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1) Overall survival (OS) results of a phase III randomized trial of standard-of-care therapy with or without enzalutamide for metastatic hormone-sensitive prostate cancer (mHSPC): ENZAMET (ANZUP 1304), an ANZUP-led international cooperative group trial.

Testosterone suppression (TS) is the backbone of treatment for metastatic hormone-sensitive prostate cancer (mHSPC). Overall survival is improved by the addition of early docetaxel (DOC) or abiraterone to TS. The randomised phase 3 ENZAMET trial assessed the effects of enzalutamide (ENZA), a potent androgen receptor (AR) inhibitor, versus a nonsteroidal anti-androgen (NSAA: bicalutamide, nilutamide, or flutamide) in addition to SOC in mHSPC.

Men (1125) with mHSPC were randomly assigned 1:1 to receive TS plus either ENZA (160 mg daily, by mouth, until clinical disease progression or prohibitive toxicity) or NSAA (conventional NSAA, by mouth until clinical disease progression or prohibitive toxicity). All participants were to receive standard background therapy with a LHRHA or surgical castration, as per standard of care. The choice of the LHRHA or surgical castration was at the discretion of the treating clinician. Randomization was stratified by: volume of disease (high vs low, according to CHAARTED); planned early DOC; planned anti-resorptive therapy, comorbidity score (ACE-27), and study site. The primary endpoint was overall survival. Subgroup analyses to assess possible modulation of the treatment effect were specified a priori and included planned early docetaxel (yes vs no) and volume of disease (high vs low).

After a median follow-up of 33 months. Overall survival was prolonged by ENZA. At 3 years, 36% NSAA vs 64% ENZA were still on their assigned study treatment. Serious adverse events (regardless of attribution) within 30 days of study treatment occurred in 42% ENZA vs 34% NSAA, commensurate with the different durations of study treatment.

ENZA significantly improved OS when added to SOC in mHSPC while the benefits appeared lower in those planned to receive early DOC.

2) Results of enfortumab vedotin monotherapy for locally advanced or metastatic urothelial cancer previously treated with platinum and immune checkpoint inhibitors.

Locally advanced or metastatic urothelial cancer (la/mUC) remains a lethal disease with limited treatment options for patients (pts) who progress on or after platinum and/or checkpoint inhibitor (CPI). Enfortumab vedotin (EV) is an antibody-drug conjugate targeting Nectin-4, which is highly expressed in UC. EV-201 is a pivotal, single-arm, two-cohort study of EV in la/mUC patients with prior CPI and platinum-containing chemotherapy (Cohort 1) or a CPI and no prior chemotherapy (Cohort 2). Here, we present preliminary data from Cohort 1.

Patients in this open-label, multicenter study received 1.25 mg/kg EV on Days 1, 8, and 15 of each 28-day cycle. The primary endpoint was confirmed overall response rate (ORR) per RECIST 1.1 by blinded independent central review. Secondary endpoints are duration of response, progression free survival (PFS), overall survival (OS), safety/tolerability.

Between October 2017 and July 2018, EV-201 enrolled 128 patient in Cohort 1 (la/mUC pts previously treated with platinum and a CPI), 125 of whom were treated with EV (70% male; median age 69 y [range 40–84 y]; 34% upper tract; a median of 2 prior systemic therapies). As of 03 January 2019, the confirmed ORR was 42% (95% CI: 33.6%–51.6%), with 9% complete response (CR). The ORR in CPI non-responders was 38% (95% CI: 27.3%–49.2%), and 36% (95% CI: 22.9%–50.8%) in patients with liver metastases (LM). Most common treatment-related adverse events (AEs), as determined by investigators, included fatigue (50%), alopecia (48%), and decreased appetite (41%). Treatment-related AEs of interest include any rash (48% all grade, 11% ≥G3) and any peripheral neuropathy (50% all grade, 3% ≥G3).

Preliminary results from this EV pivotal study demonstrated a clinically meaningful ORR, consistent with the phase 1 trial, in la/mUC pts with prior platinum and CPI, including LM patients, where there is a high unmet need. EV was well tolerated with a manageable safety profile in these patients.

3) MONALEESA-7: Addition of Ribociclib to Endocrine Therapy in Premenopausal Women with HR-Positive, HER2-Negative Breast Cancer

The phase III MONALEESA-7 study (NCT02278120) is the first trial to focus exclusively on women younger than age 59 who were premenopausal and had advanced breast cancer for which they had not received prior endocrine therapy. Specifically, is the first dedicated trial of endocrine therapy (ET) ± a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor in premenopausal patients with hormone receptor–positive (HR+)/HER2− ABC. The study met its primary endpoint of significantly longer progression-free survival (PFS) with ribociclib (RIB; a CDK4/6 inhibitor) + ET vs placebo (PBO) + ET (median, 23.8 vs 13.0 mo; HR, 0.55; $P< 0.0001$.

A total of 672 women were enrolled in the study (N=672) with HR+/HER2− ABC. Investigators randomly assigned women to receive treatment with oral RIB or a PBO. All women enrolled also received goserelin, as injectable endocrine therapy, and one of three other therapies: the nonsteroidal aromatase inhibitors letrozole or anastrozole, or tamoxifen.

