

CLINICAL TRIALS AND OBSERVATIONS

Carfilzomib significantly improves the progression-free survival of high-risk patients in multiple myeloma

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Key Points

- KRd has a favorable benefit-risk profile compared with Rd, regardless of baseline cytogenetic risk status, in patients with relapsed MM.
- KRd improves but does not abrogate the poor prognosis associated with high-risk cytogenetics in patients with relapsed MM.

The presence of certain high-risk cytogenetic abnormalities, such as translocations (4;14) and (14;16) and deletion (17p), are known to have a negative impact on survival in multiple myeloma (MM). The phase 3 study ASPIRE (N = 792) demonstrated that progression-free survival (PFS) was significantly improved with carfilzomib, lenalidomide, and dexamethasone (KRd), compared with lenalidomide and dexamethasone (Rd) in relapsed MM. This preplanned subgroup analysis of ASPIRE was conducted to evaluate KRd vs Rd by baseline cytogenetics according to fluorescence in situ hybridization. Of 417 patients with known cytogenetic risk status, 100 patients (24%) were categorized with high-risk cytogenetics (KRd, n = 48; Rd, n = 52) and 317 (76%) were categorized with standard-risk cytogenetics (KRd, n = 147; Rd, n = 170). For patients with high-risk cytogenetics, treatment with KRd resulted in a median PFS of 23.1 months, a 9-month improvement relative to treatment with Rd. For patients with standard-risk cytogenetics, treatment with KRd led to a 10-month improvement in median PFS vs Rd. The overall response rates for KRd vs Rd were 79.2% vs 59.6% (high-risk cytogenetics) and 91.2% vs 73.5% (standard-risk cytogenetics); approximately fivefold as many patients with high- or standard-risk cytogenetics achieved a complete response or better with KRd vs Rd (29.2% vs 5.8% and 38.1% vs 6.5%, respectively). KRd improved but did not abrogate the poor prognosis associated with high-risk cytogenetics. This regimen had a favorable benefit-risk profile in patients with relapsed MM, irrespective of cytogenetic risk status, and should be considered a standard of care in these patients. This trial was registered at www.clinicaltrials.gov as #NCT01080391. (*Blood*. 2016;128(9):1174-1180)

Introduction

Despite an improvement in response and survival rates,^{1,2} relapse after initial therapy remains common in patients with multiple myeloma (MM).² This highlights a need not only for novel treatment approaches, but a greater understanding of how certain patient features may affect prognosis.

The presence of high-risk cytogenetic abnormalities is not uncommon in patients with MM; deletion (del) 17p and translocation (t) 4;14

are found in ~11% and 14% of MM patients, respectively, and are known to have a negative effect on survival and prognosis.³⁻⁵ In a large group of patients with newly diagnosed MM (NDMM) who were treated with high-dose therapy and autologous stem cell transplantation within the Intergroupe Francophone du Myelome, median event-free survival was significantly shorter (15 months) for patients with del(17p) compared with patients without del(17p) (35 months; $P < .001$).⁴ In

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Table 1. Patient demographics and baseline disease characteristics

