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> Effects of antacids on sunitinib efficacy

Primary efficacy analysis results from the SORCE trial (RE05): adjuvant sorafenib for renal cell carcinoma at intermediate or high risk of relapse

Authors: Eisen TQG et al.

Summary: The phase 3 SORCE trial, led by the MRC CTU at UCL, randomised patients with primary RCC (84% clear-cell histology, and 53% and 47% at intermediate and high risk of recurrence, respectively) to receive 3 years of sorafenib (n=639), 1 year of sorafenib followed by 2 years of placebo (n=642) or 3 years of placebo (n=430); the starting dosage of sorafenib was initially 400mg twice daily, amended to once daily during the trial. None of the preplanned and prepowered analyses revealed any differences among the groups for disease-free survival (primary endpoint; HR 1.01 [95% CI 0.83–1.23] for 3 years of sorafenib versus placebo), OS or restricted mean survival time (6.81 vs. 6.82 years for 3 years of sorafenib versus placebo [p=0.99]). Over half the participants discontinued treatment early despite treatment adaptations. The grade 3 hand-foot syndrome rate was 24% among sorafenib recipients.

Comment: Adjuvant therapies for preventing cancer recurrence and improving overall cure are attractive to patients and their doctors. With the effectiveness of VEGFR TKIs in improving survival in metastatic RCC, a number of clinical trials testing these agents in resected high-risk RCC have been undertaken, testing drugs such as sunitinib, pazopanib, axitinib and, in the SORCE trial, sorafenib. Patients were offered a randomisation of surveillance versus 1 or 3 years of sorafenib. Like other adjuvant studies, toxicity appeared higher than in the metastatic setting, and dose intensity was hard for patients to tolerate. Like every other clinical trial in this setting, survival was unchanged by taking an adjuvant VEGFR TKI, and the commercially sponsored S-TRAC study remains the only study to show a difference in the artificial surrogate endpoint, progression-free duration. The SORCE trial was strongly supported by Australian sites via ANZUP, and further adjuvant studies are ongoing with immunotherapy agents.

Effect of antacids intake on the therapeutic efficacy of sunitinib (SUN) in metastatic renal cell carcinoma (mRCC) patients (pts)

Authors: Schlack K et al.

Summary: The effect of antacid therapy on the efficacy of sunitinib was reported for a real-world population of 550 patients with metastatic RCC from the German STAR-TOR registry who received first-line sunitinib. Antacid use at baseline was documented for 69% of the patients. No relevant differences were seen between antacid users and nonusers for any adverse event. Compared with antacid nonusers, antacid users had a lower overall response rate (15.1 vs. 27.4% [p=0.007]) and a shorter OS duration (20.3 vs. 25.7 months [p=0.01]).

Comment: A major challenge for all healthcare professionals is Donald Rumsfeld’s favourite non sequitur … the unknown unknowns where you don’t know what you don’t know. One of these was reported in this poster, which shows that people taking antacids while also taking sunitinib for metastatic RCC experience poorer response and worse, poorer OS. Registration and reimbursement are just the beginning; much remains to be learned for every drug in every disease, and stage 4 trials are essential to enable us to avoid these kinds of catastrophes, and conversely to find opportunities to make medicines more effective.
Prior tyrosine kinase inhibitors (TKI) and antibiotics (ATB) use are associated with distinct gut microbiota 'guilds' in renal cell carcinoma (RCC) patients

Authors: lebb a V et al.

