Medicom International Conference Series in Urology

2021 Genitourinary Cancers Symposium

American Society of Clinical Oncology

11-13 FEBRUARY 2021

PEER-REVIEWED CONFERENCE REPORT

Apalutamide in prostate cancer

In the ACIS trial, the addition of apalutamide to abiraterone acetate plus prednisone/prednisolone reduced the risk of radiographic progression or death in men with mCRPC who had not received prior chemotherapy.

read more on PAGE 4

Superior outcomes with nivolumab + cabozantinib in RCC

An in-depth analysis of CheckMate 9ER of nivolumab plus cabozantinib versus sunitinib demonstrated superior clinical outcomes and health-related quality of life in patients with renal cell carcinoma.

read more on PAGE 7

Enfortumab vedotin promosing for bladder cancer

In the phase 3 EV-301 trial, treatment with enfortumab vedotin resulted in prolonged overall survival rates in patients with previously treated locally advanced or metastatic urothelial carcinoma compared with treatment with chemotherapy.

read more on PAGE 15

MEDICOM MEDICAL PUBLISHERS

Editor Dr Stefan Rauh, Centre Hospitalier Emile Mayrisch, Esch, Luxembourg

Contents

COLOPHON

Editor	**Dr Stefan Rauh** Centre Hospitalier Emile Mayrisch, Luxembourg
Advisory Board	Dr Saeed Dabestani Lund University, Sweden
	Prof. Axel Merseburger University Hospital Schleswig-Holstein, Germany
Publishing Director	Paul Willers
Editorial Manager	Lisa Colson
Editorial Coordinators	Deirdre Boucherie Sanne Lauriks
Medical Writer	Dr Kelly Schoonderwoerd
Production Manager	Desiree Heijl
Graphic Design	MOOZ grafisch ontwerp
Layout	Wim Kempink
Cover Image	Shutterstock
ISSN	2468-8762 21:2

MEDICOM MEDICAL PUBLISHERS

Head Office
Medicom Medical Publishers
Faas Eliaslaan 5
3742 AR Baarn
The Netherlands

Postal address
Medicom Medical Publishers
PO Box 90
3740 AB Baarn
The Netherlands

Telephone +31 85 4012 560
E-mail publishers@medicom-publishers.com

Letter from the Editor

Dr Stefan Rauh

Dear Reader,

I hope you will enjoy our Medicom Conference Report of this year's ASCO GU Symposium. As usual, I'll just sample some abstracts as "teasers":

As you will see, we are coming closer to implementing a personalised medicine approach to prostate cancer, with both new prognostic and predictive markers identified.

LuPSMA has been used in daily practice for years in some European countries – now there's more evidence that this was/is justified.

A new target, a new conjugate – very promising results in advanced bladder cancer treatment.

This comes at a price – and we are increasingly at odds to pay for. Please read the interesting article on the necessary overhaul of licensing and reimbursement of oncology drugs.

So, how about repurposing a cheap drug? Is there a new role for ACE inhibitors in bladder cancer treatments? It may be a little early for that, as this is retrospective data – and there's a long history of supposedly promising but finally inefficient repurposed drugs in oncology. Still..

Please enjoy our congress report.

Yours, sincerely,
Stefan Rauh

Biography
Dr Stefan Rauh is currently working as haemato-oncologist in the oncology department of Centre Hospitalier Emile Mayrisch, Esch, Luxembourg. He is mainly involved in clinical work but also in research and teaching activities and is interested in public policy and international cooperation projects in oncology. He is member of the ESMO Practicing Oncologist's Working Group since 2011 (chair 2014–2018), member of the ESMO Public Policy Committee, and has been an ESMO Executive Board member in 2015–2016. He is co-author of the 2017 ESMO European Cancer Patient Coalition (ECPC) Patient Survivorship Guide and an invited expert for the ECPC.

Conflict of Interest:
Nothing to declare.

Prostate Cancer

Lu177 as a promising new therapy for metastatic prostate cancer

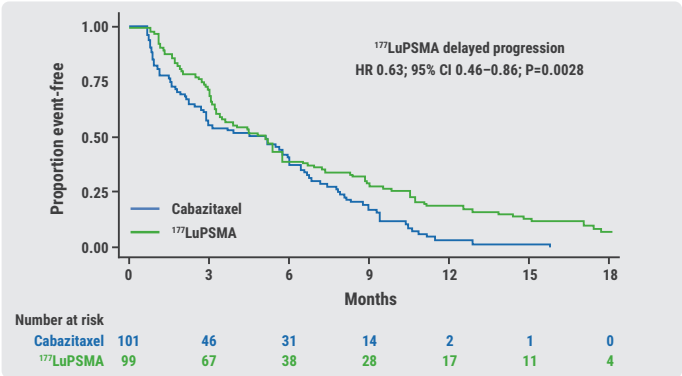
Radionuclide therapy directed towards prostatespecific membrane antigen (PSMA) showed promising results in men with docetaxel-treated metastatic castration-resistant prostate cancer (mCRPC) [1]. A phase 2 trial comparing the use of radionuclide therapy using lutetium-177 (Lu177) with chemotherapy using cabazitaxel found greater reductions in prostate-specific antigen (PSA) levels, longer periods of progression-free survival (PFS), and greater tumour objective response rates (ORR) in patients treated with Lu177.

The cell surfaces of prostate cancers strongly express PSMA – even more so in cases of mCRPC. For this reason, PSMA is used both for imaging prostate cancer and as a target for radionuclide therapy.

Dr Michael Hofman (Peter MacCallum Cancer Centre, Australia) discussed the open-label, randomised, multicentre, phase 2 TheraP trial (NCT03392428), which assessed the activity and safety of Lu177-labelled PSMA (LuPSMA) for the treatment of mCRPC [1]. Included men with docetaxel-treated mCRPC and high PSMA expression (n=200) were randomised to receive either ≤6 cycles of radionuclide therapy with LuPSMA or ≤10 cycles of chemotherapy with cabazitaxel.

The primary outcome measure was PSA response rate, defined as the proportion of participants in each group with a ≥50% reduction in PSA from baseline. In the Lu177 group, 65 men (66%) achieved this outcome, compared with 37 men (37%) in the cabazitaxel group (see Figure).

Figure: Primary outcome measure of progression-free survival [1]



CI, confidence interval; HR, hazard ratio; ^{177}LuPSMA, lutetium-177-labelled prostate-specific membrane antigen.

Secondary outcome measures included 9 parameters and were analysed after a median follow-up period of 18.4 months. PFS was 19% (95% CI 12–27%) in the radiotherapy group versus 3% (95% CI 1–9%) in the cabazitaxel group (HR 0.63; 95% CI 0.46–0.86; P=0.003; 173 events). Comparable results were found for both radiographic PFS (HR 0.64; 95% CI 0.46–0.88; P=0.007; 160 events) and PSA-PFS, which was defined as the time from randomisation to PSA progression (HR 0.60; 95% CI 0.44–0.83; P=0.002; 172 events). ORR was 49% (95% CI 33–65%) in the Lu177 group and 24% (95% CI 11–38%) in the chemotherapy group (P=0.019). Overall survival will be monitored for 4 years; this data is not yet available since the study only reached its completion date January 2021. To date, 90 deaths are reported. Regarding pain outcomes, 60% of participants in the radiotherapy arm and 43% of participants in the cabazitaxel arm reported pain (RR 1.42; 95% CI 0.84–4.48; P=0.10) at the end of follow-up.

Adverse events (AEs) were monitored from the time of first study dose to 12 weeks after treatment completion. Fewer grade 3 and 4 AEs occurred in the Lu177 group than in the cabazitaxel group (33% vs 53%). The top 3 grade 3 or 4 AEs experienced in the Lu177 group were thrombocytopenia, anaemia, and fatigue; in the cabazitaxel group, they were neutropenia, anaemia, and diarrhoea.

Concerning health-related quality of life outcomes, global health status scores were similar between the groups: LuPSMA was 64 (95% CI 61–67) versus 60 for cabazitaxel (95% CI 57–64). Nonetheless, the Lu177 group reported favourable outcomes compared with the cabazitaxel group in the domains fatigue (34 vs 40; P<0.05), social functioning (79 vs 73; P<0.05), insomnia (24 vs 29; P<0.05), and diarrhoea (8.3 vs 15.6; P<0.001). No domains were favourable in the chemotherapy group.

Dr Hofman concluded that these interim results support the use of LuPSMA as an alternative to cabazitaxel in men with docetaxel-treated mCRPC.

1. Hofman M. 177Lu-PSMA-617 (LuPSMA) versus cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel: Updated results including progression-free survival (PFS) and patient-reported outcomes (PROs) (TheraP ANZUP 1603). Abstract 6, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

Role of prostate cancer genomics is evolving

Compelling preliminary evidence supports the use of genomics to inform clinical decision-making for the management of prostate cancer. A genome-wide RNA array could serve as an independent prognostic predictor of oncological outcomes.

Dr Ashley Ross (Feinberg School of Medicine, Northwestern University, Chicago, USA) reviewed outcomes of interventions in prostate cancer that considered the Genomic Classifier (GC) score of participants [1]. The Decipher test is a genome-wide RNA expression array that yields a GC score based on 22 genes associated with oncologic pathways. It has been highly validated and is widely available. The GC score ranges from 0–1, with a score of 0–0.45 representing a low risk of clinical progression and a score of 0.60–1.0 representing a high risk of clinical progression.

Dr Ross suggested that the 22-gene GC was an independent prognostic predictor of clinical outcomes following prostatectomy. Dr Ross further demonstrated that adjuvant radiation (defined as radiation administered before reaching a prostate-specific antigen [PSA] value of 0.1 ng/mL) can be considered for patients with >1 of the following risk factors: seminal vesicle invasion, microscopic lymph node involvement, a high Gleason grade group, or a high GC score (i.e. >0.60).

