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Subcutaneous Daratumumab Safe and Effective, Warranting Continued Development

Daratumumab is a first-in-class anti-CD38 monoclonal antibody that has been recently approved in the United States in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma (MM) who have received at least 1 prior therapy, and previously as monotherapy for the treatment of patients with MM who have received at least 3 prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), or who are double refractory to a PI and an IMiD.[1]

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Impressive Results for Daratumumab Combinations in Relapsed Myeloma

The updated results of 2 phase 3 trials of daratumumab, an anti-CD38 antibody, in combination with standard-of-care doublet regimens in patients with relapsed, refractory (RR) multiple myeloma (MM) were presented at oral sessions at the 2016 annual meeting of the American Society of Hematology.

The results of these 2 trials formed the basis of the recent approval of in the United States in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with MM who have received

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Subcutaneous Daratumumab Safe and Effective, Warranting Continued Development *(continued from cover)*

Daratumumab is administered via intravenous (IV) infusion, which can take several hours. A more rapid method of administration might reduce administration costs and improve patient adherence and quality of life. Initiation of an open-label, dose-escalation phase 1b study of subcutaneous (SC) daratumumab with recombinant human hyaluronidase in patients with relapsed or refractory MM (MMY1004; PAVO; NCT02519452) was described during a poster session at the 2016 annual meeting of the American Society of Clinical Oncology.[2]

Then, at the 2016 annual meeting of the American Society of Hematology, December 3-6 in San Diego, Saad Z. Usmani, MD, Department of Hematologic Oncology and Blood Disorders, Levine Cancer Institute/Carolinas HealthCare System, Charlotte, North Carolina, gave an update[3] of the results from this study in an oral presentation.[4] The aim of this study was to determine the safety, pharmacokinetics (PK), and efficacy of SC daratumumab.

SC delivery of daratumumab is being tested in combination with the recombinant human hyaluronidase enzyme (rHuPH20) to facilitate systemic absorption of daratumumab after SC infusion into the abdominal wall. rHuPH20 temporarily breaks down the hyaluronan barrier in subcutaneous tissues, allowing deposition and absorption of injected drugs. Coformulations of trastuzumab and rituximab with rHuPH20 are approved in Europe, but not in the United States.

This dose-finding, proof-of-concept study enrolled patients with measurable relapsed, refractory MM who had received at least 2 prior lines of therapy, including a PI and an IMiD, but not including prior anti-CD38 therapy. In part 1 of the study, sequential cohorts were enrolled to receive daratumumab at dose levels of 1200 mg plus rHuPH20 30,000 units (n = 8), and 1800-mg daratumumab plus rHuPH20 45,000 units (n = 45), to determine the recommended SC dose for part 2. Dr Usmani noted that a fixed dose, rather than one calculated for individual patient body weight, was selected to improve the convenience of administration.

Daratumumab-rHuPH20 was administered in 28-day cycles, once weekly for 8 weeks, then every 2 weeks for 16 weeks, and once every 4 weeks thereafter. The 1200-mg dose of daratumumab was infused in a volume of 60 mL over 20 minutes; the 1800-mg dose was infused in a volume of 90 mL over 30 minutes using a syringe pump at rotating sites on the abdomen. Pre (1 hour prior to infusion)- and post-infusion medications included paracetamol, diphenhydramine, montelukast, and methylprednisolone, standard for daratumumab IV studies.

Primary end points were the trough concentration (C_{trough}) of daratumumab at day 1 of cycle 3 and safety. Secondary end points included the overall response rate (ORR), complete response (CR) rate, duration of response, and time to response.

All patients had received a prior IMiD, including lenalidomide, and all had received a prior PI, with all but 2 patients in the 1800-mg group having received prior bortezomib. Other baseline demographic and clinical characteristics of interest for the 2 treatment groups are shown in the **Table**. These patients resemble those enrolled in daratumumab IV monotherapy studies.

The clinical cut-off date was November 15, 2016, with a median follow-up

TABLE. Key Baseline Demographic and Clinical Characteristics

Characteristic	1200-mg daratumumab (n = 8)	1800-mg daratumumab (n = 45)
Age, median years (range)	66 (49-78)	63 (36-79)
Prior lines of therapy, median (range)	5 (2-10)	4 (2-11)
Prior ASCT, % (n)	63 (5)	82 (37)
Refractory to PI and IMiD, % (n)	63 (5)	58 (26)
Refractory to last line of therapy, % (n)	88 (7)	71 (32)

ASCT indicates autologous stem cell transplant; iMiD, immunomodulatory agent; PI, proteasome inhibitor.

time of 6.4 months for the 1200-mg group and 4.3 months for the 1800-mg group; median duration of treatment was 2.6 and 3.4 months, respectively. Discontinuations occurred in 88% of patients in the 1200-mg group and in 33% of patients in the 1800-mg group, with the primary reason being progressive disease (63% and 27%, respectively). There was one death in each group due to MM. The adverse event (AE) profile for SC daratumumab was consistent with that of the IV formulation; AEs included anemia, thrombocytopenia, upper respiratory tract infection, insomnia, and decreased appetite. There were nodiscontinuations due to treatment-emergent AEs in the higher dose group.

Daratumumab can be safely combined with rHuPH20, and the subcutaneous administration of the combination was well tolerated, with a low rate of infusion-related reactions.

— Saad Z. Usmani, MD

Infusion-related reactions (IRRs) were grade 1 and 2 in the higher dose group, occurred in 24% of patients, and resembled IRRs previously observed with IV daratumumab. One patient in the lower dose group had grade 3 dyspnea. There were no grade 4 IRRs. All IRRs occurred during or within 4 hours of the first infusion; there were no IRRs with subsequent infusions in either group. Abdominal wall SC injections were well tolerated.

PK for the 1800-mg SC dose were consistent with those for the 16 mg/kg IV dose of daratumumab, with comparable C_{trough} and variability. Maximum serum concentration (C_{max}) for the SC 1800-mg dose was similar to that of the 16 mg/kg IV dose; the C_{max} was lower for the SC 1800-mg dose during the initial weekly administration. C_{trough} for the SC 1800-mg dose was higher than that for the SC 1200-mg dose.

Responses were observed in both dose groups but were deeper in the 1800-mg group. ORR was 25%, with 2 partial responses (PR) in the 1200-mg group. ORR was 38% in the 1800-mg group, including 13 with PR, 3 with very good PR, and 1 with stringent CR.

Dr Usmani concluded that daratumumab can be safely combined with rHuPH20 and that the SC administration of the combination was well tolerated, with a low rate of IRRs. Both the PK profile of the 1800-mg dose and its efficacy was consistent with that of the approved daratumumab 16 mg/kg IV dose in a similar patient population. These results support the continued development of SC daratumumab. ■

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Impressive Results for Daratumumab Combinations in Relapsed Myeloma *(continued from cover)*

at least 1 prior therapy, expanding the original indication as monotherapy for the treatment of patients with MM who have received at least 3 prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), or who are double refractory to a PI and an IMiD.[1]

Interim results of these trials have been published recently. The POLLUX trial investigated daratumumab in combination with lenalidomide and dexamethasone versus lenalidomide and dexamethasone[2]; the CASTOR trial investigated daratumumab in combination with bortezomib and dexamethasone versus bortezomib and dexamethasone.[3]

Adding Daratumumab to Lenalidomide Significantly Improves Outcomes

Philippe Moreau, MD, Hematology, University Hospital Hôtel-Dieu, Nantes, France, presented some of the updated data from the POLLUX trial,[4] an open-label, active-controlled phase 3 study (NCT02076009).[5]

Patients were randomly assigned 1:1 to receive lenalidomide and dexamethasone with or without daratumumab over 28-day treatment cycles. A total of 283 patients were treated with a 25-mg oral dose of lenalidomide daily for the first 21 days of each cycle, in addition to a weekly 40-mg dose of dexamethasone orally. The 286 patients assigned to triple combination treatment received 16 mg/kg of daratumumab intravenously (IV) every week in cycles 1 and 2, every other week in cycles 3 to 6, and every 4 weeks thereafter. Both treatment groups continued therapy until disease progression (PD).[2,4]

The primary end point was progression-free survival (PFS). Secondary end points included time to progression (TTP), overall survival (OS), overall response rate (ORR), complete response (CR) rate, very good partial response (VGPR) rate, minimal residual disease (MRD), time to response, and duration of response.

The publication reported results from a protocol-specified interim analysis.[2] Dr Moreau reported on subgroup analyses to further examine the efficacy data according to prior treatment exposure.

The study enrolled patients with RRMM who had received at least 1 prior therapy, which could have included lenalidomide if the disease was not refractory to it. Nearly all patients had 1 to 3 prior lines of therapy; most had received a PI and about half had received an IMiD, including lenalidomide in 18% of each group.

In all patients who had received 1 to 3 prior lines of therapy, the 18-month PFS in the daratumumab group (n = 272) was 77%, and in the control group (n = 264) was 50%, at a median follow-up of 18.4 months (HR, 0.36; 95% CI, 0.26-0.49; P <.0001). The 18-month PFS was similar for patients who had received 1 to 3 prior lines of therapy and were also lenalidomide naïve. The 18-month PFS for lenalidomide-exposed patients receiving 1 to 3 prior lines of therapy was 79% for the daratumumab group and 59% for the control group (HR, 0.45; 95% CI, 0.20-0.99; P = .042).

For all patients who had received 1 to 3 prior lines of therapy, the ORR was 94% in the daratumumab group, including 47% CR and 31% VGPR; in the control group, ORR was 77%, with 20% CR and 26% VGPR (P <.0001). Responses continue to deepen in the daratumumab group over time with longer follow-up. The response rates were similar in lenalidomide-naïve patients who had received 1 to 3 prior lines of therapy: 93% ORR for the daratumumab group and 77% for the control; in lenalidomide-exposed patients, the ORR were lower, 87% versus 67%, respectively (P <.0001).[2] However, the outcomes were significantly better in the daratumumab groups than in the control groups. The addition of daratumumab similarly was associated with improved PFS and ORR in patients whose myeloma was resistant to the last line of therapy or refractory to bortezomib.

The addition of daratumumab to lenalidomide and dexamethasone improved responses and PFS in patients with either high-risk or standard-risk cytogenetics. There were no new safety signals identified in either treatment group.

Saad Z. Usmani, MD, Levine Cancer Institute/Carolinas HealthCare System, Charlotte, North Carolina, also presented data from the POLLUX trial, including additional data on outcomes based on high-risk cytogenetics within the subgroups receiving 1 to 3 prior lines of therapy, at a median follow-up of 17.3 months.[6]

Dr Usmani reported on PFS by time from last therapy or treatment-free interval (TFI), defined as the duration between the end/start date of last line of prior therapy and the date of random assignment to POLLUX. The 18-month PFS was significantly higher (P <.0001) for patients in the daratumumab arm versus those in the control arm, whether the TFI was >12 months (83% vs 60%, respectively) or ≤12 months (70% vs 37%, respectively).

Patients whose myeloma was refractory to the last therapy also benefitted from the addition of daratumumab, with an 18-month PFS of 65% for the daratumumab combination (ORR, 87%) versus 36% for the control (ORR, 64%; P = .0015 for PFS and P = .0011 for ORR). Responses were deeper in the daratumumab group (CR, 47%; VGPR, 26%) versus the control group (CR, 15%; VGPR, 19%).

The addition of daratumumab improved PFS independently of cytogenetic risk, with high-risk cytogenetic status defined as having at least 1 of the following abnormalities as assessed via fluorescence in situ hybridization or karyotyping by local laboratory assessment: translocation (t)(4;14), t(14;16), or deletion (del) 17p, as shown in **Table 1**. There was no difference in OS between treatment groups overall or by number of prior lines of therapy at the time of follow-up.

TABLE 1. PFS in the POLLUX Trial by Cytogenetic Risk

	Treatment Group	
	Daratumumab lenalidomide dex	**Lenalidomide dex**
	High-risk cytogenetics	
Median PFS	Not reached (n = 28)	10.2 mo (n = 37)
	HR, 0.44; 95% CI, 0.19-1.039; *P* = .0475	
ORR	85% (n = 27)	67 (36)
	Standard-risk cytogenetics	
Median PFS	Not reached (n = 133)	17.1 mo (n = 113)
	HR, 0.30; 95% CI, 0.18-0.49; *P* <.0001	
ORR	95% (n = 132)	82.4% (n = 111)
	P = .0020	

Dex indicates dexamethasone; ORR, overall response rate; PFS, progression-free survival.

TABLE 2. PFS in the CASTOR Trial by Cytogenetic Risk

	Treatment Group	
	Daratumumab bortezomib dex	**Bortezomib dex**
	High-risk cytogenetics	
Median PFS	11.2 mo (n = 44)	7.2 mo (n = 51)
	HR, 0.49; 95% CI, 0.27-0.89; *P* = .0167	
ORR	82% (n = 44)	62% (n = 47)
	P = .039	
	Standard-risk cytogenetics	
Median PFS	Not reached (n = 123)	7.0 mo (n = 135)
	HR, 0.29; 95% CI, 0.20-0.43; *P* <.0001	
ORR	85% (n = 118)	74% (n = 131)
	P = .0003	

Dex indicates dexamethasone; ORR, overall response rate; PFS, progression-free survival.

Dr Moreau concluded that the POLLUX data support the use of combination daratumumab plus lenalidomide and dexamethasone regardless of prior lenalidomide treatment or bortezomib refractoriness. Dr Usmani concluded that the POLLUX data support the use of combination daratumumab plus lenalidomide and dexamethasone in patients who have received at least 1 prior therapy, regardless of their cytogenetic risk status or refractoriness of prior therapy. He noted that the safety profile resembled that seen for the agents in prior clinical trials.

