

A Phase I/II Study of Arsenic Trioxide, Bortezomib, and Ascorbic Acid (ABC) Combination Therapy in Relapsed or Refractory Multiple Myeloma

James R. Berenson,^{1,2} Jeffrey Matous,³ Delina Ferretti,² Regina A. Swift,¹ Russell Mapes,¹ Blake Morrison,⁴ Howard S. Yeh^{1,2}

¹Institute for Myeloma and Bone Cancer Research, West Hollywood, CA; ²Oncotherapeutics, Inc., West Hollywood, CA; ³Rocky Mountain Cancer Centers, Denver, CO; ⁴Millennium Pharmaceuticals, Inc., Cambridge, MA

Introduction

Because the vast majority of patients with multiple myeloma (MM) develop resistance to chemotherapy, an urgent need exists for additional therapeutic options to overcome chemoresistance. Arsenic trioxide (ATO) and bortezomib (B) have each shown efficacy when used as a single agent in patients with relapsed or refractory MM.^{1,2} Preclinical in vitro studies in severe combined immunodeficient (SCID) mice have shown that the ATO/B combination has a significant synergistic effect on human MM cells.³ Both ATO and B are believed to exert their antimyeloma effect by (1) inhibiting the activation of NF- κ B, a transcriptional activator that plays a key role in the pathogenesis of hematologic cancers like MM; and (2) promoting mitochondrial cytochrome c release and activation of caspase-dependent apoptosis.^{4,5} In addition, preclinical studies have shown that ascorbic acid (AA) enhances the cytotoxic effects of ATO.⁶ Taken together, these observations suggest that the ATO/B/AA (ABC) combination might be effective in the treatment of patients with MM and that the synergy of these agents may allow the use of a lower-dose well-tolerated regimen. Therefore, the safety/tolerability and efficacy of the ABC combination were evaluated in a Phase I/II study in patients with relapsed or refractory MM.

Objectives

- Primary
 - To assess the safety and tolerability of ABC combination therapy in patients with relapsed or refractory MM
- Secondary
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 - CR: No serum or urine M-protein by immunofixation
 - PR: \geq 50% decrease in serum M-protein; \geq 90% decrease in 24-hour urine M-protein
 - MR: 25% to 49% decrease in serum M-protein; 50% to 89% decrease in 24-hour urine M-protein
 - To determine the time to response, time to progression of disease, progression-free survival, and overall survival
 - To evaluate the effects on renal failure associated with MM

Study Design

Treatment Schema (Table 1)

- During each 3-week cycle, patients received intravenous infusions of B (0.7, 1.0, or 1.3 mg/m²), followed by ATO (0.125 or 0.25 mg/kg) and then AA (1 g), on days 1, 4, 8, and 11 (6 treatment cohorts). This was followed by a 10-day rest period.
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- Patients were eligible for maintenance therapy with the same treatments given once every other week.

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ATO, arsenic trioxide; B, bortezomib
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Inclusion Criteria

- \geq 18 years of age
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- KPS \geq 60
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 - If bone marrow is extensively infiltrated, baseline platelet count \geq 10 \times 10⁹/L, hemoglobin \geq 8.0 g/dL, and neutrophil count \geq 0.5 \times 10⁹/L
- Normal liver and renal function

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Patient Demographics

- A total of 22 patients with relapsed or refractory MM were enrolled (Table 2).
- Patients received a median of 4 prior different therapies (range, 3-9). Notably, 2 patients received prior arsenic trioxide and 5 patients received prior bortezomib therapy.
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Thalidomide/lenalidomide	4
Bortezomib	5
Peripheral stem cell transplant	2
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Mean β_2 -microglobulin (range), mg/dL	5.1 (1.6–19.5)

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Adverse event	No. of patients	Cohort
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Abdominal pain	1	2
Back pain	1	4
Increased QTc	1	3
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Severe decrease in quality of life	1	3

*All adverse events were grade 1 or 2, unless otherwise noted.

