Highlights in genitourinary cancers

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From June 1st till June 5th, Chicago was host for the 55th annual ASCO meeting. This report will highlight the most important studies concerning genitourinary cancers presented during the meeting.

PROSTATE CANCER (PC)

Several new treatment modalities for PC were presented on ASCO. An overview is given in *Table 1*.

The phase III trial GETUG-AFU 16 explored the addition of androgen deprivation therapy (ADT) to salvage radiotherapy (RT) after biochemical recurrence following prostatectomy. As RT + ADT resulted in an increased metastatic-free survival (MFS) after 9 years of follow up, standard addition of ADT to salvage RT could postpone aggressive treatment without increased toxicity or decline in quality-of-life (QoL).[1]

The phase III study ENZAMET determined the possible addition of docetaxel or abiraterone acetate to testosterone suppression in metastatic hormone-sensitive prostate cancer (mHSPC) patients to improve overall survival (OS). Interim survival data demonstrate a significantly improved OS by adding enzalutamide to SOC for mHSPC.[2] Also the phase III trial TITAN assessed the addition of the androgen receptor (AR) inhibitor apalutamide to ADT in mHSPC. A clear improvement in progression-free survival (PFS) and OS were observed, with manageable toxicity profile and no changes in QoL.[3] Both the ENZAMET and TITAN study indicate a clear shift of AR inhibitors for treatment of hormone-sensitive PC.

Numerous trials assessed new treatment options for non-metastatic and metastatic castrate-resistant prostate cancer (nmCRPC and mCRPC). The phase III trial ARAMIS evaluated the use of the AR antagonist darolutamide in the nmCRPC setting. Darolutamide clearly prolongs MFS, is well tolerated, maintains QoL, and delays worsening of pain and disease-related symptoms compared to placebo.[4]

The phase II TAXOMET study reported no clinically meaningful addition of metformin to docetaxel for treatment of mCRPC patients. Data from the STAMPEDE trial (SOC + metformin) is expected.

The Alliance A031021 phase III trial compared the combination of enzalutamide + abiraterone acetate versus enzalutamide only. The combination showed no benefit in OS with more treatment-related AEs. The combination of enzalutamide + abiraterone acetate is therefore not recommended.[6]

The phase Ib/II trial KEYNOTE-365 explored the possibility of administering pembrolizumab + enzalutamide in patients who progressed on abiraterone acetate within six months. Promising results were observed (doubling of objective response rate [ORR] compared to pembrolizumab in monotherapy) indicating the possible role of immune checkpoint inhibition (ICI) in the mCRPC setting. The phase III trial KEYNOTE-641 is currently ongoing.[7]

The phase II TOPARP-B trial assessed the use of the poly(ADP)-ribose polymerase inhibitor olaparib in mCRPC patients with DNA damage repair alterations. The trial demonstrated antitumor activity, especially in patients with *BRCA1/2* loss, *PALB-2* mutations and *ATM* mutations.[8]

Additionally, another phase II trial evaluated cabazitaxel versus enzalutamide or abiraterone acetate in poor prognosis mCRPC patients. It was found that cabazitaxel gives high clinical benefit for poor risk mCRPC patients, although no gain in OS was observed. ctDNA fraction, AR amplification and *TP53* mutations proved to have prognostic value although larger study groups are needed to confirm this

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TABLE 1. New treatment modalities for prostate cancer.