Daratumumab Plus Bortezomib Provides Sustained Progression-Free Survival

Maria-Victoria Mateos, MD, PhD, University Hospital of Salamanca/IBSAL, Salamanca, Spain, presented an updated analysis of the CASTOR trial based, like the reports here of POLLUX, on prior lines of therapy, including outcomes based on cytogenetic status and MRD.[7] CASTOR is a multicenter, randomized, open-label, active-controlled, phase 3 study (NCT02136134).[8]

Patients with RRMM who had received at least 1 prior line of therapy were randomly assigned 1:1 to bortezomib 1.3 mg/m^2 subcutaneously on days 1, 4, 8, and 11 of 8 21-day cycles and 20-mg dexamethasone on days 1, 2, 4, 5, 8, 9, 11, and 12 of the 8 cycles (n = 247), or to the same dose and schedule of bortezomib and dexamethasone plus daratumumab 16 mg/kg IV weekly for the first 3 cycles and every 3 weeks for cycles 4 to 8 (n = 251). On completion of cycle 8, patients in the bortezomib and dexamethasone control group were observed, and patients in the daratumumab group continued to receive it once every 4 weeks.

The primary end point was PFS. Secondary end points included TTP, OS, ORR, VGPR, CR, and MRD. High-risk cytogenetic status based on local laboratory assessments was defined as having at least 1 of the following abnormalities via karyotyping or fluorescence in situ hybridization: del 17p, t(4;14), or t(14;16).

About three-quarters of the patients in both groups had standard-risk cytogenetics; about half had received 1 prior therapy and about 90% had received 1 to 3 prior therapies. At the primary analysis at a median of 7.4 months of follow-up, the primary end point had been met, and the independent data and safety monitoring committee recommended that patients in the control arm with PD receive daratumumab monotherapy.[3]

The data from CASTOR support the use of combination daratumumab with bortezomib and dexamethasone in patients with relapsed refractory multiple myeloma.

— Maria-Victoria Mateos, MD, PhD

Dr Mateos reported updated efficacy results. Responses continued to deepen in the daratumumab group with continued follow-up. The 12-month PFS was 60% in the daratumumab group and 22% in the control group at a median follow-up of 13 months (HR, 0.33; 95% CI, 0.26-0.43; P <.0001). ORR was 84% for the daratumumab group (including 26% CR and 35% VGPR) and 63% for the control group (P <.0001) (including 10% CR and 19% VGPR). For patients receiving 1 prior line of therapy, ORR was 91% in the daratumumab group versus 74% in the control group (P = .0014). For those receiving 2 to 3 prior lines, ORR was 79% and 58%, respectively (P = .0022).

The 12-month PFS for patients receiving 1 prior line of therapy was 77% in the daratumumab group and 25% in the control group (HR, 0.22; 95% CI, 0.14-0.34; P <.0001), versus 44% and 22%, respectively, in patients who had received 2 to 3 prior lines (HR, 0.51; 95% CI, 0.36-0.73; P = .0002). Therefore, the addition of daratumumab to bortezomib plus dexamethasone improved outcomes regardless of prior lines of therapy. This was true even if patients had received bortezomib as their 1 prior line of therapy. However, patients receiving 1 prior line of therapy had the most benefit.

The addition of daratumumab improved PFS independently of cytogenetic risk in all evaluable patients, as shown in **Table 2**. In his presentation, Dr Usmani pointed out that in the OLLUX trial, PFS was not reached for groups with either standard or high-risk cytogenetics, although in the CASTOR trial, PFS was reached in the high-risk cytogenetic group, so the combination of daratumumab plus lenalidomide and dexamethasone might be able to overcome high-risk cytogenetics. There was no difference in OS between treatment groups overall or by number of prior lines of therapy at the time of follow-up.

The rate of hematologic adverse events (AEs) was higher in the daratumumab arm; the rate of discontinuations due to treatment-emergent AEs was 9% in each arm. No new infusion-related reactions were reported.

Dr Mateos concluded that the data from CASTOR support the use of combination daratumumab with bortezomib and dexamethasone in patients with RRMM, particularly those who have received only 1 prior line of therapy.

Unprecedented Minimal Residual Disease Rates Associated With Daratumumab

Hervé Avet-Loiseau, MD, PhD, Centre Hospitalier Universitaire Rangueil, Unité de Genomique du Myelome, Toulouse, France, gave a separate presentation on evaluation of MRD in RRMM in both POLLUX and CASTOR, the first comprehensive and prospective study of MRD to date in randomized phase 3 clinical trials in patients with RRMM.[9] MRD was assessed by next-generation sequencing of the B-cell receptor (immunoglobulin) on bone marrow aspirates at sensitivities of 0.01% (1 cancer cell per 10,000 nucleated cells, or 10^{-4}), 0.001% (10^{-5}), and 0.0001% (10^{-6}) using the ClonoSEQ assay.[10] Therefore, the threshold of 10^{-6} required evaluation of a minimum of 1 million cells.

Dr Avet-Loiseau noted that, in the future, MRD assessment might become a primary end point for clinical studies because it is associated with prolonged PFS and OS in newly diagnosed patients with MM. The International Myeloma Working Group guidelines currently recommend an MRD-sensitivity threshold of at least 10^{-5} using next-generation sequencing of next-generation flow cytometry.[11]

The MRD negative rate per treatment arm was determined as the proportion of patients with negative MRD at any time point after the first dose and compared using the likelihood-ratio test. MRD was assessed in POLLUX (blinded to treatment group) at the time of suspected CR and at 3 and 6 months post suspected CR for patients who maintained this response. Similarly, in CASTOR, MRD was assessed for patients at the time of suspected CR (blinded to treatment group) and at 6 months and 12 months after first dose (at the end and 6 months after the end of bortezomib dexamethasone background therapy, respectively).

To allow for a stringent, unbiased evaluation of MRD in these studies, the entire intent-to-treat (ITT) population was evaluated when patients were considered MRD positive if they had only MRD-positive test results or had no MRD assessment. In POLLUX, 63% in the daratumumab group and 87% in the control group did not receive an MRD assessment, and for CASTOR, 76% in the daratumumab group and 87% in the control group were not assessed for MRD.

Dr Moreau presented MRD data from the POLLUX trial.[4] MRD in the ITT population was evaluated at 3 sensitivity thresholds: 10^{-4}, 10^{-5}, and 10^{-6}. The MRD rates at a threshold of 10^{-5} were reported for POLLUX,[4,6] and in the ITT population and the subgroups receiving 1 to 3 prior lines of therapy, the MRD negativity rate was statistically significantly higher (P <.001 for the ITT population, all receiving 1 to 3 prior lines, and lenalidomide naïve; P <.01 for lenalidomide exposed; P <.05 for bortezomib refractory). PFS was longer in MRD-negative patients than in MRD-positive patients; PFS was longer for MRD-positive patients in the daratumumab group than in the control group.

Dr Mateos presented MRD data from the CASTOR trial.[7] MRD-negative rates were at least 3-fold higher across all thresholds for the patients receiving the daratumumab combination in the ITT group and the 1 prior line of therapy group compared with patients receiving bortezomib and dexamethasone alone, which was statistically significant for all groups except the 1 prior line group at a threshold of 10^{-6}.

PFS was longer for patients who were MRD negative at a threshold of 10^{-5} for the ITT group and those receiving 1 prior line of therapy. In fact, PFS appeared to be similar between the 2 treatment groups for patients who were MRD negative. Patients who were MRD positive who received daratumumab had a longer PFS than MRD-positive patients in the control group.

Dr Avet-Loiseau pointed out that MRD rates were consistently higher in patients with CR or stringent CR in both the POLLUX and CASTOR trials who had received the daratumumab-containing combination. The time to MRD at 10^{-5} for the daratumumab arms in both trials was shorter than for the control arms, and rates of MRD negativity increased over time. He reiterated that patients in the daratumumab arms who were MRD positive still had a PFS benefit compared with the control arms.

In both studies, the only patients with high-risk cytogenetics who were MRD negative were those in the daratumumab arms. So far, none of these have converted to MRD positive or had PD.

Dr Avet-Loiseau concluded that the magnitude of daratumumab-induced MRD negativity in patients with RRMM was unprecedented. The benefit of MRD-negative status is being explored in ongoing studies in patients with newly diagnosed MM.

Dr Usmani was asked during his presentation if it made sense to treat a patient with RRMM with other agents to try to achieve MRD before adding an antibody to therapy. Dr Usmani thought that the best therapy currently available was the combination of daratumumab, lenalidomide, and dexamethasone, and that the question of treatment sequencing would be best answered in further clinical trials. There are ongoing trials of daratumumab with standard-of-care regimens in the upfront setting. ■

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Selinexor Active in Early Trials in Hematologic Malignancies

Although new agents with novel mechanisms of action have recently been approved for patients with multiple myeloma (MM), the disease remains incurable. MM eventually becomes refractory to all available agents, so patients with relapsed and refractory (RR)MM continue have unmet therapeutic needs, and additional agents with new mechanisms of action are still needed. Likewise, patients with acute myeloid leukemia (AML) have a poor prognosis and are also in need of novel agents that are effective and tolerable.

Selinexor is a member of a new class of agents known as selective inhibitors of nuclear export (SINEs). Selinexor inhibits exportin 1 (XPO1), the nuclear exporter for the majority of tumor suppressor proteins, the glucocorticoid receptor, and oncoprotein mRNAs. When XPO1 is inhibited by selinexor, the tumor suppressor proteins are retained and activated in the nucleus, corticosteroids are able to activate the glucocorticoid receptor, and the oncoprotein mRNAs that are retained in the nucleus are unable to be translated and expressed in the cytoplasm.[1]

Based on promising results from preclinical studies, trials have been initiated in patients with a variety of malignancies. Among these, several early phase studies of selinexor, which is administered orally, in RRMM and AML have shown encouraging results and were presented at the 2016 annual meeting of the American Society of Hematology.

Promising Results in Heavily Pretreated Refractory Multiple Myeloma

Selinexor Plus Dexamethasone in Heavily Pretreated Myeloma

Dan T. Vogl, MD, Perelman Center for Advanced Medicine, University of Pennsylvania, presented results of "Selinexor and low dose dexamethasone (Sd) in patients with lenalidomide, pomalidomide, bortezomib, carfilzomib and anti-CD38 Ab refractory multiple myeloma (MM): STORM study."[2,3]

STORM was a phase 2 study of selinexor and dexamethasone in patients with MM refractory to their last therapy, as well as, individually, to bortezomib, carfilzomib, lenalidomide, and pomalidomide ("quad" refractory), with a subset also refractory to an anti-CD38 Ab ("penta" refractory) (NCT02336815).[4] Dr Vogl noted that patients with penta-refractory MM truly had no other treatment options and represent an unmet medical need that will only grow as patients move through all of the currently available effective myeloma therapies.

Patients received 80-mg selinexor and 20-mg dexamethasone twice weekly; initially, patients received 6 doses of each drug in each 28-day cycle on a 3-weeks-on, 1-week-off schedule (group 1). Partway through the study, the protocol was amended to allow more therapeutic dosing in the setting of treatment interruptions for toxicity, and patients received 2 doses of each drug weekly for 4 weeks (group 2). Selinexor doses were reduced to 60 mg twice weekly for most toxicities or to 80 mg once weekly for thrombocytopenia or fatigue. Short dose interruptions were also utilized for thrombocytopenia or fatigue.

The primary end point included the overall response rate (ORR), defined as the total of the stringent complete response (sCR) rate, CR rate, very good partial response (PR) rate, and PR rate. Secondary end points included progression-free survival (PFS) and overall survival (OS).

Patients enrolled included 48 with quad-refractory disease and 31 with penta-refractory disease. There was a median of 7 prior lines of therapy in both groups, including glucocorticoids, alkylating agents, stem cell transplant (SCT), and anthracyclines. Of quad-refractory patients, 40 received 6 doses and 8 received 8 doses per cycle; of penta-refractory patients, 11 received 6 doses and 20 received 8 doses because more penta-refractory patients were enrolled later in the study.

The most common adverse events (AEs) were nausea, anorexia, fatigue, thrombocytopenia, and anemia. These were mostly grade 1 or 2; grade 3 AEs included gastrointestinal toxicities and fatigue, and there were grade 3 and 4 hematologic toxicities. Hyponatremia was an unexpected side effect in nearly half of patients, but it was generally asymptomatic, even when reaching grade 3; in some cases, hyponatremia as thought to be an artifact related to high serum paraprotein levels. Toxicity of selinexor led to dose interruptions in 52% of patients and dose reductions in 37%; only 18% of patients discontinued treatment due to toxicity.

To manage these toxicities, the following recommendations were made: prophylactic antiemetics for all patients, appetite stimulants for patients with significant weight loss, hematopoietic growth factors as needed, thrombopoietin receptor agonists for dose-limiting thrombocytopenia, and salt supplementation for hyponatremia.

Efficacy was evaluated by an independent review committee. ORR (≥PR) for all patients was 21%, including 5% VGPR. ORR was 21% for quad-refractory patients and 20% for penta-refractory patients. Clinical benefit rates (≥ minimal response, MR) were 33% overall, 29% in the quad-refractory patients, and 37% in the penta-refractory patients. ORR was similar whether patients received 6 doses per month (20%) or 8 doses per month (22%).

ORR was 35% in patients with high-risk cytogenetic abnormalities, including 3 patients with deletion of the p53 gene (deletion 17p) achieving response, with an ORR of 38%. The median time to response was 1 month, and median duration of response (DOR) was 5 months. Median OS was 9.3 months and median PFS was 2.1 months for all patients. For patients with at least MR, OS was not reached and median PFS was 5.5 months.

Dr Vogl said these results were impressive in such a heavily pretreated population with highly refractory MM, suggesting a true clinical benefit for those whose disease responds to selinexor. He concluded that the combination of selinexor and low-dose dexamethasone has encouraging activity in this patient population, with an ORR of 21% and a median DOR of 5 months, including patients with ongoing responses at 7 and 9 months of therapy, and benefit in patients with high-risk cytogenetic abnormalities.

The combination was well tolerated, and improved strategies for managing AEs has allowed patients to remain on therapy. Enrollment has begun to another cohort of 122 patients with penta-refractory myeloma to confirm these results.

The combination of selinexor and low-dose dexamethasone has encouraging activity in patients with heavily pretreated multiple myeloma and with high-risk cytogenetic abnormalities.