	High risk		Standard risk		Unknown*	
	KRd (n = 48)	Rd (n = 52)	KRd (n = 147)	Rd (n = 170)	KRd (n = 201)	Rd (n = 174)
Age, median y (range)	60.5 (44.0-79.0)	60.5 (41.0-84.0)	65.0 (38.0-87.0)	67.0 (36.0-84.0)	63.0 (40.0-87.0)	64.0 (31.0-91.0)
18 to 64 y, n (%)	33 (68.8)	32 (61.5)	66 (44.9)	67 (39.4)	112 (55.7)	89 (51.1)
65 to 74 y, n (%)	11 (22.9)	17 (32.7)	63 (42.9)	75 (44.1)	68 (33.8)	63 (36.2)
≥75 y, n (%)	4 (8.3)	3 (5.8)	18 (12.2)	28 (16.5)	21 (10.4)	22 (12.6)
ECOG PS, n (%)						
0	18 (37.5)	34 (65.4)	66 (44.9)	79 (46.5)	81 (40.3)	62 (35.6)
1	23 (47.9)	15 (28.8)	68 (46.3)	78 (45.9)	100 (49.8)	93 (53.4)
2	7 (14.6)	3 (5.8)	13 (8.8)	13 (7.6)	20 (10.0)	19 (10.9)
FISH, n (%)						
t(4;14)	33 (68.8)	31 (59.6)	0	0	—	—
t(14;16)	2 (4.2)	8 (15.4)	0	0	—	—
del(17p)						
≥60% of plasma cells	17 (35.4)	20 (38.5)	0	0	—	—
<60% of plasma cells	1 (2.1)	1 (1.9)	3 (2.0)	7 (4.1)	—	—
Creatinine clearance – mean mL/min ± SD	85.3 ± 23.9	91.7 ± 29.1	84.2 ± 28.1	83.3 ± 28.5	85.4 ± 30.7	86.7 ± 32.1
<50 mL/min, n (%)	2 (4.2)	2 (3.8)	9 (6.1)	17 (10.0)	14 (7.0)	13 (7.5)
≥50 mL/min, n (%)	46 (95.8)	49 (94.2)	138 (93.9)	152 (89.4)	186 (92.5)	157 (90.2)
Missing, n (%)	0	1 (1.9)	0	1 (0.6)	1 (0.5)	4 (2.3)
Serum β ₂ -microglobulin level, n (%)						
<2.5 mg/L	9 (18.8)	8 (15.4)	25 (17.0)	35 (20.6)	43 (21.4)	34 (19.5)
≥2.5 mg/L	39 (81.3)	44 (84.6)	122 (83.0)	135 (79.4)	158 (78.6)	140 (80.5)
Number of prior lines of therapy, median (range)	2.0 (1-4)	2.0 (1-3)	2.0 (1-3)	2.0 (1-4)	2.0 (1-3)	2.0 (1-3)
Prior therapy, n (%)						
Bortezomib	39 (81.3)	35 (67.3)	90 (61.2)	105 (61.8)	132 (65.7)	120 (69.0)
Lenalidomide	13 (27.1)	12 (23.1)	28 (19.0)	35 (20.6)	38 (18.9)	31 (17.8)

ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation.
*The unknown risk subgroup included patients who had FISH assessment, but the results of 1 or more genetic subtypes were not available.

transplant-ineligible patients with NDMM treated with the MM reference therapy lenalidomide and dexamethasone (continuous Rd or Rd for 18 cycles), or melphalan-prednisone-thalidomide, the 3-year overall survival (OS) rates were 39.6% to 46.8% in patients with high-risk cytogenetics and 64.8% to 77.1% in patients who were not high risk.⁶ Similar findings are evident in patients with advanced relapsed or refractory disease where the presence of t(4;14) predicts shorter survival for patients treated with Rd (9.4 vs 15.4 months; *P* = .005).⁷

There are, however, limited and inconsistent data on the effect of new agents in patients with MM and high-risk cytogenetic abnormalities.⁸⁻¹⁰ Studies have demonstrated that treatment with the first-in-class proteasome inhibitor bortezomib benefits patients with high-risk cytogenetic abnormalities. These results are nonetheless conflicting, with some studies showing a benefit for bortezomib treatment in patients with del(17p) but not t(4;14), and other studies showing a benefit in patients with t(4;14).¹¹⁻¹³

Carfilzomib is an epoxyketone proteasome inhibitor that binds selectively and irreversibly to the constitutive proteasome and immunoproteasome; as a single agent, carfilzomib has previously shown an encouraging overall response rate (ORR) of 25.8% in patients with relapsed and refractory MM who harbored high-risk cytogenetic abnormalities.⁹

Carfilzomib is approved in the United States for use in combination with dexamethasone or with Rd for the treatment of patients with relapsed or refractory MM (1-3 prior lines of therapy) and as a single agent for the treatment of patients with relapsed or refractory MM (1 or more prior lines of therapy). Carfilzomib is also approved in the European Union when used in combination with Rd for patients with relapsed MM (1 or more prior lines of therapy).

The approval of carfilzomib for use in combination with Rd in patients with relapsed or refractory MM was based on interim results

from the randomized, phase 3 study ASPIRE, which compared carfilzomib, lenalidomide, and dexamethasone (KRd) with Rd.² In brief, for the preplanned interim analysis of the ASPIRE study, treatment with KRd led to a significant reduction in the risk of disease progression or death when compared with Rd (hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.57-0.83; *P* = .0001). The median progression-free survival (PFS) was 26.3 months in the KRd group vs 17.6 months in the Rd group. OS favored the KRd group (HR, 0.79); however, the result did not cross the prespecified stopping boundary at the interim analysis of OS.

This preplanned subgroup analysis of the ASPIRE study was conducted to evaluate KRd vs Rd according to baseline cytogenetic risk status according to fluorescence in situ hybridization (FISH).

