ESMO Asia 2017 Congress

17-19 November 2017

Singapore

Table of Contents

Summary

The third European Society for Medical Oncology (ESMO) Asia Congress was established as the premiere conference for oncology professionals throughout the Asia and the Asian Pacific regions. Held in Singapore from 17 to 19 November, 2017 this congress was endorsed by 21 regional oncology societies, and was hosted by the Singapore Society of Oncology (SSO). In total 613 abstracts were selected for presentation and discussion. Summaries of a representative sample of the diverse scientific findings presented at ESMO Asia 2017 Congress follows.

INTRODUCTION

The third European Society for Medical Oncology (ESMO) Asia Congress was established as the premiere conference for oncology professionals throughout the Asia and the Asian Pacific regions. Held in Singapore from 17 to 19 November, 2017 this congress was endorsed by 21 regional oncology societies, and was hosted by the Singapore Society of Oncology (SSO).

The ESMO Asia 2017 welcomed 2'382 delegates who primarily came from Asia (85.78%) but also from Europe (7.32%), Australia and the Pacific (4.13%), North America (2.42%), Africa (0.31%) as well as Central and South America (0.04%)

In addition to delegates, the conference was attended by 251 industry representatives and exhibitors, 185 faculty members, and 33 journalists. Participants came from 61 countries, with Singapore (11.7%) and Japan (11.5%) providing the highest proportion of delegates followed by China (9.2%), Taiwan (7.4%), Thailand (6.3%) and India (6.3%). Approximately 5% of delegates each came from Vietnam, the Republic of Korea, Indonesia, and Malaysia.

The majority (34%) of the 1114 participants who provided demographic information during registration were medical oncologists, but 9.21% were clinical oncologists, 7.65% were surgical oncologists, 4.45% were basic researchers, and 2.73% were clinical researchers. The remainder of participants included, haemato-oncologists, internal medicine and gastrointestinal specialists, radiation oncologists, pathologists and pharmacists, as well as other medical professionals representing every aspect of oncology.

Breast cancer was the primary topic of interest (41.6%), while 35.6% of attendees indicated that gastrointestinal and 30.8% said non-small cell lung cancer (NSCLC) were their primary areas of interest. Approximately 25% of attendees each indicated that other lung cancer, and head and thoracic cancer were their fields of interest. Clinical research topped the list of topics of interest at 42.3% followed by anti-cancer agents at 39.0%, and cancer biology at 33.8%. Immunotherapy, biological therapy, cancer treatment and co-morbidities, tumour immunology, and translational research were all listed as the foremost topics of interest by more than 20% of the delegates who responded to this survey at registration.

The 613 abstracts chosen for presentation and discussion addressed these areas and topics of interest: Between 60 to 71 abstracts were on gastrointestinal cancer, including both colorectal and non-colorectal tumours, NSCLC, and head and neck cancer. Approximately 32 to 45 abstracts focused on breast and gynaecological cancers, supportive care and biomarkers, with 15 to 29 abstracts each covering the areas of haematological malignancies, basic science, genitourinary cancer, sarcoma, CNS tumours, melanoma and other skin tumours, tumour biology and pathology, immunotherapy of cancer, and sarcoma. The majority (80.6%) of the abstracts were presented in detail as posters, with a representative author present in most cases. The oral and poster discussion sessions featured faculty that placed abstract findings into clinical perspective and discussed how the new findings may impact the current standard of care.

Summaries of a representative sample of the diverse scientific findings presented at ESMO Asia 2017 Congress follows.

