SAR650984, A CD38 Monoclonal Antibody in Patients with Selected CD38+ Hematological Malignancies

Data From a Dose-Escalation Phase I Study (TED10893)*

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CD38 Expressed in Hematological Malignancies

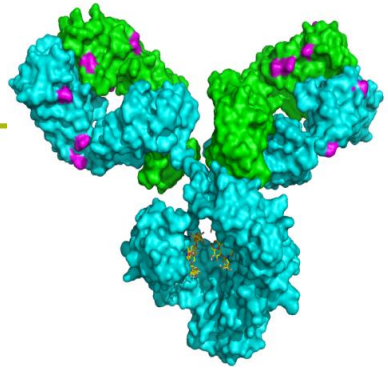
- Transmembrane glycoprotein and ectoenzyme
- High receptor density on multiple myeloma cells

CD38 Expression in Hematological Malignancies

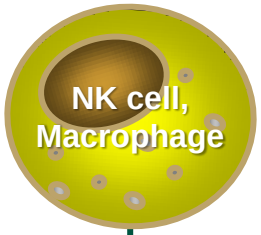
Disease	CD38+ Expression
Multiple myeloma	80-100%[1]
Non-Hodgkin's lymphoma	30-80%[2,3]
Acute myeloid leukemia	58%[4]
B chronic lymphocytic leukemia	20-25%[5]

1. Lin et al , Am J Clin Pathol 2004;121:482-488, 2. Angelopoulou et al, Eur J Haematol 2002;68:12-21,
3. Schwonzen et al, Brit J Haematol 1993;83:232-239, 4. Keyhani et al , Leukemia Res 1999;24:153-159
5. Domingo-Domènech et al, Haematologica 2002;87:1021-1027.

SAR650984: A Humanized IgG1 Monoclonal Antibody



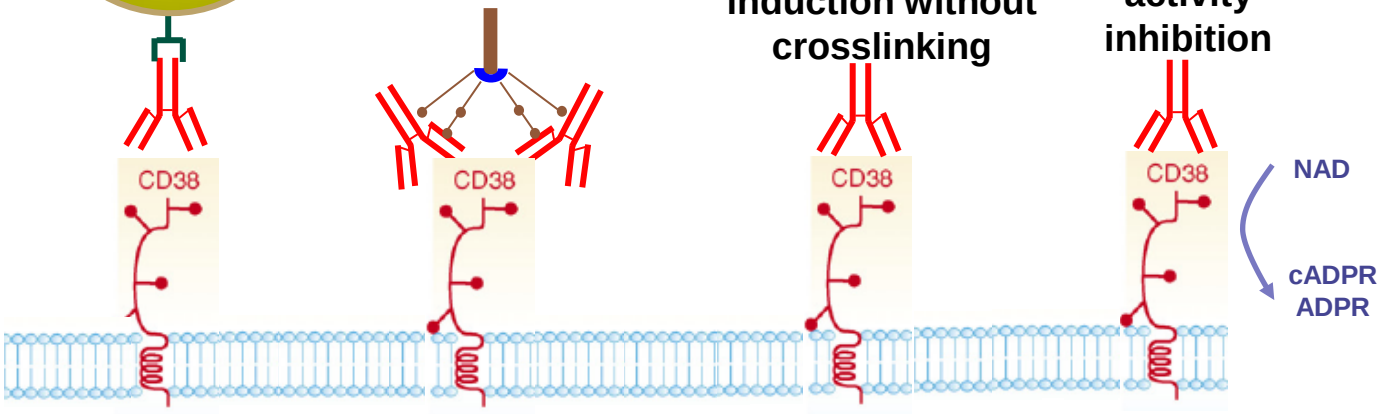
1. Antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis (ADCP)