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- All 22 patients were evaluable for efficacy.
- Clinical responses were evident in 6 of the 22 patients, giving an objective response rate of 27% (Table 4). Two patients showed PR, and 4 showed MR.
- Of the 16 patients who did not show clinical response, 9 showed stable disease (SD). Therefore, the disease control rate (CR + PR + MR + SD) was 68%.
- Six patients showed progressive disease (PD), and 1 patient failed to complete 1 full cycle of therapy.
- At 12 months from the start of ABC therapy, the progression-free and overall survival rates were 34% and 74%, respectively (Figures 1 and 2).
- Only 1 of the 6 patients receiving the lowest dose of B (0.7 mg/m²) showed a clinical response (1 MR), whereas 5 of the 16 patients receiving the higher doses (1.0 or 1.3 mg/m²) responded (2 PR and 3 MR) (Table 5).

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Progression-free survival rate at 12 months	34%
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Figure 1. Kaplan-Meier estimates of progression-free survival among patients who received ABC therapy (N = 22)

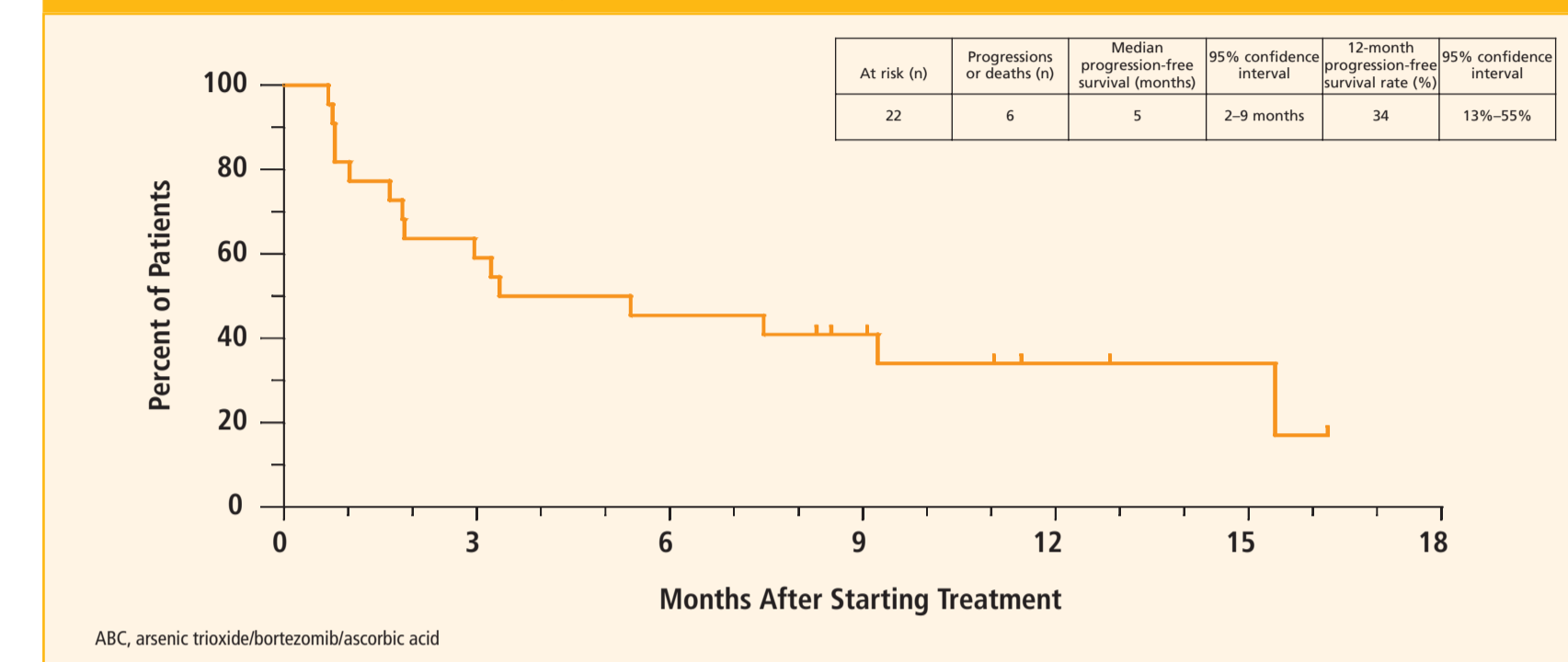
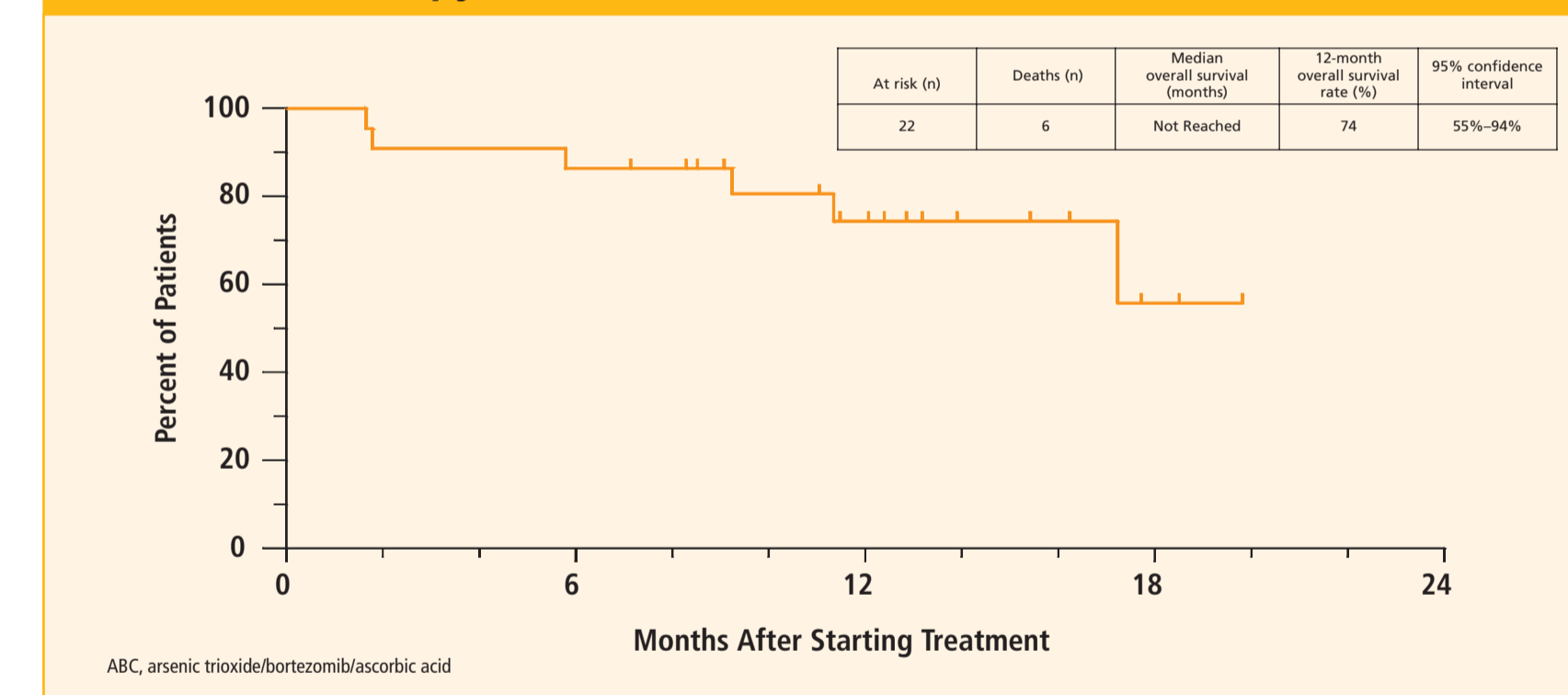


Figure 2. Kaplan-Meier estimates of overall survival among patients who received ABC therapy (N = 22)



