

# Higher incidence of injection site reactions after subcutaneous bortezomib administration on the thigh compared with the abdomen

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# Background-1

Subcutaneous (sc) rather than intravenous administration of bortezomib (Bor) is becoming more common for treating multiple myeloma (MM) because scBor results in lower incidence and severity of peripheral neuropathy and has equivalent efficacy.

*Moreau. Haematologica 2008; Moreau. Lancet Oncol 2011  
Lonial. Curr Hematol Malig Rep. 2011; Arnulf. Haematologica 2012*

## Background-2

Bor is an irritant cytotoxic agent when it leaks out; therefore, it is recommended that injections of scBor should be rotated among 8 different sites on the abdomen and thigh. However, detailed information about injection site reactions (ISR) have not been sufficiently documented.

*Moreau. Haematologica 2008; Moreau. Lancet Oncol 2011  
Lonial. Curr Hematol Malig Rep. 2011; Arnulf. Haematologica 2012*

# Design and Methods

We retrospectively analyzed the incidence and severity of ISR following scBor administration in 15 Japanese patients with MM. The frequencies of grade 0, grade 1 and grade 2 ISR in the thigh were compared with those in the abdomen using the  $\chi^2$ -test. The body mass index (BMI) of patients with grade 0–1 or 2 ISRs in the thigh was compared using the Mann–Whitney U-test.

# Design and Methods

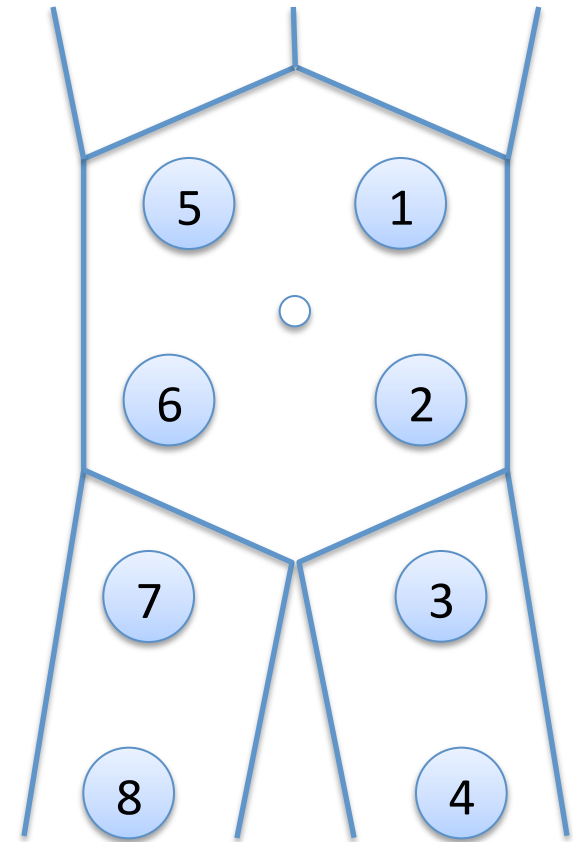
## Procedure of scBor Administration

scBor concentration: 2.5 mg/ml

3.0 mg Bor reconstituted with  
1.2 ml normal saline.

scBor injection sites: 8 different sites

The injection site is rotated  
among 8 different sites—  
upper and lower quadrants of  
the right and left abdomen  
and proximal and distal sites  
on both thighs.



# Design and Methods

## Evaluation of ISR

The tolerability of scBor at the injection site was evaluated systematically 2–hrs after injection and every day during the first treatment cycle during hospitalization. After the second cycle, ISRs were evaluated at every visit, and between visits patients documented their own ISRs in a detailed diary.

*Table 1. Grading of ISR according to NCI CTC ver. 4.0*

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
tenderness with or without associated symptoms	pain, lipodystrophy, edema, or phlebitis	ulceration, necrosis, severe tissue damage, or any indication for operative intervention	ISRs with life-threatening consequences, requiring urgent intervention	death

# Treatment Regimen with scBor

## scBD

scBor (1.3mg/m<sup>2</sup>) day 1, 8, 15, and 22

dexamethasone (40 mg/body) day 1, 8, 15, and 22

## scVCD (once-weekly)

scBor (1.3 mg/m)

cyclophosphamide ( 300 mg/m<sup>2</sup>)

dexamethasone (40 mg/body)