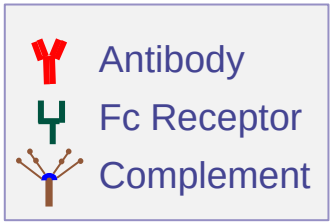


2. Complement-dependent cytotoxicity (CDC)

3. Direct apoptosis induction without crosslinking

4. CD38 enzymatic activity inhibition

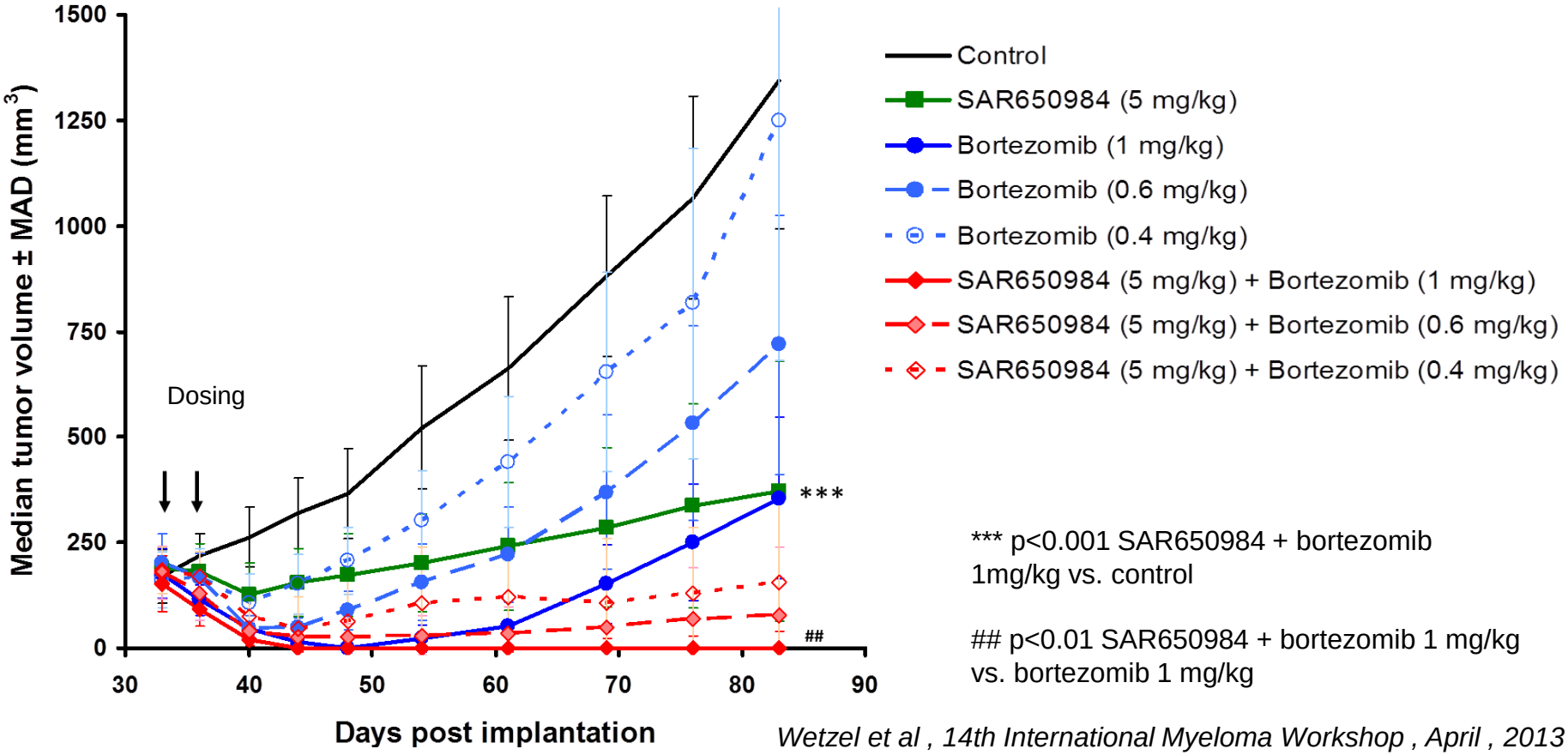




SAR650984: Potent *In Vivo* Activity

- Potent single agent *in vivo* anti-tumor efficacy
- Enhanced *in vivo* activity in combination with bortezomib, lenalidomide, carfilzomib, and melphalan in MM tumor models

Combination of SAR650984 and bortezomib in NCI-H929 MM xenograft model



*** p<0.001 SAR650984 + bortezomib 1mg/kg vs. control

p<0.01 SAR650984 + bortezomib 1 mg/kg vs. bortezomib 1 mg/kg

Wetzel et al , 14th International Myeloma Workshop , April , 2013

SAR650984: Phase I Dose Escalation Study

Primary Objective

- Determine maximum tolerated dose (MTD)/maximum administered dose (MAD)

Secondary Objective

- Characterize safety profile
- Evaluate pharmacokinetic (PK) profile
- Assess pharmacodynamics, immunogenicity, and preliminary disease response