— Dan T. Vogl, MD

Selinexor in Combination With Pomalidomide and Dexamethasone

Selinexor is being studied in combination with several backbone treatments of MM in the phase 1b/2 STOMP trial (NCT02343042).[5] This is a phase 1 dose escalation and phase 2 expansion combination study in patients with RRMM. Different arms of the study were investigating the combination of selinexor and dexamethasone with either pomalidomide, bortezomib, or lenalidomide. Christine Chen, MD, Princess Margaret Cancer Center, Toronto, Ontario, was lead author of a poster presenting the results of the selinexor in combination with pomalidomide and low-dose dexamethasone (SPd) arm of the STOMP trial.[6,7]

The primary objectives of this arm of the study were to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D); secondary objectives included ORR and DOR for each arm of the study independently. Additional objectives include the tolerability and preliminary efficacy.

Patients in the SPd arm had RRMM and had received at least 2 prior therapies, including lenalidomide and a proteasome inhibitor (PI). The dose of selinexor was escalated once weekly, starting at 80 mg, or twice weekly, starting at 60 mg; pomalidomide was administered at 4 mg daily on days 1 to 21, and dexamethasone at 40 mg weekly in each 28-day cycle.

There have been 20 patients enrolled with a median age of 61 years who had received a median of 5 prior regimens. The dose of selinexor has been escalated to 100 mg (dose level 2) in the 80-mg weekly cohort and to 80 mg (dose level 2) in the 60-mg twice-weekly cohort.

The most common AEs considered to be treatment-related include anorexia, nausea, fatigue, and thrombocytopenia. These are consistent with AEs observed with selinexor and pomalidomide administered separately. Gastrointestinal toxicities were grade 1 or 2 and manageable with antiemetics. One grade 3 dose-limiting toxicity (DLT), fatigue, occurred in the selinexor 60-mg twice-weekly group. Grade 3 and 4 toxicities included thrombocytopenia, neutropenia, and anemia; there were no incidents of febrile neutropenia or bleeding.

There were 15 patients evaluable for response as of November 28, 2016. Median PFS was 10.3 months at a median follow-up of 7.6 months. ORR was 60% (n = 9 patients), including 20% VGPR and 40% PR.

The investigators concluded that selinexor can be safely combined with pomalidomide and low-dose dexamethasone in patients with heavily pretreated MM. This all-oral regimen is generally well tolerated and is inducing rapid and durable responses in heavily pretreated MM even as dose escalations are continuing.

Determination of the recommended phase 2 dose is ongoing, with an evaluation of pomalidomide 3 mg daily plus selinexor 100 mg weekly to reduce the incidence of cytopenias.

Selinexor in Combination With Bortezomib and Dexamethasone

Nizar J. Bahlis, MD, Southern Alberta Cancer Research Institute, Calgary, presented the arm of the STOMP trial[8] that investigated the combination of selinexor plus bortezomib and dexamethasone in patients with RRMM.[9]

Patients with refractory MM were enrolled for treatment if they had at least 1 prior therapy. As long as they were not relapsed or refractory to bortezomib in their most recent line of therapy, patients with prior PI treatment were also enrolled for study. The doses of selinexor were escalated as in the SPd arm. Bortezomib was administered subcutaneously at 1.3

mg/m^2 once or twice weekly; dexamethasone was administered at a dose of 40 mg weekly in the weekly selinexor group, and patients in the twice-weekly selinexor group received a 20-mg dose.

As of November 1, 2016, there were 33 patients enrolled, 22 of whom were in the escalation group (phase 1) and 11 of whom were in the dose-expansion group. Patients had a median of 4 prior regimens, with 91% having received a prior PI and 73% having MM refractory to the prior PI; 91% had also received a prior immunomodulatory drug (IMiD), and 39% had MM refractory to prior lenalidomide and pomalidomide.

The most common grade 1 and 2 AEs were fatigue, anorexia, nausea, and weight loss. The most common grade 3 and 4 AEs included thrombocytopenia, anemia, and neutropenia. There was one DLT of grade 4 thrombocytopenia without bleeding. The MTD has not been reached in the 80-mg selinexor twice-weekly cohort.

ORR in the phase 1 group (n = 22) was 77%, with 1 sCR, 2 CR, 4 VGPR, and 10 PR. In PI-refractory patients, the ORR was 67%; 100% of the 7 patients with PI–nonrefractory MM had a response of PR or better. Median DOR was 7.8 months. Most patients (82%) had reductions in their M-protein from baseline of greater than 50%, and reductions of at least 90% were found in 36% of patients.

The recommended phase 2 dose was determined to be selinexor 100 mg once weekly, bortezomib 1.3 mg/m^2 once weekly, and dexamethasone 40 mg once weekly, based on tolerability and efficacy. In 17 patients treated at this dose, AEs were similar to those in the phase 1 group, and mostly grade 1 to 2, with 1 instance each of grade 3 diarrhea, fatigue, thrombocytopenia, and abdominal pain. The expansion cohort will enroll 20 patients.

Dr Bahlis concluded that selinexor in combination with bortezomib and dexamethasone is well tolerated, with low rates of major AEs. These agents have minimal clinically significant overlapping toxicities. AEs were primarily grade 1 and 2 and manageable. This combination is highly active in refractory MM. A phase 3 randomized study of selinexor plus bortezomib and dexamethasone versus bortezomib and dexamethasone is planned to begin early in 2017.

Selinexor Plus Carfilzomib and Dexamethasone in RRMM

Andrzej J. Jakubowiak, MD, PhD, University of Chicago Medical Center, reported on final results of the phase 1 MMRC trial (NCT02199665)[10] of selinexor, carfilzomib, and dexamethasone in RRMM.[11,12] The primary objectives were to assess the MTD and determine the RP2D of a selinexor, carfilzomib, and dexamethasone combination in patients with RRMM; secondary and exploratory objectives were to determine safety and tolerability and obtain preliminary efficacy data, including responses, activity in patients with carfilzomib-refractory MM, and time-to-event end points.

The study enrolled patients with RRMM that progressed after at least 2 prior treatment regimens for MM. For the dose-escalation portion of the trial, patients received 30 mg/m^2 to 40 mg/m^2 selinexor on days 1, 3, 8, 10, 15, and 17; 20 mg/m^2 to 56 mg/m^2 carfilzomib intravenously (IV) on days 1, 2, 8, 9, 15, 16; and dexamethasone 20 mg for cycles 1 to 4 and 10 mg for cycles 5 and thereafter in 28-day cycles in up to 5 dose levels. The carfilzomib dose was initiated at 20 mg/m^2 on days 1 and 2 of the first cycle at all dose levels. The expansion portion of the trial was to enroll up to 12 additional patients with carfilzomib-refractory MM at the RP2D. DLTs were evaluated through day 1 of cycle 2.

The dosage of selinexor for the initial 2 escalation-dose levels was calculated by body surface area, unlike the previous 2 combination studies, which used fixed doses throughout. After the first 2 escalation-dose levels, the selinexor dose was fixed at 60 mg/dose. The RP2D was determined to be 60 mg of selinexor, 27 mg/m^2 carfilzomib, and 20 mg of dexamethasone.

The median age of the 21 enrolled patients was 64 years. Patients had received a median of 4 prior lines of therapy. High-risk cytogenetics were identified in 57% of patients. All patients had received prior PIs and IMiDs; prior therapies included carfilzomib, bortezomib, lenalidomide, and autologous SCT in 95% of patients; 81% of patients had received prior pomalidomide. All patients had MM refractory to prior therapy, including the last line of therapy.

Over half of patients discontinued due to progressive disease. AEs included thrombocytopenia, anemia, lymphopenia, gastrointestinal disorders, fatigue, and dyspnea. Thrombocytopenia was the predominate grade 3 and 4 AE, occurring in 64% of patients; 27% of patients had grade 3 or 4 lymphopenia or neutropenia. Serious AEs included 1 incident each of upper respiratory infection and upper gastrointestinal bleeding.

Responses were evaluable in 19 patients; the ≥PR rate was 47% after 1 cycle and increased to 63% as the best response; the ≥VGPR rate increased from 11% after 1 cycle to 26% as the best response. In the 12 patients with carfilzomib-refractory MM, the best response was a ≥PR rate of 67% and a ≥VGPR rate of 17%. Median DOR was 3.3 months for patients with a response of ≥PR. At a median follow-up of 8.2 months, the PFS was 3.7 months and OS was not reached.

Dr Jakubowiak concluded that the combination of selinexor, carfilzomib, and dexamethasone appears to be safe, with an acceptable tolerability in patients with RRMM. The predominant toxicities of thrombocytopenia and neutropenia were manageable with dose modifications. The combination shows encouraging activity in a heavily pretreated population with RRMM, including patients with myeloma refractory to carfilzomib, suggesting that the addition of selinexor to a carfilzomib-based regimen may overcome carfilzomib resistance.

Further investigation is warranted, including administration of the combination on a weekly schedule and evaluation in a less heavily pretreated population. A trial of selinexor, carfilzomib, and dexamethasone versus carfilzomib and dexamethasone (NT02628704) is planned.[13]

The combination of selinexor, carfilzomib, and dexamethasone shows encouraging activity in a heavily pretreated population with relapsed refractory multiple myeloma.

— Andrzej J. Jakubowiak, MD, PhD

Second-Generation SINE Has Improved Tolerability Over Selinexor

A second-generation orally dosed SINE, KPT-8602, has a mechanism of action similar to that of selinexor, and with reduced brain penetration. This has been associated with a better side-effect profile than selinexor in preclinical studies, including reduced anorexia and weight loss.

R. Frank Cornell, MD, Department of Medicine, Division of Hematology-Oncology, Vanderbilt-Ingram Cancer Center, Nashville, Tennessee, presented results of a phase 1/2 trial of KPT-8602 in patients with RRMM[14,15] (NCT02649790).[16]

In phase 1 of the trial, part A determined the RP2D or MTD of single-agent KPT-8602; part B determined the RP2D or MTD of KPT-8602 combined with dexamethasone. The expansion phase 2 was planned to determine safety, tolerability, and preliminary efficacy of the combination. Patients with RRMM previously treated with at least 3 prior lines of therapy, including an alkylator, IMiD, PI, and steroid, and refractory to the most recent regimen were enrolled.

Results were reported for 12 patients in part A. Patients are currently being enrolled for the fifth dose-escalation cohort to receive 40-mg KPT-8602 daily for 5 days each week in 28-day cycles. No DLTs have occurred in 9 patients evaluated for safety. No anorexia or grade 2 or higher nausea has been observed. There is no apparent dose relationship to grade 1 and 2 nausea, diarrhea, or fatigue. Hematologic AEs were as expected for the patient population.

Responses seem encouraging, although the median time on study is short, and numbers of patients are small. The study is ongoing, with continued dose escalation. The addition of dexamethasone is expected to improve response in MM. Protocol amendments are planned to include patients with AML and chronic lymphocytic anemia, as well as solid tumors.

Longer-term follow-up of these studies and additional randomized, controlled, double-blind trials will be needed to confirm the efficacy and tolerability of selinexor for patients with MM.

Selinexor Shows Activity in Acute Myelogenous Leukemia

Results from early-phase trials of selinexor in combination with standard therapies for AML were also presented.

Amy Y. Wang, MD, University of Chicago Medical Center,[17,18] presented results of a phase 1 study of selinexor with high-dose cytarabine and mitoxantrone for remission induction of acute AML (NCT02573363).[19] Standard induction chemotherapy for AML combines high-dose cytarabine with mitoxantrone. This study was based on the known tolerability and efficacy of selinexor as a single agent and in combination with cytarabine regimens in RR AML, as well as a favorable ORR of 55% for cytarabine plus mitoxantrone at the Chicago Medical Center for patients with RR AML.

This study tested the hypothesis that adding selinexor to cytarabine plus mitoxantrone would have synergistic antileukemic effects. The primary end point was to determine the MTD of selinexor in the combination. Secondary objectives included the CR rate after induction, toxicities during induction, consolidation, maintenance, relapse-free survival, OS, and SCT success rate.

During the induction phase of the trial, patients were treated with an oral dose of selinexor on days 2, 4, 9, and 11. On day 1 and 5 of the induction phase, patients received IV cytarabine over 3 hours at an age-dependent dosage of 1.5 to 3 mg/m^2 followed immediately by IV mitoxantrone over 1 hour at 20 to 30 mg/m^2. The initial 60-mg dose of selinexor was followed by dose escalation to a target level of 80 mg, determined to be the RP2D. Once a dose level was declared tolerable, more patients could be enrolled at that level to provide additional safety, tolerability, and efficacy data. Patients who entered remission while receiving the study treatment proceeded to SCT or consolidation chemotherapy treatment with cytarabine plus selinexor followed by 1 year of maintenance therapy with weekly selinexor monotherapy.

Of the 20 patients enrolled so far, 17 received the higher selinexor dose (80 mg); 70% were female, with a median age of 62 years; 60% had de novo AML; the rest, secondary AML; 60% were newly diagnosed, 40% had RR AML. As of November

15, 2016, 19 patients completed induction therapy and were evaluable for safety and efficacy.

Serious AEs occurred in 26% of patients; there was 1 death during induction from hemorrhagic stroke in a patient with a low platelet count. The most common noninfectious AEs were of severity grade 1 or 2 and were manageable with supportive care. AEs included diarrhea, anorexia, electrolyte abnormalities, nausea, vomiting, and fatigue.

The ORR was 68.4% in patients treated with either dose of selinexor with a CR/CRi (remission with incomplete count recovery) rate of 63%. Median time to CR was 35 days, shorter in those who received granulocyte-colony stimulating factor. Responses were higher in patients who were newly diagnosed, had a favorable risk profile, or were aged ≤60 years. Of patients in remission, 6 underwent postinduction allogeneic SCT, 4 received consolidation therapy, 2 are planning SCT, and 1 patient awaits blood-count recovery.

The selinexor-cytarabine-mitoxantrone regimen is feasible and tolerable at selinexor doses up to 80 mg.

— Amy Y. Wang, MD

The selinexor-cytarabine-mitoxantrone regimen is feasible and tolerable at selinexor doses up to 80 mg. Additional molecular correlative studies will evaluate bone marrow and blood samples for markers that might predict response and relapse. The combination warrants further investigation in a larger study.