Finally, men who have a low GC score (i.e. <0.45) and receive early salvage radiation should consider the omission of androgen deprivation therapy, as analyses have demonstrated only minimal effect on distant metastases and cancer-specific mortality, and decreased overall survival in these situations. However, in men with intermediate or high GC scores receiving early salvage radiation therapy, all 3 of these parameters were improved.

1. Ross A. Use of Genomics to Guide Treatment Decisions in Post-prostatectomy Patients. ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

Apalutamide prolongs progression-free survival in prostate cancer

The addition of apalutamide to abiraterone acetate plus prednisone/prednisolone (AAP) reduced the risk of radiographic progression or death in men with metastatic castration-resistant prostate cancer (mCRPC) who had not received prior chemotherapy [1].

Both activated androgen receptors and elevated androgen production promote prostate cancer; therefore, treatment is directed towards both blocking androgen receptors and suppressing androgen production. Apalutamide is an androgen receptor inhibitor and abiraterone acetate is an androgen inhibitor that works via ligand suppression. Abiraterone acetate is administered in combination with either prednisone or prednisolone. The ACIS trial (NCT02257736) hypothesised that additional benefit could be conferred by combining these therapies.

Dr Dana Rathkopf (Memorial Sloan Kettering Cancer Center, New York, USA) shared the results of the phase 3, randomised, double-blind ACIS trial designed to compare radiographic progression-free survival (rPFS) in mCRPC patients receiving apalutamide in addition to AAP with rPFS in mCRPC patients with receiving placebo plus AAP. None of the 982 patients in the study had been previously treated with chemotherapy.

The primary endpoint was investigator-assessed rPFS over a time frame defined as time from randomisation until death, loss to follow-up, withdrawal of consent, or end of study, whichever occurred first, up to 5 years. Progression of soft tissue lesions was defined according to the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. After a median follow-up of 25.7 months, the median rPFS in the apalutamide plus AAP group was 22.6 months, versus 16.6 months in the placebo plus AAP group (HR 0.69; 95% CI 0.58–0.83; P<0.0001). These results equated to an extension of rPFS of 6 months and a 31% reduction in risk of rPFS in chemotherapy-naïve mCRPC patients.

Secondary outcomes were overall survival, prostate-specific antigen (PSA) response, time to initiation of opioid use, time to initiation of chemotherapy, and time to pain progression (as measured by the Brief pain inventory-short form scale). The first interim analysis for overall survival also occurred after a median period of 25.7 months, and the apalutamide plus AAP treatment arm showed a longer median OS than the placebo plus AAP treatment arm, although not statistically significant. The apalutamide plus AAP group demonstrated a significantly higher rate of ≥50% decline in PSA compared with placebo plus AAP (RR 1.09; 95% CI 1.02–1.17; P=0.015). Time to PSA response, time to initiation of opioid use, time to initiation of chemotherapy, and time to pain progression did not differ significantly between the 2 treatment groups.

In terms of treatment-emergent adverse events, 310/490 (63.3%) participants in the apalutamide plus AAP group reported grade 3 to 4 adverse events, compared with 275/489 (56.2%) participants in the placebo plus AAP group. No new safety concerns were identified.

1. Rathkopf D. Final results from ACIS, a randomised, placebo-controlled double-blind phase 3 study of apalutamide and abiraterone acetate plus prednisone (AAP) versus AAP in patients with chemo-naive metastatic castration-resistant prostate cancer (mCRPC). Abstract 9, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

Dose-intensified radiation therapy fails to provide better outcomes in prostate cancer

A dose-intensified salvage radiotherapy protocol administered to men with adenocarcinoma of the prostate who had undergone radical prostatectomy failed to prolong freedom from biochemical progression of the disease.

Prof. Pirus Ghadjar (Charité Universitätsmedizin Berlin, Germany) presented the results of the SAKK 09/10 trial (NCT01272050), an open-label, multicentre, randomised phase 3 trial that sought to compare the effectiveness of 2 salvage radiotherapy regimes for the treatment of patients who had relapsing prostate cancer following radical prostatectomy [1]. Relapse was defined as 2 consecutive rises in prostate-specific antigen (PSA) level with the second rising value >0.1 ng/mL, or 3 consecutive rises.

Patients (n=350) were randomised 1:1 to receive either conventional-dose radiotherapy (64 Gray [Gy] in 32 fractions administered over 6.4 weeks) or dose-intensified radiotherapy (70 Gy in 35 fractions administered over 7 weeks) directed to the prostate bed.

The primary endpoint was freedom from biochemical progression (defined as PSA ≥0.4 ng/mL and rising). At 6 years, freedom from biochemical progression was 62.3% versus 61.3% for the 64 Gy versus the 70 Gy arm, respectively, with an HR of 1.14 (95% CI 0.82–1.60; log-rank P=0.44).

Secondary endpoints included clinical progression-free survival, time to hormonal treatment, and overall survival. These outcome measures were not significantly different between the treatment groups.

Genitourinary (GU) and gastrointestinal (GI) toxicity were tracked as well. GU toxicity was not significantly different between the groups; however, the higher-dose protocol was associated with increased GI toxicity.

1. Ghadjar P. Dose-intensified versus conventional dose-salvage radiotherapy for biochemically recurrent prostate cancer after prostatectomy: Six-year outcomes of the SAKK 09/10 randomised phase 3 trial. Abstract 194, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

Intrinsic tumour biology may be predictive of treatment response in prostate cancer

Molecular determinants may help to identify patients that will derive the best responses to apalutamide for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC). This was concluded based on data from the biomarker cohort of the phase 3 SPARTAN trial.

The SPARTAN trial (NCT01946204) was a multicentre, randomised, double-blinded, phase 3 trial investigating apalutamide for the treatment of nmCRPC [1]. Included men (n=1,207) were randomised 1:2 to receive either apalutamide plus androgen deprivation therapy (ADH; n=401) or placebo plus ADH (n=806) until disease progression, withdrawal of consent, unacceptable toxicity, or death. At the primary endpoint analysis presented at ASCO 2020 and published in the *New England Journal of Medicine*, both metastasis-free survival and overall survival were significantly improved in the apalutamide arm [2,3].

Prof. Felix Feng (University of California San Francisco, USA) presented results from his team's analysis of the molecular signatures obtained from the biomarker cohort of the SPARTAN trial (n=233). For this analysis, participants were subdivided into those with early progression (EP) of the disease and those who were long-term responders (LTR). Using archival tissue samples from the biomarker cohort of the SPARTAN trial, researchers aimed to identify molecular signatures associated with either EP or LTR responses to treatment – either by apalutamide (n=60) or placebo (n=37).

Patients with EP or LTR had similar baseline characteristics. Increased immune activity, decreased tumour vascularisation, or decreased proliferative capacity at baseline were associated with LTR in the apalutamide group but not the placebo group (see Table). The inverse was true for EP in the apalutamide group, while increased hormonal independence or metastatic capacity at baseline was associated with EP in the placebo group. Tumours with increased expression of signatures suggestive of T-cell proliferation demonstrated a more favourable response

to apalutamide; this response was true in both basal and luminal tumours.

Table: Molecular signatures in the apalutamide + ADT group. Based on [1]

Signature classification	Transcriptional signatures	Differential expression		P-value LTR vs EP
Immune activity	T-cell stimulation: ICOS	↑ LTR	↓ EP	0.003
	T-cell proliferation: IL-2 signalling	↑ LTR	↓ EP	0.072*
	Antigen presentation: TAP2	↑ LTR	↓ EP	0.025
Tumour vascularisation	Tumour hypoxia	↓ LTR	↑ EP	0.061*
	Angiogenesis	↓ LTR	↑ EP	0.038*
Proliferative capacity	Prostate tumour proliferation score 1	↓ LTR	↑ EP	0.053
	Prostate tumour proliferation score 2	↓ LTR	↑ EP	0.053*

* Reached nominal statistical significance in Cox regression analysis only.
EP, early progression; ICOS, inducible co-stimulatory; IL, interleukin; LTR, long-term responders; TAP2, transporter associated with processing 2.

Prof. Feng concluded that these molecular signatures may be useful to predict which patients with nmCRPC will derive the most favourable treatment responses to apalutamide and other androgen receptor signal inhibitors.

1. Feng F. Molecular determinants associated with long-term response to apalutamide in nonmetastatic castration-resistant prostate cancer (nmCRPC). Abstract 8, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.
2. Small EJ, et al. Abstract 5516, ASCO Virtual Meeting, 29–31 May 2020.
3. Smith MR, et al. N Engl J Med. 2018; 378: 1408–1418.

Final TITAN trial results favour use of apalutamide

Apalutamide plus androgen deprivation therapy (ADT) in men with metastatic castration-sensitive prostate cancer (mCSPC) demonstrated improved overall survival (OS) and reduced risk of death compared with placebo.

The phase 3, randomised, placebo-controlled, double-blind TITAN trial (NCT02489318) investigated whether the addition of apalutamide to ADT would improve radiographic progression-free survival (rPFS) or OS in men with mCSPC [1]. Of the 1,052 participants, 525 received apalutamide, while 527 received a placebo. Investigators performed their first interim analysis after a median follow-up period of 22.7 months. At that time, both OS and rPFS were significantly better in the apalutamide group (OS, HR=0.67; rPFS, HR=0.48) than in the placebo group.

This analysis coincided with the unblinding of TITAN, giving patients from the placebo arm the opportunity to proceed to the open-label extension phase of the trial. Of the 527 patients in the placebo arm, 208 (39.5%) chose to cross over to receive apalutamide. Dr Kim Chi (British Columbia Cancer and Vancouver Prostate Centre, Canada) presented the TITAN results following the crossover, after nearly 4 years of follow-up.

The crossover group underwent treatment for a median duration of 15.4 months, as compared with a median treatment duration of 39.3 months for the apalutamide group, and 20.2 months for the placebo group as a whole.