day 1, 8, 15, and 22

# Patient Characteristics (n=15)

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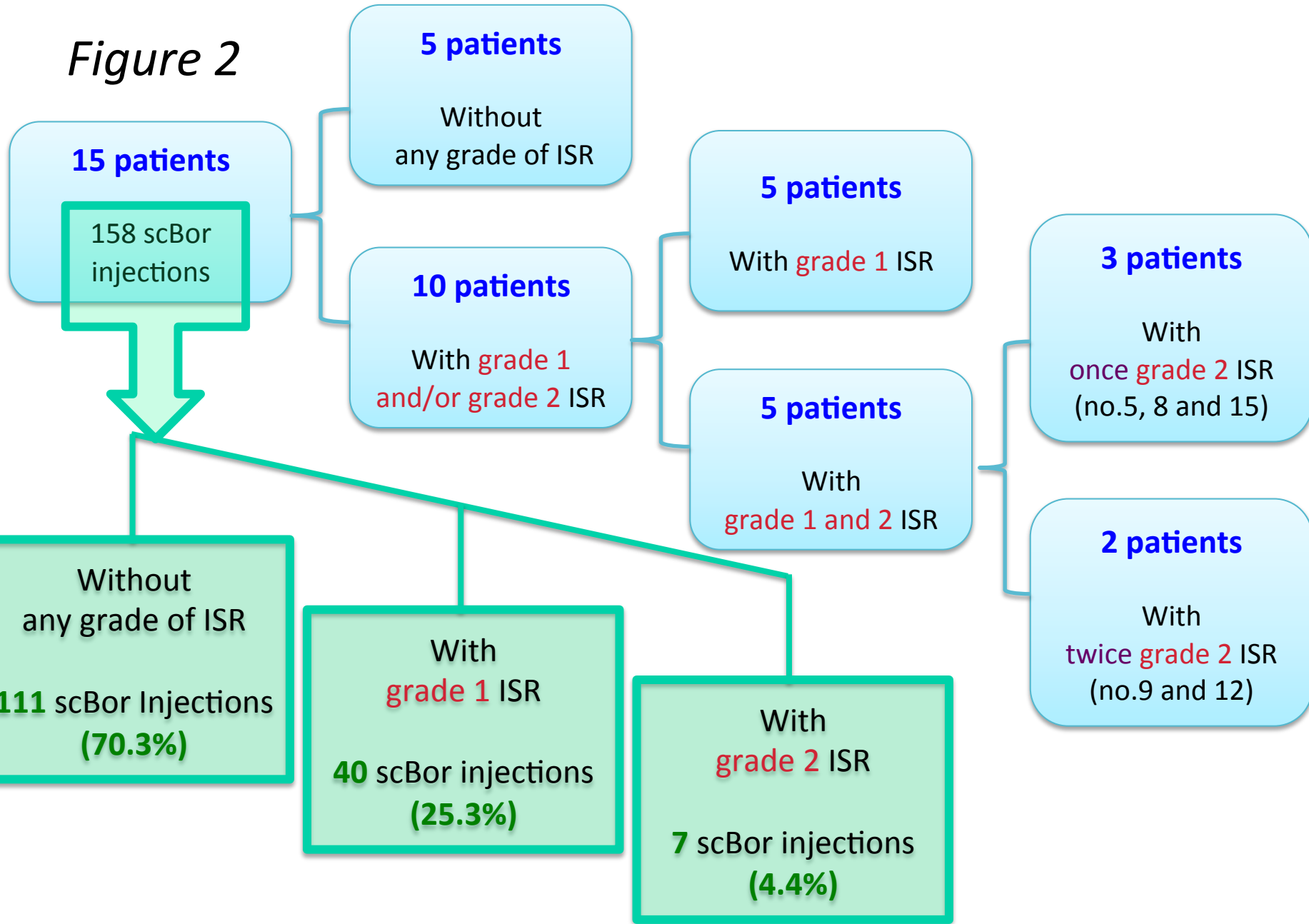
Age	70 (range 54–85)
Disease status	
Newly diagnosed	7
Relapsed / refractory	8
ivBor prior to scBor	5
Median dosage (range) (mg/m <sup>2</sup> )	17.6 (5.2–70.6)
Regimens including scBor	
BD (once-weekly)	4
VCD (once-weekly)	9
BD→VCD	2
Median dosage of scBor (range) (mg/m <sup>2</sup> )	10.4 (5.2–30.6)