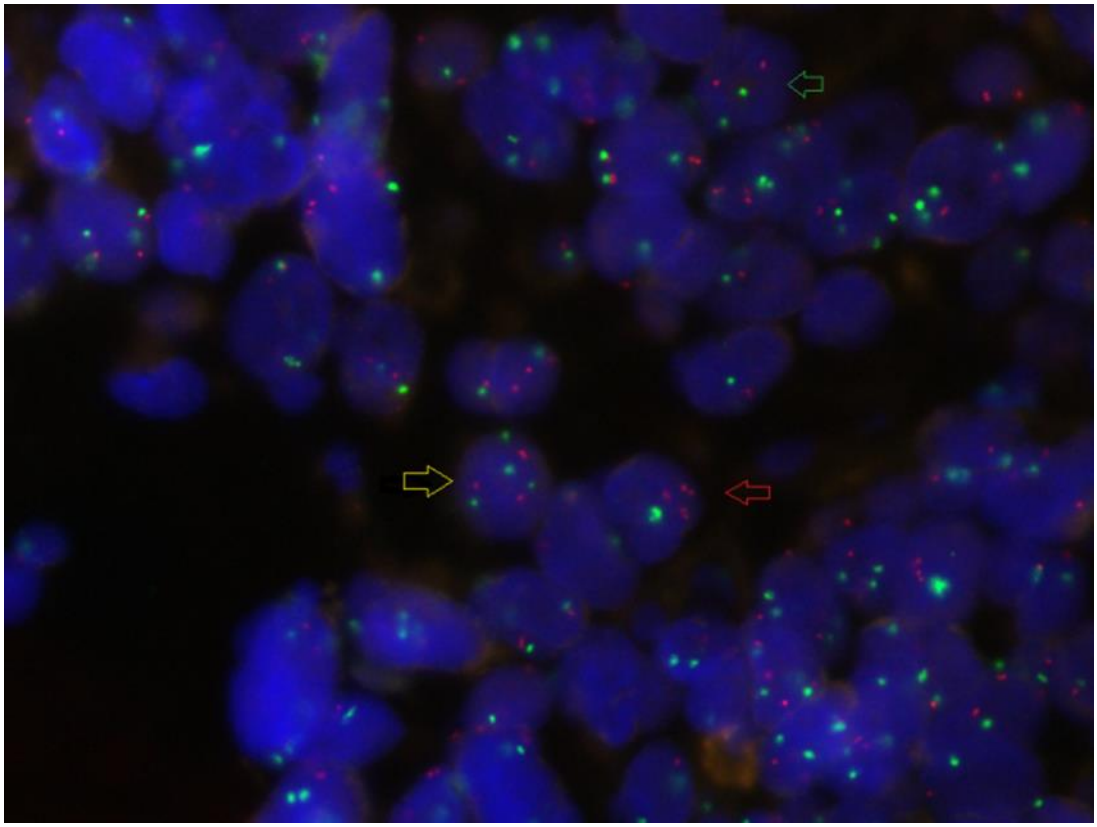
BIOMARKERS

MYC amplification in oesophagogastric cancer investigated to provide a novel-biomarker driven treatment approach

Data generated by Michael Davidson and colleagues from The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, UK from ongoing prospective screening done as part of the i*MYC* study revealed *MYC* amplification by fluorescence in situ-hybridisation (FISH) occurred in a quarter of tumour samples obtained from patients with advanced oesophagogastric cancer. A component of i*MYC* is the screening of oesophagogastric tumours for *MYC* amplification using a dual probe FISH assay that was developed by the investigators. The assay was used to assess *MYC* amplification using probes for the centrometric component of chromosome 8 and the coding region of the *MYC* gene, which was used to distinguish between increased copies of chromosome 8 and extra copies of *MYC*. The i*MYC* study was designed to investigate ibrutinib by a biomarker-driven treatment approach in patients with oesophagogastric cancer. The study was based upon preclinical work demonstrating a synthetically lethal interaction between BTK-inhibition with ibrutinib and *MYC* amplification in oesophagogastric cancer.