Final analyses continue to show superior OS outcomes in the apalutamide group; 48-month survival rates were 65% in the apalutamide group versus 52% in the placebo group. This corresponded to a 35% reduction in the risk of death, which became a 48% reduction of death risk with the inclusion of the crossover patients. Health-related quality of life outcomes did not differ between groups, and the safety profile was consistent with that reported previously. Dr Chi concluded that these final results from TITAN support the use of apalutamide in men with mCSPC.

1. Chi K. Final analysis results from TITAN: A phase III study of apalutamide versus placebo (PBO) in patients (pts) with metastatic castration-sensitive prostate cancer (mCSPC) receiving androgen deprivation therapy (ADT). Abstract 11, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

Penile Cancer

Prognosis of penile cancer associated with HPV status

Determination of human papillomavirus (HPV) status should be done routinely at diagnosis of penile cancer. HPV-positive penile cancer has a much better prognosis than HPV-negative penile cancer, independent of age, stage, comorbidities, or treatment method [1].

Dr Adithya Chennamadhavuni (University of Iowa, USA) shared the results of his team's analysis of data from the National Cancer Database (NCDB). The analysis focussed on characteristics and outcomes of 486 men who were diagnosed with penile cancer between 2004 and 2016 and who had a known HPV status. Among 486 patients with penile squamous cell cancer, 139 (29%) had tested positive for HPV. These findings are consistent with those of previous studies, which have documented that HPV is present in 30–50% of penile cancers. The majority of participants were white, <65 years old, from low-income areas, and had either public or no insurance coverage. These characteristics were similar in HPV-negative versus HPV-positive patients.

Most HPV-positive patients presented with an early-stage tumour; at time of diagnosis, 77% had a moderately to poorly differentiated tumour. Regardless of treatment modality, a superior 5-year overall survival rate was found among HPV-positive patients: 62% versus 50% in HPV-negative patients. The risk of death in patients who had tested negative for HPV was 1.49 times that of the risk of death in patients who had tested positive for HPV. Multivariable analysis demonstrated that survival rates were superior in patients who were <65 years old, had a low Charlson-Deyo comorbidity index score (0–1), and had been diagnosed at an earlier stage of the disease.

According to Dr Chennamadhavuni, this analysis reinforces that HPV status has a bearing on the prognosis of penile cancer and should therefore be performed routinely at time of diagnosis.

1. Chennamadhavuni A. Prognostic significance of human papilloma virus (HPV) in penile cancer: A National Cancer Database (NCDB) study. Abstract 5, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

Renal Cancer

Superior clinical outcomes and QoL with nivolumab plus cabozantinib in RCC

Patients with renal cell carcinoma (RCC) treated with nivolumab plus cabozantinib demonstrated both superior clinical outcomes and superior health-related quality of life outcomes compared with patients treated with sunitinib. This was found in an in-depth analysis of the CheckMate 9ER trial.

The CheckMate 9ER trial (NCT03141177) is a phase 3, open-label, randomised controlled trial investigating whether nivolumab combined with cabozantinib is a safe and effective intervention compared with sunitinib in patients with previously untreated advanced or metastatic RCC [1]. Included patients (n=651) were randomised to nivolumab plus cabozantinib (n=323) or sunitinib (n=328) as first-line therapy until either progression of the cancer or unacceptable toxicity, with a maximum treatment duration of 2 years.

Primary and secondary outcomes were reported previously and published recently, with the primary aim of progression-free survival being superior for nivolumab plus cabozantinib after a median follow-up of 18.1 months (HR 0.51; P<0.0001) [2,3]. Both key secondary outcome measures overall survival (OS) and objective response rate (ORR) were superior in the nivolumab plus cabozantinib group (HR 0.60; OS, P=0.001; ORR, P<0.0001).

The current analysis, presented by Prof. David Cella (Robert H. Lurie Comprehensive Cancer Centre, Northwestern University, Illinois, USA), focused on in-depth health-related quality of life patient-reported outcomes, utilising 2 instruments: the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-19) and the 3-level version of the EuroQol-5 Dimensions scale (EQ-5D-3L) [1]. Participants in both study arms were invited to complete the questionnaires at baseline (>93% completion rate) and common on-treatment and follow-up visits (≥80% completion rate).

Participants receiving nivolumab plus cabozantinib reported a smaller treatment burden than those receiving sunitinib. Patients in the nivolumab plus cabozantinib treatment arm had both a decreased risk of confirmed deterioration and a delay in deterioration. Patients in the nivolumab plus cabozantinib arm demonstrated a significantly better FKSI-19 total score (mean change 2.9; P<0.0001) and subscale scores of disease-related symptoms (DRS; mean change 1.55; P<0.0001), DRS-physical, DRS-emotional, and functional well-being (P<0.05 for all subscores). EQ-5D-3L scores were in favour of nivolumab plus cabozantinib compared with sunitinib for both utility index (mean change 0.05; P=0.0005) and visual analogue scale (mean change 3.26; P=0.0011).

Overall, these results demonstrated that patients with untreated advanced or metastatic RCC can benefit from both favourable clinical outcomes and improved quality of life when treated with nivolumab plus cabozantinib instead of sunitinib.

1. Cella D, et al. Patient-reported outcomes of patients with advanced renal cell carcinoma (aRCC) treated with first-line nivolumab plus cabozantinib versus sunitinib: The CheckMate 9ER trial. Abstract 285, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.
2. Choueiri TK, et al. Presentation 6960, ESMO Virtual Congress 2020, 19–21 September.
3. Choueiri TK, et al. N Engl J Med 2021, 4 March; 384:829–841.

Lenvatinib plus pembrolizumab prolongs survival in renal cell carcinoma

A phase 3 trial discovered statistically significant prolonged progression-free survival (PFS) and objective response rates (ORR) in patients with renal cell carcinoma (RCC) treated with lenvatinib plus pembrolizumab versus patients treated with sunitinib alone. Overall survival (OS) was prolonged in patients receiving lenvatinib plus pembrolizumab, but not in those receiving lenvatinib plus everolimus compared with sunitinib. Safety of these combinations was deemed equivalent to the safety profiles of the individual agents.

Dr Robert Motzer (Memorial Sloan Kettering Cancer Centre, New York, USA) presented the results of the CLEAR trial (NCT02811861) [1,2]. This was a multi-centre, randomised, open-label phase 3 trial comparing the efficacy and safety of combination therapy lenvatinib plus either pembrolizumab or everolimus with that of single therapy sunitinib as first-line therapy for patients with advanced RCC. Patients (n=1,069) were randomised 1:1:1 to 1 of 3 treatment arms.

The primary endpoint was PFS as determined by an independent review committee. At the median follow up at 27 months, PFS was significantly longer in the lenvatinib plus pembrolizumab arm compared with the sunitinib arm (median 23.9 months vs 9.2 months; HR 0.39; 95% CI 0.32–0.49; P<0.001). PFS was also significantly longer in the lenvatinib plus everolimus treatment arm than in the sunitinib arm (median 15 months vs 9 months; HR 0.65; 95% CI 0.53–0.80; P<0.001).

Secondary endpoints included OS and ORR. OS was significantly lengthened in the lenvatinib plus pembrolizumab group (HR 0.66; 95% CI 0.49–0.88; P=0.005), but not in the lenvatinib plus everolimus group (HR 1.15; 95% CI 0.88–1.50; P=0.3). ORR was significantly improved in both dual therapy arms: in the lenvatinib plus pembrolizumab arm, ORR was 71% with a complete response rate of 16%; in the lenvatinib plus everolimus arm, ORR was 54% with a complete response rate of 10%; in the sunitinib arm, ORR was 36%, with a complete response rate of 4% (OR 2.15; 95% CI 1.57–2.93).

1. Motzer R. Phase 3 trial of lenvatinib (LEN) plus pembrolizumab (PEMBRO) or everolimus (EVE) versus sunitinib (SUN) monotherapy as a first-line treatment for patients (pts) with advanced renal cell carcinoma (RCC) (CLEAR study). Abstract 269, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.
2. Motzer R, et al. N Engl J Med. 2021 Feb 13. doi: 10.1056/NEJMoa2035716. Online ahead of print.

Inflammatory markers may guide treatment decisions in metastatic renal cell cancer

The common inflammatory marker C-reactive protein (CRP) is independently associated with time from diagnosis to initiation of treatment in metastatic renal cell cancer (mRCC). Therefore, this easily accessible test can be used to help guide clinical decision-making on when to initiate systemic therapy.

Some mRCC patients experience a prolonged time between initial diagnosis and disease progression. Systemic treatment of mRCC can be both toxic and non-curative; therefore, patients who experience an indolent disease

course are usually placed on active surveillance, delaying treatment until there are signs of disease progression. However, it can be challenging to identify which patients will be appropriately managed by active surveillance and to determine when patients on active surveillance should begin systemic anti-cancer therapy (SACT). To predict survival in mRCC, inflammatory biomarkers and a patient's International Metastatic Database Consortium (IMDC) risk score are used.

Ms Vishwani Chauhan (University of Edinburgh, UK) presented the current retrospective study that included patients diagnosed with mRCC who were on active surveillance [1]. The relationship was assessed between 6 key inflammatory biomarkers (i.e. haemoglobin, white cell count, neutrophil count, platelets, CRP, and albumin) and time to initiation of SACT.

The primary endpoint was time from diagnosis to initiation of SACT. Of the 126 patient records examined, 66 patients (52.4%) initiated SACT, with a median time between diagnosis and SACT initiation of 17.2 months. Of the remaining 60 patients, 17 (13.5%) had died while on active surveillance; this group had a median survival time of 40.4 months. The final 43 patients (34.1%) remained on active surveillance and were followed for a median period of 39.6 months.

Both CRP and albumin were predictive of duration of active surveillance (P=0.01 and P=0.049, respectively). Multivariate analysis revealed that only CRP was independently associated with time between diagnosis and initiation of SACT (P=0.035).

These results suggest that some patients diagnosed with mRCC may be appropriately managed by active surveillance for a considerable period and suggest that monitoring of CRP levels can contribute to the timing of the decision to initiate SACT.