Patients and methods

Study design and participants

ASPIRE was a randomized, open-label, multicenter, phase 3 study that evaluated KRd vs Rd in patients with relapsed MM (1-3 prior lines of therapy). Full study details have been described elsewhere.² The primary end point was PFS in the intention-to-treat (ITT) population, and secondary end points included OS, ORR, duration of response (DOR), health-related quality of life, and safety. Patients were randomly assigned (1:1 ratio) to receive KRd or Rd in 28-day cycles until withdrawal of consent, disease progression, or the occurrence of unacceptable toxicities. All patients received lenalidomide (25 mg; oral) on days 1 to 21 and dexamethasone (40 mg; oral or intravenous) on days 1, 8, 15, and 22. For patients in the KRd group, carfilzomib was administered as 10-minute intravenous infusion on days 1, 2, 8, 9, 15, and 16 during cycles 1 to 12 (20 mg/m² days 1 and 2 of cycle 1; 27 mg/m² thereafter). Carfilzomib was omitted on days 8 and 9 during cycles 13 to 18 and was discontinued after 18 cycles.

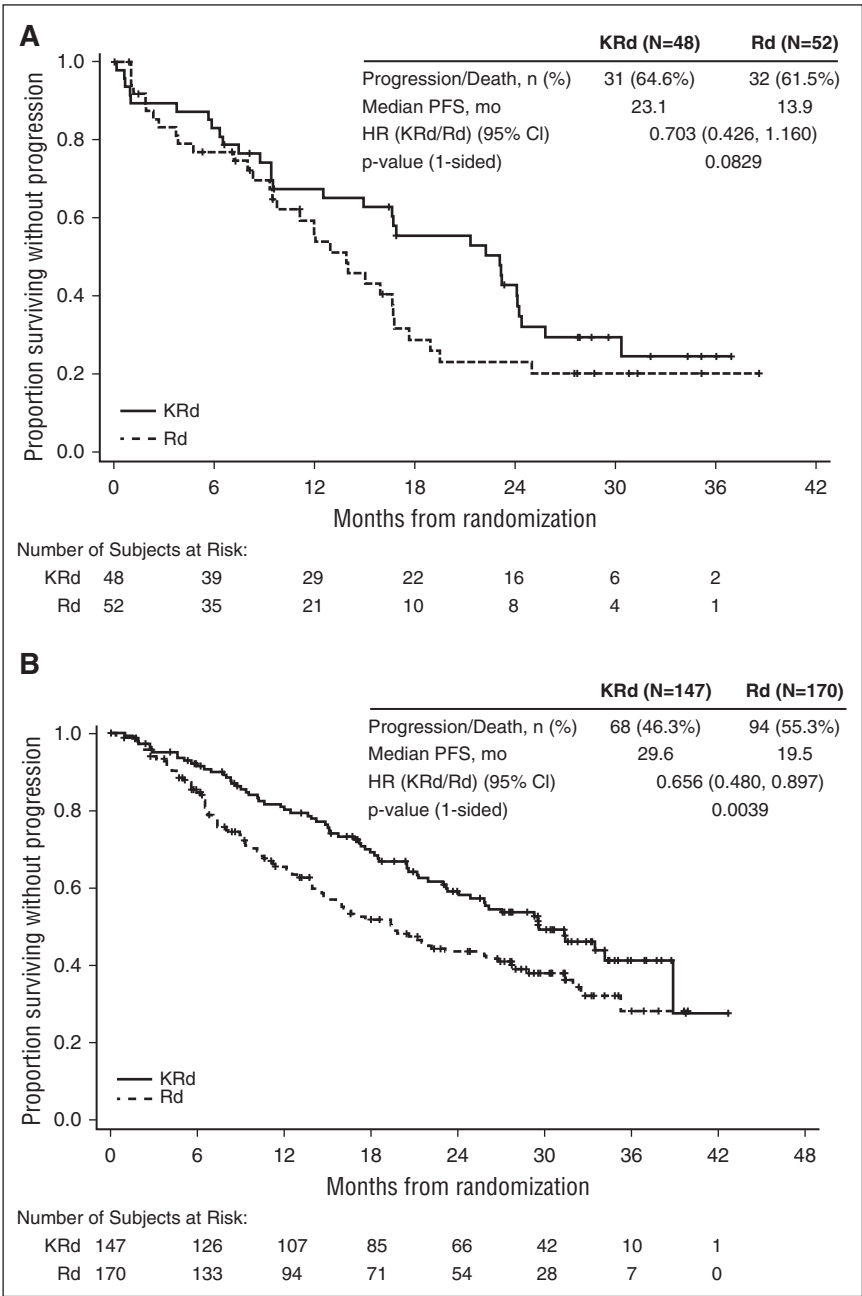


Figure 1. Kaplan-Meier estimate of PFS by cytogenetic risk status at baseline. (A) Patients in the high-risk subgroup. (B) Patients in the standard-risk subgroup.