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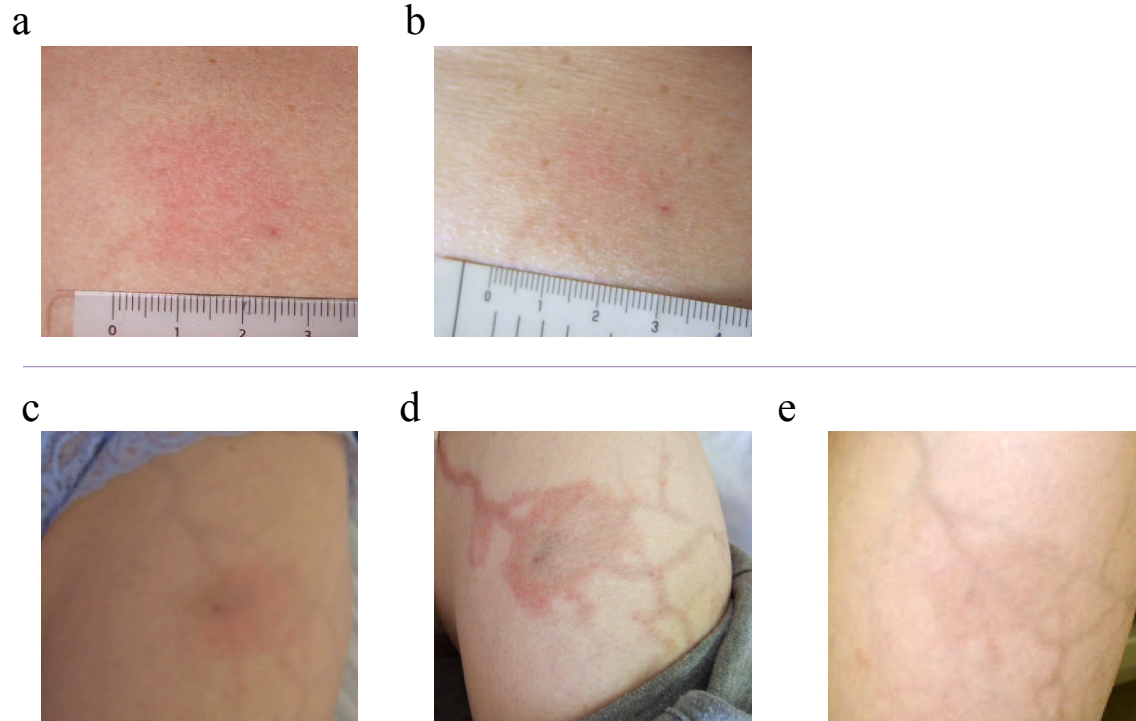