After a median follow-up of 34.6 months (min, 28.0 months), 173 patients (26%) were still on treatment, with 116 (35%) of them still receiving RIB and 57 (17%) still receiving PBO. Overall survival was evaluated after 192 deaths (83 in the RIB arm, 109 in the PBO arm). RIB + ET demonstrated a significantly longer OS than PBO + ET (HR, 0.712 [95% CI, 0.54-0.95]; p = 0.00973). The result crossed the prespecified stopping boundary for superior efficacy. The researchers observed that after 42 months of follow-up, for patients receiving RIB, the survival rate was 70% when given with ET, compared with 46% when given with PBO. In patients who received an NSAI (n=495), RIB + ET demonstrated a consistent OS improvement vs PBO + ET (HR, 0.699 [95% CI, 0.50-0.98]). Posttreatment therapy use was balanced between treatment arms—68.9% in the RIB arm and 73.2% in the PBO arm.

In this this phase III trial, RIB + ET demonstrated a clinically and statistically significant longer OS than ET alone in premenopausal patients with HR+/HER2− ABC. This is the first time that a CDK4/6 inhibitor or any targeted agent + ET has demonstrated significantly longer OS vs ET alone as initial endocrine-based therapy.

4) KEYNOTE-062: Pembrolizumab With or Without Chemotherapy vs Chemotherapy in Advanced Gastric or GEJ Adenocarcinoma

The randomized, phase III KEYNOTE-062 trial achieved its primary endpoint, showing that for patients with programmed cell death ligand 1 (PD-L1)-positive (combined positive score ≥1, CPS ≥1), HER2-negative, advanced gastric or gastroesophageal junction (GEJ) cancer, initial therapy with pembrolizumab resulted in noninferior overall survival compared with standard chemotherapy. Additionally, pembrolizumab showed clinically meaningful improvement in overall survival among patients with tumors that had high levels of PD-L1 expression. At 2 years, 39% of patients who received pembrolizumab alone were alive, compared with 22% of people who received standard chemotherapy. The trial also evaluated combined treatment with pembrolizumab and standard chemotherapy, and it found this regimen did not improve survival relative to chemotherapy alone.

The investigators randomly assigned patients, in equal numbers, to receive Pembrolizumab 200 mg Q3W for up to 2 years, Pembrolizumab+chemotherapy (cisplatin 80 mg/m^2 + 5-FU 800 mg/m^2/d on d1-d5 Q3W [or capecitabine 1000 mg/m^2 BID on d1-d14 Q3W per local guideline]) or placebo Q3W + chemotherapy. Randomization was stratified by region, disease status, and fluoropyrimidine treatment. Final analysis cutoff date was 26 March 2019.

The trial enrolled 763 patients with a median age of 62 years; 26% had previous gastric surgery to remove a tumor. In total, 69% had gastric cancer and 30% had GEJ cancer. Investigators focused on HER2-negative cancers alone, which studies have shown have a higher chance of recurrence after treatment, to limit factors that could affect outcomes. PD-L1 expression was assessed via CPS. Previous studies of gastric or GEJ cancers have demonstrated that patients with a PD-L1 CPS ≥1 may benefit from pembrolizumab, whereas a PD-L1 CPS ≥10 or more indicates a higher likelihood of benefit. In the current trial, all patients had a PD-L1 CPS ≥1, and 281 (37%) of them had a PD-L1 CPS ≥10. From this pool of patients 257 randomized to Pembrolizumab+Chemotherapy arm, 256 to Pembrolizumab and 250 to chemotherapy+placebo arm. The patients were followed for a median of 11.3 months.

Pembrolizumab was noninferior to chemotherapy for overall survival in patients with CPS ≥1 per prespecified margins while it prolonged overall survival in CPS ≥10 patients (median 17.4 vs 10.8 months; HR 0.69; 95% CI 0.49-0.97). Pembrolizumab+chemotherapy vs chemotherapy was not superior for overall survival in patients with CPS ≥1 or CPS ≥10, with a favorable trend for Pembrolizumab+chemotherapy arm. Pembrolizumab+chemotherapy did not significantly prolong progression free survival in CPS ≥1 group of patients. Overall response rate was higher for Pembrolizumab+chemotherapy arm vs chemotherapy one. The rates of serious side effects were lowest among patients treated with pembrolizumab alone. Grade 3 or higher toxic treatment-related adverse events were found in 17% of people receiving pembrolizumab, 73% of people receiving pembrolizumab and chemotherapy, and 69% of those receiving chemotherapy alone. The most common adverse events were nausea and fatigue.

In conclusion, Pembrolizumab was noninferior to chemotherapy for overall survival in patients with a CPS ≥1 with

clinically meaningful improvement for overall survival in CPS ≥10 group. *Pembrolizumab+chemotherapy did not show superior overall survival and progression free survival in CPS ≥1 and overall survival in CPS ≥10. The safety profile was more favorable for Pembrolizumab vs chemotherapy.*

5) Docetaxel, trastuzumab, pertuzumab versus trastuzumab emtansine as neoadjuvant treatment of HER2-positive breast cancer: Results from the Swedish PREDIX HER2 trial identifying a new potential de-escalation standard?