The study protocol was approved by the institutional review boards of participating institutions, and all patients provided written informed consent.

Cytogenetic subgroup assessments

Bone marrow samples to quantify percentage myeloma cell involvement and for FISH to define cytogenetic risk status at baseline were collected at study entry, and investigations performed at 2 central laboratories. FISH was performed on sorted CD138⁺ plasma cells with probes used to detect t(4;14), t(14;16), and del(17p). Patients were classified into cytogenetic subgroups. The high-risk subgroup consisted of patients with genetic subtypes t(4;14) or t(14;16), or with del(17p) as determined by the central laboratories. The standard-risk subgroup consisted of all other patients with known baseline cytogenetic status, and the unknown risk subgroup included patients who had a FISH assessment but for whom the result of 1 or more genetic subtypes was not available. For the analysis reported here, the stringent cutoff value of 60% for the proportion of plasma cells

with del(17p) was used to be consistent with the recommendations from the International Myeloma Workshop Consensus Panel 2.¹⁴

Statistical analysis

Efficacy analyses were based on the ITT population (all randomly assigned patients). The safety population included all patients who received at least 1 dose of the study treatment.

The per arm distribution of PFS, including the median, was estimated for each cytogenetic subgroup using the Kaplan-Meier method. HRs were estimated using Cox regression. *P* values are descriptive and unadjusted for multiplicity.

The ORRs for each treatment arm and cytogenetic subgroup were calculated as the proportion of patients who had a best overall response of partial response or better (stringent complete response [sCR], complete response [CR], very good partial response, or partial response) as their best response across the entire treatment duration. A Clopper-Pearson 95% CI was calculated for each ORR.

Table 2. Response by cytogenetic risk status at baseline

	High risk		Standard risk		Unknown	
	KRd (n = 48)	Rd (n = 52)	KRd (n = 147)	Rd (n = 170)	KRd (n = 201)	Rd (n = 174)
Best overall response, n (%)*						
CR or better	14 (29.2)	3 (5.8)	56 (38.1)	11 (6.5)	56 (27.9)	23 (13.2)
Very good partial response	15 (31.1)	11 (21.2)	55 (37.4)	66 (38.8)	81 (40.3)	46 (26.4)
Partial response	9 (18.8)	17 (32.7)	23 (15.6)	48 (28.2)	36 (17.9)	39 (22.4)
Progressive disease	2 (4.2)	6 (11.5)	2 (1.4)	2 (1.2)	3 (1.5)	8 (4.6)
ORR, n (%)*	38 (79.2)	31 (59.6)	134 (91.2)	125 (73.5)	173 (86.1)	108 (62.1)
95% CI†	65.0% to 89.5%	45.1% to 73.0%	85.4% to 95.2%	66.2% to 80.0%	80.5% to 90.5%	54.4% to 69.3%
Odds ratio for KRd vs Rd (95% CI)‡	2.919 (1.140-7.470)		3.805 (1.945-7.443)		3.987 (2.376-6.690)	
DOR, median mo	22.2	14.9	30.4	20.4	28.6	24.3
95% CI	16.0-29.4	9.9-24.0	24.9 to NE	13.9-30.5	15.0 to NE	12.0 to NE

*Determined by Independent Review Committee according to International Myeloma Working Group Uniform Response Criteria. Patients evaluated for ORR had a best overall response of partial response or better.

†Clopper-Pearson interval.

‡The odds ratio and 95% CI were estimated using the Mantel-Haenszel method.

Treatment effects in the subgroups for ORR were represented by an odds ratio and corresponding 95% CI that were calculated using the Mantel-Haenszel method.

Data for this study were collected and analyzed by the sponsor (Onyx Pharmaceuticals Inc., an Amgen subsidiary). All authors had access to the primary clinical trial data.

Results

Patients and enrollment

Between July 2010 and March 2012, 792 patients from North America, Europe, and the Middle East were enrolled and randomized (KRd, n = 396; Rd, n = 396) as previously reported.² In total, 417 patients had known cytogenetic risk status; 100 patients (24%) were categorized as the high-risk cytogenetic subgroup (KRd, n = 48 [25%]; Rd, n = 52 [23%]), and 317 patients (76%) were categorized as the standard-risk subgroup (KRd, n = 147 [75%]; Rd, n = 170 [77%]). There were 375 patients in the unknown risk subgroup (KRd, n = 201; Rd, n = 174). The cutoff date for the interim analysis was June 16, 2014.²

In both treatment arms, baseline demographics and disease characteristics were generally balanced across cytogenetic subgroups (Table 1). Median duration of treatment was longer with KRd vs Rd for the high-risk subgroup (73.6 vs 43.1 weeks) and the standard-risk subgroup (86.6 vs 61.4 weeks).

