Patients with melanoma related brain metastases achieve reduced risk of progression and better overall survival if they receive radiotherapy before immunotherapy as opposed to the other way round. The meta-analysis study, abstract RADT-04, presented at the Society of Neuro Oncology Meeting, 21–24 November, held in Houston, Texas, suggested that optimal results could be achieved when the time interval between the two sequenced treatments was around two weeks.

“Our study shows that sequence matters and that radiotherapy followed by checkpoint inhibitors maximises the therapeutic benefits for patients with melanoma that has metastasised to the brain,” says study presenter Philip Haddad, a medical oncologist from Louisiana State University Health Science Center and Overton Brooks VA Medical Center, both in Shreveport Louisiana.

Brain metastases occur in approximately half of patients with cutaneous melanoma and are the third most common metastatic site. While checkpoint inhibitors and radiotherapy are both used, either alone or in combination, for melanoma brain metastases, no consensus or guidelines currently exist around the optimal treatment sequence for the combined treatment. The rationale for using radiotherapy and immune checkpoint inhibitors together derives from evidence that radiotherapy synergises with immune checkpoint inhibitors to produce a more robust response.

For the meta-analysis, Haddad and colleagues identified six retrospective comparative studies (that were not randomised), involving 213 patients with median age of 62 years and a median follow-up of 22 months. The studies, which were published between 2015 and 2022, all reported progression free survival and overall survival, with any studies involving concurrent checkpoint inhibitors and radiotherapy excluded from the analysis. In four of the studies the checkpoint inhibitor used was ipilimumab, in one study ipilimumab plus nivolumab, and in one study an unnamed checkpoint inhibitor. Five of the studies used stereotactic radiosurgery and one a combination of whole brain radiotherapy and stereotactic radiosurgery.

The results showed a clear progression free survival disadvantage when immunotherapy is used prior to radiotherapy (HR=1.77; 95%CI 1.21–2.60; P=0.003; I_2=13.5%).

Similarly, starting treatment with immune checkpoint inhibitors followed by radiotherapy showed a trend towards poorer overall survival compared to the reverse sequence, although this finding was of borderline significance (HR=1.39; 95%CI 0.97–1.99; P=0.07; I_2=0%). All but one of the studies trended towards worse survival associated with an immune checkpoint inhibitor-first strategy.

The protocols in the studies had a range of intervals between radiotherapy and immunotherapy of 0.5 to 4 months, with the 0.5-month interval study demonstrating the greatest benefit and the study with the 4-month interval the least benefit.

“At this point the best evidence that we have for melanoma patients with brain metastases to achieve longer survival is to sequence radiotherapy before immunotherapy and for the optimum gap between treatments to be around two weeks,” Haddad tells *Cancerworld*.

The mechanism of action, he adds, is likely to be that radiation upfront induces injury to the tumour. “This exposes antigens to the immune system that rushes in to engage the cancer, while the immunotherapy acts to prevent the hostile cancer environment from shutting off this beneficial immune response,” he explains.

The next step, says Haddad, would be to conduct an umbrella platform trial with an adaptive design where the two sequences could be compared to a third arm giving the treatments concurrently. “There are studies coming along suggesting that combining radiotherapy and checkpoint inhibitors may be more effective. But before we can test this approach against sequencing in a clinical trial, we

need to know the optimum sequence, which this analysis shows to be radiotherapy followed by immune therapy," says Haddad.

In any future trial, other questions that will need to be addressed include the optimal time interval between the sequenced treatments, the most effective checkpoint inhibitor (whether ipilimumab or nivolumab alone or ipilimumab plus nivolumab), the optimum dose of radiotherapy, and whether radiotherapy should be given in one dose or fractionated. "Unfortunately, it's unlikely that pharmaceutical companies who already have established markets would be willing to fund such trials. The initiative has to come from national cooperative trialist groups," says Haddad.

The benefit of radiotherapy followed by immunotherapy, Haddad believes, is likely to hold for other cancers that have metastasised to the central nervous system. He cites a study by Jacob Eckstein, published in *Adv Radiat Oncol* in 2023, which showed that, in 128 patients with lung, breast, or kidney cancer that had metastasised to the spinal cord, overall survival was improved in patients who received stereotactic radiosurgery prior to immunotherapy.