Trial	GETUG-AFU16	ENZAMET	TITAN	ARAMIS	TAXOMET	A031021	KEYNOTE-365	TOPARP-B	NCT02254785
Reference	1	2	3	4	5	6	7	8	9
Phase	III	III	III	III	II	III	Ib/II	II	II
Type of patients	BCR after RP	mHSPC	mHSPC	nmCRPC (PSADT ≤ 10 mo)	mCRPC	mCRPC	mCRPC (post AA)	mCRPC with DNA damage repair alterations (≥ 1 prior taxane)	Poor prognosis mCRPC
Number of patients	743	1125	1052	1509	99	1311	69	98	95
Randomisation	1:1	1:1	1:1	2:1	1:1	1:1	–	1:1	1:1
Therapy	RT + ADT vs. RT	TS + Enza vs. TS + non-steroidal ADT	ADT + Apa vs. ADT + Pbo	ADT + daroluta-mide vs. ADT + Pbo	DOCE + metfor-min vs. Doce + Pbo	Enza + AA vs. Enza	Pembro + Enza	Olaparib 400 mg BID vs. olaparib 300 mg BID	Caba vs.. Enza / AA
mFU	112 mo	34.0 mo	22.6 mo		41.1 mo	–	9.0 mo	17.6 mo	–
mMFS	NR vs. NR HR = 0.73 (0.54 – 0.98)	–	–	40.4 vs. 18.4 mo HR = 0.41 (0.34 – 0.50)	–	–	–	–	–
mPFS	NR vs. 108 mo HR = 0.54 (0.43 – 0.68)	NR vs. 27 mo HR = 0.40 (0.33 – 0.49)	NR vs. 22.1 mo HR = 0.48 (0.39 – 0.60)	–	7.4 vs. 5.6 mo	52.2 vs. 20.7 mo HR = 0.85 (0.74 – 0.97)	6 mo	5.4 vs. 5.4 mo	1L: 7.4 vs. 4.7 mo HR = 0.94 (0.57 – 1.56) 2L: 3.7 vs. 2.9 mo HR = 0.92 (0.46 – 1.86)
mOS	NR vs. NR HR = 0.93 (0.63 – 1.39)	NR vs. NR HR = 0.67 (0.52 – 0.86)	NR vs. NR HR = 0.67 (0.51 – 0.89)	NR vs. NR HR = 0.71 (0.50 – 0.99)	24.6 vs. 19.7 mo	34.2 vs. 32.5 mo HR = 0.90 (0.78 – 1.05)	NR	–	37.0 vs. 15.5 mo HR = 0.77 (0.41 – 1.44)
Clinical benefit rate	–	–	–		–	–	–	–	1L: 88 vs. 70 % 2L: 63 vs. 74 %
PSA decline > 50%	–	–	–		66 vs. 63 %	80 vs. 82 %	26 %	37 vs. 30 %	1L: 61 vs. 62 % 2L: 41 vs. 48 %
ORR	–	–	–		28 vs. 28 %	–	20 %	24 vs. 16 %	1L: 23 vs. 17 % 2L: 20 vs. 0 %
Grade 3/4 AEs	No increase in toxicity	–	42 vs. 41 %		–	69 vs. 56 %	41 %	–	1L: 48 vs. 6 %

AA, abiraterone acetate; ADT, androgen deprivation therapy; AE, adverse event; Apa, apalutamide; BCR, biochemical recurrence; Caba, cabazitaxel; Enza, enzalutamide; HR, hazard ratio; mFU, median follow up; mHSPC, metastatic hormone-sensitive prostate cancer; mMFS, median metastatic-free survival; mo, months; NR, not reached; mOS, median overall survival; mPFS, median progression-free survival; (n)mCRPC, (non-)metastatic castrate-resistant prostate cancer; ORR, objective response rate; Pbo, placebo; Pembro, pembrolizumab; PSADT, PSA doubling time; RP, radical prostatectomy; RT, radiotherapy; TS: testosterone suppression.

finding.[9]

Finally, the phase III trial CABADOC determined the patient preference between cabazitaxel and docetaxel for first-line chemotherapy in mCRPC. Although cabazitaxel and docetaxel have similar efficacy when used as first-line treatment option, more patients prefer cabazitaxel. Preferable choice was mostly influenced by fatigue, patient-defined QoL, hair loss, and pain.[10]

RENAL CELL CARCINOMA (RCC)

It remains a constant point of discussion when to start systemic therapy in metastatic RCC (mRCC) patients, especially in patients with low tumor burden or slow growing disease. The Canadian Kidney Cancer information system identified 1711 patients who immediately started systemic therapy (N=848); started systemic therapy ≥6 months after diagnosis of mRCC (N=370) or never received systemic therapy (N=493). Five year-OS was significantly lower for patients who immediately started systemic therapy (32.1 versus 70.2%). After adjusting for IMDC risk criteria and age, both OS (HR 0.46, 0.38-0.56) and time to treatment failure (HR 0.79, 0.69-0.92) were greater for delayed versus immediate systemic treatment. These data suggest that a subset of patients may be safely observed without immediate initiation of systemic therapy, which could be explained by the fewer metastatic sites and increased performance of metastasectomies in this patient group. Prospective validation in the contemporary immunotherapy era is required.[11]

Next, several treatment modalities for mRCC were presented at ASCO. An overview is given in *Table 2*.