Efficacy by cytogenetic subgroup

The addition of carfilzomib to Rd reduced the risk of disease progression or death in both the high-risk and standard-risk cytogenetic subgroups (Figure 1), consistent with previous findings from the overall ITT population.² Median PFS in the high-risk subgroup (n = 100) was 23.1 months (95% CI, 12.5-24.2) for KRd vs 13.9 months (95% CI,

9.5-16.7) for Rd (HR, 0.70; 95% CI, 0.43-1.16). Median PFS in the standard-risk subgroup (n = 317) was 29.6 months (95% CI, 24.1 to not estimable [NE]) for KRd vs 19.5 months (95% CI, 14.8-26.0) for Rd (HR, 0.66; 95% CI, 0.48-0.90). For patients with unknown cytogenetic risk status, median PFS was 28.4 months (95% CI, 22.1-32.3) for KRd vs 17.6 months (95% CI, 14.0-22.2) for Rd (HR, 0.74; 95% CI, 0.56-0.98).

Table 2 shows response by cytogenetic risk status at baseline. The addition of carfilzomib to Rd increased the ORR in both the high-risk cytogenetic subgroup (79.2% [KRd] vs 59.6% [Rd]; odds ratio, 2.919 [95% CI, 1.140-7.470]) and standard-risk subgroup (91.2% [KRd] vs 73.5% [Rd]; odds ratio, 3.805 [95% CI, 1.945-7.443]). In the high-risk subgroup, 29.2% (KRd) and 5.8% (Rd) of patients achieved a CR or better, including 16.7% (KRd) and 3.8% (Rd) with an sCR. In the standard-risk subgroup, 38.1% (KRd) and 6.5% (Rd) of patients achieved a CR or better, including 15.0% (KRd) and 3.5% (Rd) with an sCR. Median DOR in the high-risk subgroup was 22.2 months for KRd vs 14.9 months for Rd. Median DOR in the standard-risk subgroup was 30.4 months for KRd vs 20.4 months for Rd.

In patients with high-risk cytogenetics and 1 prior line of therapy, the median PFS was 24.1 months in the KRd subgroup (n = 23) and 14.0 months in the Rd subgroup (n = 18); in patients with high-risk cytogenetics and at least 2 prior lines of therapy, the median PFS was 22.2 months in the KRd subgroup (n = 25) and 12.0 months in the Rd subgroup (n = 34) (Table 3). In patients with high-risk cytogenetics, the median PFS for KRd vs Rd was 22.2 months vs 9.5 months for patients with prior bortezomib exposure and 23.2 months vs 17.6 months for patients without prior bortezomib exposure; the median PFS for KRd vs Rd was 24.1 months vs 9.7 months for patients with prior lenalidomide exposure and 22.2 months vs 15.9 months for patients without prior lenalidomide exposure. In patients with standard-risk cytogenetics, the median PFS for KRd vs Rd was 25.9 months vs 19.5 months for patients with prior bortezomib exposure and 33.5 months vs

Table 3. Efficacy by prior lines of therapy and cytogenetic risk status at baseline

	High risk				Standard risk			
	1 Prior line		≥2 Prior lines		1 Prior line		≥2 Prior lines	
	KRd (n = 23)	Rd (n = 18)	KRd (n = 25)	Rd (n = 34)	KRd (n = 70)	Rd (n = 72)	KRd (n = 77)	Rd (n = 98)
PFS, median mo	24.1	14.0	22.2	12.0	29.6	17.7	31.4	19.5
ORR, n (%)*	17 (73.9)	11 (61.1)	21 (84.0)	20 (58.8)	62 (88.6)	56 (77.8)	72 (93.5)	69 (70.4)

*Determined by Independent Review Committee according to International Myeloma Working Group Uniform Response Criteria. Patients evaluated for ORR had a best overall response of partial response or better.