Summary: These researchers performed a network analysis of gut microbiota from patients with RCC treated with nivolumab to explore relationships of 'guilds' of bacterial communities with prior exposure to antibiotics (n=11), axitinib (n=13), sunitinib (n=49), other TKIs (n=20) and clinical outcomes. The response rate with nivolumab treatment was 48%. Cross-validation of overall faecal microbiota composition stratified the patients with different predictive power: antibiotics 84%, axitinib 81%, sunitinib 69% and outcome 49%. The network analysis identified six guilds (G1–G6). Of these, guild G1–G2 behaved in opposite ways and were topologically separated by negative correlations. Both were related to nonresponse, while G1 was dominated by species related to antibiotics. In contrast, G2 was mainly represented by species related to no antibiotic exposure and greater susceptibility to prior TKI exposure (where axitinib and sunitinib behaved in an opposite way) compared with the other guilds. Guild G4 was mainly inhabited by species related to TKIs other than axitinib and sunitinib. It was determined that definite bacterial species were able to drive the stratification into guilds of the global RCC network, such as Akkermansia muciniphila for response and Dorea formicigena for no antibiotic exposure.

Comment: In a similar theme, workers from the Institut Gustave Roussy have presented further work on the relationship of the faecal microbiome to treatment outcomes in kidney cancer patients in particular in the context of immunotherapy agents. As noted before, there are negative influences associated with the recent use of antibiotics, but most intriguingly, there are also associations with the recent use of some TKIs. For example, recent sunitinib was associated with a negatively influencing microbiome, whereas axitinib did not have an association. This obviously has intriguing implications for treatment sequencing, and in particular combination therapy with immunotherapy agents and TKIs. Interventional trials cannot be far away.

Efficacy of immune checkpoint inhibitors (ICI) and genomic alterations by body mass index (BMI) in advanced renal cell carcinoma (RCC)

Authors: LaiLai A-KA et al.

Summary: The impact of BMI in patients with RCC treated with PD-1/ PD-L1-based immune checkpoint inhibitor was explored along with potential genomic alterations in this retrospective analysis of 735 patients with median follow-up of 13.5 months; 76% of the patients were male, 85% had clear-cell histology and 60% were intermediate-risk. Thirty-one percent of the patients had received first-line immune checkpoint inhibitors and 31% received combination immune checkpoint inhibitor therapy, and when these treatments were started, 37% and 63% had BMIs of <25 and ≥25 kg/m², respectively. Compared with patients from the lower BMI group, those in the higher BMI group had a better 1-year OS rate (79% vs. 66% adjusted HR 0.75 [0.57–0.97]), but there was no significant difference for ORR or median time to treatment failure. There was also no significant difference between the low and high BMI groups for genomic alterations or tumour mutational burden among patients with clear-cell RCC and available next-generation sequencing data (n=519).

Comment: Finally in the theme of risk factors (perhaps in this case not modifiable), an analysis of the IMDC database has reported that the baseline BMI is linearly associated with treatment outcome in people with metastatic kidney cancer taking immune checkpoint inhibitors. A similar association has been reported with VEGFR TKIs in this disease. In an exploratory analysis, there were no gross differences in the mutational spectrum of patients with high and low BMI; i.e. at first blush this is not simply due to poor prognosis genomics being associated with more aggressive clinical courses.

A phase II trial of TKI induction followed by a randomized comparison between nivolumab or TKI continuation in renal cell carcinoma (NIVOSWITCH)

Authors: Grünwald V et al.

Summary: Patients with metastable advanced or metastatic clear-cell RCC (31%, 65% and 4% favourable-, intermediate- and poor-risk, respectively) who had a PR (59%) or stable disease (41%) after sunifinb 50mg or pazopanib 800mg once daily for 10–12 weeks were randomised to continue their TKI treatment (n=24) or switch to intravenous nivolumab 240mg or 480mg every 2–4 weeks (n=25) until progression or intolerance. In an intent-to-treat analysis, the best overall response rate did not differ significantly between the nivolumab versus TKI continuation arms when assessed from the start of induction therapy (64% vs. 70% [p=0.76]), but the rate was lower for nivolumab recipients when assessed from randomisation (16% vs. 48% [p=0.029]). The respective any-grade adverse event rates in the nivolumab and TKI continuation arms were 96% and 100%, with rates of 44% and 67% for grade 3–5 events and 40% and 38% for serious events.