Kendra L. Sweet, MD, Moffitt Cancer Center, Tampa, Florida, presented a poster on a phase 1 study of selinexor in combination with daunorubicin and cytarabine in patients with newly diagnosed, poor-risk AML[20,21] (NCT01607892).[22] Prior treatment for an antecedent hematologic disorder was allowed.

During the induction phase, patients were treated with 100 mg/m^2 of cytarabine daily by continuous IV infusion on days 1 to 7. For the first 3 days, patients received a daily dose of 60 mg/m^2 daunorubicin (7 + 3). Patients received either a 60-mg (cohort 1) or 80-mg (cohort 2) oral dose of selinexor on days 1, 3, 8, 10, 15, and 17; selinexor was given at the same dose for all phases of the study. If indicated, re-induction therapy was permitted with 5 + 2 cytarabine plus daunorubicin with selinexor at the induction dosage. Once patients achieved CR, they received 1 to 2 cycles of consolidation treatment with 5 + 2 plus selinexor followed by up to 12 months of selinexor maintenance therapy on days 1 and 8 in a 21-day cycle. Patients could proceed to hematopoietic SCT at any time after achieving CR.

Of 21 patients enrolled, 18 were evaluable for response. The P2D of selinexor was 80 mg twice weekly for combination therapy. The most common treatment-related AEs included febrile neutropenia, diarrhea, and hyponatremia at grade 3 or 4 severity. Blood-count recovery resembled that for 7 + 3 alone. In all treated patients evaluable for response, ORR was 56%, including 44% CR and 12% CRi, which the authors denoted as encouraging results for this treatment. Investigators suggest the combination of selinexor with 7 + 3 warrants further investigation in a trial comparing the combination to 7 + 3 alone.

Ramiro Garzon, MD, The Ohio State University, Columbus, presented the results of a phase 1 trial of selinexor in combination with decitabine in patients with newly diagnosed or refractory high-risk AML (NCT02093403)[23] in a poster.[24,25] This dose-escalation study determined the safety, feasibility, MTD, RP2D, and preliminary clinical activity of the combination.

Patients received 10-day decitabine induction(s) at 20 mg/m^2 on days 1 to 10 for up to four 28-day cycles in combination with selinexor once daily, twice weekly beginning on day 11. Patients with <5% marrow blasts after any cycle received 5-day decitabine maintenance with selinexor, as described.

At the maximum administered dose of 55 mg/m^2, 3 patients had not reported any ≥3 drug-related toxicities; however, an amendment was made for selinexor after treatment-related low-level gastrointestinal toxicities of nausea and anorexia led to discontinuation of study treatment in 2 patients at the first-dose level: selinexor at a dose of 60 mg was given twice weekly for only 2 weeks instead of 3 weeks, on days 11, 13, 18, and 20 of each cycle. Six additional patients were enrolled at 60 mg of selinexor, with improved tolerability found to be the RP2D.

The most common AEs of grade 3 severity or higher included asymptomatic hyponatremia, febrile neutropenia, sepsis, hypertension, hyperglycemia, hypophosphatemia, and lung infections. Discontinuations were due to intolerable therapy-related toxicities (10 patients), refractory AML (6 patients), death in induction or remission (1 each), transplantation (3 patients), or uncontrolled infection (1 patient).

Of 24 patients enrolled, 19 had RR AML with a median of 3 prior lines of therapy; of these, 3 died during induction, unrelated to therapy. The ORR overall was 37.5%. Of the remaining 16 patients in the RR AML group, there were 2 CR, 2 CRi, and 1 marrow CR. Two of the 5 previously untreated patients had CR, and 2 had CRi. Six patients with RR AML underwent allogeneic SCT.

Although selinexor in combination with standard-of-care therapies in high-risk AML offers somewhat promising results, the toxicities of some combinations present a problem. It remains to been seen whether the further development of the second-generation SINE, KPT-8602, may resolve these issues. ■

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Treatment Intensity Cannot Be Effectively Reduced in Low-Risk Childhood Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer. Life expectancy for children with ALL has improved with current intensive therapy, although it is associated with toxicity; it may not be required for patients with low-risk (LR) disease.

Martin Schrappe, MD, Christian-Albrechts University Kiel and University Medical Center Schleswig-Holstein, Kiel, Germany, gave a plenary session talk,[1] "Reduced intensity delayed intensification in standard-risk (SR) patients defined by minimal residual disease in childhood acute lymphoblastic leukemia: results of an international randomized trial in 1164 patients (trial AIEOP-BFM ALL 2000)"[2] at the 2016 annual meeting of the American Society of Hematology.

Stephen P. Hunger, MD, Perelman School of Medicine at the University of Pennsylvania, introduced Dr Schrappe's presentation. He noted that overall survival (OS) of children with ALL has improved dramatically over the last half century. Fifty years ago, the expected survival for children with ALL was about 10%. Today, a child diagnosed with ALL has an expected survival of greater than 90%, and improvements are continuing.

Modern therapy includes multiple phases that last several years, including intensive phases of therapy that last 6 to 10 months, and maintenance or continuation therapy, which is low intensity, lasting 18 to 30 months. Currently, event-free survival (EFS) exceeds 85% and OS exceeds 90%. Mortality caused by toxicity is 2% to 4% overall. However, long-term adverse events are a significant concern because survivors can have an additional life expectancy of 70 to 80 or more years.

Patients with LR ALL, defined as an EFS of 93% to 95% and OS of ≥98% with contemporary ALL therapy, can be identified using a variety of risk factors, including clinical features, such as age and initial white blood cell count (WBC) at time of diagnosis; the presence of favorable sentinel genetic alterations, such as the ETV6/RUNX1 fusion or high hyperdiploidy; and most importantly, early response to treatment measured by sensitive minimal residual disease (MRD) technologies. Therefore, contemporary therapy likely over treats many, if not most, patients with LR ALL.

Dr Hunger outlined the challenges in treating patients with LR ALL, which include the following:

- How should LR ALL be defined?
- How can the minimum therapy needed for cure be identified?
- What are the most appropriate clinical trial end points? EFS or OS?

Dr Hunger suggested that randomized trials testing reduction in treatment intensity are challenging to conduct but are the best way to answer these critical questions. During Dr Schrappe's presentation of the results from a large randomized trial, the open question as to what treatment for childhood SR ALL is optimal, least toxic, and most effective was unanswered. Dr Schrappe said the definitions for LR or SR are interesting because they are so different. SR ALL is a completely misleading term, he said: without adequate treatment, there is no SR ALL because ALL is, by definition, a fatal disease. Treatment itself remains the strongest prognostic factor in childhood, and probably every category of ALL. And treatment depends on the socioeconomic environment, ie, where one lives and how well one is equipped. In some countries, the availability of diagnostic tools is quite limited; this should not be forgotten, he said.

Examples of classification systems include WBC, age, and early response assessment, the cheapest being assessment of response to prednisone using a peripheral blood smear, which is highly predictive of outcome. The NCI (National Cancer Institute)-SR/HR (high-risk) classification system combines WBC and age. Other classification systems are based on immunophenotyping or genetics, eg, ETV6/RUNX1, hyperdiploidy, and more recently, the detection of MRD by flow cytometry or polymerase chain reaction (PCR) techniques.

This allows the detection of disease even when the patient appears to be in remission. An MRD pilot trial in Italy, the Netherlands, Austria, and Germany showed that MRD was prognostic in childhood ALL.[3] It was a prospective, blinded analysis of MRD in the bone marrow of patients with ALL treated in trials. They found 3 distinct risk groups in the 129 patients. LR was determined in the 55 patients (43%) who had a 3-year relapse rate of 2%, whereas the 19 patients (15%) of the HR group had a relapse rate of 75% and disease unresponsive to therapy that was detectable at high levels after induction (at 5 weeks) and after consolidation (at 12 weeks). The intermediate-risk group fell between LR and HR, with a 3-year relapse rate of 23% in the 55 patients (43%).

On the basis of these results, the trial AIEOP-BFM-ALL 2000 [NCT00430118 (BFM)[4] and NCT00613457 (AIEOP)[5]] was designed. In this study, risk stratification was defined as follows:

- SR: MRD negative with 2 PCR markers for IgH and T-cell receptor rearrangements in week 5 and week 12 after introduction and consolidation therapy, respectively; marker sensitivity $\geq 10^{-4}$; no clinical or biological HR criteria, including poor response to induction, or HR genetic features

- Medium risk: MRD positive at week 5 and/or week 12 and MRD at week 12 $<10^{-3}$ with 2 markers; or MRD not classifiable; no clinical or biological HR features
- HR: MRD $\geq 10^{-3}$ at week 12 or poor response to prednisone or nonremission at the end of induction therapy or translocation (t)(9;22) or t(4;11)

Patients in the trial had B-precursor acute lymphoblastic leukemia (pB-ALL), which accounted for 42.3% (n = 1248) of patients in the SR group; only 16.2% (n = 75) of patients with T-cell leukemia were in the SR group. Patients were aged 1 to 17 years, with 85% aged 1 to 9 years (an age group that is prognostically favorable); infant leukemia was excluded. Demographics were typical of ALL, and 71.5% had very low WBC counts.

The data reported by Dr Schrappe were intended to determine whether well-selected patients with SR ALL can be treated with less-intensive therapy. Trial results have been published; results show the benefit of early intervention but suggest that MRD might not be the perfect surrogate for response.[6]

The 2 interventions reported at this session were administered in the trial to patients with SR disease, reduced-intensity protocol III (P-III) versus standard-intensity protocol II (P-II) for delayed re-intensification in order to reduce treatment burden in the group of patients with best treatment response and lowest risk of relapse. The reduced-intensity P-III reduced dexamethasone by 30%, vincristine by 50%, doxorubicin by 50%, and cyclophosphamide by 50%, and the duration of therapy was shortened by 3 weeks.

There were 4937 patients registered in trial AIEOP-BFM-ALL 2000; of these, 4839 patients were eligible and 1346 patients were eligible for random assignment in SR. There were 64 patients in the SR group not eligible due to early events; 182 refused to be randomly assigned, so 1164 patients were randomly assigned in SR, 86.5% of the eligible and accessible patients.

At a median follow-up of 8.6 years, there was no significant difference in the 5-year EFS between the 2 treatment groups in the intent-to-treat population, with an EFS of 94.7% in the P-II group and 90.7% in the P-III group ($P = .12$).

There was no reduction in toxicity in the group receiving the reduced-intensity treatment. Although in the early phase, P-III was less toxic, with fewer grade 3 and 4 infections, which is an overall indication of toxicity, in the late phase, reduced-intensity therapy was associated with a higher rate of infections than the standard protocol, and the rate of second malignancies was also higher. Dr Schrappe said the reasons for this are not known.

When analyzing results by treatment given, there was a significant difference between treatments ($P = .041$), with a higher 5-year EFS in the standard-intensity arm (94.9%) versus reduced intensity (90.6%). There were no differences between groups in the cumulative incidence of relapse at 5 years or in OS at 5 years in the as-treated population.

However, there was a significant difference in 5-year EFS in the as-treated population for patients with SR pB-ALL; EFS was 90.6% in the reduced-intensity P-III group and 95.2% in the P-II group ($P = .043$). In patients with SR pB who were ETV6/RUNDC1 negative, EFS at 5 years was 87.7% in the reduced-intensity P-III group and 94.2% in the P-II regular intensity group ($P = .027$).

For SR patients aged ≥10 years, the cumulative incidence of relapse at 5 years as treated for the reduced-intensity P-III group was 81.6%, and 95.2% for the regular-intensity P-II group ($P = .037$).

In conclusion, Dr Schrappe said that in this trial, only the most favorable patients, selected by excellent MRD-negative response, were randomly assigned treatment aimed at reduction of cumulative doses of critical agents. Unfortunately, patients with pB-ALL who were less intensively treated experienced 50% more relapses than patients receiving standard-intensity treatment. He believes that only the randomized approach in a large cohort of ALL patients could detect this significant and clinically relevant difference. Any treatment modification in patients with such an excellent prognosis as the SR group defined in this trial should be carried out with great caution and under controlled conditions. ■

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Newer Therapies in Development for Multiple Myeloma Show Promise

Although the prognosis for patients with multiple myeloma (MM) continues to improve with the development of new agents with novel mechanisms of action, MM usually becomes refractory to even the newest generation proteasome inhibitors (PI), immunomodulatory drugs (IMiDs), and even the recently approved monoclonal antibodies (mAbs). This results in a population of patients with relapsed and refractory (RR)MM that is difficult to treat and has a poor prognosis. Progress in developing even newer agents, including those with immunotherapeutic activity, was reported at the 2016 annual meeting of the American Society of Hematology.

Nelfinavir Overcomes Proteasome Resistance in Refractory Multiple Myeloma

Christoph Driessen, MD, PhD, Department of Oncology and Haematology, Kantonsspital St. Gallen, St. Gallen, Switzerland, presented the results of a phase 2, multicenter trial (NCT02188537)[1] of the protease inhibitor nelfinavir in combination with bortezomib and dexamethasone in patients with PI-refractory MM.[2]

Nelfinavir inhibits the protease of HIV; this protease has no known human homologues. Nelfinavir was approved as oral therapy for HIV[3] and is available in generic form. The treatment is known to induce the activation of unfolded protein response (UPR) and upregulate IRE1/XBP1 expression; these activities overcome PI resistance in vitro and in preclinical models.

In a phase 1 trial, nelfinavir induced UPR and upregulated IRE1/XBP1 in peripheral blood mononuclear cells, with no dose-limiting toxicities (DLT). The recommended phase 2 dose (RP2D) was identified as 2 × 2500 mg (which is twice the dose recommended for treatment of HIV), in combination with standard bortezomib plus dexamethasone.

The objective of the phase 2 study was to determine whether, in patients with PI-refractory MM, the addition of nelfinavir to the approved regimen of bortezomib and dexamethasone had sufficient activity to merit further investigation.