Summary

- ABC combination therapy led to objective responses in 27% of this group of heavily pretreated MM patients.
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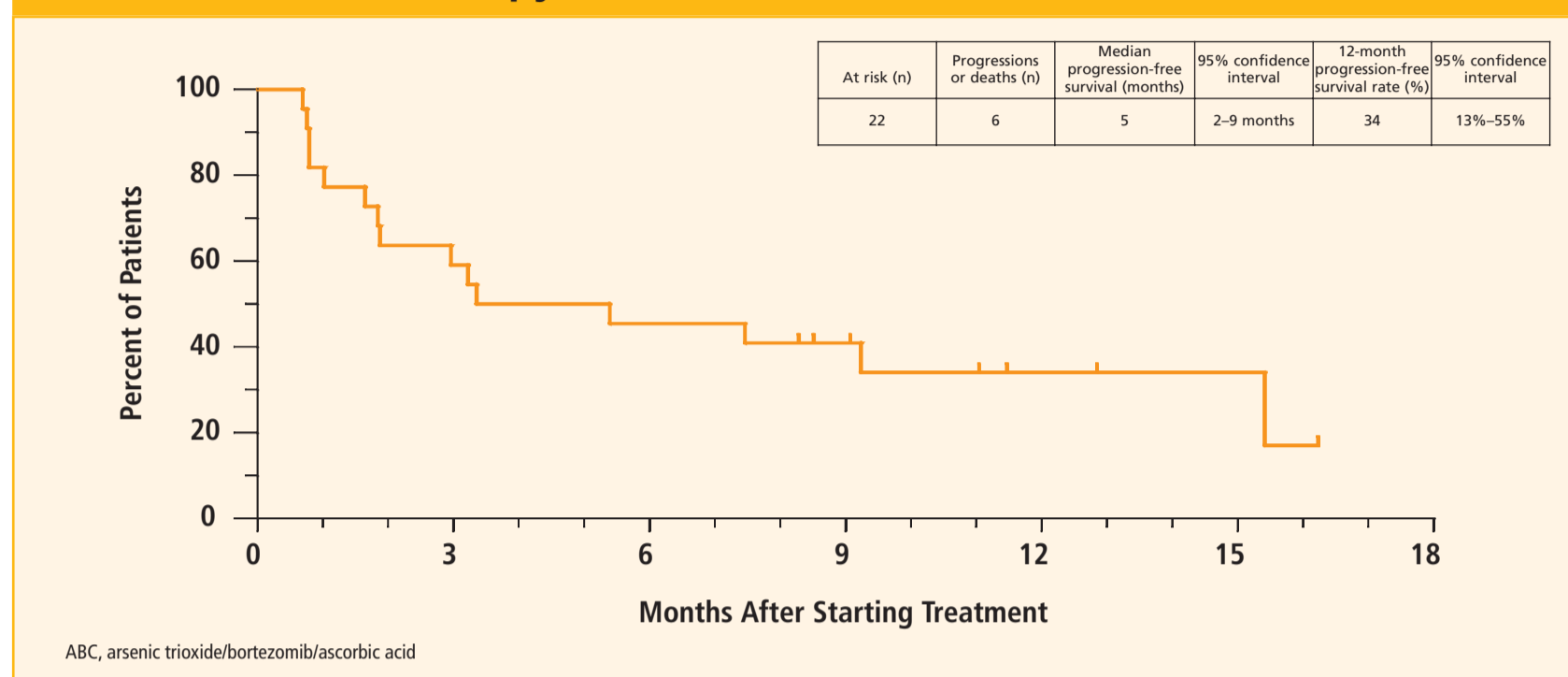
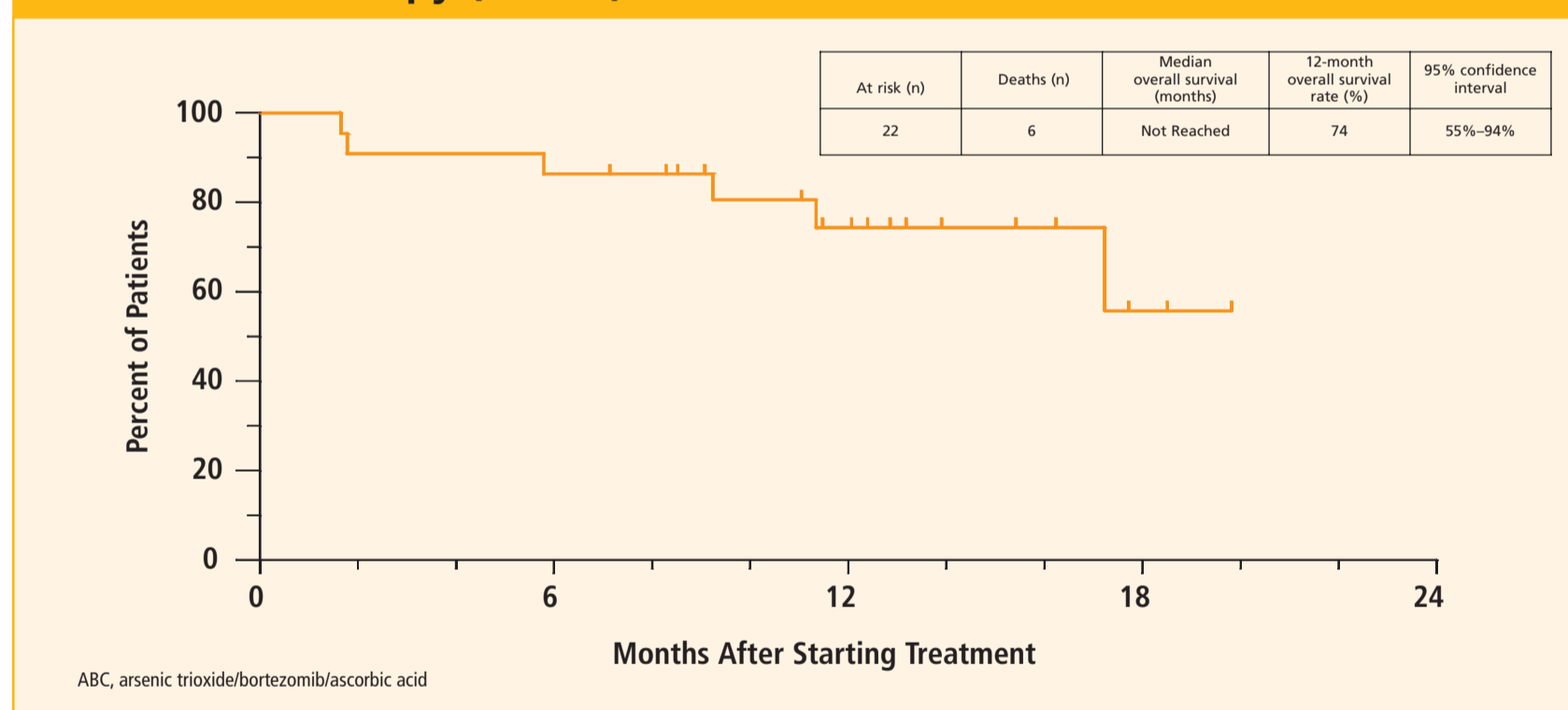