SAR650984: Phase 1 Study Population

Key Inclusion Criteria

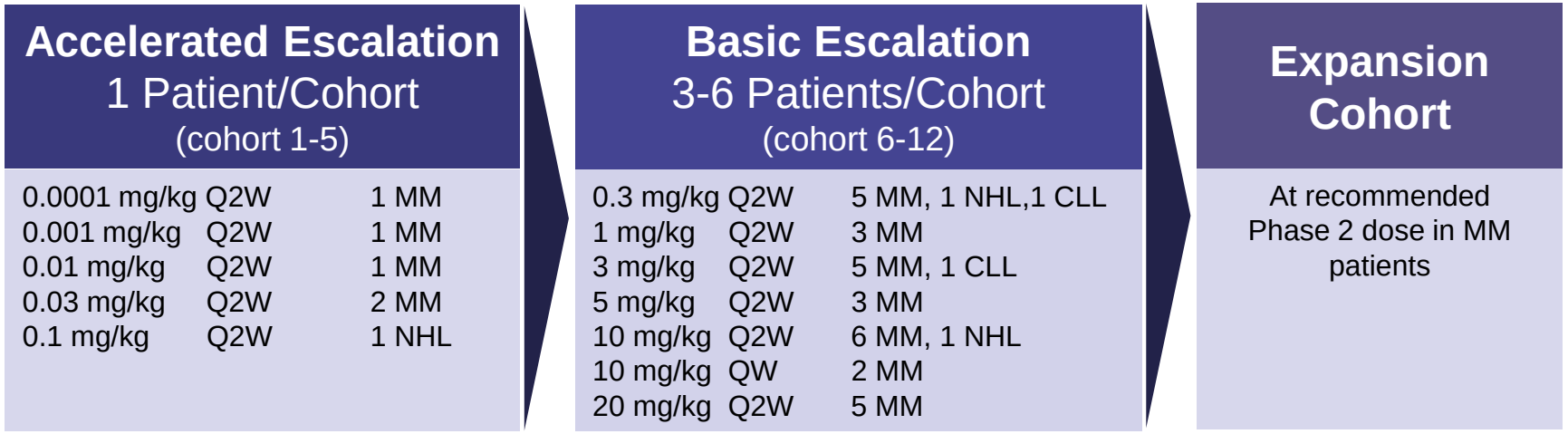
- Adults with selected hematologic malignancies and confirmed CD38 expression (FC or IHC)
  - **Multiple Myeloma**
  - **Chronic Lymphocytic Leukemia (CLL)**
  - **Non-Hodgkins Lymphoma**
  - **Acute Leukemias (AML, ALL)**
- Relapsed disease failing standard therapy
  - **Multiple Myeloma patients only from cohort 11 (10mg/kg QW) onwards**
- No limit on prior lines of therapy

Key Exclusion Criteria

- Poor performance status (KPS<60)
- Active or ongoing infection

SAR650984: Phase I Study Design

- Administered every 2 weeks (Q2W) or weekly (QW)
- DLT evaluation period is 28 days
- Disease assessment every 28 days
- Dose escalation phase followed by an expansion cohort



- MM= Multiple Myeloma; NHL = Non-Hodgkins Lymphoma; CLL = Chronic Lymphocytic Leukemia
- Patients treated prior to Sep 13, 2013 are presented

SAR650984: Baseline Characteristics

- **39 treated patients**
  - Median age = 65.0 (40 - 85)
- **Prior therapies of myeloma patients (n=34)**
  - Median = 6 (2 – 14)
  - At doses ≥ 0.3 mg/kg - all patients received prior lenalidomide and bortezomib
  - At doses ≥ 10 mg/kg - 69% of patient received carfilzomib and/or pomalidomide

	Accelerated Doses	0.3 mg/kg Q2W	1 mg/kg Q2W	3 mg/kg Q2W	5 mg/kg Q2W	10 mg/kg Q2W	10 mg/kg QW	20 mg/kg Q2W	Overall
# of Patients (# of Myeloma patients)	6 (5)	7 (5)	3 (3)	6 (5)	3 (3)	7 (6)	2 (2)	5 (5)	39 (34)
# of Prior treatments, All pts - Median (range)	5 (4 - 9)	6 (1 - 12)	8 (7 - 9)	7 (3 -14)	4 (4 - 10)	5 (2 - 9)	8.5 (4 -13)	5 (4 - 7)	6 (1- 14)
Prior carfilzomib	0	0	0	3	1	4	2	2	12
Prior pomalidomide	0	0	2	0	2	0	1	2	7

SAR650984: Grade 3-4 Drug-Related TEAEs and Drug-Related SAEs (All Treated Patients)

Grade 3-4 drug related TEAEs / Drug related SAEs	3 mg/kg Q2W (N = 6)	5 mg/kg Q2W (N = 3)	10 mg/kg Q2W (N = 7)	10 mg/kg QW (N = 2)	20 mg/kg Q2W (N = 5)	Overall (N = 39)
Any Events	1 / 1	0 / 1	2 / 2	2 / 1	1 / 2	6 / 7
Pneumonia	1 / 1	-	2 / 2	-	-	3 / 3
Apnea	-	-	-	-	1 / 1	1 / 1
Hyperglycaemia	-	-	1 / 0	-	-	1 / 0
Hypophosphataemia	-	-	-	1 / 0	-	1 / 0
Obstruction Gastric	-	-	-	1 / 1	-	1 / 1
Pyrexia	1 / 1	-	-	-	-	1 / 1
Flushing	-	0 / 1	-	-	-	0 / 1
Hypoxia	-	0 / 1	-	-	-	0 / 1
Infusion Related Reaction	-	-	-	-	0 / 1	0 / 1
Nasal Congestion	-	0 / 1	-	-	-	0 / 1
Vomiting	-	0 / 1	-	-	-	0 / 1