This was a prospective, single-arm, multicenter, open-label, phase 2 trial with no industry support. Patients received 2500 mg of nelfinavir twice daily on days 1 to 14 for a maximum of 6 cycles of 21 days, in combination with bortezomib 1.3 mg/m^2 intravenously (IV) or subcutaneously (SC) on days 1, 4, 8, 11 and dexamethasone 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12. Patient follow-up was conducted until beginning a new therapy regimen or death. Dr Driessen said that the number of cycles was limited because the trial had no industry support, and a grant was needed to buy the drugs on the commercial market.

The primary end point was response, with best response at least partial response (PR). Secondary end points included adverse events (AEs), time to next therapy, or progressive disease (PD). Patients were heavily pretreated and were required to be IMiD exposed or intolerant, with MM refractory to the most recent PI-containing therapy.

The study enrolled 34 patients, with a mean age of 67 years, with a median of 5 prior lines of therapy; 76% had prior autologous stem cell transplant (ASCT); 39% had poor-risk cytogenetic features, and the median time since last therapy was less than a month. Patients had MM refractory to bortezomib (100%), lenalidomide (79%), and pomalidomide (44%).

The patients received a mean of 4.5 therapy cycles. The best response ≥PR, which was the primary outcome, was 65% (n = 22), with 15% very good (VG)PR and 50% PR. Of the 13 patients with poor-risk cytogenetics, 77% had a best response of ≥PR. Time to new antimyeloma therapy or death for all patients was a median of 16 weeks. PD on therapy was observed for 38% of patients.

Efficacy per prior drug treatment in patients with a best response of PR or better was 65% (22 of the 34 patients enrolled) in those with prior bortezomib exposure (by definition, the whole patient population) and also 65% in bortezomib-refractory MM. In patients exposed to bortezomib and lenalidomide, the PR or better rate was 65%; it was 70% (19 of 27 patients) in patients with MM refractory to both agents. In patients exposed to bortezomib, lenalidomide, and pomalidomide, 56% (9 of 16 patients) had a response of ≥PR, and 60% of those whose MM was refractory to these 3 agents had a 60% response of ≥PR (9 of 15). Only 2 patients had received bortezomib, lenalidomide, and carfilzomib, and 1 had a response of ≥PR.

The AEs were as expected for a heavily pretreated population of patients with MM. Grade 1/2 diarrhea was quite common and treated with prophylactic loperamide. There were 4 grade 5 AEs (deaths) resulting from infectious complications (sepsis and pneumonia). It is not known if this is a true signal due to the small number of patients in the trial. Antibiotic prophylaxis was not required.

Dr Driessen said that nelfinavir plus bortezomib and dexamethasone has substantial activity in advanced, PI-refractory MM. The activity of this combination was preserved in PI and IMiD double-refractory MM and in patients with poor-risk cytogenetics. The toxicity profile resembled that of bortezomib in heavily pretreated patients. The median time to next treat-

(continued on page 23)

DARZALEX® + Rd or Vd after first relapse in multiple myeloma

DISCOVER MORE

with the first and only CD38-directed monoclonal antibody (mAb)[1]

Indication

DARZALEX® (daratumumab) is indicated in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Rd=lenalidomide and dexamethasone; Vd=bortezomib and dexamethasone.

Important Safety Information

Warnings and precautions include: infusion reactions, interference with serological testing, neutropenia, thrombocytopenia, and interference with determination of complete response

In patients who received DARZALEX® in combination with lenalidomide and dexamethasone, the most frequently reported adverse reactions (incidence ≥20%) were: neutropenia (92%), thrombocytopenia (73%), upper respiratory tract infection (65%), infusion reactions (48%), diarrhea (43%), fatigue (35%), cough (30%), muscle spasms (26%), nausea (24%), dyspnea (21%) and pyrexia (20%). The overall incidence of serious adverse reactions was 49%. **Serious adverse reactions were:** pneumonia (12%), upper respiratory tract infection (7%), influenza (3%) and pyrexia (3%).

In patients who received DARZALEX® in combination with bortezomib and dexamethasone, the most frequently reported adverse reactions (incidence ≥20%) were: thrombocytopenia (90%), neutropenia (58%), peripheral sensory neuropathy (47%), infusion reactions (45%), upper respiratory tract infection (44%), diarrhea (32%), cough (27%), peripheral edema (22%), and dyspnea (21%). The overall incidence of serious adverse reactions was 42%. **Serious adverse reactions were:** upper respiratory tract infection (5%), diarrhea (2%) and atrial fibrillation (2%).

Please see Important Safety Information and brief summary of full Prescribing Information on following pages.

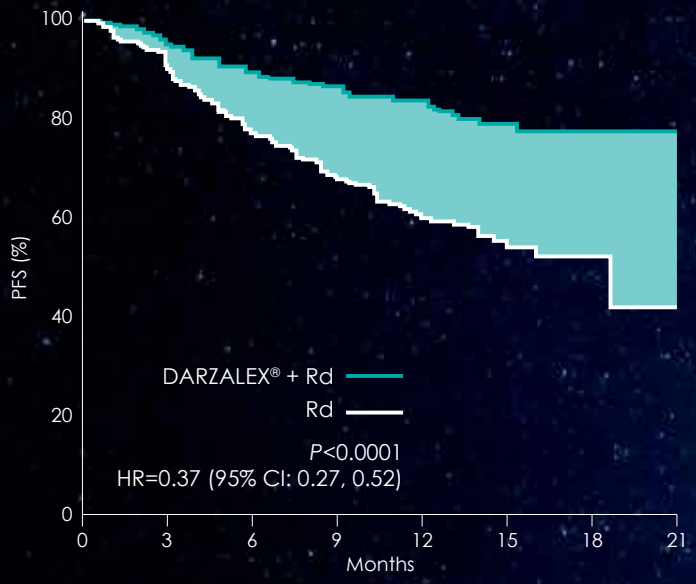
DARZALEX®
(daratumumab)
injection for intravenous infusion
100 mg/5 mL, 400 mg/20 mL

DARE TO DREAM

Superior efficacy in combination

POLLUX

DARZALEX® (daratumumab) + Rd significantly improved PFS vs Rd alone[1]



63%
reduction in the risk of disease progression or death with DARZALEX® + Rd

POLLUX was an open-label, randomized, active-controlled phase 3 trial comparing treatment with DARZALEX® 16 mg/kg + Rd (n=286) to Rd alone (n=283) in multiple myeloma patients who received a minimum of 1 prior therapy. Patients were treated until unacceptable toxicity or disease progression. Efficacy was evaluated by PFS based on International Myeloma Working Group (IMWG) criteria.[1]

91.3% **ORR** with DARZALEX® + Rd vs **74.6%** with Rd alone (*P*<0.0001). CR or better was 42.3% with DARZALEX® + Rd vs 18.8% with Rd alone. VGPR was 32.2% vs 24.4%, and PR was 16.8% vs 31.4% with DARZALEX® + Rd vs Rd alone, respectively.[1]

PFS=progression-free survival; HR=hazard ratio; ORR=overall response rate; CR=complete response; VGPR=very good partial response; PR=partial response.

Important Safety Information

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Infusion Reactions

DARZALEX® can cause severe infusion reactions. Approximately half of all patients experienced a reaction, most during the first infusion. Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing an infusion. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, laryngeal edema and pulmonary edema. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension.

Pre-medicate patients with antihistamines, antipyretics, and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt infusion for reactions of any severity and institute medical management as needed. Permanently discontinue therapy for life-threatening (Grade 4) reactions. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion.

To reduce the risk of delayed infusion reactions, administer oral corticosteroids to all patients following DARZALEX® infusions. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX®. Type and screen patients prior to starting DARZALEX®.

Neutropenia

DARZALEX® may increase neutropenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. DARZALEX® dose delay may be required to allow recovery of neutrophils. No dose reduction of DARZALEX® is recommended. Consider supportive care with growth factors.

Janssen Oncology

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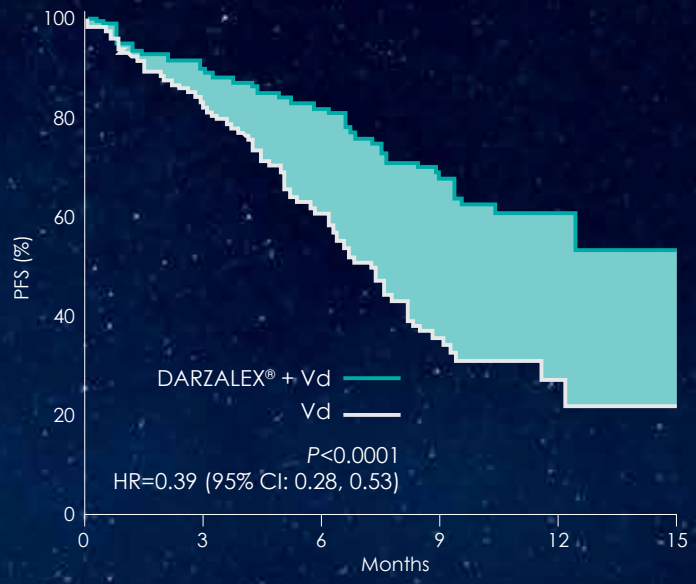
 12/16 062716-161102

CASTOR

DARZALEX® + Vd significantly improved PFS vs Vd alone[1]



61%
reduction in the risk of disease progression or death with DARZALEX® + Vd

CASTOR was an open-label, randomized, active-controlled phase 3 trial comparing treatment with DARZALEX® 16 mg/kg + Vd (n=251) to Vd alone (n=247) in multiple myeloma patients who received a minimum of 1 prior therapy. DARZALEX® was given until disease progression. Efficacy was evaluated by PFS based on International Myeloma Working Group (IMWG) criteria.[1,2]

79.3% **ORR** with DARZALEX® + Vd vs **59.9%** with Vd alone (*P*<0.0001). CR or better was 18.3% with DARZALEX® + Vd vs 8.5% with Vd alone. VGPR was 38.2% vs 19.0%, and PR was 22.7% vs 32.4% with DARZALEX® + Vd vs Vd alone, respectively.[1]

Important Safety Information (cont'd)

Thrombocytopenia

DARZALEX® may increase thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. DARZALEX® dose delay may be required to allow recovery of platelets. No dose reduction of DARZALEX® is recommended. Consider supportive care with transfusions.

Interference with Determination of Complete Response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

Adverse Reactions

In patients who received DARZALEX® in combination with lenalidomide and dexamethasone, the most frequently reported adverse reactions (incidence ≥20%) were: neutropenia (92%), thrombocytopenia (73%), upper respiratory tract infection (65%), infusion reactions (48%), diarrhea (43%), fatigue (35%), cough (30%), muscle spasms (26%), nausea (24%), dyspnea (21%) and pyrexia (20%). The overall incidence of serious adverse reactions was 49%. Serious adverse reactions were pneumonia (12%), upper respiratory tract infection (7%), influenza (3%) and pyrexia (3%).

In patients who received DARZALEX® in combination with bortezomib and dexamethasone, the most frequently reported adverse reactions (incidence ≥20%) were: thrombocytopenia (90%), neutropenia (58%), peripheral sensory neuropathy (47%), infusion reactions (45%), upper respiratory tract infection (44%), diarrhea (32%), cough (27%), peripheral edema (22%), and dyspnea (21%). The overall incidence of serious adverse reactions was 42%. Serious adverse reactions were upper respiratory tract infection (5%), diarrhea (2%) and atrial fibrillation (2%).

DRUG INTERACTIONS

Effect of Other Drugs on Daratumumab: The coadministration of lenalidomide or bortezomib with DARZALEX® did not affect the pharmacokinetics of daratumumab.

Effect of Daratumumab on Other Drugs: The coadministration of DARZALEX® with bortezomib did not affect the pharmacokinetics of bortezomib.

063483-161117

Please see brief summary of full Prescribing Information on adjacent pages.

For more information, visit **www.darzalexhcp.com**

References: 1. DARZALEX® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Palumbo A, Chanan-Khan A, Weisel K, et al; the CASTOR Investigators. *N Engl J Med.* 2016;375(8):754-766.

DARZALEX®
(daratumumab)
injection for intravenous infusion
100 mg/5 mL, 400 mg/20 mL

DARE TO DREAM

DARZALEX® (daratumumab) injection, for intravenous use
Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

DARZALEX is indicated:

- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.
- as monotherapy, for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infusion Reactions

DARZALEX can cause severe infusion reactions. Approximately half of all patients experienced a reaction, most during the first infusion.

Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion.

Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, laryngeal edema and pulmonary edema. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension *[see Adverse Reactions]*.

Pre-medicate patients with antihistamines, antipyretics and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt DARZALEX infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX therapy for life-threatening (Grade 4) reactions. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion *[see Dosage and Administration (2.1) in Full Prescribing Information]*.

To reduce the risk of delayed infusion reactions, administer oral corticosteroids to all patients following DARZALEX infusions *[see Dosage and Administration (2.2) in Full Prescribing Information]*. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum[1] *[see References]*. The determination of a patient's ABO and Rh blood type are not impacted *[see Drug Interactions]*.

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX. Type and screen patients prior to starting DARZALEX.

Neutropenia

DARZALEX may increase neutropenia induced by background therapy *[see Adverse Reactions]*.

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. DARZALEX dose delay may be required to allow recovery of neutrophils. No dose reduction of DARZALEX is recommended. Consider supportive care with growth factors.

Thrombocytopenia

DARZALEX may increase thrombocytopenia induced by background therapy *[see Adverse Reactions]*.

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. DARZALEX dose delay may be required to allow recovery of platelets. No dose reduction of DARZALEX is recommended. Consider supportive care with transfusions.

Interference with Determination of Complete Response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein *[see Drug Interactions]*. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

ADVERSE REACTIONS

The following serious adverse reactions are also described elsewhere in the labeling:

- Infusion reactions *[see Warning and Precautions]*.
- Neutropenia *[see Warning and Precautions]*.
- Thrombocytopenia *[see Warning and Precautions]*.

Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflects exposure to DARZALEX (16 mg/kg) in 717 patients with multiple myeloma including 526 patients from two Phase 3 active-controlled trials who received DARZALEX in combination with either lenalidomide (DRd, n=283; Study 3) or bortezomib (DVd, n=243; Study 4) and four open-label, clinical trials in which patients received DARZALEX either in combination with lenalidomide (n=35), or as monotherapy (n=156).