1. Chauhan V. Prognostic biomarkers of systemic inflammation in patients on active surveillance for metastatic renal cell carcinoma (mRCC): A biobank analysis. Abstract 348, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

Clinical trial exclusion criteria may lead to lack of evidence in real-world patients: how do the excluded fare?

In a study reviewing data from patients that would otherwise be excluded from clinical trials, no difference was found in overall survival (OS) in patients with hypertension versus patients without hypertension receiving systemic therapy for metastatic renal cell carcinoma (mRCC). Further studies are indicated to analyse responses of patients with hypertension.

Clinical trial exclusion criteria often include conditions commonly seen in real-world patients, such as autoimmune disease, cardiovascular conditions, and uncontrolled hypertension. As a result, while clinical trial outcomes often demonstrate favourable responses in participants who meet the inclusion criteria as delineated, there is a paucity of research that evaluates whether these favourable results will extend to real-world patients who were precluded from trial participation by the exclusion criteria.

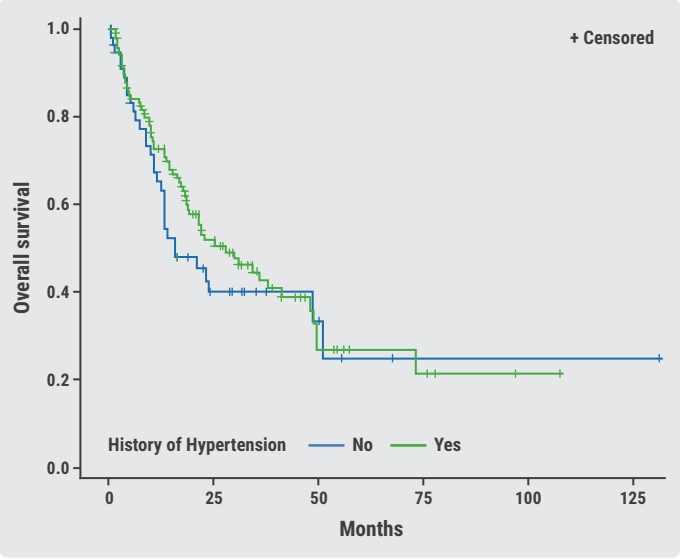
In the current analysis, Dr Diana Maslov (Ochsner Health System, Louisiana, USA) and colleagues retrospectively reviewed data from trials that allowed patients with hypertension to participate [1]. Identified were patients with mRCC who had participated in clinical trials investigating target therapies for mRCC (most commonly tyrosine kinase inhibitors [TKIs]) that did not exclude patients with hypertension. Patient characteristics, treatment type, and response to treatment (using Response Evaluation Criteria in Solid Tumours version 1.1) were analysed. Furthermore, a list of common clinical trial exclusion criteria was compiled, such as hypertension, heart, liver or renal failure, and presence of autoimmune disease.

Of the 198 patients, 142 (71.72%) had a history of uncontrolled hypertension. Most patients (n=154, 77.8%) received single TKIs; specifically, 84 received pazopanib (42.4%), 43 received sunitinib (13.6%), and 27 received cabozantinib (13.6%). The remaining 44 patients (22.2%) underwent combination therapy; specifically, 21 received axitinib plus pembrolizumab (10.6%) and 23 received ipilimumab plus nivolumab (11.6%). The median duration of therapy was 5.17 months.

The analysis for survival included 165 (83.3%) of the patients; OS was not significantly affected by a history of hypertension (P=0.38; see Figure). The median OS for patients with hypertension was 15.90 months compared with 27.80 months for patients without hypertension, yielding an OS for all patients of 22.80 months.

Similarly, there was no difference in response rate between patients with hypertension versus patients without hypertension (P=0.65). Finally, there was no difference in progression-free survival between those participants who

Figure: OS in patients with and without hypertension [1]



had a history of hypertension and those who did not (P=0.97). The investigators call for more and larger studies to analyse the effects in more recently approved therapies for mRCC in real-world practice.

1. Maslov D. The impact of hypertension on response rates in patients with renal cell carcinoma. Abstract 287, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

Axitinib offers hope for improving renal cell cancer surgical outcomes

Prof. Grant Stewart (University of Cambridge, UK) reported that the tyrosine kinase inhibitor axitinib elicited a 31% response rate in a phase 2 clinical trial exploring its effect on venous tumour thrombus (VTT) in renal cell cancer (RCC) [1].

VTT is found in 4–15% of RCC cases and the associated surgery for VTT removal bears a high morbidity and mortality rate (5–15% risk of mortality). Outcomes associated with extirpative surgery for VTT in RCC are poor, with only a 40–65% 5-year survival rate in non-metastatic RCC. Complication rates increase with the extent of the VTT. The current study aimed to determine whether surgical outcomes could be improved by pre-surgical treatment with axitinib. It was hypothesised that axitinib may help to decrease the extent of the VTT, thereby necessitating less invasive surgery and potentially improving survival rates.

The NAXIVA trial (NCT03494816) was a single-arm, single-agent, open-label, phase 2, feasibility study that evaluated the response of VTT to axitinib in 21 patients (15 males and 6 females) with a median age of 69 years, who had either metastatic or non-metastatic, clear cell RCC with venous invasion. Blood, urine, and tissue samples provided biomarkers to evaluate treatment response. All patients were scheduled for nephrectomy and inferior vena cava (IVC) tumour thrombectomy following 8 weeks of receiving steadily increasing doses axitinib (if tolerated). The starting dose of axitinib was 5 mg, then 7 mg, and finally a proposed maximum dose of 10 mg. Follow-ups were scheduled for 6 and 12 weeks after surgery.

The primary endpoint was the percentage of patients who showed a decreased level of VTT extension in accordance with the Mayo classification scheme, following 8 weeks of treatment with axitinib. At the end of the treatment period, 26.58% demonstrated a reduction in VTT extent.

The investigators also employed 4 secondary outcome measures: the percentage of change in VTT height; the percentage of patients with a change in surgical management strategy at week 9 as compared with week 1; complications delineated in accordance with the Clavien-Dindo classification scheme; and response rate as assessed using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. At week 9, VTT height showed a median reduction of 21.49% (SD, 27.60%). Of the 17 patients who progressed to surgery, 7 (41.1%) were able to undergo a less invasive surgical procedure, and 2 (11.7%) experienced complications graded as Clavien-Dindo ≥3. The response rate according to RECIST was 61.90% SD, 14.29% PR, and 9.52% PD.

The researchers concluded that the prospective data provided by the NAXIVA trial is positive. The use of axitinib prior to surgery for RCC could decrease VTT extension and thus enable a less invasive surgical approach. These changes have the potential to reduce the morbidity and mortality currently associated with extirpative surgery for VTT in RCC, as well as to increase survival time. Research is currently being conducted to identify predictors of response.

1. Stewart G. NAXIVA: A phase II neoadjuvant study of axitinib for reducing extent of venous tumour thrombus in clear cell renal cell cancer (RCC) with venous invasion. Abstract 275, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

Cabozantinib as possible new first-line therapy in translocation renal cell carcinoma

Cabozantinib may be a reasonable therapeutic option for patients with microphthalmia-associated transcriptional

factor (MiT) translocation renal cell carcinoma (TRCC) [1]. This is a welcome development for a cancer that currently lacks a standardised treatment approach under either National Comprehensive Cancer Network (NCCN) guidelines or the European Society for Medical Oncology (ESMO) framework.

MiT-family TRCCs are an aggressive subgroup of RCC (making up only about 1 to 5% of all RCCs), which strongly express cellular mesenchymal-epithelial transition factor (c-MET, a tyrosine kinase receptor). Current first-line therapy for these cancers consists of the use of vascular endothelial growth factor receptor (VEGFR)-directed agents; the progression-free survival (PFS) associated with this approach ranges from 3 to 8.4 months.

Cabozantinib is a tyrosine kinase inhibitor (TKI) that inhibits VEGFR, MET, and AXL (also a tyrosine kinase receptor). Dr Jonathan Thouvenin (Institut de Cancerologie Strasbourg Europe, France) reported results from his team's international, multicentre, retrospective analysis of 24 patients with MiT-family TRCC who had been treated with cabozantinib at any time. Determined were 3 endpoints: objective response rate (ORR) using Response Evaluation Criteria in Solid Tumors [RECIST], PFS, and overall survival (OS). The median age of the patients was 43.5 years and 17 (70.8%) were female. The majority (17, 70.8%) had undergone previous nephrectomy. The lungs were the most frequent site of metastasis (62.5%), followed by retroperitoneal lymph nodes (45.8%), and bone (37.5%).

Most patients had undergone previous treatment; 16/24 (66.7%) had received monotherapy and 6/24 (25.0%) combination therapy. Specifically, 11 (45.8%) had received monotherapy VEGFR TKIs; 5 (20.8%) had received monotherapy immune checkpoint inhibitors; 4 (16.7%) had been treated with a combination of VEGFR TKIs and immune checkpoint inhibitors; and 2 (8.3%) had been treated with a combination of immune checkpoint inhibitors.

Of the 24 patients, 7 (29.2%) had received cabozantinib as a first-line therapy, 9 (37.5%) had received it as a second-line therapy, and the remaining 8 (33.3%) as a third-line (or beyond) therapy. Only 4 patients (16.7%) achieved an ORR; 1 (4.2%) was deemed complete and 3 (12.5%) were deemed partial. Of the remaining 20 patients, 11 (45.8%) had stable disease, whereas 9 (37.5%) suffered disease progression. Following a median follow-up of 14 months, the median PFS was 8.4 months (95% CI 3.57–11.57). The median OS was 17 months (CI 95% 10.4–NA).

Treatment-related grade 3–4 adverse events were experienced by 9 patients (37.5%). A further 5 (20.8%) experienced treatment-related adverse events to the extent that they decided to discontinue therapy. There were no treatment-related deaths.