No Grade 3-4 drug-related TEAEs / drug-related SAEs below 3mg/kg (N=16)

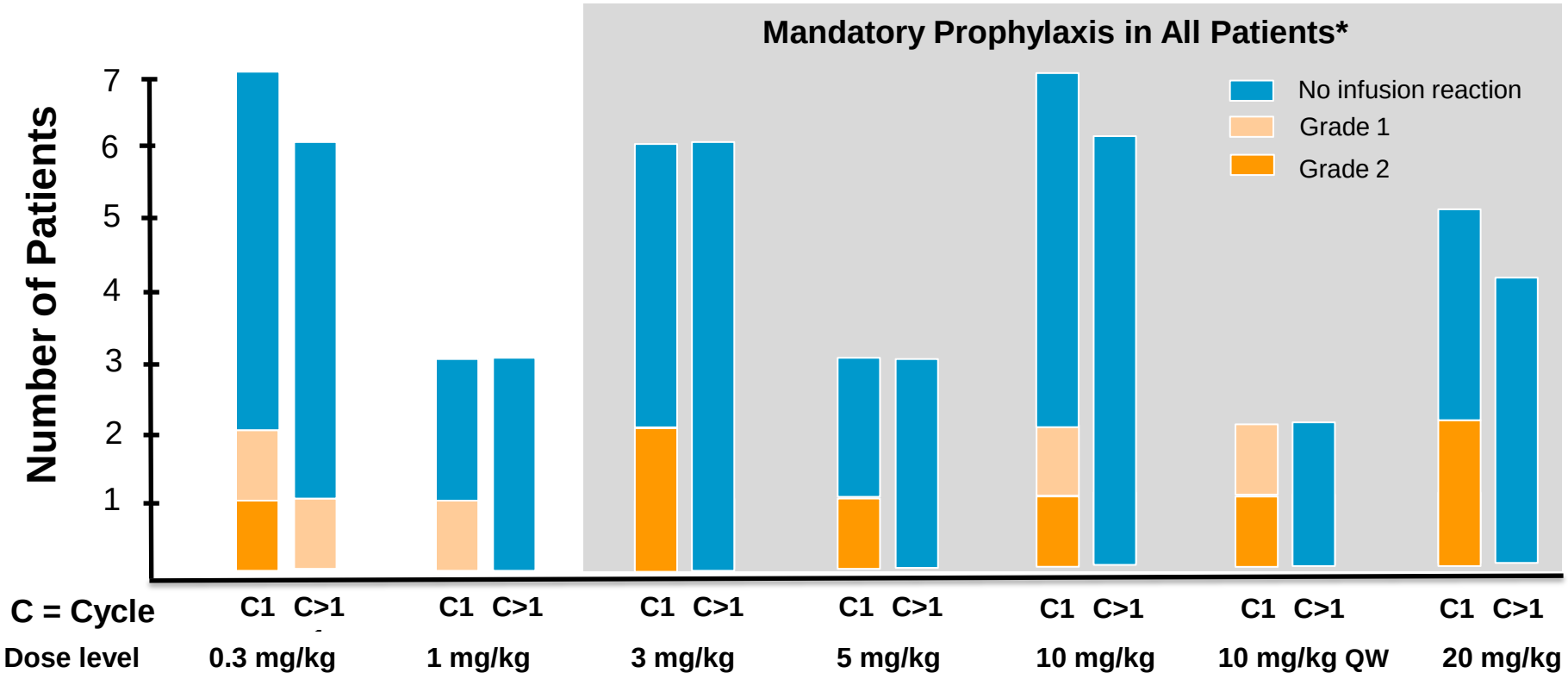
SAR650984: TEAEs occurring in ≥ 10% of the patients (All Treated Patients)

All grades/ Grade 3-4	Patients (N = 39)
Any events	**39 / 18**
Fatigue	17 / 0
Nausea	13 / 0
Fever	10 / 1
Cough	9 / 0
Anemia	8 / 2
Headache	8 / 0
Vomiting	7 / 0
Hypercalcaemia	6 / 2
Diarrhea	6 / 0

All grades/ Grade 3-4	Patients (N = 39)
Dyspnea	6 / 0
Hypokalaemia	5 / 2
Bone pain	5 / 0
Chills	5 / 0
Constipation	5 / 0
Thrombocytopenia	4 / 3
Abdominal pain	4 / 1
Decreased appetite	4 / 0
Dysgeusia	4 / 0