Table 4. Efficacy by specific cytogenetic abnormality at baseline (high-risk subgroup)

Cytogenetic abnormality	High-risk subgroup			
	t(4;14) Only		del(17p) Only in ≥60% of plasma cells	
	KRd (n = 30)	Rd (n = 25)	KRd (n = 13)	Rd (n = 13)
PFS, median mo	23.1	16.7	24.5	11.1
ORR, n (%) [*]	24 (80.0)	18 (72.0)	10 (76.9)	6 (46.2)

^{*}Determined by Independent Review Committee according to International Myeloma Working Group Uniform Response Criteria. Patients evaluated for ORR had a best overall response of partial response or better.

19.8 months for patients without prior bortezomib exposure; the median PFS for KRd vs Rd was 21.3 months vs 16.0 months for patients with prior lenalidomide exposure and 29.6 months vs 19.5 months for patients without prior lenalidomide exposure.

Efficacy by specific cytogenetic abnormalities in the high-risk subgroup is shown in Table 4. Median PFS in the high-risk KRd subgroup for patients with either the (4;14) translocation only or the (17p) deletion only was similar to the overall median PFS for this subgroup (23.1 months vs 24.5 months vs 23.1 months, respectively). Median PFS in the high-risk Rd subgroup for patients with either the (4;14) translocation only or the (17p) deletion only differed slightly compared with the overall median PFS for this subgroup (16.7 months vs 11.1 months vs 13.9 months, respectively).

Safety

The safety and tolerability profiles of KRd vs Rd in patients with high- and standard-risk cytogenetics (Table 5) were similar to those in the overall population.² Grade ≥3 treatment-emergent adverse events (TEAEs) were reported at similar rates between KRd and Rd groups in the standard-risk subgroup (85.6% and 84.5%, respectively), and more frequently with KRd vs Rd in the high-risk subgroup (89.1% and 78.4%, respectively).

Discussion

This preplanned subgroup analysis of the ASPIRE study indicates that KRd improved outcomes in patients with high- and standard-risk cytogenetics compared with Rd. The interaction between treatment effect and cytogenetic subgroup was tested for PFS, and no significant interaction was identified. For patients with high-risk cytogenetics, who were defined using the highest cutoff possible for the presence of del(17p) (≥60%), treatment with KRd resulted in a median PFS of nearly 2 years, which was a 9-month improvement compared with patients treated with Rd. For patients with a standard cytogenetic risk status at baseline, treatment with KRd also led to a 10-month improvement in median PFS vs treatment with Rd. Notably, the PFS benefit for KRd vs Rd in patients with standard-risk cytogenetics was comparable with that in patients with high-risk cytogenetics, with similar reductions in the risk of disease progression or death.

Higher ORRs and longer DOR were also demonstrated for both the KRd high-risk subgroup compared with the control arm (79.2% vs 59.6%, and 22.2 months vs 14.9 months, respectively), and the KRd standard-risk subgroup compared with the control arm (91.2% vs 73.5%, and 30.4 months vs 20.4 months, respectively). Approximately fivefold as many patients with high- or standard-risk baseline cytogenetics achieved a CR or better with KRd compared with Rd. The depth of response as indicated by minimal residual disease (MRD) beyond CR was not assessed in the ASPIRE study. Previous studies have shown that MRD negativity is associated with improved outcomes in MM^{15,16} and merits evaluation in future relapsed MM studies. Although limited by the number of patients with known cytogenetics and a lack of MRD data, this subgroup analysis adds weight to the primary findings of the ASPIRE study in that KRd maintains a favorable benefit-risk profile for patients with relapsed MM, irrespective of cytogenetic risk status at baseline.

Further analyses for PFS and ORR in the high-risk subgroup, by specific baseline cytogenetic abnormalities and prior treatment, demonstrated a consistency of benefit for KRd vs Rd in patients with 1 vs 2 or more prior lines of therapy, prior exposure to bortezomib or lenalidomide, and t(4;14) or del(17p) only. The number of patients in these particular analyses was small, and robust conclusions cannot be drawn as to the relative contribution each cytogenetic abnormality may have on PFS or ORR. It is important to note that the definition of high-risk disease depends on disease characteristics (eg, cytogenetics) and the efficacy of available treatment options.¹⁷ Risk stratification by historical cytogenetic abnormalities such as t(4;14) or del(17p) may no longer remain relevant for therapies capable of producing robust outcomes in patients harboring these abnormalities.

