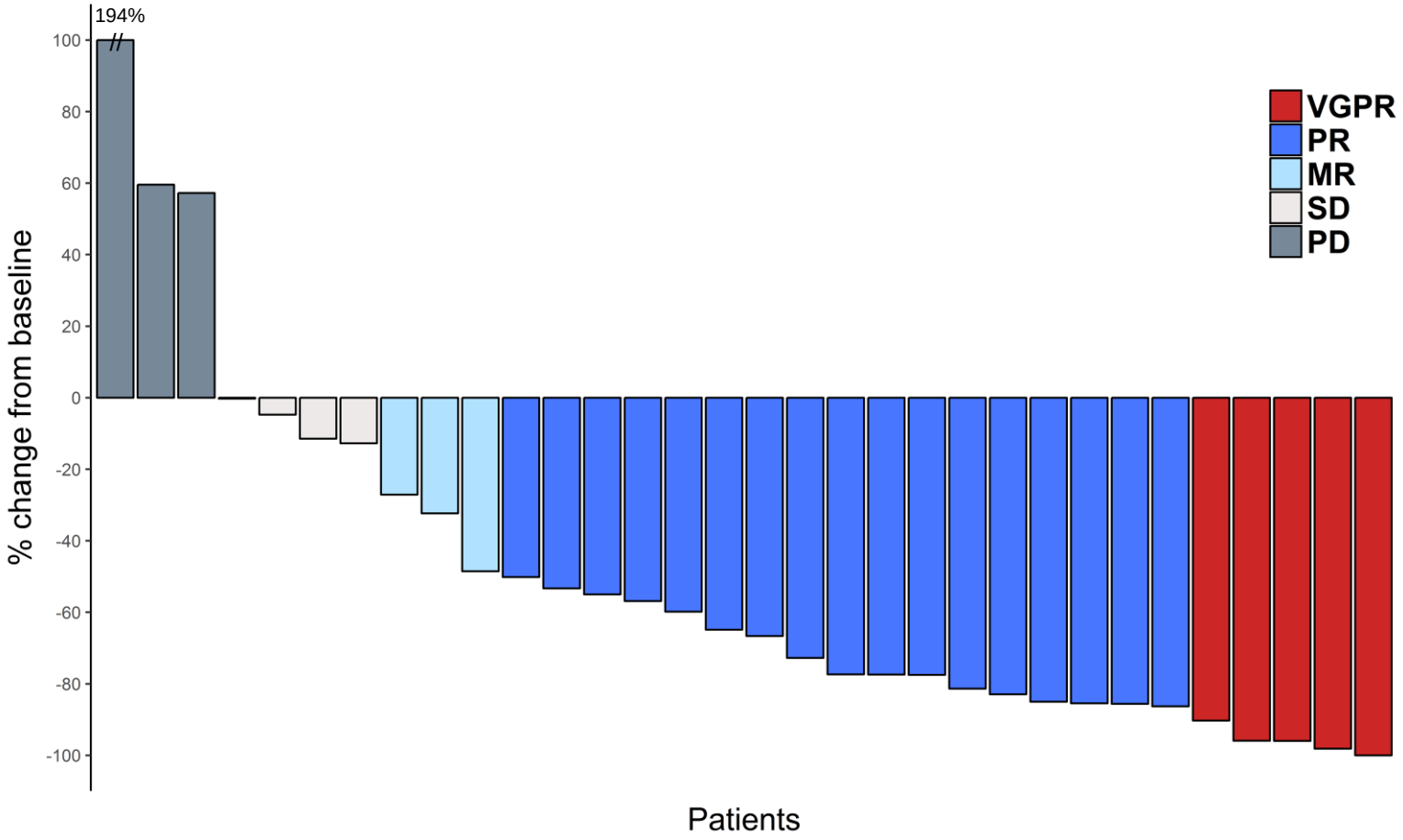
Prior drug exposure

	Total - 34 patients n (%)	
	Exposed	**Refractory**
Bortezomib (BTZ) Number of lines, median (min-max)	34 (100%) 2 (1-5)	34 (100%)
Lenalidomide (LEN)	34 (100%)	27 (79%)
Pomalidomide (POM)	16 (47%)	15 (44%)
Carfilzomib (CFZ)	2 (6%)	2 (6%)
BTZ + LEN + POM + CFZ	1 (3%)	1 (3%)

