

# CAR T-Cell Therapy Is a Desirable Option in Second-Line Multiple Myeloma



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**D**uring the 2024 International Myeloma Society Annual Meeting, colleagues gathered to discuss the latest advancements in multiple myeloma. They highlighted the latest clinical trials and their impact on frontline treatments, current approaches and emerging therapies, and the role of chimeric antigen receptor (CAR) T-cell therapy.

Through this conversation, the experts were able to share their experiences and how they approach treatments at the various institutions.

## Treatment Options in Newly Diagnosed Multiple Myeloma

Key trials in this population were highlighted with an assessment of their efficacy outcomes (**Table**).<sup>1-3</sup> Gertz asked what the current standard of care (SOC) was and whether there were certain patients who should be deviated.

For patients who are at standard risk, there is currently only lenalidomide (Revlimid) maintenance approved by the FDA.<sup>4</sup> Dhakal believes the data from the phase 2 PERSEUS trial (NCT03710603) are promising and are readying daratumumab (Darzalex) plus lenalidomide maintenance for this population. For those who are high risk, he prefers triplet maintenance. One instance in which deviation from SOC may occur is in patients who have renal failure.

Banerjee discussed the deviation from SOC PERSEUS data because of the bortezomib (Velcade) dosing. He used it once per week in order to avoid neuropathy. A lenalidomide backbone is still used. For patients who are high risk he considers adding a proteasome inhibitor.

“Dr Dhakal’s point is very well taken in we don’t know what the optimal maintenance is. PERSEUS did not [randomly assign] patients to daratumumab, lenalidomide vs lenalidomide. It enrolled patients who got D-VRd [daratumumab, bortezomib, lenalidomide, and dexamethasone] went on to get daratumumab plus lenalidomide and those who did not. There are still some unanswered questions there,” Banerjee said.

Shared decision-making between patients and clinicians came

**TABLE. Top Trials in Newly Diagnosed Multiple Myeloma<sup>1-3</sup>**

TRIAL	NCT	TREATMENT	PFS	CR OR BETTER
<b>PERSEUS</b>	NCT03710603	D-VRd vs VRd	4 years, 84.3% vs 67.7% (HR, 0.42; <i>P</i> < .0001)	87.9% vs 70.1% ( <i>P</i> < .0001)
<b>ISKIA</b>	NCT03104842	IsaKRd vs KRd	1 year, 95% in both arms	74% vs 72% ( <i>P</i> < .001)
<b>CASSIOPEIA</b>	NCT02541383	D-VTd vs VTd	Median, 83.7 months vs 52.8 months	76.9% vs 49.8% ( <i>P</i> < .001)

CR, complete response; D-VRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; D-VTd, daratumumab, bortezomib, thalidomide, and dexamethasone; IsaKRd, isatuximab, carfilzomib, lenalidomide, and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; PFS, progression-free survival; VRd, bortezomib, lenalidomide, and dexamethasone; VTd, bortezomib, thalidomide, and dexamethasone.

into play. Lee often discusses the next steps for patients who are standard risk. He most commonly does this because of the risk-benefit ratio for high-dose chemotherapy and autologous stem cell transplant. In these situations, patients may defer to transplant or consider completing 8 cycles of D-VRd followed by maintenance.

Gertz mentioned that because we are now in the daratumumab era, he wanted to know how Chari felt about the phase 3 DETERMINATION trial (NCT01208662) and whether these results were valuable.<sup>5</sup>

When DETERMINATION was presented, a question was posed about the pros and cons of transplant. Chari highlighted the primary end point was progression-free survival (PFS) because of the results observed with transplant. He believes a new study is needed to displace transplant either through CAR T-cell therapy or quadruplet therapies. For any patient younger than 70 years, he does recommend transplant.

Sidana noted that transplant has remained the SOC for all patients unless someone opts out based on toxicity or a long-term risk. The DETERMINATION data showed lower outcomes in patients who were high risk and did not receive a transplant. For patients who are standard risk and value PFS, a transplant is recommended. However, if they value short-term quality of life, other treatment options may be discussed.

“I am not using dual maintenance in every patient because of the data we saw from [the phase 3] CASSIOPEIA trial [NCT02541383]. Initially, all the data keep evolving with longer follow-ups. For patients who are standard risk, I’m using lenalidomide maintenance. It is convenience, it is the added benefit that needs to be proven. However, because patients who are high risk do not have great outcomes and have inferior PFS, I’m willing to add more therapy along with the adverse effects that come with it and the inconvenience that comes with it. Typically, it’s either a [proteasome inhibitor] and lenalidomide or anti-CD38 and lenalidomide in those patients,” Sidana said.

Based on the data, Gertz wondered whether there was a specific reason to prefer lenalidomide over thalidomide. Prada has never

had the chance to use thalidomide outside of a few select cases when patients had severe cytopenia or a high disease burden.

In the community setting, Prada typically uses daratumumab because of its subcutaneous administration. Recently, isatuximab (Sarclisa) was approved with bortezomib, lenalidomide, and dexamethasone for patients with newly diagnosed multiple myeloma not eligible for autologous stem cell transplant.<sup>6</sup> With this approval, Prada thinks that she will begin to use isatuximab in the frontline setting.

**Treatment Options for Transplant Not Preferred or Transplant-Ineligible Patients**

Chari wondered that if the phase 3 MAIA trial results (NCT02252172) have been stated as the best medicine, how do oncologists move past it? For him, the more important data are from the phase 3 IMROZ trial (NCT03319667).<sup>7,8</sup> For MAIA, the follow-up was shorter and the data cutoff was approximately 8 months after discontinuing bortezomib.