Combination Treatment with Lenalidomide

Adverse reactions described in Table 1 reflect exposure to DARZALEX (DRd arm) for a median treatment duration of 13.1 months (range: 0 to 20.7 months) and median treatment duration of 12.3 months (range: 0.2 to 20.1 months) for the lenalidomide group (Rd) in Study 3. The most frequent adverse reactions (≥20%) were infusion reactions, diarrhea, nausea, fatigue, pyrexia, upper respiratory tract infection, muscle spasms, cough and dyspnea. The overall incidence of serious adverse reactions was 49% for the DRd group compared with 42% for the Rd group. Serious adverse reactions with at least a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (12% vs Rd 10%), upper respiratory tract infection (7% vs Rd 4%), influenza and pyrexia (DRd 3% vs Rd 1% for each).

Adverse reactions resulted in discontinuations for 7% (n=19) of patients in the DRd arm versus 8% (n=22) in the Rd arm.

Table 1: Adverse reactions reported in ≥ 10% of patients and with at least a 5% frequency greater in the DRd arm in Study 3

Adverse Reaction	DRd (N=283) %			Rd (N=281) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Infusion reactions[a]	48	5	0	0	0	0
Gastrointestinal disorders						
Diarrhea	43	5	0	25	3	0
Nausea	24	1	0	14	0	0
Vomiting	17	1	0	5	1	0
General disorders and administration site conditions						
Fatigue	35	6	< 1	28	2	0
Pyrexia	20	2	0	11	1	0
Infections and infestations						
Upper respiratory tract infection[b]	65	6	< 1	51	4	0
Musculoskeletal and connective tissue disorders						
Muscle spasms	26	1	0	19	2	0
Nervous system disorders						
Headache	13	0	0	7	0	0
Respiratory, thoracic and mediastinal disorders						
Cough[c]	30	0	0	15	0	0
Dyspnea[d]	21	3	< 1	12	1	0

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see description of Infusion Reactions below.

[b] upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection

[c] cough, productive cough, allergic cough

[d] dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment from baseline listed in Table 2.

Table 2: Treatment-emergent hematology laboratory abnormalities in Study 3

	DRd (N=283) %			Rd (N=281) %		
	Any Grade	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Anemia	52	13	0	57	19	0
Thrombocytopenia	73	7	6	67	10	5
Neutropenia	92	36	17	87	32	8
Lymphopenia	95	42	10	87	32	6

Key: D=Daratumumab, Rd=lenalidomide-dexamethasone.

Combination Treatment with Bortezomib

Adverse reactions described in Table 3 reflect exposure to DARZALEX (DVd arm) for a median treatment duration of 6.5 months (range: 0 to 14.8 months) and median treatment duration of 5.2 months (range: 0.2 to 8.0 months) for the bortezomib group (Vd) in Study 4. The most frequent adverse reactions (>20%) were infusion reactions, diarrhea, peripheral edema, upper respiratory tract infection, peripheral sensory neuropathy, cough and dyspnea. The overall incidence of serious adverse reactions was 42% for the DVd group compared with 34% for the Vd group. Serious adverse reactions with at least a 2% greater incidence in the DVd arm compared to the Vd arm were upper respiratory tract infection (DVd 5% vs Vd 2%), diarrhea and atrial fibrillation (DVd 2% vs Vd 0% for each).

Adverse reactions resulted in discontinuations for 7% (n=18) of patients in the DVd arm versus 9% (n=22) in the Vd arm.

Table 3: Adverse reactions reported in ≥ 10% of patients and with at least a 5% frequency greater in the DVd arm Study 4

Adverse Reaction	DVd (N=243) %			Vd (N=237) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Infusion reactions[a]	45	9	0	0	0	0
Gastrointestinal disorders						
Diarrhea	32	3	< 1	22	1	0
Vomiting	11	0	0	4	0	0
General disorders and administration site conditions						
Edema peripheral[b]	22	1	0	13	0	0
Pyrexia	16	1	0	11	1	0
Infections and infestations						
Upper respiratory tract infection[c]	44	6	0	30	3	< 1
Nervous system disorders						
Peripheral sensory neuropathy	47	5	0	38	6	< 1
Respiratory, thoracic and mediastinal disorders						
Cough[d]	27	0	0	14	0	0
Dyspnea[e]	21	4	0	11	1	0

Key: D=daratumumab, Vd=bortezomib-dexamethasone.

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see description of Infusion Reactions below.

[b] edema peripheral, edema, generalized edema, peripheral swelling

[c] upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection

[d] cough, productive cough, allergic cough

[e] dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment are listed in Table 4.

Table 4: Treatment-emergent hematology laboratory abnormalities in Study 4

	DVd (N=243) %			Vd (N=237) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Anemia	48	13	0	56	14	0
Thrombocytopenia	90	28	19	85	22	13
Neutropenia	58	12	3	40	5	<1
Lymphopenia	89	41	7	81	24	3

Key: D=Daratumumab, Vd=bortezomib-dexamethasone.

Monotherapy

The safety data reflect exposure to DARZALEX in 156 adult patients with relapsed and refractory multiple myeloma treated with DARZALEX at 16 mg/kg in three open-label, clinical trials. The median duration of exposure was 3.3 months (range: 0.03 to 20.04 months). Serious adverse reactions were reported in 51 (33%) patients. The most frequent serious adverse reactions were pneumonia (6%), general physical health deterioration (3%), and pyrexia (3%).

Adverse reactions resulted in treatment delay for 24 (15%) patients, most frequently for infections. Adverse reactions resulted in discontinuations for 6 (4%) patients.

Adverse reactions occurring in at least 10% of patients are presented in Table 5. Table 6 describes Grade 3–4 laboratory abnormalities reported at a rate of ≥10%.

Table 5: Adverse reactions with incidence ≥10% in patients with multiple myeloma treated with DARZALEX 16 mg/kg

	DARZALEX 16 mg/kg N=156		
	Incidence (%)		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**
Infusion reaction[a]	48	3	0
General disorders and administration site conditions			
Fatigue	39	2	0
Pyrexia	21	1	0
Chills	10	0	0
Respiratory, thoracic and mediastinal disorders			
Cough	21	0	0
Nasal congestion	17	0	0
Dyspnea	15	1	0
Musculoskeletal and connective tissue disorders			
Back pain	23	2	0
Arthralgia	17	0	0
Pain in extremity	15	1	0
Musculoskeletal chest pain	12	1	0
Infections and infestations			
Upper respiratory tract infection	20	1	0
Nasopharyngitis	15	0	0
Pneumonia[b]	11	6	0
Gastrointestinal disorders			
Nausea	27	0	0
Diarrhea	16	1	0
Constipation	15	0	0
Vomiting	14	0	0
Metabolism and nutrition disorders			
Decreased appetite	15	1	0
Nervous system disorders			
Headache	12	1	0
Vascular disorders			
Hypertension	10	5	0

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see below.

[b] Pneumonia also includes the terms streptococcal pneumonia and lobar pneumonia.

Table 6: Treatment emergent Grade 3-4 laboratory abnormalities (≥10%)

	Daratumumab 16 mg/kg (N=156)		
	All Grade (%)	Grade 3 (%)	Grade 4 (%)
Anemia	45	19	0
Thrombocytopenia	48	10	8
Neutropenia	60	17	3
Lymphopenia	72	30	10

Infusion Reactions

In clinical trials (monotherapy and combination treatments; N=717) the incidence of any grade infusion reactions was 46% with the first infusion of DARZALEX, 2% with the second infusion, and 4% with subsequent infusions. Less than 1% of patients had a Grade 3 infusion reaction with second or subsequent infusions.

The median time to onset of a reaction was 1.5 hours (range: 0.02 to 72.8 hours). The incidence of infusion modification due to reactions was 41%. Median durations of infusion for the 1st, 2nd and subsequent infusions were 7.0, 4.3, and 3.5 hours respectively.

Severe (Grade 3) infusion reactions included bronchospasm, dyspnea, laryngeal edema, pulmonary edema, hypoxia, and hypertension. Other adverse infusion reactions (any Grade, ≥5%) were nasal congestion, cough, chills, throat irritation and vomiting.

Herpes Zoster Virus Reactivation

Prophylaxis for Herpes Zoster Virus reactivation was recommended for patients in some clinical trials of DARZALEX. In monotherapy studies, herpes zoster was reported in 3% of patients. In the randomized controlled combination therapy studies, herpes zoster was reported in 2% each in the

DRd and Rd groups respectively (Study 3) and in 5% versus 3% in the DVd and Vd groups respectively (Study 4).

Infections

In patients receiving DARZALEX combination therapy, Grade 3 or 4 infections were reported with DARZALEX combinations and background therapies (DVd: 21%, Vd: 19%; DRd: 28%, Rd: 23%). Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. Discontinuations from treatment were reported in 3% versus 2% of patients in the DRd and Rd groups respectively and 4% versus 3% of patients in the DVd and Vd groups respectively. Fatal infections were reported in 0.8% to 2% of patients across studies, primarily due to pneumonia and sepsis.

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. In clinical trials of patients with multiple myeloma treated with DARZALEX as monotherapy or as combination therapies, none of the 111 evaluable monotherapy patients, and 1 (0.4%) of the 234 combination therapy patients, tested positive for anti-daratumumab antibodies. This patient administered DARZALEX as combination therapy, developed transient neutralizing antibodies against daratumumab. However, this assay has limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab; therefore, the incidence of antibody development might not have been reliably determined.

Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication and the underlying disease. Therefore, comparison of the incidence of antibodies to daratumumab with the incidence of antibodies to other products may be misleading.

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding[1] *[see References]* or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, K-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, consider other methods to evaluate the depth of response.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no human data to inform a risk with use of DARZALEX during pregnancy. Animal studies have not been conducted. However, there are clinical considerations *[see Clinical Considerations]*. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX may cause fetal myeloid or lymphoid-cell depletion and decreased bone density. Defer administering live vaccines to neonates and infants exposed to DARZALEX in utero until a hematology evaluation is completed.

Data

Animal Data

Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. In cynomolgus monkeys exposed during pregnancy to other monoclonal antibodies that affect leukocyte populations, infant monkeys had a reversible reduction in leukocytes.

DARZALEX® (daratumumab) injection

Lactation

Risk Summary

There is no information regarding the presence of daratumumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for DARZALEX and any potential adverse effects on the breast-fed child from DARZALEX or from the underlying maternal condition.

Females and Males of Reproductive Potential

Contraception

To avoid exposure to the fetus, women of reproductive potential should use effective contraception during treatment and for 3 months after cessation of DARZALEX treatment.

Pediatric Use

Safety and effectiveness of DARZALEX in pediatric patients have not been established.

Geriatric Use

Of the 156 patients that received DARZALEX monotherapy at the recommended dose, 45% were 65 years of age or older, and 10% were 75 years of age or older. Of 561 patients that received DARZALEX with various combination therapies, 40% were 65 to 75 years of age, and 9% were 75 years of age or older. No overall differences in safety or effectiveness were observed between these patients and younger patients *[see Clinical Studies (14) in Full Prescribing Information]*.

OVERDOSAGE

The dose of DARZALEX at which severe toxicity occurs is not known.

In the event of an overdose, monitor patients for any signs or symptoms of adverse effects and provide appropriate supportive treatment.

REFERENCES

1. Chapuy, CI, RT Nicholson, MD Aguad, et al., 2015, Resolving the daratumumab interference with blood compatibility testing, Transfusion, 55:1545-1554 (accessible at http://onlinelibrary.wiley.com/doi/10.1111/trf.13069/epdf).

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Infusion Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of infusion reactions:

- itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing *[see Warnings and Precautions and Adverse Reactions]*.

Neutropenia

- Advise patients that if they have a fever, they should contact their healthcare professional *[see Warnings and Precautions and Adverse Reactions]*.

Thrombocytopenia

- Advise patients to inform their healthcare professional if they notice signs of bruising or bleeding *[see Warnings and Precautions and Adverse Reactions]*.

Interference with Laboratory Tests

Advise patients to inform healthcare providers including blood transfusion centers/personnel that they are taking DARZALEX, in the event of a planned transfusion *[see Warnings and Precautions and Drug Interactions]*.

Advise patients that DARZALEX can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response *[see Warnings and Precautions and Drug Interactions]*.

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ment was 16 weeks; individual patients had substantially longer treatment benefit, keeping in mind that the maximum duration of treatment in this trial was 18 weeks. Nelfinavir may universally boost the cytotoxic activity of bortezomib, and possibly other PIs in other settings. With future generic bortezomib becoming available, the combination of nelfinavir plus bortezomib and dexamethasone has the potential to become a fully generic, affordable, active therapy option for patients with PI-refractory MM.

Dr Driessen concluded that nelfinavir in combination with bortezomib and dexamethasone is a reasonable, active, safe, and widely available treatment option for patients with PI-refractory MM. The objective response rate (ORR) of 65% observed in this population of patients with very advanced, heavily pretreated, mostly dual-refractory MM is exceptional. He thought the results warrant further development of nelfinavir as a sensitizing drug for PI-based treatments and as a promising new agent for MM therapy. When asked about a phase 3 study, he said the results of this trial need to be confirmed, and it was not clear what the comparator in a phase 3 trial would be.

Venetoclax Could Be the First Targeted Therapy for Multiple Myeloma

Monotherapy Study

Antiapoptotic proteins, including BCL-2, BCL-xL, and MCL-1, promote the survival of MM cells. Venetoclax is a potent, selective, orally bioavailable, small-molecular inhibitor of BCL-2. It was initially approved in the United States in 2016 and indicated for the treatment of chronic lymphocytic leukemia (CLL) with deletion (del) 17p as detected by an FDA-approved test after 1 prior therapy. The Vysis CLL FISH Probe Kit is FDA approved for selection of patients with CLL for treatment with venetoclax.[4]

Overexpression of BCL-2 mediates MM tumor cell survival and has been associated with resistance to chemotherapeutics. Venetoclax helps restore the process of apoptosis in CLL and has demonstrated cytotoxic activity in tumor cells that overexpress BCL-2.[4]

Venetoclax has also been shown to induce cell death in MM cells, particularly those positive for the translocation t(11;14), which correlates with higher ratios of BCL-2 to MCL-1, and BLC-2 to BCL-2L1 (BCL-xL) mRNA; it is being investigated as monotherapy and in combination therapy in patients with MM.