The phase III trial E2810 evaluated the effect of pazopanib on MFS in mRCC treatment-naïve patients with no evidence of disease following metastasectomy. The primary end point was not reached and adjuvant pazopanib in this patient cohort is thus not recommended.[12]

The phase III CARMENA trial previously indicated that cytoreductive nephrectomy (CN) is not advised in mRCC. Updated results strengthen this statement. However, it was shown that patients with only 1 IMDC risk criteria could still benefit from CN.[13]

A phase II trial by Gao *et al.* evaluated the benefit of concomitant CN or metastasectomy in mRCC patients receiving first-line ICI. The authors suggest that ICI plus concomitant CN or metastasectomy is safe and shows promising clinical utility. Furthermore, response to therapy and survival outcome might be correlated to several biomarkers, such as CD8 tumor infiltrating lymphocytes and tumor IFN.[14]

The phase II CheckMate 920 study determined the clinical efficacy of ICI in patients with brain metastases. The current results show encouraging efficacy results with safety profile comparable to previous reported studies.[15]

Finally, several subanalyses of large phase III studies were presented in which the effect of ICI on sarcomatoid mRCC and IMDC intermediate and poor risk mRCC were assessed. IMmotion 151, CheckMate 214 and KEYNOTE-426 all showed high benefit from ICI for patients with sarcomatoid features and intermediate and poor risk patients.[16-18]

The fact that sarcomatoid mRCC respond well to ICI can be partly explained by the retrospective analysis done by Bakouny *et al.* After performing next-generation sequencing on sarcomatoid and rhabdoid mRCC tumors, analysis showed that genomic alterations in *BAP1* were significantly more frequent in sarcomatoid and rhabdoid mRCC (25 *vs.* 4.3%) while other genomic alterations and tumor mutational burden were similar. This could account for the fact that sarcomatoid and rhabdoid mRCC tumors have better outcomes on ICIs compared to non-ICI-based therapies.[19]

In addition, patient reported outcomes from the IMmotion 150 suggested that atezolizumab, alone or with bevacizumab, maintained daily function with minimal symptom interference versus sunitinib.[20]

UROTHELIAL CARCINOMA (UC)

Numerous novel therapies for treatment of (metastatic) urothelial carcinoma (mUC) were presented at ASCO. An overview is given in *Table 3*.

First, the most ideal adjuvant therapy following cystectomy in patients with locally advanced disease was determined. Comparison between adjuvant RT or chemotherapy proved comparable MFS, although local control is improved in the RT arm. Based on this study, this treatment option could be offered for patients unfit or unwilling to receive chemotherapy.[21]

The CALGB 90601 phase III study assessed the added value of bevacizumab to chemotherapy in treatment-naïve mUC. No OS benefit was shown. A small gain in PFS was observed, although not clinically significant. Bevacizumab has therefore no place in first-line therapy.[22]

The HCRN GU14-180 phase II trial explored the role of maintenance ICI in patients who are stable after first-line chemotherapy. Maintenance ICI proved effective and prolonged PFS. Further validation is even though still required to verify if maintenance ICI "deepens" responses achieved with first-line chemotherapy.[23]

Response to ICI may be dampened by *FGFR3* mutations. The phase Ib/II FIERCE-22 trial therefore explored the efficacy of the combination of the FGFR3 inhibitor vofatamab and ICI. The combination seems well tolerated and prolongs PFS, especially in patients with wild type *FGFR3*. Further investigation is ongoing.[24]

TABLE 2. New treatment modalities for metastatic renal cell carcinoma.

