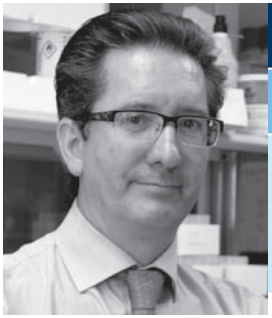

INTERVIEW

Jesus F San-Miguel, MD, PhD

Dr San-Miguel is Professor of Hematology and Head of the Hematology Department at the University Hospital of Salamanca and Director of the Biomedical Research Institute of Salamanca in Salamanca, Spain.

Tracks 1-15

Select Excerpts from the Interview

Track 5

DR LOVE: Would you comment on the use of post-transplant maintenance lenalidomide in multiple myeloma (MM), what we've learned from the updated data presented in Paris by the CALGB and the issue of secondary cancer?

DR SAN-MIGUEL: The post-transplant lenalidomide maintenance data in patients with MM are attractive. The duration of PFS was nearly doubled

in both the French and CALGB trials (Attal 2010; McCarthy 2011; [2.1]). Although no benefit has been observed in the French trial with regard to OS, a benefit is already evident in the reduced number of deaths with lenalidomide maintenance in the CALGB. However, the enthusiasm for these benefits was initially somewhat counteracted by the issue of second cancers.

Most of the agents we use to treat cancer can induce a higher risk of secondary tumors, and so far in the French trial the incidence in the treatment arm is between 7% and 8%. In the control arm, the incidence is significantly lower. Ultimately, though, the event-free survival continues to be in favor of lenalidomide maintenance.

2.1

Post-transplant Lenalidomide Maintenance Therapy for Patients with Multiple Myeloma

	IFM 2005-02[1]		CALGB-100104[2]	
	Lenalidomide (n = 307)	**Placebo** (n = 307)	**Lenalidomide** (n = 231)	**Placebo** (n = 229)
Median PFS[1] or TTP[2]	41 mo	24 mo	48 mo	31 mo
	$p < 10^{-8}$		$p < 0.0001$	
Deaths	19%*	17%*	9%	16%

PFS = progression-free survival; TTP = time to progression
* Difference not significant

[1] Attal M et al. *Proc 13th International Myeloma Workshop* 2011; [2] McCarthy PL et al. *Proc 13th International Myeloma Workshop* 2011.

Track 7

DR LOVE: Would you discuss the options for initial up-front therapy for transplant-ineligible patients with MM?

DR SAN-MIGUEL: For the elderly, melphalan/prednisone (MP) has been standard for more than 30 years. However, now we have 3 agents — thalidomide (T), lenalidomide (R) and bortezomib (V) — that, in combination with MP or corticosteroids, have become the new treatment standard.

The addition of thalidomide to MP (MPT) yields a significant benefit in terms of response rate and PFS in at least 5 of the 6 randomized trials, and in 3 of them a benefit is also apparent in OS, leading to an approximate 6-month prolongation in both OS and PFS (Fayers 2011).

Lenalidomide in combination with MP (MPR) has been recently tested in a large randomized trial. This trial compared MP to MPR with a third arm evaluating lenalidomide as continuous treatment until disease progression, and the response rate was significantly higher with the lenalidomide-based regimens. Furthermore, an additional significant benefit was observed in PFS for patients receiving continuous lenalidomide compared to MP and MPR. No difference in OS was observed (Palumbo 2010).

Bortezomib was evaluated in the VISTA study, which was a large randomized trial that compared MPV to MP alone. The difference in response rate was significant, with an 8-month benefit in PFS and a significant benefit in OS observed with the addition of bortezomib. These data were striking because benefit in PFS was clear almost from the outset (San Miguel 2008).

Nevertheless, bortezomib was associated with some toxicity, particularly peripheral neuropathy. For this reason, the Spanish group pioneered the concept of reducing the dose by moving to a weekly dosing schedule from a twice-weekly dosing schedule. In the GEM-2005 trial, by reducing the dose of bortezomib from twice weekly to weekly we were able to significantly decrease the peripheral neuropathy. Gastrointestinal symptoms were also significantly reduced. Most important, we were able to maintain, if not increase, the efficacy of the regimen (Mateos 2010b).

Track 8

DR LOVE: Would you discuss the Phase III study evaluating subcutaneous versus intravenous (IV) bortezomib in MM that was recently published in *The Lancet Oncology* (Moreau 2011; [2.2])?

DR SAN-MIGUEL: The study was a 2-to-1 randomization comparing subcutaneous administration of bortezomib to IV treatment, and approximately 220 patients were randomly assigned. The data are attractive for several reasons. First, the incidence of Grade 3 or higher peripheral sensory neuropathy is quite low with subcutaneous administration, 6% or less.

Second, the response rate was near 55%, and the PFS was almost 11 months, which is longer than the 6-month PFS reported previously in the APEX trial. Interestingly, even on the IV arm, it was more than 9 months in this study. The question is, why is the PFS longer, even with IV administration? I believe it's because physicians now know how to use bortezomib better. They are reducing the toxicity by decreasing dose as soon as a signal indicates to do so. This allows the patient to stay on treatment which results in prolonged survival.

2.2

MMY-3021: A Phase III Trial of Subcutaneous (SC) versus Intravenous (IV) Administration of Bortezomib in Relapsed Multiple Myeloma

Response	Bortezomib SC (n = 145)	Bortezomib IV (n = 73)
Overall response rate	42%	42%
Complete response	6%	8%
Nonhematologic adverse events		
Any peripheral neuropathy (any grade)	38%	53%
Any peripheral neuropathy (Grade ≥3)	6%	16%

Moreau P et al. *Lancet Oncol* 2011;12(5):431-40.

Tracks 12, 14

DR LOVE: Would you talk a little about some of the new agents that are emerging in MM?

DR SAN-MIGUEL: Pomalidomide is a third-generation IMiD with efficacy similar to lenalidomide — about 60% of patients at high risk responded, and a PFS of approximately 11 months was achieved. Even patients with lenalidomide-refractory disease respond to pomalidomide — 20% to 30% respond, with a 5- to 7-month PFS (Lacy 2010).

Carfilzomib is a second-generation proteasome inhibitor and is similar to bortezomib in terms of response, with a PFS of around 1 year in bortezomib-naïve disease in patients who achieved VGPR. In patients with bortezomib-refractory disease, approximately 20% respond to carfilzomib. Another important point is the lack of associated peripheral neuropathy.

At ASH 2010, Dr Jakubowiak presented data on carfilzomib, lenalidomide and dexamethasone (CRd) in newly diagnosed MM. The response rate to CRd was 100% (Jakubowiak 2010). Almost 40% are complete responses, which is similar to the RVD regimen, so I believe these agents will move quickly to the up-front setting. ■

SELECT PUBLICATIONS

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Fayers PM et al. **Thalidomide for previously untreated elderly patients with multiple myeloma: Meta-analysis of 1685 individual patient data from 6 randomized clinical trials.** *Blood* 2011;118:1239-47.

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Mateos MV et al. **Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: A randomised trial.** *Lancet Oncol* 2010a;11(10):934-41.

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Palumbo A et al. **A Phase 3 study to determine the efficacy and safety of lenalidomide combined with melphalan and prednisone in patients ≥ 65 years with newly diagnosed multiple myeloma.** *Haematologica* 2010;95(51);**Abstract 0566**.

San Miguel JF et al. **Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma.** *N Engl J Med* 2008;359(9):906-17.