As might be expected for both treatment groups, efficacy outcomes were generally better for patients with standard-risk cytogenetics than those with high-risk cytogenetics. Although KRd treatment resulted in 9- to 10-month improvements in PFS compared with Rd for patients with high-risk or standard-risk cytogenetics, the absolute median PFS was ~6 months shorter for both arms in the high-risk cytogenetics subgroup. Median PFS in the high-risk subgroup was also shortened relative to the overall ITT population for both KRd (23.1 and 26.3 months, respectively) and Rd (13.9 and 17.6 months, respectively).² In contrast, median PFS in the standard-risk subgroup was longer relative to the overall ITT population for both KRd (29.6 and 26.3 months, respectively) and Rd (19.5 and 17.6 months, respectively).²

Table 5. Adverse events, treatment discontinuations, and deaths in the safety population

	High risk		Standard risk		Unknown	
	KRd (n = 46)	Rd (n = 51)	KRd (n = 146)	Rd (n = 168)	KRd (n = 200)	Rd (n = 170)
Any grade ≥3 TEAE, n (%)	41 (89.1)	40 (78.4)	125 (85.6)	142 (84.5)	162 (81.0)	132 (77.6)
Treatment discontinuations of any study drug attributable to adverse events, n (%)	12 (26.1)	12 (23.5)	33 (22.6)	45 (26.8)	57 (28.5)	40 (23.5)
Deaths within 30 d of last dose, n (%)	4 (8.7)	2 (3.9)	9 (6.2)	12 (7.1)	17 (8.5)	19 (11.2)

TEAE, treatment-emergent adverse event.

The safety and tolerability profiles of KRd vs Rd in high-risk and standard-risk patients were consistent with those previously reported for the overall ITT population,² and no new safety signals were identified in this subgroup analysis.

Studies evaluating other novel agents have found that they can improve the poor prognosis associated with high-risk cytogenetic abnormalities. Bortezomib can overcome the adverse prognosis associated with t(4;14), but it is unclear whether it can for del(17p).¹¹⁻¹³ The MM-003 and IFM 2010-02 studies of pomalidomide with low-dose dexamethasone found that this combination overcame the poor outcomes associated with del(17p) in patients with relapsed/refractory MM.^{3,18} In the ELOQUENT-2 study of elotuzumab, lenalidomide, and dexamethasone vs Rd in patients with relapsed or refractory MM, PFS HR favored the elotuzumab, lenalidomide, and dexamethasone group compared with the Rd group across key subgroups, including patients with t(4;14), del(17p), and 1q21.¹⁹ In the TOURMALINE-MM1 study of ixazomib, lenalidomide, and dexamethasone vs Rd in patients with relapsed and/or refractory MM, the PFS HR favored the ixazomib, lenalidomide, and dexamethasone vs Rd in both high risk cytogenetic patients and those with del(17p).²⁰ It is worth noting that for these studies the cutoff values for the proportion of plasma cells with del(17p) varied from any detectable presence of mutation considered as a positive result³ (ie, if any cell in the analyzed sample was positive for the mutation, then the patient was considered to be del(17p) positive)¹⁹ to positive if $\geq 60\%$ of plasma cells carried the mutation.¹⁸

Overall, the results presented in this analysis indicate that KRd had a favorable benefit-risk profile compared with Rd in patients with relapsed MM, irrespective of baseline cytogenetic risk status. Two single-arm, phase 2 studies have shown that KRd is active in patients with NDMM, independent of cytogenetic risk status.^{21,22} Given the improvements in median PFS for high-risk (9 months) and standard-risk (10 months) patients and the high CR or better rates with KRd irrespective of cytogenetic risk status (29% and 38%, respectively) reported here in relapsed MM, evaluation in large NDMM studies is warranted. These NDMM studies may have important clinical implications regarding discussions of risk-adapted therapy (eg, reduced therapy for standard-risk patients) vs optimal therapy for all patients.

In conclusion, this preplanned subgroup analysis of the ASPIRE study demonstrated that KRd has a favorable benefit-risk profile compared with Rd, regardless of baseline cytogenetic risk status. KRd improves but does not abrogate the poor prognosis associated with high-risk cytogenetics in patients with relapsed MM and should be considered a standard of care in these patients, irrespective of baseline cytogenetic risk status.

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References

- Pulte D, Gondas A, Brenner H. Improvement in survival of older adults with multiple myeloma: results of an updated period analysis of SEER data. *Oncologist*. 2011;16(11):1600-1603.
- Stewart AK, Rajkumar SV, Dimopoulos MA, et al; ASPIRE Investigators. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2015;372(2):142-152.
- Dimopoulos MA, Weisel KC, Song KW, et al. Cytogenetics and long-term survival of patients with refractory or relapsed and refractory multiple myeloma treated with pomalidomide and low-dose dexamethasone. *Haematologica*. 2015;100(10):1327-1333.
- Avet-Loiseau H, Attal M, Moreau P, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myélome. *Blood*. 2007;109(8):3489-3495.
- Avet-Loiseau H, Hulin C, Campion L, et al. Chromosomal abnormalities are major prognostic factors in elderly patients with multiple myeloma: the intergroupe francophone du myélome experience. *J Clin Oncol*. 2013; 31(22):2806-2809.