# Patients' and ISRs' Flow (n=15)

Figure 2

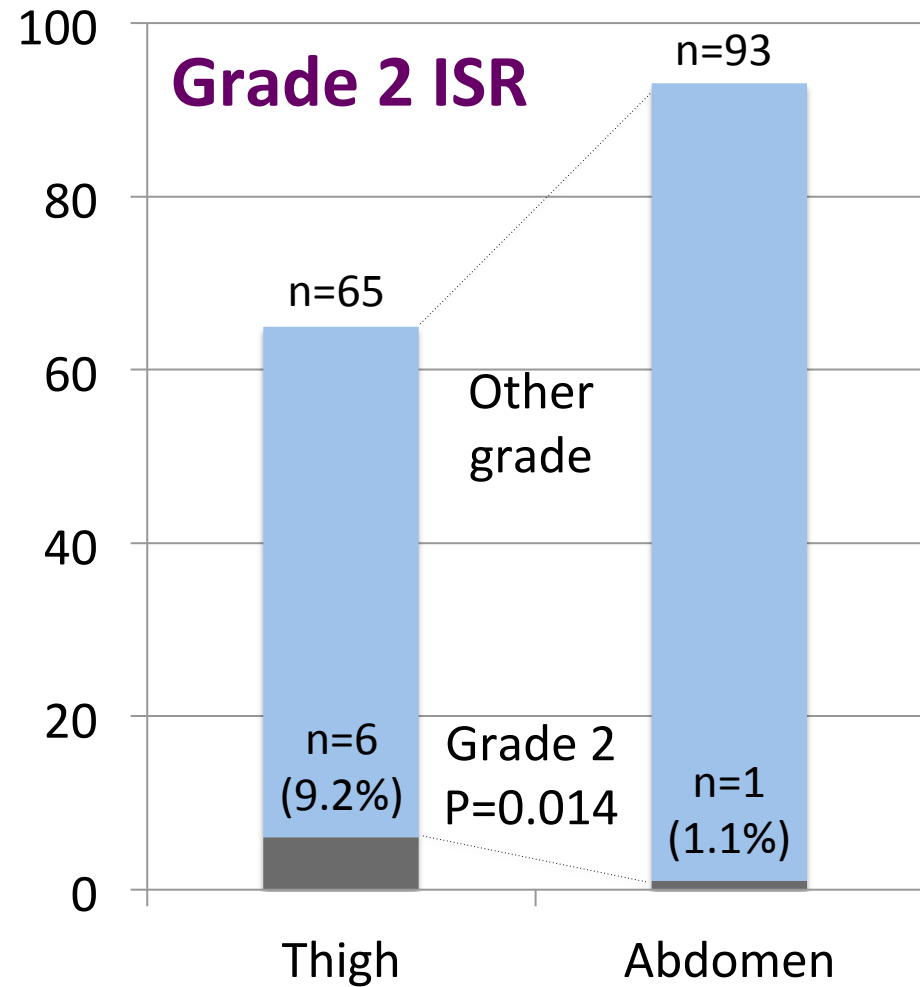
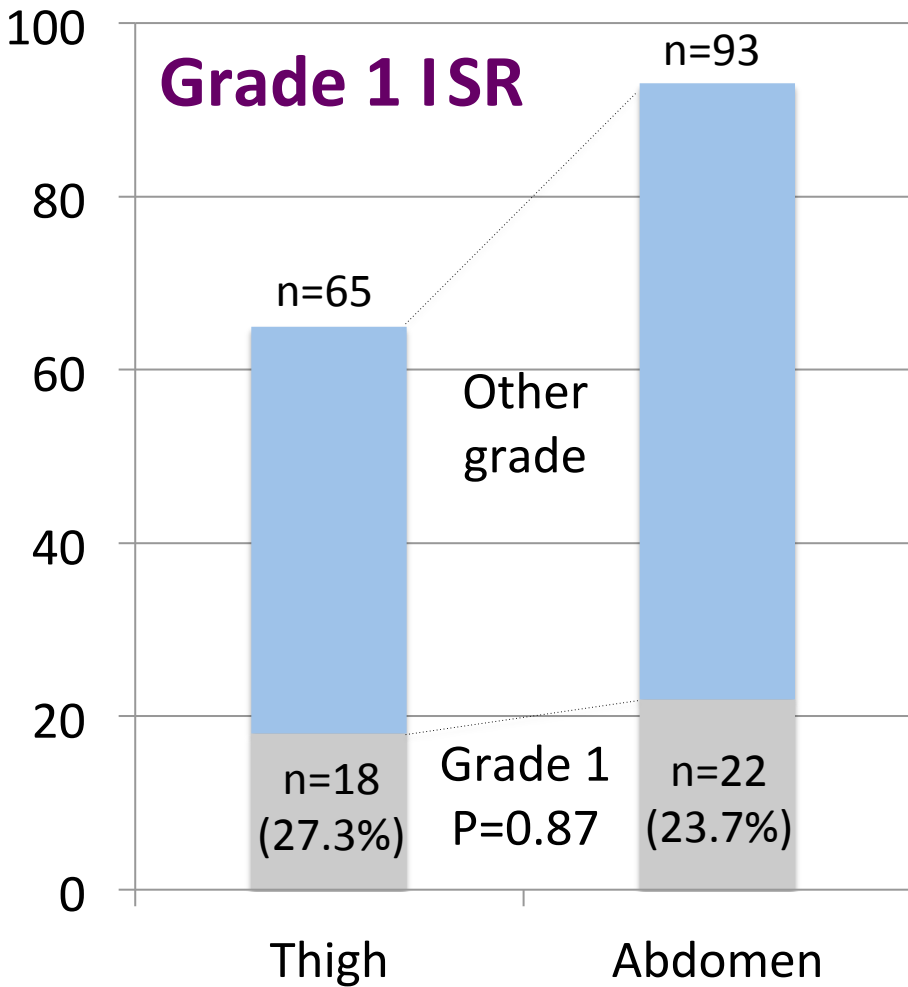


# Representative case (patient no. 9) with skin erythema



A 65-year old female (patient 9) with skin erythema, (a) classified as grade 1 ISR, 2 days after the 1<sup>st</sup> scBor injection on the left upper abdomen  
(b) Skin erythema quickly resolved without treatment 3 days after the injection  
(c) Two days after the 3<sup>rd</sup> scBor injection on the proximal left thigh, skin erythema recurred and progressively increased in size with phlebitis and finally progressed to grade 2 ISR 3 days after the 3<sup>rd</sup> injection. This ISR lesion did not expand further; therefore, no treatment was required and ISR resolved after 24 days.  
(d) Pigmentation persisted 43 days after the 3<sup>rd</sup> scBor injection

# Incidence of ISR (thigh vs. abdomen)



## Major toxicities (NCI CTC ver. 4.0)

	n (%)
Thrombocytopenia (grade 3)	0
New grade 3 thrombocytopenia	0
Grade 3 baseline thrombocytopenia	0
Neutropenia (grade 3)	3 (20%)
New grade 3 neutropenia	2 (13%)
Grade 3 baseline neutropenia	1 (7%)
Anemia (grade 3)	3 (20%)
New grade 3 anemia	0
Grade 3 baseline anemia	3 (20%)
Peripheral neuropathy (new/worse)	0/4
Grade 1/2 peripheral neuropathy	3 (20%)
Grade 3/4 peripheral neuropathy	1 (7%)
Infection (grade 3)	2 (13%)
Liver dysfunction (>grade 3)	0 (0%)

# Conclusion

We conclude that 4 different sites at the abdomen, avoiding the thigh, would be feasible and more suitable for scBor injection because ISR may be less common and severe and rapidly disappear within the interval before the next injection. Further large, prospective studies are required to assess the safety and efficacy of scBor.