Neoadjuvant therapy produces high rates of pathological complete response (pCR) and is the standard of care in HER2 positive breast cancer; however, the optimal treatment regimen remains to be established.

In this randomized phase II study patients ≥18 years with HER2 positive breast cancer >20mm or verified lymph node metastases were randomized to 6 courses of docetaxel, trastuzumab and pertuzumab (DTP, group A/docetaxel 75-100 mg IV + trastuzumab 600 mg SC + pertuzumab 840 mg IV starting dose, subsequently 420 mg IV) or trastuzumab emtansine (T-DM1, group B/trastuzumab emtansine 3.6 mg/kg IV), q 21 days. The protocol allowed switch to the competing treatment upon lack of response or drug-related severe toxicity. Patients received postoperative epirubicin+cyclophosphamide, trastuzumab for a total of one year and endocrine therapy. Accrual was completed in October 2018 after randomization of 202 patients, data on pCR were available for 190 at the time for this abstract submission. Median age, 52 years (26-74), menopausal status, histological type and grade were well balanced between the treatment groups. 62.6% of the tumors were hormone receptor (HR) positive.

Primary endpoint was pathological objective response. 190 patients completed the protocol-specified preoperative treatment. pCR was achieved in 45.3% of patients, 46.4% in patients treated with DTP and 44.1% with T-DM1 (chi-sq., p=0.75). In HR-positive tumors, pCR was obtained in 35.3% of patients, 35.9% in group A *vs.* 34.6% in group B (p=0.87); in HR-negative tumors, the overall pCR rate was 62.0%, 66.7% in group A *vs.* 57.9% in group B (p=0.45). Severe (grade 3/4) toxicity was reported at 68 occasions related to DTP, compared with 16 related to T-DM1, 26 vs. 3 caused by febrile neutropenia. Significantly better quality of life was reported by patients treated with T-DM1.

Data from PREDIX HER2 trial on TDM-1 demonstrates similar efficacy and less toxicity, in particular for patients with HER2 and HR positive cancers, being a potential new standard for neoadjuvant therapy.

6) SOPHIA primary analysis: A phase 3 study of margetuximab + chemotherapy versus trastuzumab + chemotherapy in patients with HER2+ metastatic breast cancer after prior anti-HER2 therapies

Pretreated HER2+ metastatic breast cancer lacks a defined standard of care, although trastuzumab is commonly used. Margetuximab has similar HER2 binding and antiproliferative effects as trastuzumab. By contrast, margetuximab's Fc region is engineered to increase affinity for both alleles of the activating Fc receptor (FcR), CD16A, and decrease affinity for the inhibitory FcR, CD32B. The low affinity CD16A-158F allele (~85% of population) has been associated with diminished clinical response to trastuzumab. In a Phase 1 trial, margetuximab demonstrated acceptable safety, anti-tumor activity, and evidence of HER2-specific antibody and T-cell responses.

SOPHIA (NCT02492711), a randomized, open-label Phase 3 trial, enrolled patients with HER2+ metastatic breast cancer after pertuzumab and 1–3 lines of prior anti-HER2 therapies for breast cancer. Patients were randomized 1:1 to margetuximab (15 mg/kg IV q3w + chemotherapy) or trastuzumab (6 [8 for loading dose] mg/kg IV q3w + chemotherapy), stratified by met sites (≤2, >2), lines of trastuzumab for met disease (≤2, >2), and chemotherapy choice (standard dose capecitabine, eribulin, gemcitabine, or vinorelbine). Primary endpoints are central blinded progression free disease (PFS) and overall survival (OS), assessed sequentially using the stratified log-rank test. Objective response rate (ORR) was a secondary endpoint. 257 PFS events were required to provide 90% power to show PFS superiority at 2-sided $\alpha = 0.05$.

Intent-to-treat analysis (536 patients: margetuximab 266; trastuzumab 270) occurred after 265 PFS events. Margetuximab prolonged PFS over trastuzumab (median 5.8 vs 4.9 months, hazard ratio [HR], 0.76; 95% CI, 0.59–0.98; *P*= 0.033). Treatment effects were more pronounced in patients with CD16A genotypes containing a 158F allele (median PFS 6.9 vs 5.1 months, HR, 0.68; 95% CI, 0.52–0.90; *P*= 0.005). In 524 patients with baseline measurable disease (margetuximab 262; trastuzumab 262), ORR was higher with margetuximab (22%; 95% CI, 17.3-27.7%) vs trastuzumab (16%; 95% CI 11.8-21.0%). Safety profiles were comparable in 529 patients who received study therapy. Grade ≥3 AEs and serious AEs occurred in 138 (52%) and 39 (15%) vs 128 (48%) and 46 (17%) patients on margetuximab vs trastuzumab, respectively.

In combination with chemotherapy in pretreated HER2+ metastatic breast cancer, margetuximab improves PFS over trastuzumab with comparable safety. CD16A genotyping suggests a differential benefit in patients with a 158F allele. OS data are maturing.