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Authorship

Contribution: H.A.-L., A.K.S., and P.M. designed the research; all authors performed the research; M.O. performed the statistical analysis; H.A.-L. and M.O. analyzed and interpreted the data; H.A.-L. wrote the initial draft of the manuscript and edited the final draft; and all authors reviewed the draft manuscript and approved the final version for submission.

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6. Avet-Loiseau H, Hulin C, Benboubker L, et al. Impact of cytogenetics on outcomes of transplant-ineligible patients with newly diagnosed multiple myeloma treated with continuous lenalidomide plus low-dose dexamethasone in the FIRST (MM-020) trial [abstract]. *Blood*. 2015;126(23). Abstract 730.
7. Avet-Loiseau H, Soulier J, Fermand JP, et al; IFM and MAG groups. Impact of high-risk cytogenetics and prior therapy on outcomes in patients with advanced relapsed or refractory multiple myeloma treated with lenalidomide plus dexamethasone. *Leukemia*. 2010;24(3):623-628.
8. Kumar SK, Lee JH, Lahuerta JJ, et al; International Myeloma Working Group. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study [published correction appears in *Leukemia*. 2012;26(5):1153]. *Leukemia*. 2012;26(1):149-157.
9. Jakubowiak AJ, Siegel DS, Martin T, et al. Treatment outcomes in patients with relapsed and refractory multiple myeloma and high-risk cytogenetics receiving single-agent carfilzomib in the PX-171-003-A1 study. *Leukemia*. 2013;27(12):2351-2356.
10. Klein U, Jauch A, Hielscher T, et al. Chromosomal aberrations +1q21 and del(17p13) predict survival in patients with recurrent multiple myeloma treated with lenalidomide and dexamethasone. *Cancer*. 2011;117(10):2136-2144.
11. Chang H, Trieu Y, Qi X, Xu W, Stewart KA, Reece D. Bortezomib therapy response is independent of cytogenetic abnormalities in relapsed/refractory multiple myeloma. *Leuk Res*. 2007;31(6):779-782.
12. Avet-Loiseau H, Leleu X, Roussel M, et al. Bortezomib plus dexamethasone induction improves outcome of patients with t(4;14) myeloma but not outcome of patients with del(17p). *J Clin Oncol*. 2010;28(30):4630-4634.
13. Cavo M, Tacchetti P, Patriarca F, et al; GIMEMA Italian Myeloma Network. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *Lancet*. 2010;376(9758):2075-2085.
14. Munshi NC, Anderson KC, Bergsagel PL, et al; International Myeloma Workshop Consensus Panel 2. Consensus recommendations for risk stratification in multiple myeloma: report of the International Myeloma Workshop Consensus Panel 2. *Blood*. 2011;117(18):4696-4700.
15. Paiva B, van Dongen JJ, Orfao A. New criteria for response assessment: role of minimal residual disease in multiple myeloma. *Blood*. 2015;125(20):3059-3068.
16. Landgren O, Owen RG. Better therapy requires better response evaluation: paving the way for minimal residual disease testing for every myeloma patient. *Cytometry B Clin Cytom*. 2016;90(1):14-20.
17. Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. *Blood*. 2016;127(24):2955-2962.
18. Leleu X, Karlin L, Macro M, et al; Intergroupe Francophone du Myélome (IFM). Pomalidomide plus low-dose dexamethasone in multiple myeloma with deletion 17p and/or translocation (4;14): IFM 2010-02 trial results. *Blood*. 2015;125(9):1411-1417.
19. Lonial S, Dimopoulos M, Palumbo A, et al; ELOQUENT-2 Investigators. Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med*. 2015;373(7):621-631.
20. Moreau P, Masszi T, Grzasko N, et al; TOURMALINE-MM1 Study Group. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;374(17):1621-1634.
21. Jakubowiak AJ, Dytfield D, Griffith KA, et al. A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. *Blood*. 2012;120(9):1801-1809.
22. Korde N, Roschewski M, Zingone A, et al. Treatment with carfilzomib-lenalidomide-dexamethasone with lenalidomide extension in patients with smoldering or newly diagnosed multiple myeloma. *JAMA Oncol*. 2015;1(6):746-754.