Trial	E2810	CARMENA	NCT02210117	CheckMate 920	IMmotion 151	CheckMate 214	KEYNOTE-426
Reference	12	13	14	15	16	17	18
Phase	III	III	II	II	III	III	III
Type of patients	Treatment-naïve (no evidence of disease following metastasectomy)	Treatment-naïve	Treatment-naïve	Treatment-naïve (asymptomatic brain metastases)	Treatment-naïve (sarcomatoid)	Treatment-naïve (sarcomatoid and IMDC intermediate / poor risk)	Treatment-naïve (sarcomatoid / IMDC intermediate / poor risk)
Number of patients	129	450	105	28	142/863	112/1096	IMDC: 592/861 sarcomatoid: 105/861
Randomisation	1:1	1:1	2:3:2	–	1:1	1:1	1:1
Therapy	Pazo vs. pbo	Sun + CN vs. sun	Nivo ± surgery vs. nivo + bev ± surgery vs. nivo + ipi ± surgery	Nivo + ipi	Atezo + bev vs. sun	Nivo + ipi vs. sun	Pembro + axi vs. sun
mFU	30 mo	61.5 mo	24.6 mo	6.5 mo	–	30 mo	–
mMFS	17.3 vs. 14.2 mo HR = 0.85 (0.55 – 1.31)	–	–	–	–	–	–
mPFS	–	–	+ surgery: 17.3 vs. 7.6 vs. 8.9 mo - surgery: 14.5 vs. 7.6 vs. 7.5 mo	9.0 mo	8.3 vs. 5.3 mo HR = 0.52 (0.34 – 0.79)	8.4 vs. 4.9 mo HR = 0.61 (0.38 – 0.97)	IMDC: 12.6 vs. 8.2 mo HR = 0.67 (0.53 – 0.85) sarcomatoid: NR vs. 8.4 mo HR = 0.54 (0.29 – 1.00)
mOS	NR vs. NR HR = 2.65 (1.02 – 6.9)	15.6 vs. 19.8 mo HR = 0.93 (0.76 – 1.15)	All: NR vs. NR vs. NR	NR	NR vs. 15.0 mo HR = 0.56 (0.32 – 0.96)	31.2 vs. 13.6 mo HR = 0.55 (0.33 – 0.90)	IMDC: NR vs. NR HR = 0.52 (0.37 – 0.74) sarcomatoid: NR vs. NR HR = 0.58 (0.21 – 1.59)
ORR	–	–	+ surgery: 86 vs. 89 vs. 69 % - surgery: 55 vs. 44 vs. 43 %	28.6 %	49 vs. 14 %	56.7 vs. 19.2 %	IMDC: 55.8 vs. 29.5 % sarcomatoid: 58.8 vs. 31.5 %
Grade 3/4 AEs	–	–	All: 38 vs. 42 vs. 47 %	21 %	40 vs. 49 %	46 vs. 40 %	–

Atezo, atezolizumab; axi, axitinib; bev, bevacizumab; HR, hazard ratio; IMDC, International Metastatic RCC Database Consortium; ipi, ipilimumab; mFU, median follow up; mMFS, median metastatic-free survival; mo, months; mOS, median overall survival; mPFS, median progression-free survival; nivo, nivolumab; NR, not reached; ORR, objective response rate; pazo, pazopanib; pbo, placebo; pembro, pembrolizumab; sun, sunitinib.

TABLE 3. New treatment modalities for advanced urothelial carcinoma.

