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Short Commentary

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Checkpoint Dilemma: KEYNOTE-564's Triumph Amidst the Failures of Its Rivals in Renal Cell Carcinoma?

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The overall survival results of Keynote 564 were recently reported with adjuvant pembrolizumab showing an overall survival (OS) benefit in intermediate and high-risk resected renal cell carcinoma (RCC) (5-year OS 87.7% VS 82.3% in favour of pembrolizumab, HR 0.66).[1] After repeated failures of adjuvant tyrosine kinase inhibitors (TKIs), this was a Cinderella moment in the therapeutic paradigm of localized RCC.Despite the unprecedented results, the trial attracted notable criticism due to the disproportionate dropout rates between the study arms, raising concerns about potential informative censoring. Subsequent sensitivity analyses, when accounting for these imbalances, attenuated the statistical significance initially observed in disease-free survival outcomes.[2] The observation that nearly 50% of patients in the control arm remained disease-free at two years underscores the existence of subgroups that fare well with surgery alone, highlighting the limitations of traditional prognostic models such as UCLA Integrated Staging System (UISS) and SSIGN. Relapse risk assessment through risk stratification models such as Leibovich score and the 16 gene recurrence score was not part of the keynote 564 trial. Approximately, 40% of patients who receive adjuvant pembrolizumab relapse within a span of 5 years. This reinforces the need for more refined, individualized risk stratification tools, such as postoperative ctDNA profiling and KIM-1 (Kidney injury molecule 1) levels to better predict recurrence in resected RCC. Even-though the benefit of adjuvant pembrolizumab was evident in all subgroups, the benefit was most evident for the M1 NED (No evidence of disease) subset and the least for pT3N0 grade1 disease. This has even led many of the experts to forego adjuvant pembrolizumab for pT3N0 grade 1 RCC with a low Leibovich score.

The other notable trial was IMmotion010 which evaluated adjuvant atezolizumab for 1 year. Despite having a longer median follow up of 44.7 months, highest percentage of M1 NED participants (no evidence of disease), more patients with regional lymph node involvement compared to Keynote 564 (11% vs 6%), this trial failed to meet its primary endpoint of DFS.[3] There is ample evidence in the metastatic setting from the negative results of Javelin Renal 101 (avelumab + axitinib)[4] and IMmotion 151 (atezolizumab + bevacizumab)[5] that PDL1 inhibition is a weak strategy in RCC. The positive takeaway from IMmotion 010 was the post-hoc exploratory analysis of KIM-1 levels, where adjuvant therapy benefitted patients more with higher KIM-1 levels post resection.

Next, we have PROSPER which evaluated a peri-operative strategy with nivolumab (2 doses,480 mg in total, followed by surgery and adjuvant therapy for a total of 9 months).[6] The biological rationale was strong suggesting that tumor infiltrating CD8+ T cells are likely to arise when the primary tumor and draining lymph nodes are in-situ. The study was negative for recurrence-free survival. Many concerns were raised regarding patient inclusion criteria and trial design. Unlike Keynote 564, PROSPER included T1 patients with a low risk of recurrence. Non clear histologies were included, where the role of immunotherapy is doubtful. The 9-months therapy duration might be suboptimal compared to keynote 564 and IMmotion010. Also, limiting the neoadjuvant phase to just 2 cycles raised a few eyebrows. Landmark trials evaluating neoadjuvant immunotherapy in melanoma(pembrolizumab), non-small cell lung cancer (nivolumab, durvalumab and pembrolizumab) have given longer courses of preoperative therapy resulting in recurrence-free survival benefit. Moreover, the study design was open-labelled, resulting in imbalances and patient attrition post-surgery.

Checkmate 914 added to the list of negative studies, which assessed the role of adjuvant nivolumab and ipilimumab versus placebo (Part A), with disappointing results.[7] The 6-month therapy duration aimed to minimize toxicities, but this strategy may be inadequate for RCC, where recurrence risk is a continuous variable and poorly predicted by existing models. This has been the learning so far from the slew of negative adjuvant TKI trials. Without proper biomarker selection, it is not worthwhile subjecting patients to this regimen which resulted in 28% grade 3/4 toxicities and only 57%

treatment completion rates.[7] Also, there were concerns regarding the protracted 6 weekly schedule of ipilimumab compared to the condensed regimen in checkmate 214 which may have effectively reduced CTLA4 inhibition without affecting tolerability.

In summary, KEYNOTE-564 achieved an overall survival benefit by enrolling a higher-risk patient cohort and administering pembrolizumab, a proven anti-PD1 agent, which has stood the test of time, over an extended duration. Clinicians must recognize that optimal patient selection, guided by clinical, pathological, and molecular markers is crucial for success. The primary challenge lies not in identifying candidates for treatment, but in discerning those who should not receive it. Focus should be on refining exclusion criteria and understanding which subgroups benefit the most. Balancing benefits in OS and PFS against potential toxicity is crucial. Lastly, integrating evidence from trials with real-world data and expert consensus will be essential to refine guidelines and improve outcomes. Adjuvant treatment should be withheld for tumours with a low to very low risk of relapse (T1, T2 up to grade 3), patients with incomplete resections or residual disease beyond the kidney. Few questions remain yet to be answered. There is no role for adjuvant immunotherapy yet for resected non-clear cell RCC, which still remains an area of unmet need. Role of PDL1 estimation in adjuvant treatment decision making is unclear with conflicting evidence and majority of experts recommending against the same. Also, data to guide treatment of patients relapsing post adjuvant immunotherapy are mostly retrospective, with single agent tyrosine kinase inhibitor (TKI) or clinical trial enrolment suggested for relapse occurring within 6 months of adjuvant pembrolizumab. Late relapses may be rechallenged with immunotherapy-TKI combinations. It is still unclear whether to use IMmotion 151 gene clusters or ccrcc1-4 gene signatures for therapeutic decision making due to the lack of prospective data. Clinicians should also keep in mind that the optimal adjuvant therapy for resected oligo-brain metastases is still a matter of debate as this subset was not included in the M1 NED category.

Key upcoming studies include RAMPART, which is investigating the efficacy of adjuvant durvalumab and durvalumab-tremelimumab combination in resected RCC, and LITESPARK-022, assessing the combination of pembrolizumab and belzutifan versus pembrolizumab monotherapy.

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