These results constitute real-world evidence that cabozantinib provided a more durable response than that seen with other first-line therapies described in the literature for MiT TRCC systemic treatment.

1. Thouvenin J. Efficacy of cabozantinib in advanced MiT family translocation renal cell carcinomas (TRCC). Abstract 274, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

Predictors of oral anti-cancer agent utilisation in renal cell carcinoma

Patients who are older, frail, and have a higher comorbidity burden are less likely to use oral anti-cancer agents (OAAs) compared with younger, more fit patients with fewer comorbidities.

Prof. Stephanie Wheeler (University of North Carolina, USA) shared the results of her team's investigation into the use of OAAs [1]. First, they note that OAAs offer several advantages; they are less invasive than intravenously administered drugs and they offer greater convenience and flexibility regarding location of administration. However, the use of OAAs also has potential disadvantages, including the risk of interactions with food or other drugs, difficulty in taking the agent due to odynophagia (i.e. painful swallowing), risk of missed doses, and, typically, increased cost.

The investigators sought to identify which patients would be more likely to adopt the use of OAAs following a diagnosis of metastatic renal cell carcinoma (mRCC). They retrospectively analysed data from the records of 713 patients contained in a registry-linked, multi-payer claims database to discover patterns associated with use of multiple OAAs (i.e. axitinib, cabozantinib, everolimus, lenvatinib, pazopanib, sorafenib, and sunitinib). All patients had been diagnosed with mRCC and were only included if they had been enrolled in the database for ≥12 months after diagnosis.

Unadjusted and adjusted risk ratios and 95% confidence limits were estimated for associations between use of OAAs

and certain patient characteristics. Results demonstrated only a 37% usage of OAAs by the patients. Moreover, there was a definite trend towards lower uptake by patients who were older, frail, and had a greater burden of comorbidities. Other patient characteristics such as sex, race/ethnicity, urban versus rural, or public versus private insurance proved not to be predictive of OAA use.

More research into these patterns is warranted so that decisions regarding highest quality patient care can be guided by appropriate guiding principles.

1. Wheeler S. Patterns and predictors of oral anticancer agent utilization in diverse metastatic renal cell carcinoma patients. Abstract 279, ASCO Genitourinary Cancers Symposium, 11-13 February 2021.

Denosumab plus pembrolizumab in advanced clear cell renal cell carcinoma

Preliminary studies have demonstrated that denosumab, an inhibitor of receptor activator of NF-κB ligand (RANKL), may potentiate the effects of the PD-1 inhibitor pembrolizumab. This potential was further studied in the KEYPAD trial in patients with unresectable or metastatic clear cell renal cell carcinoma (ccRCC).

Dr Craig Gedye (Calvary Mater Newcastle, Australia) discussed the KEYPAD trial (NCT03280667) at ASCO GU 2021 [1]. While some benefit is derived from treatment with vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin (mTOR) inhibitors, the prognosis for patients with unresectable or metastatic ccRCC remains poor, as the disease inevitably progresses. Cytokine immunotherapy, although highly toxic, has met with some success.

KEYPAD is a single-arm, multicentre, phase 2 trial aiming to investigate the activity and safety of combining denosumab with pembrolizumab in unresectable or metastatic ccRCC. The study will recruit 70 adults who will receive 200 mg pembrolizumab intravenously every 3 weeks (Q3W) combined with 120 mg denosumab subcutaneous on days 1, 8 and 22 and then Q3W until disease progression, toxicity, or participant withdrawal, up to a maximum of 2 years.

The primary completion date is scheduled for December 2022. The primary outcome measure will be the objective tumour response rate, as measured by Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. Secondary outcome measures to be tracked are progression-free survival, disease control rate, time to objective tumour response, time to first skeletal-related event, frequency and severity of adverse events, and frequency of treatment delays and discontinuation due to toxicity.

Dr Gedye concluded that favourable outcomes may lead to a new standard of care and would offer new hope for those afflicted with unresectable or metastatic ccRCC.

1. Gedye C. Denosumab and pembrolizumab in clear cell renal carcinoma (KEYPAD): A Phase 2 trial (ANZUP1601). Abstract TPS367, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

Testicular Cancer

New prediction model for brain metastasis in germ cell tumours

Researchers have identified 5 variables that can predict brain metastasis in germ cell tumours (GCTs). Clinicians can use the resulting prediction model to identify high-risk patients.

The presence of brain metastasis is a negative prognostic factor in patients who have a GCT; Dr Ryan Ashkar (Indiana University Simon Comprehensive Cancer Centre, Indiana, USA) and his team sought to identify factors to establish a model to predict patients at risk for developing brain metastasis [1]. To this end, 2,291 patients from a prospectively maintained database were identified who had been treated for testicular cancer at Indiana University between January 1990 and September 2017.

Patients were separated into 2 groups based on the presence (n=154; 6.7%) or absence (n=2,137; 93.3%) of brain metastasis. Kaplan-Meier analysis demonstrated a 2-year

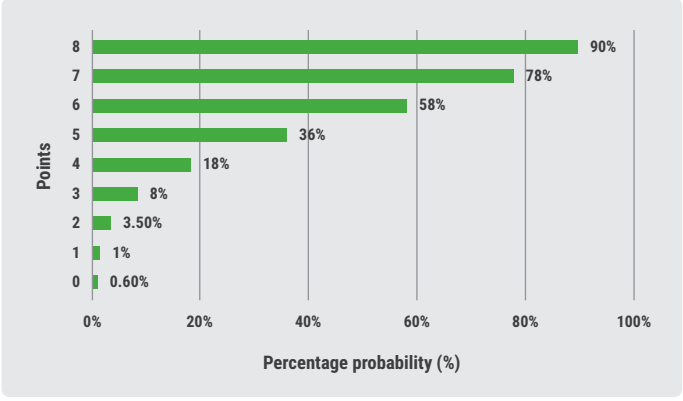
progression-free survival of 17% versus 65% (P<0.001) in those with brain metastasis versus those without. The same method showed an overall survival rate of 62% in patients with brain metastasis compared with 91% (P<0.001) in those without.

The data was then divided into datasets for training and validation of the model with equal numbers of events in each dataset. Logistic regression was used to identify a predictive model for the presence of brain metastasis. The resulting model identified weighted variables that can be used to predict progression to brain metastasis:

- age of ≥40 at time of diagnosis (1 point);
- b-hCG level ≥5,000 prior to chemotherapy (1 point);
- the presence of bone or pulmonary metastases, with pulmonary metastases further subdivided into those <3 cm or ≥3 cm:
  - bone metastasis (1 point);
  - pulmonary metastasis <3 cm (2 points);
  - pulmonary metastasis ≥3 cm (3 points); and
- histology demonstrating a predominance of chorio-carcinomatous cells (2 points).

The total number of points yields a corresponding probability of progression to brain metastasis (see Figure).

Figure: Probability of brain metastasis, as characterised by the prediction model [1]



Dr Ashkar concluded that this model can predict the occurrence of brain metastasis in patients with metastatic GCTs and recommend its use by clinicians to identify patients at risk of developing brain metastasis.

1. Ashkar R. Prediction model for brain metastasis (BM) in patients with metastatic germ-cell tumours (mGCT) accounting for size of pulmonary metastases. Abstract 378, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

Reduction in radiation exposure is possible in testicular seminoma surveillance

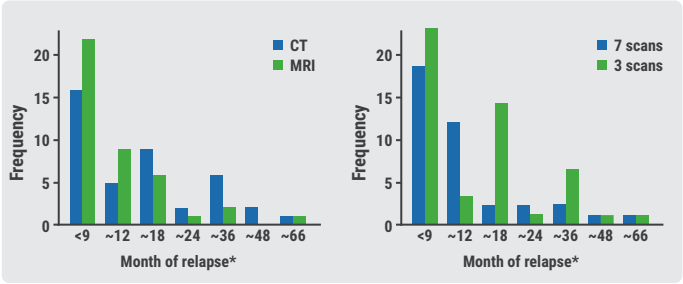
Magnetic resonance imaging (MRI) is non-inferior to computed tomography (CT) for the surveillance of stage 1 testicular seminoma. Over a 6-year period, a 3-scan schedule was non-inferior to a 7-scan schedule regardless of imaging modality in the phase 3 TRISST trial.

Stage 1 testicular seminoma has an almost 100% survival rate. Current international guidelines for the management of this cancer recommend CT surveillance of the abdomen/retroperitoneum following orchiectomy, with no adjuvant chemotherapy. While avoidance of chemotherapy avoids the risks and side effects associated with it, there are still long-term adverse health effects resulting from repeated exposure to radiation via multiple CT scans.

Prof. Robert Huddart (Royal Marsden Hospital and Institute of Cancer Research, UK) presented the results of the TRISST trial (NCT00589537) [1]. This phase 3, multicentre, factorial, non-inferiority trial aimed to assess whether CT could be safely replaced with MRI and whether the frequency of imaging could be safely decreased in surveillance of men with stage 1 seminoma. Investigators randomised 669 men to 1 of 4 arms, 2 of which were monitored with CT, and 2 of which were monitored with MRI. Each imaging modality arm had 2 different frequency schedules: one scanned patients at 6, 12, 18, 24, 36, 48, and 60 months; the other scanned patients at 6, 18, and 36 months. Patients randomised to the 3-scan arms only remained there in the absence of disease progression. All patients were followed for 6 years.

The primary outcome measure was the proportion of patients relapsing with Royal Marsden Hospital stage ≥2C disease.

Figure: Relapse frequency for MRI versus CT and 3-scan versus 7-scan schedule [1]



* +/- 3-month window for 12 and 18 months; +/- 6-month window for 24 months onwards.

Of the 669 trial participants, 358 (54%) were deemed to be low-risk and 82 (12%) relapsed (see Figure). Only 10 of these 82 were graded as a stage ≥2C relapse. Most relapses were diagnosed at the time of scheduled imaging; additionally, relapse beyond 3 years was rare.