SAR650984: Patients with Infusion Reactions

Patients treated at doses of 0.3 mg/kg Q2W or higher



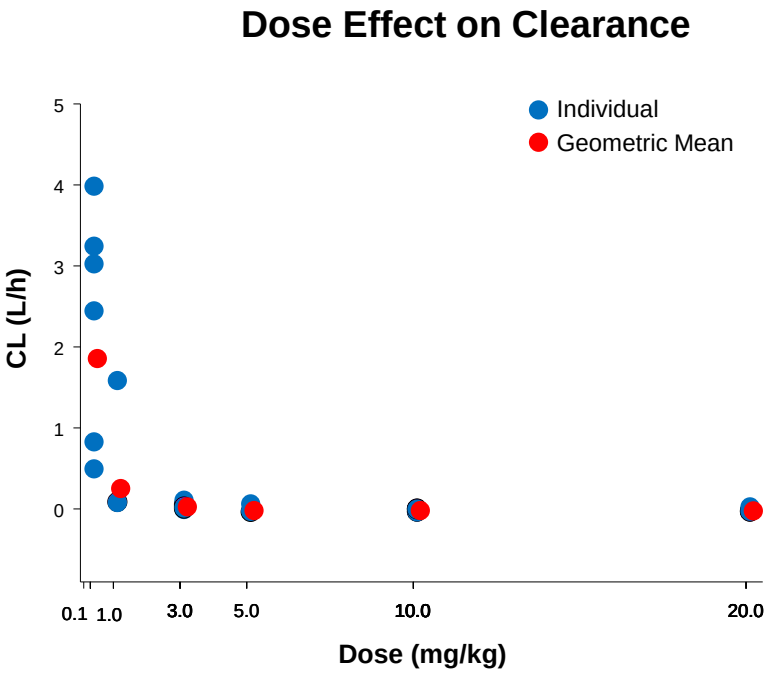
*methylprednisolone 100 mg IV, diphenhydramine 50 mg IV, ranitidine 50 mg IV, and acetaminophen 650-1000 mg po (or equivalents)

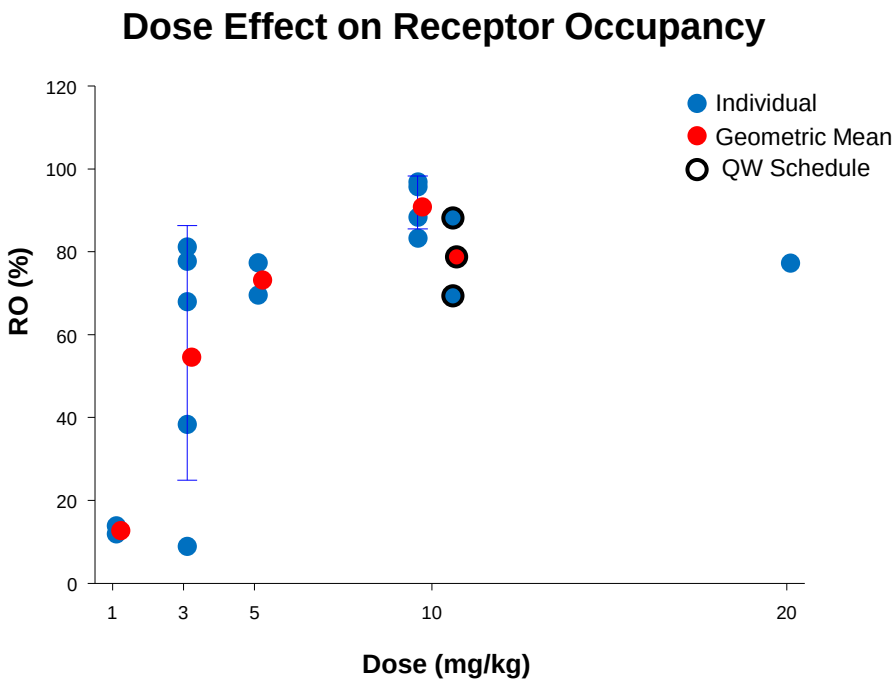
Symptoms of Infusion Reactions (N; max severity):

Nausea (5; G 2); Pyrexia (4; G 1); Drug hypersensitivity, Chills (3; G 2); Headache (3; G 1); Vomiting , Hypoxia (2; G 2); Cytokine release syndrome, Dyspnea, Flushing, Nasal congestion, Bronchospasm, Tracheal stenosis, Laryngospasm (1; G 2); Influenza-like illness, Abdominal pain, Blurred vision, Lacrimation increased, Rhinorrhea, Cough, Restlessness (1; G 1)