Shaji Kumar, MD, Division of Hematology, Mayo Clinic, Rochester, Minnesota, presented the safety and efficacy results of a phase1, open-label, multicenter study (NCT01794520)[5] of venetoclax monotherapy in RRMM.[6]

The primary objectives of this study included safety, tolerability, maximum tolerated dose (MTD), RP2D, and pharmacokinetics (PK). Secondary and exploratory objectives included ORR, time to progression (TTP), duration of response (DoR), and predictive biomarkers in patients with RRMM.

After a 2-week lead in period with weekly dose escalation, patients in the dose-escalation cohorts (n = 30) received daily venetoclax doses of 300 mg, 600 mg, 900 mg, or 1200 mg, and patients in the safety expansion cohort (n = 36) were treated with 1200 mg of venetoclax. Patients with PD during venetoclax monotherapy were allowed to continue in the study if they elected to receive venetoclax plus dexamethasone.

The 66 patients enrolled in the study had a median age of 63 years; 39 (62%) patients had International Staging System (ISS) stage II or III MM. The median number of prior therapies was 5 (range: 1 to 15), and 62 (94%) patients had received bortezomib (70% had bortezomib-refractory MM), 62 (94%) had received lenalidomide (77% had lenalidomide-refractory MM), and 50 (76%) had prior ASCT. Thirty (46%) patients had MM with t(11;14), reflecting the interest in a drug that can address this translocation; 18% had del 17p.

Nelfinavir plus bortezomib and dexamethazone has substantial activity in advanced, proteasome inhibitor-refractory multiple myeloma.

— Christoph Driessen, MD, PhD

Median treatment time on venetoclax monotherapy was 2.4 months; 17 (26%) received venetoclax plus dexamethasone after PD for a median of 1.4 months. Of the 66 patients enrolled, 51 patients (77%) discontinued study treatment. PD lead to discontinuation in 39 patients; 5 patients cited AEs/toxicity for cancelation from therapy, 2 withdrew consent, 1 patient was lost to follow-up, and 4 patients did not have a specified reason.

Of the 66 patients enrolled, 2 patients had DLTs of abdominal pain and nausea at the 600-mg dose. Dose escalation was continued due to suspicion that these DLTs might not be drug related. Common AEs in ≥20% of patients included nausea (48%), diarrhea (36%), neutropenia (32%), thrombocytopenia (32%), fatigue (27%), anemia (23%), back pain (21%), and vomiting (21%). Grade 3 and 4 AEs were seen in 68% of patients; those in ≥10% of patients included thrombocytopenia (26%), neutropenia (20%), lymphopenia (15%), anemia (14%), and de-

creased white blood cell counts (12%). Hematologic AEs were managed with dose modifications. Gastrointestinal AEs were primarily grade 1 and 2 and were manageable.

Serious AEs included pneumonia (8%), sepsis (5%), pain, pyrexia, cough, and hypotension (3% each). Although venetoclax is associated with a risk of tumor lysis syndrome (TLS),[4] no TLS was reported in this study. Eight deaths were reported: 6 due to PD, with 1 due to lung disorder and 1 due to brain hemorrhage after injury; neither was considered by the investigator as related to venetoclax.

ORR for all patients was 21% (14/66), including 15% VGPR or better, with 3% stringent complete response (sCR), 4% CR, and 8% VGPR. Most of the objective responses were in the 30 patients with t(11;14); ORR for this subgroup was 40%, including 4% sCR, 10% CR, and 13% VGPR. Dr Kumar called these results striking. For the 36 patients who did not have t(11;14), ORR was 6%, including 3% each sCR and VGPR. For the 2 patients with response in the non-t(11;14)/undetermined group, 1 had a translocation of chromosome 14 with an unidentified partner and the other had no cytogenetics data available. ORR was similar across subgroups by refractoriness to prior therapy.

The median TTP in all patients was about 2.5 months; TTP was 6.6 months in the t(11;14) group. Response was fairly durable for these heavily pretreated patients who had a response. Median DoR is about 10 months.

In the t(11;14)-positive subgroup, responses were analyzed by the BCL-2:BCL-2L1 ratio. BCL-2 and BCL-2L1 (BCL-xL) quantitation was determined using a droplet digital polymerase chain reaction (PCR) test on CD138-selected bone marrow cells collected at baseline. Bootstrapping and Aggregating Thresholds from Trees (BATTing) was used to estimate threshold BCL-2:BCL-2L1 for selection of patients likely to have a clinical response versus nonresponse. Those patients (n = 9) with a high ratio had the best responses, with an ORR of 88%, including 11% sCR, 33% CR, and 11% VGPR. Median TTP in these patients is about 12 months. The 15 patients with a low ratio had an ORR of 20%, including 13% VGPR.

Dr Kumar concluded that venetoclax monotherapy in RRMM had an acceptable safety profile among this heavily pretreated population of patients with MM, with particular efficacy in patients with t(11;14). A higher ORR (40% vs 6%) and deeper responses of ≥VGPR (27% vs 6%) were seen for patients who had t(11;14) versus those who did not have that translocation. Venetoclax activity in patients with t(11;14) was independent of refractoriness to prior therapies. A higher ORR (88% vs 20%) was seen in patients with t(11;14) who had a high BCL-2:BCL-2L1 ratio.

The results of this study confirm the antimyeloma activity of venetoclax as a single agent in patients with t(11;14) RRMM and support further study of venetoclax in combination therapies. Dr Kumar thought that venetoclax should be used in combination with dexamethasone, which probably sensitizes MM cells to venetoclax. He said that venetoclax could change the outcome for many patients with MM, and it could be the first biomarker-driven drug in MM.

As monotherapy, there is a role for venetoclax in the subgroup of patients with the favorable biomarker t(11;14); for the patients without t(11;14), venetoclax will need to be combined with another agent. He pointed out that once a biomarker is established for patients with t(11;14), those without should be examined to determine what else might be associated with a favorable outcome.

Combination Study

Bortezomib is known to suppress MCL-1 antiapoptotic activity in MM cells; this activity is enhanced in vitro when bortezomib is combined with venetoclax, making the cells more sensitive to therapy. Philippe Moreau, MD, Department of Hematology, Nantes University Hospital, Nantes, France, presented the results of a phase 1b, open-label, dose-escalation trial of venetoclax combined with bortezomib and dexamethasone in patients with RRMM.[7]

The primary objectives of this study were similar to the venetoclax monotherapy trial, to determine safety, tolerability, MTD, RP2D, and PK. Secondary and exploratory objectives included ORR, TTP, DoR, and exploratory biomarkers.

Venetoclax could change the outcome for many patients with multiple myeloma, and it could be the first biomarker-driven drug for multiple myeloma.

— Shaji Kumar, MD

Patients who had received prior bortezomib within 30 days of the first dose of venetoclax or who had grade 3 or 4 neuropathy were excluded. Venetoclax was escalated from 50 mg to 1200 mg daily. Bortezomib doses were standard, administered SC twice a week for the first 8 cycles, then weekly for cycles 9 to 11. After cycle 12, venetoclax was administered as a single agent.

The study enrolled 66 patients, with 54 in the dose-escalation cohort and 12 in the safety expansion at R2PD of 800 mg. Median age was 64 years, and 39 (59%) had ISS stage II or III MM. The median number of prior therapies was 3; 39% had

TABLE. Objective Responses Overall and by Prior Therapy Subgroup[7]

	ORR, %	sCR, %	CR, %	VGPR, %	PR, %
All patients (N = 66)	67	5	15	23	24
Bortezomib nonrefractory (n = 39)	90	8	20	36	26
Bortezomib refractory (n = 26)	31	0	4	4	23
Bortezomib sensitive (n = 27)	89	7	19	30	33
Bortezomib naïve (n = 12)	92	9	25	50	8
1-3 prior lines of therapy (n = 37)	89	9	24	32	24
>3 prior lines of therapy (n = 29)	38	0	4	10	24
Bortezomib nonrefractory and 1-3 prior lines of therapy (n = 30)	97	10	23	41	23

CR indicates complete response; ORR, objective response rate; PR, partial response; sCR, stringent CR; VGPR, very good PR.

MM refractory to prior bortezomib, 53% had MM refractory to prior lenalidomide, and 61% had MM refractory to the last line of treatment.

Only 30% of patients remain on study; the primary reason for discontinuation was PD. There were 5 deaths, 4 due to PD and 1 due to respiratory syncytial virus infection (not considered by the investigator as related to venetoclax). Most AEs, particularly those grade 3 and 4, were related to dexamethasone.

At the maximum venetoclax dose, the MTD was not reached; 800-mg venetoclax was chosen for the expansion phase because the PK of this dose were favorable for daily administration.

The ORR for all patients was 67%, including 5% sCR, 15% CR, 23% VGPR, and 24% PR. Objective responses for patients by subgroup are summarized in the **Table**.[7] The best responses were seen in patients with MM not refractory to bortezomib and particularly those who had received 1 to 3 prior lines of therapy who were bortezomib naïve.

Median TTP for patients with bortezomib-nonrefractory disease was 11.3 months, and for patients whose MM was bortezomib refractory, TTP was 1.8 months. Median DoR for patients with bortezomib-nonrefractory MM was 8 months, and for patients with bortezomib-refractory MM it was 4 months. TTP was 11.6 months in patients with 1 to 3 prior lines of treatment versus 4.3 months for patients with more than 3 prior lines of treatment, and DoR was 11 versus 5 months, respectively.

BCL-2 gene expression, determined, as in the venetoclax monotherapy study, on selected plasma cells, was correlated with clinical response. In patients (n = 18) with high levels of BCL-2 expression, ORR was 94%, with 33% sCR/CR, 37% VGPR, and 28% PR. For those with low expression of BCL-2 (n = 27), ORR was 59%, with 7% sCR/CR, 15% VGPR, and 37% PR.

Dr Moreau concluded that the addition of venetoclax to bortezomib and dexamethasone did not appear to add toxicity and was well tolerated. The toxicity of the combination was primarily related to the bortezomib component. No TLS was observed. The MTD for the combination was not reached. Responses were highest among patients with MM not refractory to bortezomib who received only 1 to 3 prior lines of therapy. Responses were more durable among patients whose MM was not refractory to prior bortezomib and those who had received 1 to 3 prior lines of therapy. High levels of BCL-2 gene expression were correlated with a higher clinical response.

The antimyeloma activity observed with this novel combination, which targets both BCL-2 and MCL-1, supports an ongoing phase 3 trial (NCT02755597)[8] with this regimen in patients with RRMM. The trial will look at biomarkers that could be used to identify patient subgroups most likely to benefit. Dr Moreau said enrollment in this trial has been rapid. He believes there would be a place for other venetoclax combination therapy, eg, with the PI ixazomib, which would be an all-oral regimen and would allow for a longer length of treatment than bortezomib because of its lower incidence of peripheral neuropathy.

Pembrolizumab Plus Pomalidomide and Dexamethasone: Promising Immunotherapy for Myeloma

Pembrolizumab, a checkpoint inhibitor, is a programmed death receptor-1 (PD-1)–blocking humanized mAb. Pembrolizumab blocks the interaction between the PD-1 receptor, which is found on T cells, and its ligands, PD-L1 and PD-L2. Upregulation of PD-1 ligands are found on some tumor cells and inhibit active T cell–immune surveillance. Blocking the interaction of PD-1 with its ligands releases inhibition of the antitumor response of T cells and decreases tumor growth.[9]

Pembrolizumab is indicated for the treatment of unresectable or metastatic melanoma; recurrent or metastatic head and neck squamous cell carcinoma after PD on or after platinum-containing chemotherapy; metastatic non–small cell lung cancers (NSCLC) that express high levels of PD-L1 using an FDA-ap-

proved test and have no EGFR or ALK genomic tumor aberrations and have not been treated with prior systemic chemotherapy metastatic NSCLC; and metastatic NSCLC with low levels of PD-L1 expression, PD on or after platinum-containing chemotherapy, and PD on prior therapy with an FDA-approved therapy for EGFR or ALK genomic tumor aberrations if these were present.[9]

Ashraf Z. Badros, MD, Greenebaum Cancer Center, University of Maryland School of Medicine, Baltimore, presented updated results of a phase 2, single-center study (NCT02289222)[10] of pembrolizumab combined with pomalidomide and dexamethasone in patients with RRMM.[11]

Myeloma cells use the activation of signaling from PD-1 receptor and interaction with PD-L1 as one mechanism of evading immune surveillance by suppressing myeloma-specific T cells. Responses to checkpoint inhibitors in solid tumors are correlated to high expression of PD-1 on tumor cells, a T-cell–rich environment irrespective of PD-1 expression, and a high mutation tumor burden. However, in MM, pembrolizumab had no single-agent activity. In the trial reported here, investigators hypothesized that in the setting of the immune stimulatory properties of pomalidomide, the blockage of the PD-1/PD-L1 interaction might restore myeloma cell–specific cytotoxic T cells, resulting in clinically relevant responses in patients with MM.

This trial enrolled 48 patients with RRMM who received 28-day cycles of pembrolizumab 200 mg IV every 2 weeks on day 1 and 14 (after a run-in phase in the first 6 patients who received 200 mg IV every 4 weeks to establish safety), plus pomalidomide 4-mg daily every 21 days and dexamethasone 40 mg weekly (20 mg in patients older than 70 years). The protocol was amended after 24 months of follow-up to allow patients to continue on this therapy.

Study objectives included measurements of safety and efficacy, including ORR, progression-free survival (PFS), OS, and correlative studies of CD3/PD-1 on bone marrow T cells and PD-L1 on plasma cells at baseline to correlate expression with response.

Patients had a median age of 64 years; they were required to have at least 2 prior lines of therapy, including both an IMiD and a PI. Patients with active autoimmune disorders requiring systemic treatment or a history of severe autoimmune disease were excluded. Patients had received a median of 3 lines of prior therapy. All patients had received both IMiDs and PIs (100% bortezomib, 98% lenalidomide, and 50% carfilzomib as salvage therapy); about 70% had prior ASCT; 73% had MM double refractory to both an IMiD and PI; 79% had MM refractory to PIs, and 90% had MM refractory to lenalidomide.