Key secondary outcome measures included disease-free survival and overall survival rates; these were 87% and 99%, respectively. Values were similar across all groups. No tumour-related deaths occurred.

Although more events occurred in those who received 3 scans instead of 7, the criteria for non-inferiority were still met for both the intention-to-treat (ITT) and the per-protocol patients (upper 90% CI <5.7%). There were fewer events in those who received MRI scans than in those who received CT scans; 2 (0.6%) versus 8 (2.5%) (1.9% decrease; 90% CI -3.5% to -0.3% [ITT]). Per protocol results were similar.

Prof. Huddart asserted that surveillance is both safe and effective in stage 1 testicular seminoma, regardless of frequency or type of imaging. Furthermore, imaging beyond 3 years may be unnecessary, as relapse after 3 years is rare. Finally, they recommend that the standard of care should recommend MRI instead of CT, in an attempt to limit radiation exposure in this young population.

1. Joffe J. Imaging modality and frequency in surveillance of stage I seminoma testicular cancer: Results from a randomized, phase III, factorial trial (TRISST). Abstract 374, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

New therapeutic option for early metastatic seminoma

The phase 2 SEMS trial demonstrated encouraging outcomes from retroperitoneal lymph node dissection (RPLND) for early metastatic (i.e. stage 2) testicular seminoma. The 2-year recurrence-free survival (RFS) rate was 87% and the overall survival rate (OS) was 100% among patients who underwent the procedure.

The National Comprehensive Cancer Network Guidelines for management of stage 2A testicular seminoma remain unchanged for several decades, recommending chemotherapy and radiation therapy. Although these interventions are associated with excellent cure rates, they are also associated with long-term morbidity as well as secondary complications such as cardiac events, secondary cancers, metabolic syndrome, and lung disease. For this reason, investigators of the SEMS trial wished to explore other therapeutic options for young men with this cancer [1].

A seminoma will typically first spread to the retroperitoneal space. RPLND is commonly employed in testicular germ cell tumours. The researchers aimed to investigate whether RPLND might also be effective for early metastatic seminoma. The SEMS trial (NCT02537548) is a single-arm, multi-institutional, phase 2 trial that is studying outcomes after RPLND in stage 1–2A testicular seminoma. Enrolled are 55 patients (median age 34 years) with testicular seminoma and isolated retroperitoneal lymphadenopathy measuring 1–3 cm to receive RPLND. The primary endpoint is RFS at 2 years. Secondary outcome measures are short-term (up to 12 months) and long-term (up to 5 years) RPLND complication rates and 5-year RFS.

Of the 55 patients in the trial, 14 had initial stage 1 disease and 41 had stage 2A–B. At a median follow-up period of 24 months post-RPLND, 10 participants experienced recurrence, yielding a recurrence rate of 18%. The median recurrence time was 8 months. Of these 10 participants, 8 received chemotherapy (i.e. 6 received 3 cycles of bleomycin/etoposide/cisplatin, 1 received 4 cycles of combination etoposide plus cisplatin, and 1 received combination carboplatin plus etoposide), and 2 required additional surgery. The 2-year RFS was 87% and OS was 100%.

Within the first year of surgery, 7 surgical complications occurred; 5 were classified as Clavien-Dindo I-II complications and 2 as Clavien-Dindo III. No patients have reported any long-term complications.

At the time of ASCO GU 2021, principal investigator Prof. Siamak Daneshmand (University of Southern California, USA) reported that these 55 patients have now been followed for 5 years and all have survived. The outcomes achieved in this trial are similar to results for non-seminomatous germ cell tumours. Thus, Prof. Daneshmand concluded that RPLND offers an effective first-line treatment option for men with testicular seminoma with retroperitoneal lymphadenopathy. The decreased long-term morbidity associated with RPLND makes it a favourable alternative.

1. Daneshmand S. SEMS Trial: Result of a prospective, multi-institutional phase II clinical trial of surgery in early metastatic seminoma. Abstract 375, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

Urothelial Cancer

Poorer outcomes in bladder cancer predicted by race/ethnicity and gender

Socioeconomic, racial/ethnic, and gender considerations influence the diagnosis and management of bladder cancer in the United States. A recent study found that Black patients and patients of the female gender experienced delayed diagnosis and are less likely to receive appropriate therapies [1].

Dr Shaakir Hasan (New York Proton Centre, USA) reported on his team's research into social disparities in the diagnosis and management of bladder cancer. Cases of bladder cancer (n=434,608) were designated from the National Cancer Database. In accordance with National Comprehensive Cancer Network Guidelines, 331,714 (76.3%) were identified as early cases, 72,154 (16.6%) as muscle invasive, 15,579 (3.6%) as locally advanced, and 15,161 (3.5%) as metastatic.

Next, they employed multivariate binomial and multinomial logistic regression analyses to identify demographic characteristics associated with (i) stage of cancer at time of diagnosis and (ii) the delivery of appropriate, guideline-recommended treatment. The analyses revealed that relative to early diagnosis, the 2 strongest predictors of diagnosis made at later stages were being Black (muscle invasive, HR 1.19; 95% CI 1.15–1.23; locally advanced, HR 1.49 95% CI 1.40–1.59; metastatic, HR 1.66; 95% CI 1.56–1.76) and of the female gender (muscle invasive, HR 1.21; 95% CI 1.18–1.21; locally advanced, HR 1.16; 95% CI 1.12–1.20; metastatic, HR 1.34; 95% CI 1.29–1.38). Multivariable cox regression analysis additionally revealed that Black patients (HR 1.13; 95% CI 1.11–1.16) and patients of the female gender (HR 1.03; 95% CI 1.02–1.05) also had reduced survival rates.

Other demographic factors predicting delayed diagnosis were older age, treatment at an academic centre (excluding metastasis), the presence of Medicaid insurance, and coming from a lower-income/less educated/more rural area. These same factors, as well as being Hispanic, were also associated with a lack of receiving appropriate, cancer-focused therapy.

This study has identified that gender, race/ethnicity, and socioeconomic status impact the diagnosis and management of bladder cancer in the United States. Further investigation is warranted to explore these health disparities so that strategies can be formulated to address and ameliorate them.

1. Hasan S. Social disparities in the diagnosis and management of bladder cancer. Abstract 403, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

Enfortumab vedotin as a promising treatment option for bladder cancer: phase 3 results

New therapy prolongs survival in the 2nd line for patients with urothelial carcinoma. Enfortumab vedotin may become the new standard of care for patients with previously treated locally advanced or metastatic urothelial carcinoma (la/mUC). In the recent phase 3 EV-301 trial, treatment with enfortumab vedotin resulted in prolonged overall survival (OS) rates in these patients compared with treatment with chemotherapy.

OS is poor in patients who have previously received platinum-based chemotherapy and checkpoint (PD-1/PD-L1) inhibitor therapy. Enfortumab vedotin is an antibody-drug conjugate approved by the FDA in 2019 that is directed against nectin-4, a molecule that is highly expressed in la/mUC.

Dr Thomas Powles (Barts Cancer Centre, UK) shared the results of the EV-301 trial (NCT03474107), an open-label, phase 3 trial comparing the OS of participants with la/mUC who were progressing during or after treatment with PD-1. They were randomised to receive either enfortumab vedotin or standard chemotherapy (i.e. docetaxel, vinflunine, or paclitaxel) [1,2]. Enrolled were 608 participants, of whom 301 were randomised to the enfortumab vedotin arm and the remaining 307 to the chemotherapy arm.

At 11.1 months follow-up, the primary endpoint of median OS was longer by 3.9 months in the enfortumab vedotin arm compared with the chemotherapy arm (12.9 vs 9.0 months; HR 0.70; 95% CI 0.56–0.89; 1-sided P=0.001). At the time of interim analysis, 301 deaths had occurred (49.5% of total number of participants). Of these deaths, 134 had occurred in the enfortumab vedotin group (44.5% of participants in this group) and 167 in the chemotherapy group (54.4% of this group).

Secondary endpoints included progression-free survival, objective response rate, and rate of adverse events. Progression-free survival in the enfortumab vedotin group was 5.6 months versus 3.7 months in the chemotherapy group (HR 0.61; 95% CI 0.50–0.75; 1-sided P<0.00001). Objective response rate was significantly superior in the enfortumab vedotin group compared with the chemotherapy group (40.6% vs 17.9%; 1-sided P<0.001). Adverse event rates were similar between groups (93.9% in the enfortumab vedotin group; 91.8% in the chemotherapy group).

Due to the superior OS achieved by patients with la/mUC treated with enfortumab vedotin together with its tolerable safety profile, Dr Powles recommended that enfortumab vedotin should become a new standard of care for this patient group.

1. Powles T. Primary results of EV-301: a phase III trial of enfortumab vedotin versus chemotherapy in patients with previously treated locally advanced or metastatic urothelial carcinoma. Abstract 393, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.
2. Powles T, et al. N Engl J Med. 2021. DOI: 10.1056/NEJMoa2035807. Online ahead of print.

Enfortumab vedotin as a promising treatment option for bladder cancer: phase 2 results

Interim data from the phase 2 EV-201 trial investigating the efficacy of enfortumab vedotin on bladder cancer is promising. In cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer (la/mUC) who had received prior therapy with an immune checkpoint inhibitor, 52% of participants achieved a confirmed objective response rate (ORR) after receiving enfortumab vedotin therapy [1].

Nectin-4 is a cell-adhesion molecule that is highly expressed in urothelial carcinoma and may contribute to tumour-cell growth and proliferation. Enfortumab vedotin, an antibody–drug conjugate directed against nectin-4, is composed of a fully human monoclonal antibody specific for nectin-4 and monomethyl auristatin E (an agent that disrupts microtubule formation) [2].

