Where do monoclonal antibodies fit into the treatment strategy for myeloma?

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Monoclonal antibodies (mAbs) offer novel opportunities for the management of patients with multiple myeloma (MM) in our efforts to cure this disease. Daratumumab is a mAb against CD38, which is licensed as monotherapy for relapsed/refractory (RR) MM patients who have received at least 3 prior lines of therapy, including an immunomodulatory drug (IMiD) and a proteasome inhibitor (PI) or in patients who are double refractory to an IMiD and a PI. License was based on data from two phase 2 studies where daratumumab, as a single agent, produced an overall response rate (ORR) of 31% in RRMM patients who have received a median number of 5 prior lines of therapies. The median duration of response was 7.6 months, the median PFS was 4 months (15 months in responders) and the median overall survival (OS) was 20 months. Phase 3 studies in earlier phases of myeloma have been recently reported. Daratumumab was given in combination with lenalidomide and low dose dexamethasone (DaraRd) versus Rd in RRMM who had received 1-3 prior lines of therapy. DaraRd produced an impressive PFS advantage in favor of DaraRd arm (the 12-month PFS rate was 83% versus 60% in Rd arm; HzR 0.37, $p<0.001$). Complete response (CR) and MRD negative rates were 43% versus 19% and 22% versus 5% for DaraRd and Rd, respectively ($p<0.0001$ for both comparisons). Similar results were produced in another phase 3 study, in a similar population, where daratumumab was given in combination with bortezomib and dexamethasone (DaraVD) versus VD: the 12-month PFS rate was 77.5% in DaraVD versus 29.4% in VD arm; HzR 0.31, $p<0.001$.

Other novel combinations based on IMiDs and mAbs are available for RRMM. Elotuzumab is a mAb against SLAMF7 and was combined with Rd (EloRd) in a phase 3 study for RRMM patients who had received 1-3 prior lines of therapy. Median PFS in the EloRd group was 19.4 months *vs.* 14.9 months in the Rd group ($p<0.001$). Pembrolizumab is a mAb against program cell death-1 (PD-1). In a phase 2 study, pembrolizumab was combined with Rd in patients who had previously received at least 2 lines of therapy. Although 96% of patients had been exposed to Rd, the ORR was 75% (56% in those refractory to Rd). Other combinations of Rd with mAbs in RRMM include the combination with indatuximab ravtansine (targeting CD138), which produced an ORR of 78% in a phase 2 study and the combination with ulocuplumab (targeting CXCR4), which produced an ORR of 53% in a phase 1b study.