Efficacy outcomes

	Total - 34 patients **Median (min-max) or n (%)**
Therapy cycles delivered within the trial	4.5 (1-6)
Best response ≥ PR (90% CI)	**22 (65%)** **(49%-76%)**
Best response categories – VGPR – PR – MR – SD – **CBR (VGPR+PR+MR)**	 5 (15%) 17 (50%) 3 (9%) 4 (12%) 25 (74%)
Poor risk CG patients (n=13) **Best response ≥ PR**	10 (77%)
Time to new anti-myeloma therapy or death (weeks), median (95% CI)	16 (13-24)
PD under trial therapy (confirmed / unconfirmed)	13 (38%) / 18 (53%)

Best response



Maximum relative change in serum M-protein or serum free light chain concentration in individual evaluable patients.

Efficacy per prior drug treatment

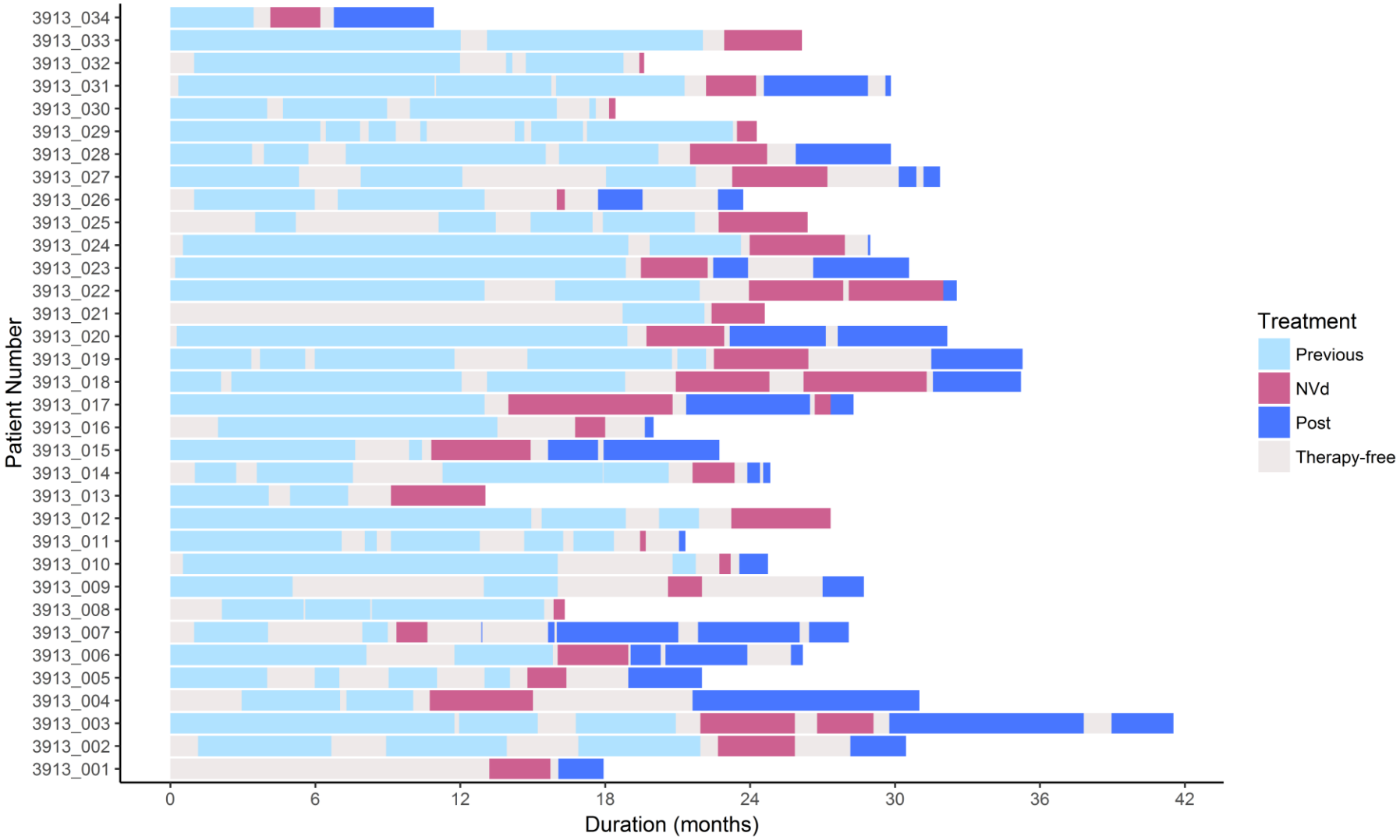
Best response ≥ PR	Total - 34 patients n (%)	
	Exposed	Refractory
Bortezomib (BTZ)	n=34 22 (65%)	n=34 22 (65%)
BTZ + Lenalidomide (LEN)	n=34 22 (65%)	n=27 19 (70%)
BTZ + LEN + Pomalidomide (POM)	n=16 9 (56%)	n=15 9 (60%)
BTZ + LEN + Carfilzomib (CFZ)	n=2 1 (50%)	n=2 1 (50%)