SAR650984: Pharmacokinetics

Clearance and Receptor Occupancy





Clearance

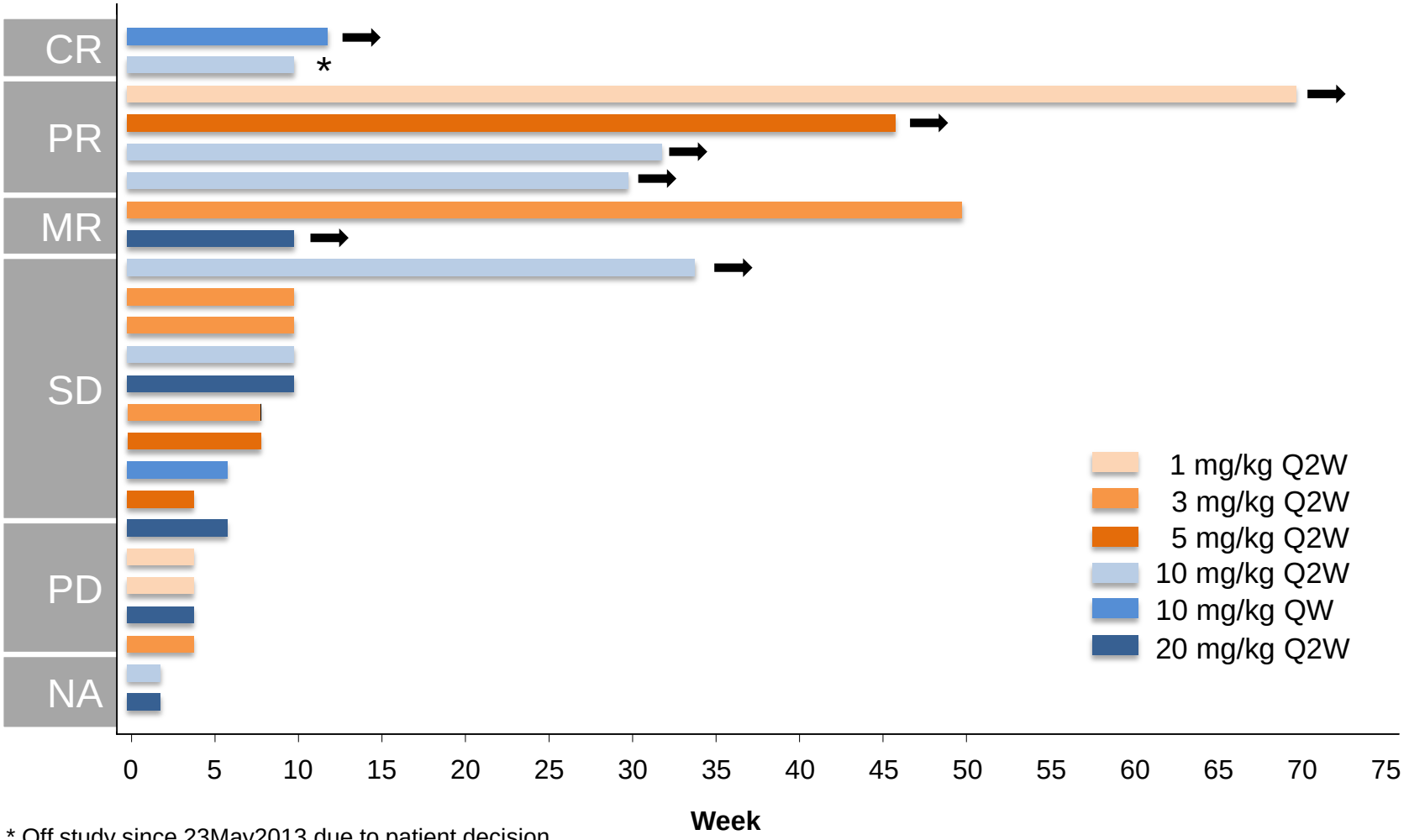
- Overall clearance decreased with increasing doses
- Decrease in clearance is less marked from 5 mg/kg Q2W compared to previous doses

Receptor Occupancy (RO)

- RO was not detectable below 1 mg/kg
- RO > 70% is observed at 5mg/kg Q2W and higher dose levels