The ongoing EV-201 trial (NCT03219333) is investigating the efficacy and safety of enfortumab vedotin administered to patients with la/mUC who have previously been treated with PD-1/PD-L1 inhibitors. The study has 2 cohorts: patients who have undergone platinum-based chemotherapy and patients who are cisplatin-ineligible/platinum-naïve. Dr Arjun Vasant Balar (NYU Langone Medical Oncology, New York, USA) shared results from the second cohort at ASCO GU 2021.

The cisplatin-ineligible cohort consisted of 89 participants who received 1.25 mg/kg enfortumab vedotin intravenously on days 1, 8, and 15 of each 28-day cycle for a median treatment duration of 6 months. The primary endpoint was ORR utilised Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 confirmed by an independent review facility. ORR was achieved by 52% of the participants and 20% of participants achieved a complete response. Median duration of response was 10.9 months, median progression-free survival was 5.8 months, and median overall survival was 14.7 months.

The safety profile matched the pre-existing safety profile of enfortumab vedotin. Four deaths were deemed to be treatment related; all occurred in patients aged >75 with multiple co-morbidities. Causes of death were acute kidney injury, metabolic acidosis, multiple organ dysfunction syndrome, and pneumonitis. Adverse events included alopecia areata (51%), peripheral neuropathy (47%), fatigue (34%), rash (61% all grade), and hyperglycaemia (10% all grade).

The researchers are optimistic that the favourable ORR and safety profile of enfortumab vedotin will make it a reasonable therapeutic option in the management of patients with la/mUC who have failed previous lines of therapy.

1. Balar A. EV-201 Cohort 2: Enfortumab vedotin in cisplatin-ineligible patients with local advanced or metastatic urothelial cancer who received prior PD-1/PD-L1 inhibitors. Abstract 394, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.
2. Powles T, et al. N Eng J Med 2021; DOI: 10.1056/NEJMoa2035807. Online ahead of print.

New standard of care recommended for patients with upper tract urothelial cancer

Results from the POUT trial demonstrated that the implementation of gemcitabine-platinum combination chemotherapy within 90 days following nephroureterectomy resulted in longer periods of disease-free survival (DFS) in patients with locally advanced upper tract urothelial cancer (UTUC).

Dr Alison Birtle (Rosemere Cancer Centre, UK) shared results from an updated analysis of the POUT trial (NCT01993979), a randomised, multi-centre, phase 3 trial assigning 260 post-nephroureterectomy patients with advanced UTUC either to surveillance only or to four 21-day cycles of adjuvant

chemotherapy. For participants in the chemotherapy arm, treatment was initiated within 90 days post-surgery and consisted of either a combination of gemcitabine-cisplatin or, in patients with impaired renal function, gemcitabine-carboplatin. Follow-up visits to monitor for signs of recurrence occurred at the same frequency in both treatment arms; namely, at 4, 7, 10, and 13 weeks corresponding to the end of each chemotherapy treatment cycle. Patients underwent imaging and cystoscopy every 6 months for 2 years and then annually up to the 5-year point.

The primary endpoint was DFS within a 3-year time frame. The occurrence of 88 deaths triggered a (pre-planned) updated analysis with data cut-off 11 January 2021; after a median follow-up period of 49.2 months, 109 (41.9%) participants had reached the primary endpoint of DFS; 64/129 (49.6%) in the surveillance group and 45/131 (34.4%) in the chemotherapy group (adjusted HR 0.54; 95% CI 0.36–0.79; P=0.002). There had also occurred 93 deaths: 52 of the 129 patients in the surveillance arm (40.3%) and 41 of the 131 patients in the chemotherapy arm (31.3%) had died.

Secondary outcome measures included overall survival, metastasis-free survival, acute and late toxicity, and quality of life. All secondary outcome measures were tracked for 5 years except quality of life, which was only monitored for up to 2 years. Updated overall survival rates are 57% (95% CI 46–66) for patients under surveillance and 65% (95% CI 71–86) for patients receiving gemcitabine-cisplatin/carboplatin (adjusted HR=0.77; 95% CI 0.50–1.17; P=0.21). Metastasis-free survival was achieved by 66 of the 129 (51.2%) participants assigned to surveillance and by 45 of the 131 (34.4%) participants assigned to chemotherapy (adjusted HR=0.55; 95% CI 0.37–0.82; P=0.003). In the chemotherapy group, 44% of participants experienced grade ≥3 treatment-emergent adverse events (AEs) compared with only 4% of participants in the surveillance group [2]. These AEs were consistent with previous AEs reported for this chemotherapy protocol. The most common AEs experienced were hypertension (25/240, 10.4%), lethargy (25/240, 10.4%), urinary tract infection (14/240, 5.8%), and hearing loss (13/240, 5.4%). Chemotherapy was not associated with any long-term toxicity. Regarding quality-of-life outcomes, no differences were seen between the groups.

Despite a non-significant improvement in overall survival, the improved DFS and metastasis-free survival outcomes achieved by patients treated with platinum-based chemotherapy within 90 days post-nephroureterectomy have prompted the researchers to recommend this protocol be considered a new standard of care for these patients.

1. Birtle AJ. Updated outcomes of POUT: A phase III randomized trial of peri-operative chemotherapy versus surveillance in upper tract urothelial cancer (UTUC). Abstract 455, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.
2. Birtle A et al. Lancet. 2020 Apr 18;395(10232):1268–77.

Signature DNA alterations in subtypes of bladder cancer

Attempts to identify a signature DNA alteration pathognomonic of differing histologic subtypes of bladder cancer have been unsuccessful to date.

Urothelial carcinomas encompass a vast array of histological morphologies, some of which are more aggressive than others. For this reason, the histomorphologic features of bladder cancer carry a prognostic significance, and different variants necessitate different treatment approaches. Dr Andrew Thomas Lenis (Memorial Sloan Kettering Cancer Centre, New York, USA) shared results from his team's genomic sequencing of bladder cancers of varying histologies in an attempt to determine whether these urothelial cancer variants had pathognomonic genomic profiles [1].

Memorial Sloan Kettering Cancer Centre developed the MSK-IMPACT™ test (authorised by the FDA in 2017) to analyse tumours for >400 mutations known to play a role in cancer. They used this test to identify gene alterations across a prospectively generated institutional cohort of >2,000 samples of bladder cancer. The cohort included patients with pure urothelial carcinoma not otherwise specified (NOS) as well as multiple variants: squamous, small cell, adenocarcinoma and urothelial carcinoma with glandular differentiation, micropapillary, nested, and plasmacytoid. The current study aimed to identify trends that corresponded to these variant subtypes.

MSK-IMPACT™ analysis revealed the following:

- the mutations in squamous cell tumours were similar to those seen in urothelial carcinoma NOS;
- nearly all small cell tumours had mutations in *TP53, RB1,* and *TERT;*
- adenocarcinomas frequently had mutations in *TP53, KRAS,* and *PIK3CA;*
- urothelial carcinomas with glandular differentiation resembled urothelial carcinoma NOS;
- micropapillary variants often showed *ERBB2* amplifications;

- nested variants often showed *RHOA* mutations and *FOXA1* amplifications; and
- plasmacytoid variants demonstrated pathognomonic *CDH1* alterations.

They also used single-cell RNA sequencing (scRNA-seq) on a subset of specimens to compare immune cell heterogeneity. This analysis identified distinct tumour cell clusters along with varying collections of immune cells in each bladder cancer subtype.

The analysis could not identify a pathognomonic DNA alternation that corresponded to the different variants of bladder cancer. However, they speculate that scRNA-seq carried out on larger cohorts may identify different immune cell profiles characteristic of different subtypes. Dr Lenis and his team will also utilise whole-exome sequencing and mutational signatures to further explore and characterise urothelial cancer variants.

1. Lenis A. Genomic characterization of bladder cancer with variant histology. Abstract 470, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

ACE inhibitors associated with superior responses in bladder cancer

A retrospective analysis of patients with muscle-invasive bladder cancer (MIBC) undergoing neoadjuvant chemotherapy (NAC) prior to radical cystectomy found that those who were taking angiotensin-converting enzyme inhibitors (ACEi) experienced increased pathologic complete responses (pCR). Researchers speculated that ACEi may amplify the effects of NAC.

The renin-angiotensin system plays a role in the proliferation of cells, blood cells, and connective tissue; it can also be involved in immunosuppression. Previous studies have suggested that ACEi and angiotensin receptor blockers (ARB) may suppress tumour growth, possibly by blocking transforming growth factor-β, which plays a role in bladder cancer.

Dr Jonathan Thomas (Beth Israel Deaconess Medical Centre, Massachusetts, USA) shared the results of his teams' retrospective review [1]. The analysis included 133 males and 54 females with MIBC who were either treated or not treated with either ACEi or ARB while they were receiving NAC prior to radical cystectomy for MIBC. Of these 187 patients, 114 (61.0%) were treated with cisplatin/gemcitabine, while 53 (28.3%) received dose-dense methotrexate-vinblastine-adriamycin-cisplatin. Among the patients reviewed, 41 (21.9%) were taking an ACEi, while 24 (12.8%) patients were taking an ARB.

Among the 41 patients taking an ACEi, 17 (41.5%) achieved a pCR versus 36 (24.7%) of the 146 patients who were not taking an ACEi. Multivariable analysis identified only ACEi intake as being associated with pCR. ARB intake was not associated with pCR.

The 5-year overall survival (OS) was 64%. The only factor associated with significantly improved OS was pCR (HR 0.18; 95% CI 0.07–0.45; P<0.001). After adjusting for pCR, ACEi was not significantly prognostic of OS (HR 1.12; 95% CI 0.60–2.09; P=0.72). That is, while ACEi intake was associated with achieving a pCR (OR 2.17; 95% CI 1.05–4.48; P=0.037), it was not prognostic of OS; it was speculated that this finding is due to the presence of other factors which could result in patient death. Both OS and pCR were unaffected by ARB intake while receiving NAC.

Next steps should include validation of these findings with external data. Additionally, investigation should be conducted into the potential impact of ACEi/ARB in other treatment settings of MIBC, including a prospective trial to explore the effect ACEi and ARB intake during NAC treatment.