Adverse events, ≥G3, n>2

	AE type	G3	G4	G5
Hematological	Anemia	10		
	(febrile) Neutropenia	1	2	1
	Thrombocytopenia	8	7	
Infections	Lung infection	7	1	
	Sepsis			3
Non-hematological	Fatigue	5		
	Peripheral sensory neuropathy	3		
	Hypertension	6		
Laboratory	Creatinine increased	4		
	Hyperglycemia	6		
	Hypokalemia	2	1	
	Hyponatremia	5		

Individual therapy characteristics

≈ 24 months prior to NFV until last follow up



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Discussion

- NVd has substantial activity in advanced, proteasome inhibitor-refractory multiple myeloma
- Activity of NVd preserved in PI+IMID double-refractory as well as in poor risk CG patients
- Toxicity profile similar to Vd in heavily pretreated patients
- Median TTNT 16 weeks, individual patients with substantially longer treatment benefit
- Nelfinavir may universally boost cytotoxic activity of proteasome inhibitors
- With future generic BTZ, NVd has potential to become a fully generic, affordable, active therapy option for PI-refractory patients

Conclusions

- Nelfinavir in combination with bortezomib and dexamethasone (NVd) is a reasonable, active, safe, and widely available treatment option for patients with proteasome inhibitor-refractory multiple myeloma.
- The objective response rate of 65% observed in this very advanced, heavily pretreated, mostly dual-refractory patient population is exceptional.
- Our results warrant further development of nelfinavir as a sensitizing drug for proteasome inhibitor-based treatments and as promising new agent for MM therapy.

Acknowledgements

Participating Centers and Investigators

Kantonsspital St. Gallen	C. Driessen, F. Hitz
Inselspital Bern	T. Pabst, U. Novak
Kantonsspital Luzern	T. Zander, M. Gregor
Universitätsspital Zürich	P. Samaras, R. Müller
Kantonsspital Aarau	N. Cantoni
Hôpital Fribourgeois	D. Betticher
Hôpitaux Universitaires de Genève	N. Mach
Universitätsspital Basel	D. Heim
Kantonsspital Chur	U. Mey

SAKK Coordinating Center

C. Berset
S. Rondeau
A. Tomaszewska
M. Baresic
H. Hawle

Financial Support

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State Secretariat for Education, Research and Innovation SERI

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