SAR650984: Time on Treatment by Best Response

Myeloma Patients Treated at Doses of 1 mg/kg Q2W or higher

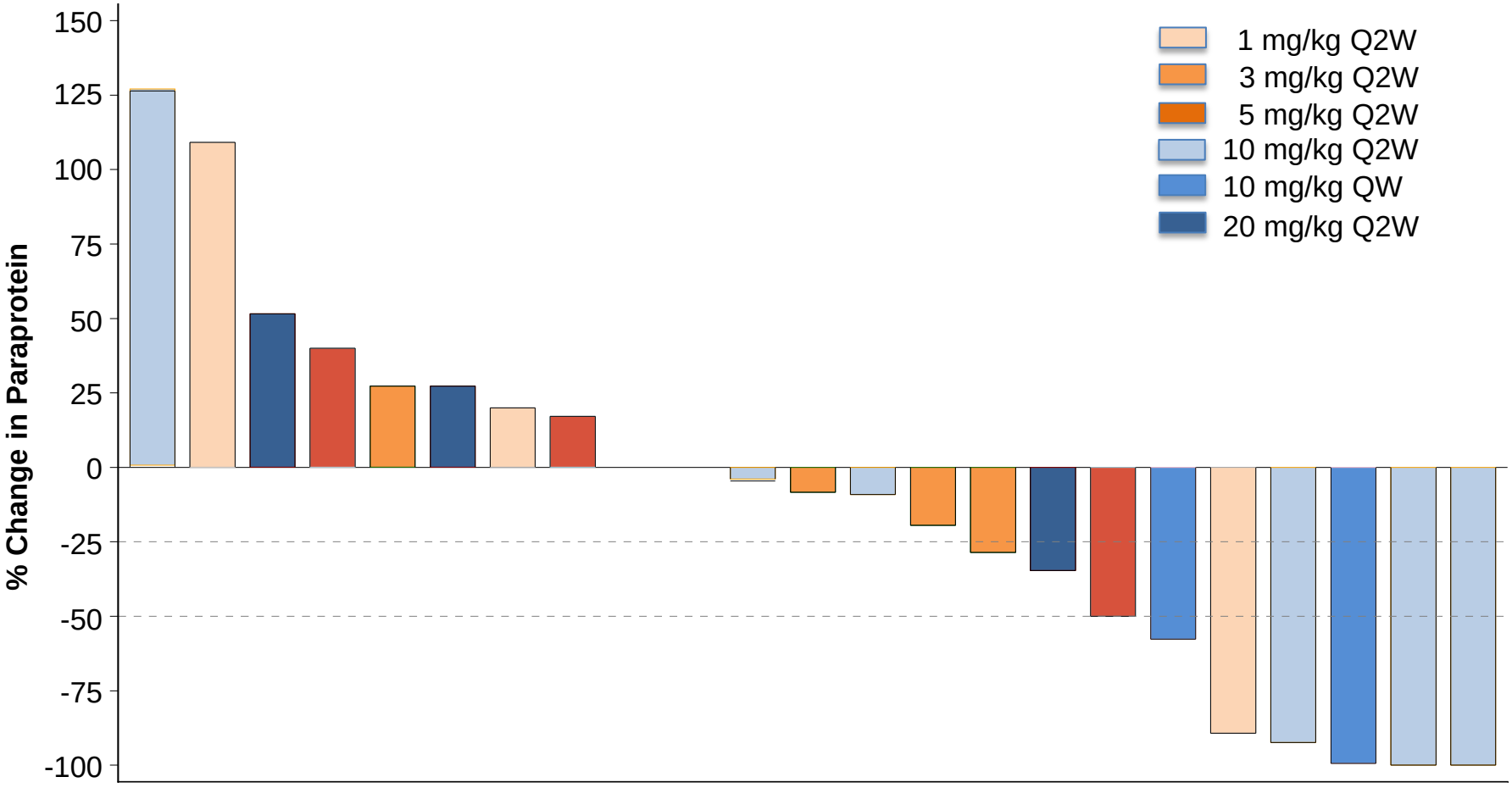


* Off study since 23May2013 due to patient decision.