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- Six patients showed progressive disease (PD), and 1 patient failed to complete 1 full cycle of therapy.
- At 12 months from the start of ABC therapy, the progression-free and overall survival rates were 34% and 74%, respectively (Figures 1 and 2).
- Only 1 of the 6 patients receiving the lowest dose of B (0.7 mg/m²) showed a clinical response (1 MR), whereas 5 of the 16 patients receiving the higher doses (1.0 or 1.3 mg/m²) responded (2 PR and 3 MR) (Table 5).

Table 4. Patient Responses to ABC Therapy (N = 22)

Objective responses	n (%)
Overall response	6 (27)
Complete response (CR)	0 (0)
Partial response (PR)	2 (9)
Minimal response (MR)	4 (18)
Disease control (CR+PR+MR+SD)	15 (68)
Objective responses by failed prior therapies	no. responses/no. who received drug previously (%)
Arsenic trioxide	0 (0)
Melphalan	1/6 (17)
Thalidomide/lenalidomide	1/4 (25)
Bortezomib	0 (0)
Peripheral stem cell transplant	1/2 (50)
Progression-free survival rate at 12 months	34%
Overall survival rate at 12 months	74%

ABC, arsenic trioxide/bortezomib/ascorbic acid; SD, stable disease

Table 5. Patient Responses by Cohort (N = 22)

Cohort	ATO dose (mg/kg)	B dose (mg/m ²)	No. of patients enrolled	Best responses
1	0.125	0.7	3	1 MR, 2 PD
2	0.125	1.0	3	1 PR, 1 SD, 1 PD
3	0.125	1.3	4*	1 PR, 2 PD
4	0.25	0.7	3	2 SD, 1 PD
5	0.25	1.0	3	3 MR
6	0.25	1.3	6	6 SD

ATO, arsenic trioxide; B, bortezomib; MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease
*One patient failed to complete 1 full cycle of therapy.