“I think we would all agree that if you’re over 70 [years of age] or frail and elderly, if you’re [given] twice-weekly bortezomib, you’re transplant eligible, right? Either way, one or the other. I hate studies that say transplant ineligible and are giving twice-weekly bortezomib. Because that’s a huge selection bias. Those of us who would be sitting in front of that patient would never allow them to sign consent for that study. Putting that aside, I think the benefit is great, but I still have a major question mark, whether 18 months of [proteasome inhibitor] exposure is going to improve PFS beyond 5 years, because the follow-up currently is only about 8 months after bortezomib was discontinued,” Chari said.

Chari further stated that the data were based on minimal residual disease (MRD) and not PFS. He wondered what the role of MRD was in today’s treatment setting. The Oncologic Drug Advisory Committee determined it can be used as a surrogate end point for accelerated approval, but there must be PFS follow-up.<sup>9,10</sup>

Results from the IMROZ trial have emphasized the need for

quadruplet therapies, according to Lee. Instead of asking whether a patient could be transplant eligible or ineligible, he more often leans toward whether they are triplet or quadruplet therapy eligible. For a triplet, he will use a DRd backbone.

Banerjee mentioned the concept of dynamic frailty. This includes patients who during initial therapy may not be able to walk well or who use a wheelchair. However, after a few cycles of CD38, they are becoming more mobile and have the potential to become transplant eligible.

Until about 2 years ago, Dhakal was continuing to pursue transplant for patients aged 70 to 80 years. However, once data came out indicating it wasn't worth it unless they could tolerate 200 mg/m<sup>2</sup> of melphalan per day, he noted it might not be worthwhile. Results from the MAIA trial still inform his clinical practice for patients who are transplant ineligible.

Sidana will use a quadruplet therapy in a certain subset of her patients if they are transplant ineligible. She does emphasize the need for longer-term data, but the benchmark is the DRd backbone. She will insert a proteasome inhibitor for those patients who are high risk.

### CAR T-Cell Therapy and Use in Multiple Myeloma

The conversation shifted to the use of CAR T-cell therapy and how it is being moved into earlier lines of therapy. Gertz wanted to know how CAR T-cell therapy fits into the second line, and especially if the practice has not reached that standard yet, what they should consider doing.

At Prada's community practice, she still does not have access to idecabtagene vicleucel (Abecma) or ciltacabtagene autoleucel (Carvykti). However, it is approved for her practice; it just hasn't been initiated. Looking at the neurotoxicity data, she said there needs to be a longer follow-up. The ideal patients to refer to CAR T-cell therapy would be those who have functional high-risk multiple myeloma and have primary refractory disease or those who progress after the first line of therapy within 18 months of achieving a complete response.

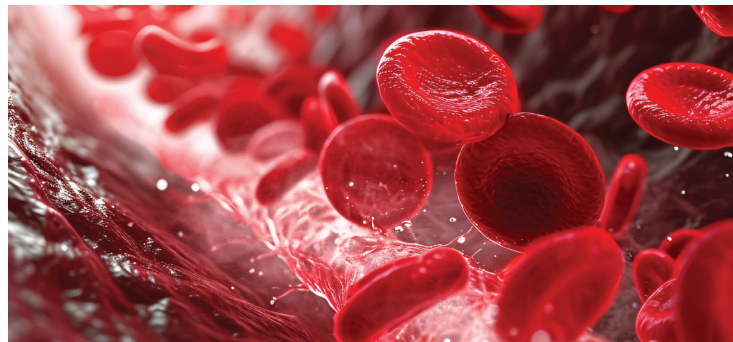
Sidana referred to the neurotoxicity mentioned as weighing the risks and benefits of the treatment. She highlighted the short-term risks, like cytokine release syndrome (CRS), of CAR T-cell therapy that are observed within the first few weeks of beginning treatment. Immune cell-associated neurotoxicity syndrome does occur within the first few days but can be reversed with steroids and typically is not severe.

"The neurotoxicity Dr Prada alluded to that a lot of us are concerned about is the delayed neurotoxicity, which takes several shapes and forms including cranial nerve palsies, but very importantly Parkinson-like features, which we don't have great treatments for and may not be reversible. To use CAR T in the earlier

line, the risk in phase 3 CARTITUDE-4 trial [NCT04181827] of Parkinsonism was very low, 0.5%. Much lower than the late line, but it is still not zero," Sidana said.<sup>11</sup>

Regarding critical care after the use of CAR T-cell therapy, Chari has not had any patients escalate to that degree of care. The CRS with these treatments remains primarily grade 1/2 and doesn't need extra monitoring once it is addressed.

Banerjee typically sees patients from Idaho, Montana, or Alaska. Because of this, he won't necessarily recommend CAR T-cell therapy in the second line. They would have to relocate and move to a big city for a month to be monitored and may continue past that. He agrees more data need to be collected for him to even consider suggesting patients move for this second-line treatment.



Gertz asked Dhakal what his strategy would be if patients developed secondary malignancies and what his approach would be regarding treatment with CAR T-cell therapy. Most patients have been triple-class exposed, so Dhakal will look to see whether they are eligible for CAR T-cell therapy. He highlighted there was an added benefit of safety as the CARTITUDE-4 trial data showed no delayed neurotoxicity.

As Dhakal looked at competing risk factors for secondary malignancies, he noted that it was still death-related to multiple myeloma. Because of this, he believes CAR T-cell therapy should be considered in the second line.

"As we learn about CAR T, one thing [that] is quite clear in the CAR T treatment is if you debulk the disease at the lowest level, you are going to get the best outcome for both safety and efficacy. For those patients, I would argue that I could still debulk [the disease] very nicely with a database regimen as a bridging therapy or maybe even prior to bridging or prior to collection, and then could still get the best benefit with the CAR T afterward because that probably would be the best situation for these patients to go in," Dhakal said. ■



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