➞ Ongoing

SAR650984: Maximal Change in Paraprotein

Myeloma Patients Treated at Doses of 1 mg/kg Q2W or Higher



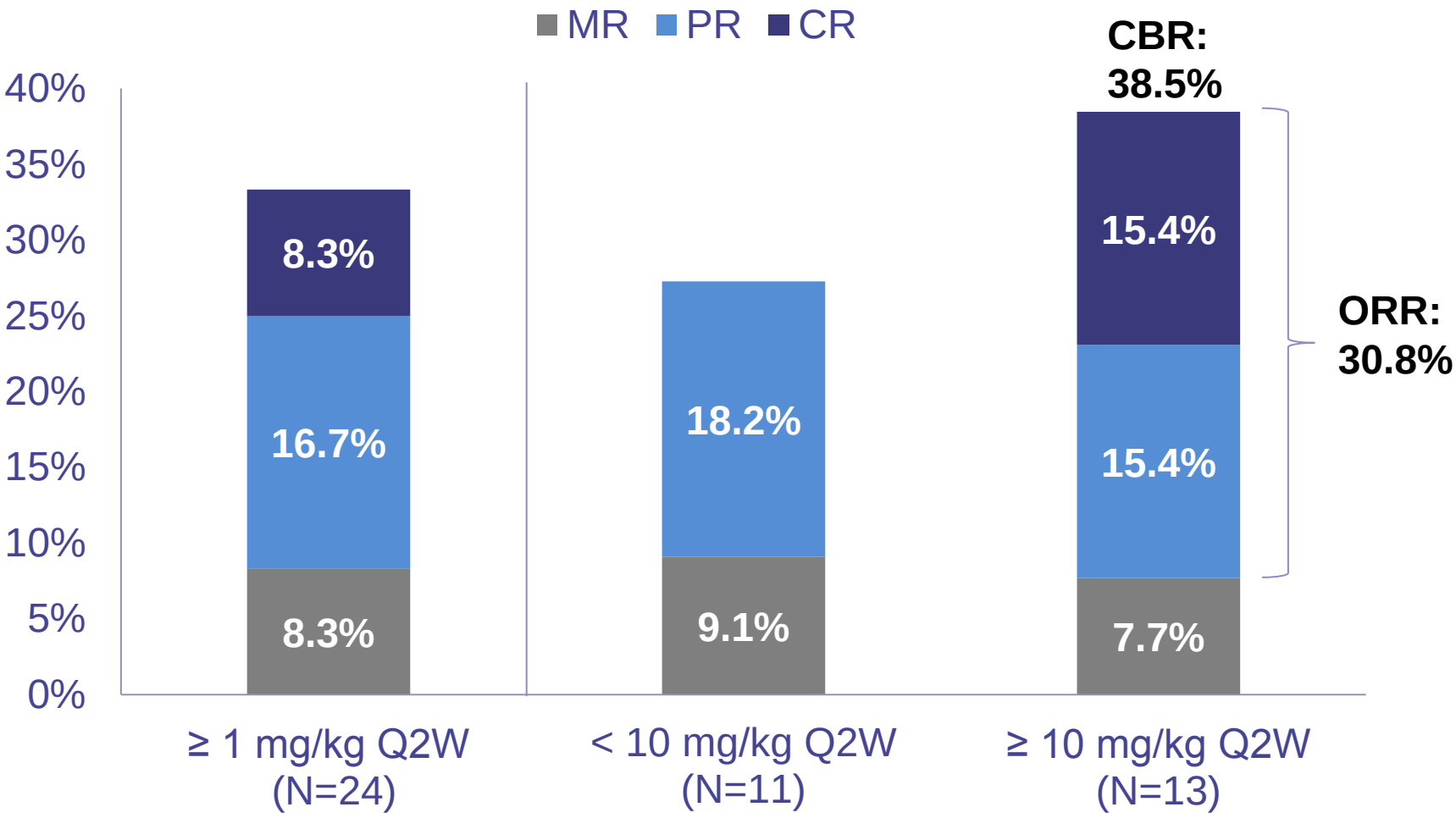
One patient at 3.0 mg/kg and 20 mg/kg with 0% change; One patient at 20 mg/kg not evaluable

SAR650984: Reduction in Bone Marrow Plasma Cells

Myeloma Patients Treated at Doses of 1 mg/kg Q2W or Higher

Cohort (N)	% Reduction in bone marrow plasma cells [Baseline value (%)]	Investigator's assessment (EBMT/IMWG criteria)
1 mg/kg Q2W (N=3)	68.8 [16]	PR
3 mg/kg Q2W (N=5)	25.0 [60]	MR
5 mg/kg Q2W (N=3)	84.9 [33]	PR
10 mg/kg Q2W (N=6)	100.0 [5]	CR
	60.5 [19]	PR
	100.0 [30]	PR
10 mg/kg QW (N=2)	100.0 [17]	CR
20 mg/kg Q2W (N=5)	80.0 [20]	MR

SAR650984: Phase 1 Response Summary



SAR650984: Phase 1 Response Summary

- Overall Response Rate (CR+PR)
  - Dosing cohorts ≥1mg/kg = **25%** (2 CR, 4 PR of 24)
  - Dosing cohorts ≥ 10 mg/kg = **31%** (2 CR, 2 PR of 13)
- Clinical Benefit Rate (CR+PR+MR)
  - Dosing cohorts ≥ 1mg/kg = **33%** (2 CR, 4 PR, 2 MR of 24)
  - Dosing cohorts ≥ 10 mg/kg = **38%** (2 CR, 2 PR, 1 MR of 13)
- Median Time to Initial Response (CR, PR, MR) = 6.1 weeks (3.4 – 12.3)
- In 8 responders the median duration of response 5.0 months (0 - 15.4)
  - 6 patients still on treatment
- Median duration of follow up is 6.5 months (1.9-16.3)

SAR650984: Phase 1 Study Conclusions

- SAR650984, an anti-CD38 mAb, has shown a favorable safety profile in hematological malignancies
  - MTD was not reached with an every other week and an every week schedule
  - Infusion reactions were predominantly Gr 1-2, and with standard prophylaxis, are only observed with first dose
- The non linear PK profile is consistent with target-mediated clearance
- Higher receptor occupancy correlates with increasing dose

SAR650984: Conclusions in Multiple Myeloma

At doses 0.0001 mg/kg to 20 mg/kg (n=34):

- Clinical Benefit Rate (CR+PR+MR) of 26.5%

At ≥ 10 mg/kg (n=24):

- Overall Response Rate (CR + PR) of **30.8%** including 2 CRs
- Clinical Benefit Rate (CR+PR+MR) of **38.5%**
  - Median of 5 prior lines of therapy
  - All patients previously treated with bortezomib and lenalidomide
  - 69% received carfilzomib and/or pomalidomide

- Clinical response correlates with clearance of plasma cells from the bone marrow

Acknowledgements

- The authors would like to thank participating patients and their families
- This study was funded by Sanofi