1. Thomas J. Impact of angiotensin inhibitors on pathologic complete response with neoadjuvant chemotherapy (NAC) for muscle-invasive bladder cancer (MIBC). Abstract 220, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

Better allocation of research dollars needed

Of nearly 80,000,000 USD in funding for bladder cancer research between 2017 and 2019, approximately half was allocated to non-priority areas. Better mechanisms in grant selections are needed to align funding more closely to stakeholder-identified high priority research areas.

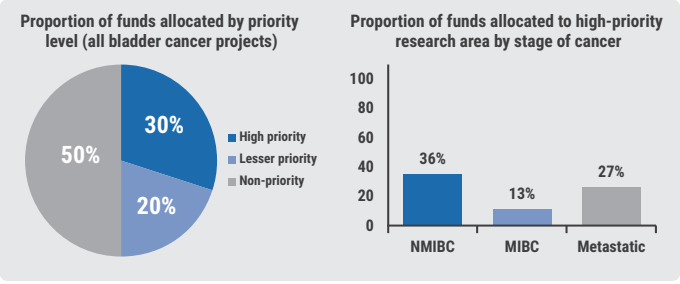
Patient-centred care includes not just delivery of clinical care but also allocation of funding to stakeholder-identified priority areas. Ms Jeenan Kaiser (University of Alberta, Canada) shared results of a recent project examining the relationship between funding patterns and priority research areas identified and compiled through the Bladder Cancer Advocacy Network [1]. Different research needs were put forward based on stage of cancer; namely, non-muscle-invasive bladder cancer (NMIBC), muscle-invasive bladder

cancer (MIBC), or metastatic bladder cancer. The top 2 priorities in each area were:

- NMIBC: 1) decision-making about radical cystectomy and timing, and 2) treatment options for intravesical Bacillus Calmette-Guérin (BCG) therapy-resistant bladder cancer;
- MIBC: 1) decision-making about bladder preservation versus radical cystectomy, and 2) type of urinary diversions; and
- metastatic bladder cancer: 1) incorporating novel treatments, and 2) treatment sequencing.

Results showed that between 2017 and 2019, 78,525,974 research US dollars funded 298 bladder cancer-focused research efforts in Canada and the US. Data was analysed based on country, year of funding, focus of the agency, stage of cancer, and the funding amount to identify if the amount of funding support was proportionate to previously identified research needs. It was found that only 30% of these research dollars ($23,268,258) directly funded research focused on high-priority research needs, while 20% ($15,575,064) was diverted towards projects which explored research areas deemed less important. The remaining 50% ($39,682,652) supported research endeavours that had not even been identified as research priorities (see Figure).

Figure: Tracking of allocation of bladder cancer research funding in the US and Canada [1]



NMIBC, non-muscle-invasive bladder cancer; MIBC, muscle-invasive bladder cancer.

Also of note is that non-bladder-cancer specific agencies allocated more funding to priority projects than bladder-specific cancer agencies.

Ms Kaiser concluded that this analysis has identified the need to improve research funding mechanisms in bladder cancer research; a greater proportion of research dollars must be allocated towards stakeholder-identified priority research needs.

1. Kaiser J. Bladder cancer research funding in Canada and the United States: A comparison between stakeholder priorities and resource allocation from 2017 to 2019. Abstract 422, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

Better prediction of favourable responses to immune checkpoint inhibitors in mUC

Response rates to treatment with immune checkpoint inhibitors are notoriously inconsistent, with some metastatic urothelial carcinoma (mUC) patients achieving durable responses and others not responding at all. Several patient characteristics may be used to predict better responses to immune checkpoint inhibitor therapy in urothelial carcinoma.

Dr Marie Alt (Princess Margaret Cancer Centre, Canada) and her team aimed to investigate whether any characteristics could be identified to predict which patients with urothelial carcinoma may have a better likelihood of achieving a favourable outcome with immune checkpoint inhibitors [1].

To this end, a retrospective, posthoc analysis was performed of data from 2 previous trials which investigated the use of durvalumab, an anti-PD-L1 monoclonal antibody, and durvalumab plus tremelimumab, an anti-CTLA-4 monoclonal antibody, in patients with mUC. The aim was to identify differences in patient characteristics between robust responders and poor responders.

Patients (n=367) were divided into 2 groups; one group consisting of patients who had survived ≥2 years (n=88; 24.0%), and the other group consisting of patients who had survived <2 years (n=279; 76.0%) from the point of receiving the first dose of the study drug. Next, a univariate analysis was performed on each baseline characteristic to identify any independent associations with long-term overall survival (OS). Finally, multivariate regression analysis was performed, including those variables that had been identified by univariate analysis. These consisted of sex, Eastern Cooperative Oncology Group Performance Status (ECOG PS), PD-L1 status, presence or absence of lymph node only disease, presence or absence of visceral disease, time from initial diagnosis to study entry, haemoglobin level, lactate dehydrogenase level, and absolute neutrophils count.

The primary outcome measure used in the analysis was long-term OS. Multivariate analysis revealed a significant association between long-term OS and ECOG PS, PD-L1 status, baseline haemoglobin level, and baseline absolute neutrophils count. Secondary outcome measures were objective response rates (ORR) and duration of response. Patients in the OS ≥2 years group had both higher ORR (71.6%) and longer duration of response than those in the OS <2 years group (ORR 5.7%).

Further investigation is warranted to determine what patient characteristics may predict a favourable response to immune checkpoint inhibitor therapy. Next steps should also explore if any biomarkers can be used to help inform prognosis.

1. Alt M. Identification of characteristics associated with long-term survival in patients with metastatic urothelial carcinoma (mUC) who received durvalumab (D) with or without tremelimumab (T) in clinical studies. Abstract 441, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

Genitourinary Oncology

Researchers call for an overhaul of licensing and funding of anti-cancer drugs

Prohibitive costs often exclude patients from accessing newly approved drugs to treat their genitourinary (GU) cancers. Yet, these rising costs may be unrelated to effectiveness: only 52% of newly approved regimens for GU cancer have demonstrated superior overall survival (OS) outcomes compared with previously approved therapies.

In the current study, presented by Dr David O'Reilly (Cork University Hospital, Ireland), the ease and cost were assessed of acquisition of newly approved systemic anti-cancer therapies (SACT) for patients with GU cancer [1]. Data was collected on licensing and reimbursement by public health insurance of all new GU cancer therapies that had been approved by the FDA between 2010 and 2020 and the relationship between cost of SACT and OS benefit was analysed.

Of 29 investigated regimens, the FDA approved 26 new regimens for GU cancer therapy during this 10-year period. Only 15/29 (52%) of these therapies were associated with a prolonged OS period; 6/29 (21%) were associated with neither prolonged OS nor progression-free survival. Furthermore, androgen receptor signalling inhibitors were more likely to have a proven OS benefit and they had a lower mean cost than non-androgen receptor signalling inhibitors. In the US, no association was found between OS benefit and price of the drug regimen (P=0.445). Regimens known to prolong OS were not more expensive than those that did not.

Of the 29 studied regimens, 21 (72%) were approved by the EMA and 12 were reimbursed in the UK, compared with only 6 in Ireland. Dr O'Reilly recommended a new approach towards the licensing and public funding of drug therapy to promote fairer access to the most efficacious drug regimes.

1. O'Reilly D. Value for money in genitourinary oncology. Abstract 1, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

Exploring a new strategy for metastatic germ cell tumours

Cure rates for patients with poor- and intermediate-risk metastatic germ cell tumours (GCTs) lag behind those for patients with good-risk metastatic GCTs. The Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) aims to improve these cure rates. The P3BEP trial aims to determine whether an accelerated chemotherapy regime is more effective than the existing standard protocol.

For patients with metastatic GCTs, cure rates are currently >90% in good-risk disease, 85% in intermediate-risk disease, and only 70% in poor-risk disease. These are the rates seen with current first-line therapy, which consists of four 3-weekly cycles of bleomycin, etoposide, and cisplatin (BEP) administered over a 12-week treatment period. ANZUP aims to determine whether shortening the treatment cycles in metastatic GCTs will yield the same superior cure rates achieved by shortening the treatment cycles in other cancers [1].

The safety and feasibility of an accelerated chemotherapy protocol in patients with intermediate- and poor-risk metastatic GCTs have already been confirmed in phase 1 and 2 trials. With these favourable results, Ms Shalini Subramaniam (NHMRC Clinical Trials Centre, University of Sydney, Australia) and colleagues have now devised an accelerated treatment

protocol which administers BEP in four 2-weekly cycles, followed by 4 doses of bleomycin, administered once per week for 4 weeks for a total intervention of 12 weeks.

The randomised, open-label, phase 3 trial P3BEP (NCT02582697) aims to randomise 500 participants (males and females) aged 11–45 years who have poor- or intermediate-risk metastatic GCTs of the mediastinum, ovary, retroperitoneum, or testis to receive either the standard chemotherapy regime or the accelerated BEP regime as described above, over a period of 12 weeks. ANZUP pointed out that this is the first trial of its kind to include adults as well as children of both sexes.

The trial consists of 2 stages; the primary endpoint for stage 1 is complete response; stage 1 analysis is expected to occur mid 2021. An interim analysis has identified no safety concerns to date. The primary endpoint for stage 2 is progression-free survival at 2 years.

Several key secondary outcome measures are monitored: initial response after 12 weeks of treatment, final response at 6 months, adverse events, health-related quality of life, treatment preference, delivered dose-intensity of chemotherapy (relative to standard BEP), and overall survival rates.

The authors conclude that a positive result of this trial may change standards of care.

1. Subramaniam S. P3BEP (ANZUP 1302): An international randomized phase III trial of accelerated versus standard BEP chemotherapy for male and female adults and children with intermediate and poor-risk metastatic germ cell tumours (GCTs). Abstract TPS 390, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.