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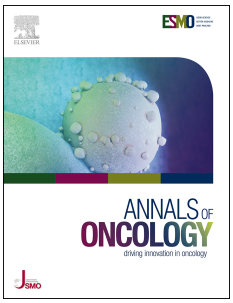

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Mark Linch, Alvin Lee

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Positioning checkpoint blockade in urothelial cancer: PURE-01 and PEANUTS

Mark Linch & Alvin Lee

Department of Oncology, University College London Cancer Institute, 74 Huntley Street, London, UK.

Immune checkpoint inhibitors (CPI) have led to a step-change in the management of advanced urothelial cancer (UC). Despite great successes in UC, response rates (RR) to monotherapy remain at only about 20%. This has led to a variety of approaches to test the optimal use of these agents, including bringing combination therapy approaches and attempts to identify predictive biomarkers earlier in the disease course.

In this issue of *Annals of Oncology,* there are back-to-back articles that explore strategies to improve the effectiveness of CPI in UC. In the first article, Giannatempo et al have performed a single centre, single-arm phase 2 study of nab-paclitaxel and pembrolizumab in patients with metastatic UC after 1 or 2 previous lines of therapy[1]. The primary endpoint was median progression-free survival (PFS), with secondary endpoints of response rate (RR), duration of response, overall survival and safety and tolerability. Biomarker analysis included PD-L1 status, mutational burden, mutational status (tumour and ctDNA), and FDG-PET assessment. 70 patients were enrolled, with a median PFS (mPFS) of 5.9 months and radiological RR of 38.6%. This is one of the first trials to report outcomes of chemoimmunotherapy (CT-IO) in the second/third line setting and demonstrates promising levels of activity. In comparison, 2nd-line treatments such as vinflunine or pembrolizumab have previously been associated with RR of about 10-20% and PFS of 2-7months [2, 3]. The main limitation of the study is the choice of nab-paclitaxel as the chemotherapy backbone to this CT-IO combination as this agent was not, and likely will not be, a standard of care in the routine clinical management of UC.

Taxanes inhibit cancer cell division through stabilization of the microtubules. More recently, taxanes have been shown to increase tumour T-cell infiltration and activation, reduce immunosuppressive Tregs and MDSCs, and lead to immunoenhancing cytokine release [4]. Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) has been shown to be selectively taken up in macrophages, leading to a functional switching between immunosuppressive (M2) and immunostimulatory (M1) macrophages [5]. Nab-paclitaxel, unlike standard paclitaxel, is formulated without the potentially allergenic Cremophor solvent and therefore does not require immunosuppressive steroid pre-medication. At the time of the PEANUT study conception, nab-paclitaxel was selected due to single-arm study data showing clinical activity in UC and pre-clinical immune modulation. The randomized controlled trial of nab-paclitaxel compared to paclitaxel in UC, which was subsequently reported, failed to demonstrate an improved PFS and higher rates of toxicity with nab-paclitaxel. The role of nab-paclitaxel as an immune adjunct in UC was further reduced after impressive

activity was shown for enfortumab vedotin (EV), another anti-microtubule agent. EV, a nectin-4 targeted form of momomethyl auristatin E (MMAE) demonstrated an overall response rate of 42% as a monotherapy in patients with UC who had received prior platinum chemotherapy and CPI[6]. The combination of EV with pembrolizumab has subsequently been tested in a phase 2 trial as a first-line therapy for metastatic UC; initial reports suggest an excellent overall response rate of 73.3% with good tolerability [7]. As such, EV is likely to be the anti-microtubule backbone for subsequent CT-IO trials.

The tried and trusted oncological paradigm of taking an effective treatment from late-stage disease and testing it earlier in the disease forms the basis of the second article. Bandini et al present updated results of the PURE-01 trial of neoadjuvant pembrolizumab for localised muscle invasive bladder cancer (MIBC)[8]. They now present the interim survival outcomes stratified by pathological response and molecular characteristics. The overall event-free survival (EFS) at 2-years was 77.9% which compares favourably with neoadjuvant chemotherapy studies[9]. Clinical T3-4 disease and low PD-L1 combined positive score were associated with worse EFS in the multivariable analyses. 4 patients refused to have a cystectomy after neoadjuvant pembrolizumab; all had significant down-staging (3 x pT0 and 1 x pTis) and all were free of disease with a median follow-up of 10 months. The authors propose to test TURBT and active surveillance as an alternative to cystectomy in patients that attained a complete pathological response and have favourable molecular features.

Utilising immunotherapy earlier in the disease course may be more effective due to lower disease burden, less pre-treatment and fitter host immunity. In the ABACUS study, 2 cycles of neoadjuvant atezolizumab prior to cystectomy was tested with a 31% pathological complete RR and 1-year relapse-free survival (RFS) of 79% [10]. Interestingly, in the small subgroup of patients that achieved downstaging to non-MIBC (NMBIC) within the PURE-01 study, the EFS was poor, indicative of a suboptimal response of NMIBC to pembrolizumab. This may be a cautionary sign but we must wait for the NMIBC trials to be completed.

In the PURE-01 study, the transcriptomic Decipher classifier was used to molecularly stratify the cohort. The best outcomes were seen with claudin-low subtypes and worst outcomes were seen with neuroendocrine–like subtypes. In the PEANUT study, individual gene mutations were not associated with mPFS. Neither studies reported TGF-B or inflammatory infiltrate transcriptomic signatures, which have previously been associated with response to CPI in UC [10, 11].

The standard of care imaging for bladder cancer remains CT chest, abdomen and pelvis. Magnetic Resonance Imaging (MRI) and FDG-PET scans are gaining traction in the local and distant staging of UC, respectively. In the PURE-01 study, complete response as assessed by pelvic MRI was a good predictor of EFS lending further weight to the use of MRI to stage localized bladder cancer. Whether MRI can be used as an alternative to TURBT in the staging of the disease is being tested in prospective studies such as BladderPath [12]. In the PEANUT

study, an exploratory biomarker was FDG-PET CT restaging after 2 cycles of CT-IO. Response at this time point was associated with mPFS, but whether this adds to the current standard of care, conventional CT, was not tested.

In summary, the PURE-01 and PEANUT studies provide interesting insights into the utilization of CPI in UC and will help to inform subsequent prospective trials in this dynamic field.

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