Trial	NCT01734798	CALGB 90601	HCRN GU14-182	FIERCE-22	NCT03333616	NCT03507166	EV-201
Reference	21	22	23	24	25	26	27
Phase	III	III	II	Ib/II	II	II	II
Type of patients	Chemo-naïve, local disease after cystectomy	Treatment-naïve (> 12 mo since adjuvant chemotherapy)	First line chemo-pretreated patients with stable disease	≥ 1 prior chemotherapy or < 12 mo since adjuvant chemotherapy	Variant histologies, treatment-naïve or pretreated (no ICI)	HER2+, pretreated (≥ 1 prior systemic therapy)	Pretreated (prior platinum chemotherapy and ICI)
Number of patients	123	506	107	7/28	19	43	128
Randomisation	2:1	1:1	1:1	–	–	–	–
Therapy	RT vs. adjuvant chemotherapy	Chemotherapy + bev vs. chemotherapy + pbo	Pembro vs. pbo	Vofatamab + pembro	Nivo + ipi	RC48-ADC	Enfortumab vedotin
mFU	–	46.2 mo	14.7 mo	–	3.6 mo		4.6 mo
mMFS	HR = 0.65 (0.35 – 1.19)	–	–	–	–	–	–
mPFS	–	7.7 vs. 6.6 mo HR = 0.79 (0.66 – 0.95)	5.4 vs. 3.2 mo HR = 0.64 (0.41 – 0.98)	NR	3.8 mo	6.9 mo	5.8 mo
mOS	HR = 0.94 (0.52 – 1.69)	14.5 vs. 14.3 mo HR = 0.87 (0.72 – 1.06)	–	–	NR	NR	11.7 mo
ORR	–	40.4 vs. 33.0 %	22 vs. 12 %	36 %	37 %	51.2 %	44 %
Grade 3/4 AEs	8 vs. 2 % (late GI toxicity)	83.5 vs. 80.7 %	53 vs. 35 %	–	16 %	–	–

Bev, bevacizumab; HR, hazard ratio; ICI, immune checkpoint inhibition; ipi, ipilimumab; mFU, median follow up; mMFS, median metastatic-free survival; mo, months; mOS, median overall survival; mPFS, median progression-free survival; nivo, nivolumab; NR, not reached; ORR, objective response rate; pbo, placebo; pembro, pembrolizumab; RT, radiotherapy.

KEY MESSAGES FOR CLINICAL PRACTICE

1. A clear shift is seen towards modern AR inhibitors for treatment of hormone-sensitive PC.
2. Combinations of docetaxel plus metformin or enzalutamide plus abiraterone are not advised for treatment of mCRPC.
3. Pembrolizumab plus enzalutamide show promising results in mCRPC (although phase III data are awaited).
4. Genetic profiling will play a role in determining the most optimal treatment option for mCRPC.
5. Active surveillance remains a valid option for mRCC, especially in patients with low tumor burden.
6. Cytoreductive nephrectomy is only recommended in patients with low risk (IMDC 1) and might be plausible in patients receiving first-line ICI.
7. ICI proves effective for mRCC patients diagnosed with asymptomatic brain metastases.
8. Sarcomatoid mRCC patients respond well to ICI, probably due to the genomic alterations (especially *BAP1* mutations) that are associated with this histologic feature.
9. Adjuvant RT for locally advanced mUC is a possible option for patients unfit or unwilling to receive chemotherapy.
10. Bevacizumab is not to be given in addition to first-line chemotherapy in mUC.
11. Maintenance ICI might "deepen" the responses achieved with first-line chemotherapy in mUC – results of first line combination trials are awaited.
12. Combination of ICI and FGFR3 inhibitors might increase the ORR in mUC due to the inhibition of the dampening effect created by *FGFR3* mutations.
13. mUC of variant histologies can respond to ICI and show a desirable safety profile.
14. Novel treatment options are coming which show efficacy in mUC patients who progressed on first-line chemotherapy and second-line ICI (enfortumab vedotin and FGFR inhibition are the most important approaches in this setting).

Patients with mUC of variant histologies have poor outcomes. A phase II trial was conducted to assess the use of ICI in this patient group. ICI showed clear efficacy with desirable safety profile. Further exploration of ICI in this patient population is therefore warranted.[25]

Despite the use of ICI in mUC, the question remains which treatment to choose after progression on ICI. Two phase II trials were reported exploring this statement. RC48-ADC, an anti-HER2 antibody-drug conjugate, proved clinically meaningful in HER2+ patients pretreated with ICI (and chemotherapy).[26] Next, enfortumab vedotin, an antibody-drug conjugate targeting Nectin-4, proved effective for patients who progressed after chemotherapy and ICI.[27]

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