Comment: When we have treatments that can benefit some patients, we then seek to refine these to extend those benefits to more patients. In this study from one of the German consortia, patients showing benefit from a first-line VEGFR TKI were randomised to continue that TKI or switch to second-line nivolumab. The switch to nivolumab did not improve response rate and had little effect on toxicity. The concept of a TKI causing some kind of immunogenic cell death and immunotherapy induction is not supported by these data, and in retrospect, with more robust benefits from immunotherapy seen in patients least likely to respond to VEGFR TKIs (as seen in Checkmate 214), this result is less surprising.

Poster abstract 959P

Abstract

Tailored immunotherapy approach with nivolumab in advanced renal cell carcinoma (TITAN-RCC)

Authors: Grimm M-O et al.

Summary: Patients with intermediate-risk (70%) or poor-risk (27%) advanced clear-cell RCC requiring first- and second-line therapy received induction nivolumab 240mg every 2 weeks, and those with significant disease progression at week 8 or either stable disease or progression at week 16 received 2–4 boost cycles of nivolumab plus ipilimumab, while those who achieved PR or CR continued with maintenance therapy, with nivolumab plus ipilimumab boosts only for progression. This efficacy analysis reported on 108 first-line and 99 second-line participants. The best overall response rates after nivolumab induction with or without nivolumab plus ipilimumab boosts were 37% and 28% in first- and second-line participants, respectively. Among 102 participants who received nivolumab plus ipilimumab boosts for either stable disease of progression by week 16, the PD/CR rate was 12% and the stable disease rate was 53%. Six percent of participants who received boosts for stable disease went on to progress, compared with 51% with early progression. Treatment-related adverse events were presented.

Comment: This is a second trial attempting to optimise treatment attempts to 'taylor' therapy by offering patients single-agent immunotherapy alone, and if this was unsuccessful, 'boosting' their immune system with combination ipilimumab plus nivolumab. Early data were presented showing that the response to nivolumab was 28%, and then in patients with stable disease/disease progression at week 16, a response rate of 38% overall was reported. Patients were also treated with this combination in second-line therapy, but this is less relevant to routine practice in Australia. Overall, only ~10% of patients experienced a response to ipilimumab plus nivolumab boost after not experiencing a response to single-agent nivolumab. These are intriguing data that merit further investigation, as the potential cost and toxicity savings may be important. Two early criticisms of this study are the primary endpoint (response rate is a poor surrogate of OS with checkpoint immunotherapy – landmark PFS is better) and the relatively long duration of therapy on first-line nivolumab of 16 weeks; if there is early progression that might have been ‘rescued’ by ipilimumab, then patients may have missed an opportunity. A robust on-treatment predictive biomarker, if available, would allow a more rapid determination of PD-1 treatment resistance. Watch this space.

Profferred Paper 2 – Genitourinary tumours, non-prostate; Abstract LBA57

Abstract

Independent commentary by Dr Craig Gedye BSc(Hons) MBChB FRACP PhD

Dr Gedye is a physician/scientist, dual trained as a medical oncologist, clinical trialist and basic science researcher. He works for patients with melanoma, brain, kidney, prostate, tests, and bladder cancer at the Calvary Mater Newcastle, and is the Clinical Research Director at the NSW Statewide Biobank. He chairs the Renal Cancer Subcommittee for ANZUP Cancer Trials Group, and is the coordinating principal investigator for the KeyRAD and UNISON trials. He undertakes translational and basic cancer research at the Hunter Medical Research Institute, University of Newcastle. Dr Gedye’s research focus is on cancer heterogeneity: why treatments work for some patients but not others. This challenging research spans the translational spectrum from patient experience to basic science.
ESMO 2019 Conference Review
Focus on Renal Cancer

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ADAPTeR: a phase II study of anti-PD1 (nivolumab) therapy as pre- and post-operative therapy in metastatic renal cell carcinoma

Authors: Au Li et al.