Figure 1. Kaplan-Meier estimates of progression-free survival among patients who received ABC therapy (N = 22)

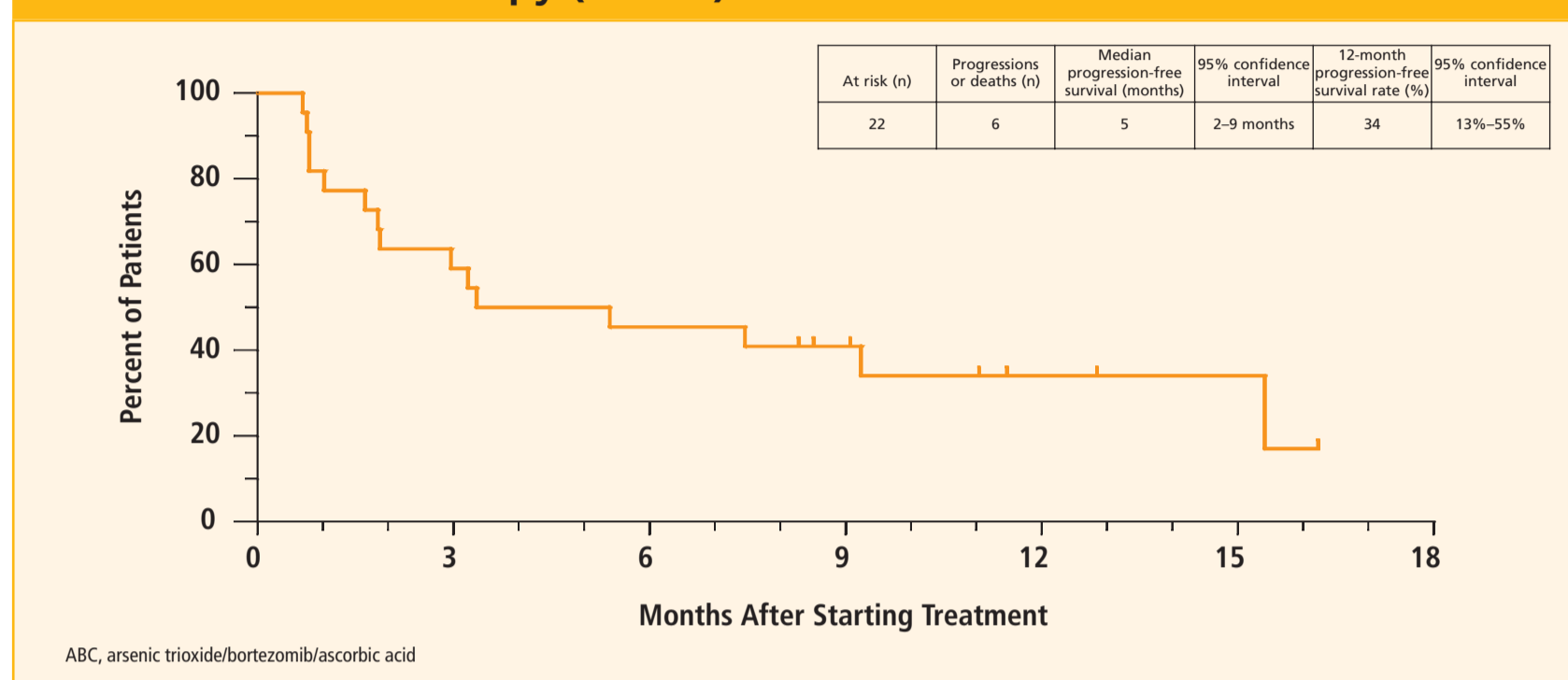
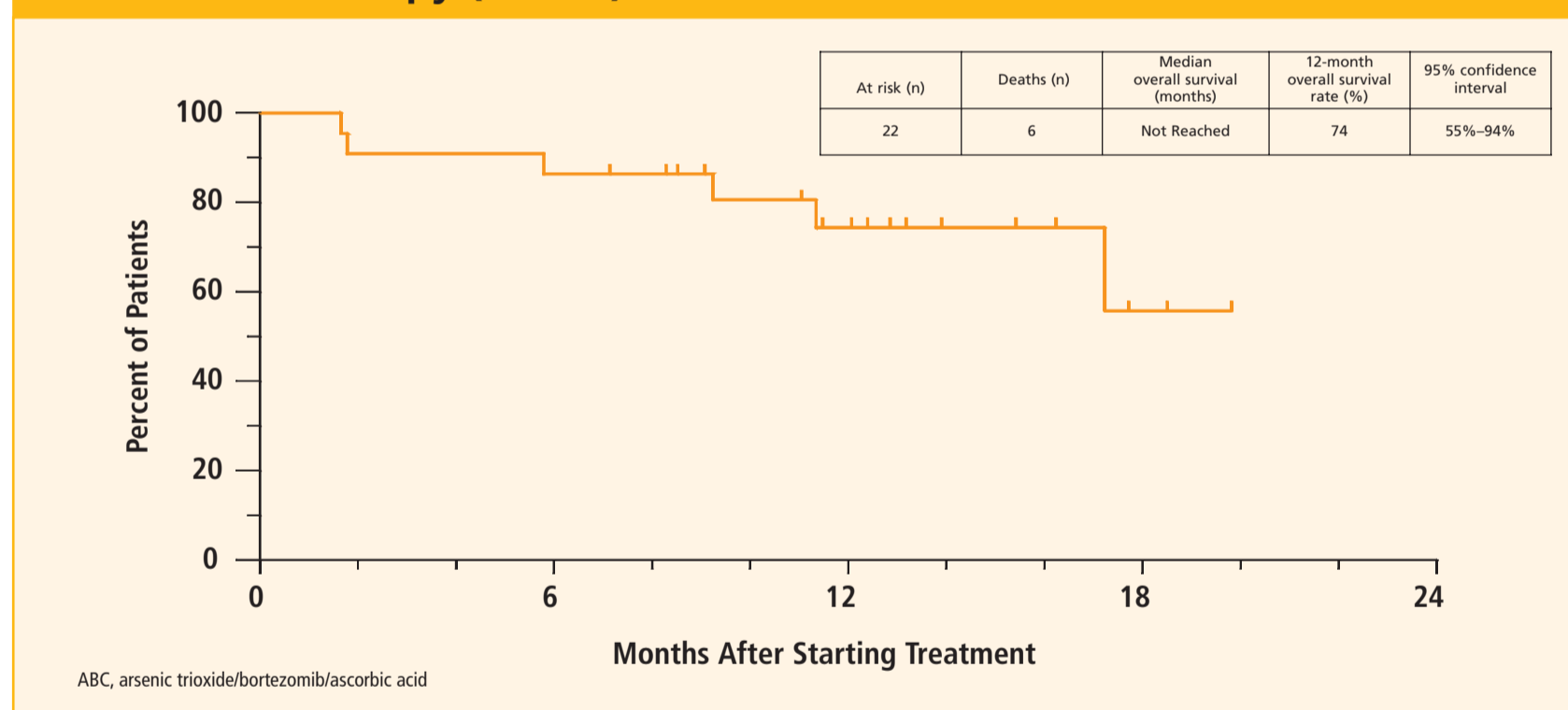


Figure 2. Kaplan-Meier estimates of overall survival among patients who received ABC therapy (N = 22)



Summary

- ABC combination therapy led to objective responses in 27% of this group of heavily pretreated MM patients.
- The therapy was well tolerated by most patients.
- Given the encouraging results of this interim analysis, further evaluation of this combination in a larger group of patients with relapsed or refractory MM is planned.

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