There were 18 (38%) patients with standard-risk cytogenetics, defined as normal, hyperdiploid, or t(11;14), and 30 (62%) patients with high-risk cytogenetics, defined as del 17p, t(14;16), t(14;20), t(4;14), or 1q+.

At a median follow-up of 10 months and a median of 8 treatment cycles, 45 patients were evaluable for efficacy of pembrolizumab treatment. Half of patients had PD, 20% died, and 22 patients continued study treatment.

All 48 patients were evaluable for safety where AEs proved as expected, and there were no infusion-related reactions (IRRs). Grade 3 and higher-severity hematologic toxicities in the patient population were anemia (21%), neutropenia (40%), lymphopenia (15%) and thrombocytopenia (8%); they were found to be manageable. Nonhematologic events of grade ≥3 included fatigue (15%), hyperglycemia (25%), upper respiratory tract infections (21%), and rash (10%). The most frequent grade ≥2 AEs included dyspnea (54%), dizziness (44%), increased creatinine (38%), edema (35%), rash (30%), constipation (30%), and arrhythmias (19%). Infections occurred despite antibiotic prophylaxis. Events of clinical significance included immune-mediated events related to pembrolizumab, consisting of interstitial pneumonitis (12%), hypothyroidism (10%), hepatitis (6%), adrenal insufficiency (4%) and vitiligo (2%). Transbronchial biopsies were performed on 6 patients with pneumonitis before treatment with steroids. Lymphocytic infiltrates with reversal of CD4:CD8 ratio were seen, with very strong PD-L1 expression that is not normally observed in normal pneumocytes. Those patients responded well to treatment and were restarted on pembrolizumab. Two patients who had recurrent episodes were taken off study, per protocol.

Dose reductions were required in about half of patients. Pomalidomide dose reductions were due to rash, neutropenia, palpitations and fatigue; dexamethasone was most commonly reduced because of hypoglycemia, and pembrolizumab was reduced for pneumonitis. Ten patients discontinued due to toxicity.

The ORR in evaluable patients (n = 45) was 65%, including 7% sCR, 2% CR, 20% VGPR; in patients with double-refractory MM (n = 32), ORR was 68%, including 3% sCR, 3% CR, and 18% VGPR; in the patients with high-risk cytogenetics (n = 27), ORR was 56%, including 7% sCR, 4% CR, and 4% VGPR. The median DoR was 16.3 months.

The median PFS was 17.4 months. PFS was significantly higher in patients with low-risk cytogenetics than for those with high-risk cytogenetics. Age, stage, and prior treatment had no effect on PFS. Median OS has not been reached.

PD-L1 expression, determined by immunohistochemical staining of formalin-fixed bone marrow biopsies obtained at baseline, was correlated with response. Only 20% of patients (n = 10) with negative PD-L1 had a response of ≥VGPR, whereas 54% of patients (n = 13) with high expression of PD-L1 had a response of ≥VGPR (P = .05). There was no significant difference in PFS between patients with positive and negative PD-L1 expression.

Tumor tissue was also tested for PD-1 expression and CD3 expression to determine the presence of T-cell infiltration.

Of 41 patients with data, 17% were both CD3 positive and PD-1 positive, 25% were CD3+/PD-1 negative, and 58% had no T-cell infiltration, defined as CD3 negative/PD-1 negative, which may be a reflection of the limitations of the technique. There was no significant difference in response among these 3 groups. Median PFS was significantly longer (17.5 months) for the patients with T-cell infiltrate that was not activated or exhausted by PD-1 expression (6.3 months, $P = .05$).

Dr Badros concluded that the combination of pembrolizumab, pomalidomide, and dexamethasone has impressive antimyeloma activity, including deep responses of sCR in patients with double-refractory MM, with durable remission and a DoR of 16 months. Side effects were manageable but high, at 50% with a 10% discontinuation rate. Dr Badros speculated that as more is learned about immune-mediated events, AEs will be more manageable. Further studies are needed to better understand the PD-1 pathway in MM and help design rational combinations to modulate PD-1 and its downstream targets to improve immunity against myeloma. He noted that the doses of pembrolizumab in this study were higher than those currently approved for solid tumors,[9] so dose adjustment might improve the immune-mediated side-effect profile of combination therapy.

The combination of pembrolizumab, pomalidomide and dexamethasone has impressive antimyeloma activity, including deep responses of stringent complete response in patients with double-refractory multiple myeloma.

— Ashraf Z. Badros, MD

BCMA Is Target of 2 New Immunotherapy Approaches for Myeloma

B-cell maturation antigen (BCMA), a cell surface receptor in the tumor necrosis factor superfamily, is restricted to B cells at later stages of differentiation and is requisite for the survival of long-lived plasma cells. BCMA is expressed primarily on the surface of plasma cells and on MM cells at variable levels. Signaling via BCMA promotes proliferation, making it a rational target for antimyeloma therapy. Chimeric antigen receptors (CAR) are engineered transmembrane proteins on the surface of T cells that recognize and target BCMA on the surface cancer cells for antimyeloma activity, as shown in preclinical studies.

Adam D. Cohen, MD, Abramson Cancer Center, University of Pennsylvania, presented 2 studies using BCMA as a target for MM therapy.

The first study described the initial safety and efficacy in a phase 1 study (NCR02546167)[12] of BCMA-specific CAR-T cells (CART-BCMA) in patients with MM.[13]

The CAR-T cells produced for this trial include a BCMA-specific extracellular region for recognition of BCMA expression MM cells and 2 intracellular signaling domains with the zeta chain of CD3 and 4-1BB to recognize signal transduction for T-cell activation on BCMA antigen binding. For the production of modified CART-BCMA cells, T-cell cultures had stable expression of modified CAR transgene using lentiviral vector and were expanded in culture using bead conjugated to anti-CD3 and anti-CD28 antibodies, which provide activating and costimulatory signals to T cells in culture.

The study is an ongoing dose-escalation study in patients with RRMM. Patients in the first cohort received 1 x 10^8 to 5 x 10^8 CART-BCMA cells alone without lympho-depleting chemotherapy to assess safety, in split-dose infusions, with 10% on day 0, 30% on day 1, and 60% on day 2. Further cohorts were planned to include the use of cyclophosphamide at 1.5 g/m^2 with 1 x 10^7 to 5 x 10^7 CART-BCMA, and a third cohort administering cyclophosphamide at 1.5 g/m^2 with 1 x 10^8 to 5 x 10^8 CART-BCMA. After activity and toxicity were observed in the first cohort, the cohorts were expanded to up to 9 patients from 3 to obtain a better sense of safety and efficacy at each dose level.

The primary objective is safety; secondary objectives include feasibility of manufacturing, efficacy, and exploratory studies, the most important of which is expansion and persistent activation of CART-BCMA cells, measured by flow cytometry and quantitative PCR. However, no prespecified levels were required for enrollment.

Patients with RRMM after at least 3 prior lines of therapy (2 if dual refractory) were eligible. There was a 2-week washout for therapy (4 for mAbs) before T-cell collection. After patients are enrolled and T cells are collected, the manufacturing process takes 2 to 3 weeks, during which time patients can receive additional therapy to keep disease from worsening. Cyclophosphamide is administered 3 days before infusion if the patient is in the cyclophosphamide cohort; then CART-BCMA cells are administered 10% on day 0, 30% on day 1, and 60% on day 2,

which allows flexibility to hold or delay doses if patients develop toxicity.

As of November, 2016, seventeen patients consented; 2 patients failed screening, 1 patient had cells manufactured but was not treated due to pneumonia followed by rapid PD, and 14 were treated, including 9 in cohort 1. In this cohort, all expressed BCMA on MM cells and achieved the minimum target dose of 1 x 10^8 CART-BCMA cells.

The median age of patients was 57 years; they had received a median of 9 prior lines of therapy, and all had MM refractory to at least 1 PI and 1 IMiD; 4 had MM refractory to the mAb daratumumab. All had high-risk cytogenetic abnormalities, and a third had extramedullary disease.

CART-BCMA cells manufactured from heavily pretreated patients with multiple myeloma are feasible.

— Adam D. Cohen, MD

Cytokine release syndrome (CRS) was the major toxicity, which occurred in 8 of the 9 patients; 5 had grade 1 or 2 CRS, and 3 had grade 3 or 4 CRS. Four patients required tocilizumab, which rapidly reduced fever and stabilized hemodynamic instability. Median hospital stay was 9 days.

There was 1 DLT in a patient with high tumor burden. This patient had CRS that resolved with treatment, but the patient then experienced grade 4, posterior reversible encephalopathy syndrome (PRES), with severe delirium, recurrent seizures, and cerebral edema on magnetic resonance imaging (MRI). This coincided with rapid expansion of CART-BCMA cells. Symptoms resolved after antiseizure medication and high-dose methylprednisolone, followed by cyclophosphamide, without long-term neurologic sequelae. Another patient developed grade 3 to 4 encephalopathy and delirium related to grade 4 CRS without MRI changes or evidence of PRES. This patient initially improved with tocilizumab, but then the patient rapidly deteriorated with rapidly progressive MM PD and candidemia, was transferred to supportive care, and died on day 24. Other grade 3 and 4 toxicities were largely associated with CRS, including electrolyte abnormalities and cytopenias.

One patient has ongoing CART-BCMA persistence, with ongoing stringent CR at 12 months after CART-BCMA infusion and MRD-negative bone marrow by flow cytometry. Three other patients had minor response or stable disease lasting 2 to 3 months before progression. Two patients had minimal expansion and no response.

The patients with the deepest and most durable responses have the greatest degree of CART-BCMA cell expansion. The patient with grade 4 PRES maintained CART-BCMA cells with a VGPR lasting 5 months but had a relapse when those cells were lost.

All patients had BCMA detectable on their MM cells at various levels. One patient had no BCMA detectable at relapse, suggesting a dim variant or possible selection for BCMA-negative MM cells.

This study shows that CART-BCMA cells manufactured from heavily pretreated patients with MM are feasible, demonstrating promising in vivo expansion and clinical activity even without lympho-depleting chemotherapy. The cohort presented had significant toxicity. Depth of response correlates with the degree of CART-BCMA expansion and CRS, with too few patients to determine whether response might correlate with BCMA expression. An expanded cohort is enrolling with lymphodepletion with cyclophosphamide to see whether this will enhance expansion, persistence, and clinical activity.

Dr Cohen said that, currently, he would see the use of CART-BCMA cell therapy only in heavily pretreated patients as salvage therapy until the technology is more thoroughly investigated and toxicity can be managed better.

The second study presented by Dr Cohen described the dose-escalation portion of a phase 1, open-label study (NCT02064387)[14] of an antibody–drug conjugate directed against BCMA in patients with RRMM.[15]

GSK2857916 is a humanized IgG1 anti-BCMA antibody conjugated to the microtubule disrupting agent monomethyl auristatin F via a stable, protease-resistant linker. Mechanisms of action include apoptosis following internalization and release of active drug, enhanced antibody–dependent cell-mediated cytotoxicity, and stimulation of an endogenous immune response. The rationale for investigating GSK2857916 in MM is supported by the restricted pattern of BCMA expression and by evidence from preclinical studies.

The primary objectives of the dose-escalation, part 1 study include safety, MTD, and RP2D. Part 1 enrolled 30 patients with RRMM previously treated with a PI, IMiD, and alkylating agent with PD within 60 days of last treatment. Patients had a median age of 60 years; 70% had 5 prior lines of therapy. All had MM refractory to an IMiD, 90% to a PI; 90% were dual refractory to both, 4 were refractory to daratumumab, and a quarter had high-risk cytogenetics.

GSK2857916 is administered every 3 weeks as a 1-hour IV infusion for 16 cycles, with no mandatory prophylaxis for IRRs for the first cycle, but it could be administered if patients had a reaction. However, premedication with steroid eye drops was used to prevent corneal damage. Doses ranged from 0.03 mg/kg to 4.6 mg/kg.

CART-BCMA therapy offers the potential for a single treatment with a long-term, durable remission, which is appealing.

— Adam D. Cohen, MD

PD is the primary reason for discontinuation; 10 patients remain on study for the dose-escalation part, and 2 patients discontinued due to AEs. The most common AE was ocular toxicity, mostly grade 1 or 2 after the first and second cycles; other AEs included nausea and grade 3 or higher transient thrombocytopenia. About a quarter of patients had IRRs, mostly grade 1 and in the first cycle.

BCMA receptor binding was assessed on bone marrow biopsies on day 8 of the first cycle, with engagement of the receptor starting at 0.12 mg/kg and greater than 80% saturation starting at 1.92 mg/kg. No antidrug antibodies were detected. Soluble BCMA was detected in the serum of patients with MM at levels higher than that of normal controls and can serve as a pharmacodynamic measure of the degree to which the antibody–drug conjugate is hitting its target. In this study, at the highest dose level, free BCMA is cleared from the serum and is associated with a rise of a complex between the antibody–drug conjugate and BCMA. The complex resolves by day 8 of each cycle and reappears at each subsequent cycle.

The ORR in the dose-escalation cohort was 27% (8 of 30 patients), including 1 sCR, 3 VGPR, and 4 PR. Responses appear to improve as dose increases. At ≤1.92 mg/kg (n = 21), the ORR was 9.5%; at ≥3.4 mg/kg (n = 9), 66.7%.

GSK2857916 was well tolerated, with no DLTs up to 4.6 mg/kg every 3 weeks, and the MTD was not reached; 3.4 mg/kg was selected for the expansion dose, which is ongoing.

When Dr Cohen was asked which BCMA treatment he would offer to a very good friend with RRMM, he responded that although it was too early to really know, the CART-BCMA offers the potential for a single treatment with a long-term, durable remission, which is appealing. That needs to be demonstrated in a large proportion of patients. Issues with manufacturing may make that difficult. The antibody–drug conjugate has the advantage of being an off-the-shelf product, so there are pros and cons to each approach. He would like to see more data, particularly DoR with both approaches, before the question can be answered. ■

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