Summary: Fifteen treatment-naive patients with metastatic clear-cell RCC received neoadjuvant nivolumab 3 mg/kg every 2 weeks before and after cytoreductive nephrectomy until progressive disease in this research. Median follow-up was 12.5 months. The side effect profile of nivolumab was deemed to be acceptable, and the overall response rate was 37%. Preliminary transcriptome analyses of pretreatment biopsies (33 samples from 14 participants; <4 regions per case) revealed enrichment for primary resistance (defined as disease progression within 2 months; n=4) with immune 'cold' tumours, as distinct from 'hot' tumours. Histological TIL scoring revealed concurrent immune phenotypic clusters. Primary-resistant cases had no on-treatment stromal and intraepithelial TILs (evaluable n=2), whereas 70–90% stromal and 30–90% intraepithelial TILs were detected on-treatment across seven regions at nephrectomy in an exceptional responder receiving treatment for >24 cycles.

Comment: Finally, early reports of another novel optimisation strategy were presented, with a single-centre study of neoadjuvant and postoperative nivolumab immunotherapy in people with metastatic RCC undergoing cytoreductive nephrectomy. In a small number of patients so far, safety was unremarkable, but the response rate of 37% is encouraging, and more intriguingly, immediate predictive biomarkers could be speculated from tumour resection specimens. Some patients had no clinical benefit and corresponding poor immune infiltrations – one can imagine NOT recommending further nivolumab, and rather enrolling in a trial or escalating therapy; likewise, other patients had clinical responses that aligned with robust intratumoural immune landscapes; this would be reassuring for ongoing monotherapy.

Poster Discussion – Genitourinary tumours, non-prostate; Abstract 907PD

ENTRATA: randomized, double-blind, phase II study of telaglenastat (tela; CB-839) + everolimus (E) vs placebo (pbo) + E in patients (pts) with advanced/metastatic renal cell carcinoma (mRCC)

Authors: Motzer RJ et al.

Summary: In the ENTRATA trial, patients with measurable metastatic RCC who had received ≥2 prior lines of systemic therapy, including ≥1 VEGFR TKI, were stratified by prior TKI line and randomised to receive oral everolimus 10mg once daily with either oral telaglenastat 30mg (n=42) or placebo (n=23) twice daily until disease progression or unacceptable toxicity. Compared with everolimus plus placebo, everolimus plus telaglenastat was associated with a longer median PFS duration (3.6 vs 1.9 months; HR 0.64 [95% CI 0.34–1.20]). The respective grade ≥3 adverse event rates for the everolimus plus telaglenastat and everolimus plus placebo arms were 80% and 60%; the most common were anaemia (17% and 17%), pneumonia (7% and 4%), abdominal pain (7% and 0%), thrombocytopenia (7% and 0%) and fatigue (4% and 9%), and the associated discontinuation rates were similar (28% and 30%). No treatment-related deaths were recorded. Consistent findings were seen in subgroup analyses. Survival data were presented at the Congress.

Comment: Several new agents for kidney cancer were reported at ESMO19. The first of these exploits a known metabolic peculiarity of clear-cell RCC: an overreliance on the tricarboxylic acid cycle and oxidative phosphorylation (you know... the Krebs cycle?... or sorry, did that give nasty flashbacks to second-year Biochemistry? – apologies.) In the ENTRATA study, the novel glutaminase inhibitor telaglenastat (CB-839) was offered to people with TKI-refractory clear-cell RCC, in combination with everolimus, versus the now traditional largely useless strawman control of these exploits a known metabolic peculiarity of clear-cell RCC: an overreliance on the tricarboxylic acid cycle and oxidative phosphorylation (you know... the Krebs cycle?... or sorry, did that give nasty flashbacks to second-year Biochemistry? – apologies.) In the ENTRATA study, the novel glutaminase inhibitor telaglenastat (CB-839) was offered to people with TKI-refractory clear-cell RCC, in combination with everolimus, versus the now traditional largely useless strawman control of everolimus alone. A small increment in PFS was seen (1.7 months) with a modest increase in toxicity, but no increase in treatment discontinuation for toxicity. The results of the CANTATA study, where telaglenastat is combined with cabozantinib at an earlier stage of disease, will be more clinically relevant and are eagerly awaited.

Proffered Paper 1 – Genitourinary tumours, non-prostate; Abstract LBA54

A first-in-human phase I/II trial of the oral HIF-2α inhibitor PT2977 in patients with advanced RCC

Authors: Jonasch E et al.

Summary: Three patients with advanced solid tumours received dose-escalated oral PT2977, a potent, selective small-molecule HIF-2α inhibitor, and 52 patients with advanced clear-cell RCC (73% intermediate-risk and 18% poor-risk) who had received ≥1 prior therapy entered an expansion phase 2 trial in which they received PT2977 120mg once daily. At the time of reporting, all-grade, all-cause adverse events with incidences ≥25% were anaemia (75%), fatigue (64%), dyspnoea (44%), nausea (33%), peripheral oedema (29%) and cough (27%), and the most common grade 3 adverse events and on-target effects of HIF-2α inhibition were anaemia (20%) and hyponatraemia (11%). The treatment-related adverse event discontinuation rate was 4%. The confirmed PR rate was 24%, the stable disease rate was 54% with a clinical benefit rate of 78%, and the estimated 40-week PFS rate was 50.1%.

Comment: As well as the distinctive metabolic reprogramming noted previously, RCC is best known as driven by angiogenesis, largely due to the loss of VHL expression which in turn drives HIF-1α overexpression. HIF-1 inhibitors have been unimpressive so far, but this poster describes the early experience of a novel HIF-2α inhibitor. HIF-2α signalling is linked in a complex fashion with HIF-1, but wasrationally selected as a potential target for RCC. This is a promising first set of data, with infrequent discontinuation due to toxicity and impressive activity at an early stage of development.

Poster Discussion – Genitourinary tumours, non-prostate; Abstract 911PD

Safety and efficacy of the oral CXCR4 inhibitor X4P-001 + axitinib in advanced renal cell carcinoma patients: an analysis of subgroup responses by prior treatment

Authors: McDermott DF et al.

Summary: Patients who had failed ≥1 prior treatment for advanced RCC (n=65) received oral X4P-001 (a selective, oral CXCR4 antagonist) at a dosage of 200mg twice daily or 400mg once daily, along with oral axitinib 5mg twice daily, in a combined phase 1/2 study; the participants’ median treatment duration was 25 weeks. Twelve of the participants remained on combination therapy at the time of reporting. Among 62 evaluable participants, the ORR was 29% (including one CR and 17 PRs) and the interim median PFS duration was 7.4 months. Among participants who had received immediate prior TKI therapy, the ORR was 18% and median PFS duration was 7.4 months, and the respective ORR and PFS duration for those who had received immediate prior immune-oncological therapy were 61% and 11.6 months. The adverse event-related study discontinuation rate was 20%. Any-grade treatment-related adverse events with incidences ≥20% were diarrhoea (54%), decreased appetite (45%), fatigue (43%), hypertension (38%), nausea (28%) and dysphonia (22%), and the most common grade ≥3 treatment-related adverse events were hypertension (22%) and diarrhoea (11%).

Comment: Finally, we saw an initial clinical report of a novel agent targeting a pleiotropic pathway in kidney cancer. CXCR4 is a chemokine that has multiple signalling effects, including angiogenesis, immune regulation and metastatic potential. Small-molecule inhibitors of CXCR4 like plerixafor have been in use in haematology for over a decade, but interest in solid tumours is growing. In combination with axitinib, this novel oral CXCR4 inhibitor was associated with tumour responses with modest durability, but reasonable toxicity leading to discontinuation in 20% of patients. The potential immune synergy will make this target and drug something to watch in the near future.

Poster Discussion 2 – Immunotherapy of cancer; Abstract 1186PD

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