Findings from the initial screening component of the trial showed that both the number of cells showing *MYC* amplification and the range of amplification intensity seen across tumour samples varied significantly. FISH analysis had so far successfully been performed on 109 archival tumour samples, with *MYC* amplification observed in 27/109 (25%) of samples. The percentage of cells demonstrating *MYC* amplification varied between samples, with a median 57.5% of cells (range 11 to 94%) showing amplification. The analysis also revealed a high degree of intra-tumour heterogeneity, with 20/27 (74%) amplified samples showing a range of amplification ratios within the tumour specimen. The investigators suggest that extra-chromosomal amplifications of the *MYC* gene may account for some of the genetic heterogeneity seen.

Example of a FISH result assessing for *MYC* amplification demonstrating heterogeneity of signalling patterns within the sample is shown on image below, with green arrow indicating a normal diploid pattern of 2 *MYC* (red) signals and 2 CEP8 (green) signals; yellow arrow indicating a polysomic pattern with multiple *MYC* and CEP8 signals; and red arrow indicating an amplified pattern with multiple extra *MYC* signals.



© Dr Michael Davidson.

Further exploratory work involved the development of a novel digital droplet polymerase chain reaction (ddPCR) test to identify *MYC* amplifications from DNA isolated from both primary tumour and circulating tumour (ct)DNA. Positive detection of amplification by ddPCR was only possible in tumour samples that had a homogenous and high-level FISH amplification pattern. NCT02884453. Davidson *et al.* Abstract 23O

Practice point and future research opportunities

The *iMYC* trial represents the first attempt at screening for and targeting *MYC* in advanced oesophagogastric cancer. Prospective data generated from the screening programme thus far illustrates the utility of FISH in assessing for *MYC* amplification, as well as demonstrating extensive heterogeneity of *MYC* amplification in this tumour type. A novel ddPCR assay to detect *MYC* amplifications from both archival tumour and ctDNA was also developed and used; the ddPCR assay did not appear to be optimal for the detection of small clonal subpopulations of amplified cells.

circLMTK2 is identified by comprehensive circular RNA and bioinformatics analysis as a possible proliferative factor and prognostic marker in gastric cancer

Jie Chen, department of Gastric Surgery, Fudan University Shanghai Cancer Centre in Shanghai, China and colleagues investigated whether circular RNAs (circRNAs) may play a role in the regulation of gene expression in gastric cancer and may serve as a prognostic marker. Circular RNAs are non-coding RNAs that have been identified as critical regulators

in some cancer types. There is increasing evidence that circRNAs represent a class of widespread and diverse endogenous RNAs that may regulate gene expression.

The investigators determined the circRNA expression profile in three paired samples of gastric cancer and adjacent normal tissue using ribo-minus RNA sequencing and a bioinformatics analysis. The circRNA candidates were identified using quantitative reverse transcription polymerase chain reaction (qRT-PCR). Additional molecular and cellular techniques were used to explore the biological function and mechanism of circRNA in gastric cancer cells. The prognostic significance was analysed using the Kaplan-Meier method and the Cox proportional hazards model.

Characterisation of circular RNA transcripts using RNA-sequence analysis of ribosomal RNA-depleted total RNA on the 3 paired tissue samples yielded 15623 distinct circRNA candidates. The investigators determined that at least 5500 distinct circRNAs were differently expressed in the gastric cancer tissue compared with matched normal tissue. One abundant circRNA derived from the LMTK2 gene was characterised, termed circLMTK, and was found to have upregulated expression in gastric cancer tissue; furthermore, silencing of circLMTK2 significantly inhibited gastric cancer cell growth. The investigators determined that the level of circLMTK2 may be an independent prognostic marker for overall survival and disease-free survival in patients with gastric cancer. Chen *et al.* Abstract 24O

Practice point and future research opportunities

This study determined the circular RNA profile of gastric cancer tissue and characterised a circular RNA that is derived from the LMTK2 gene, circLMT2, that is differentially expressed in gastric cancer tissue and may serve as a new proliferative factor and prognostic marker in gastric cancer.

BREAST CANCER

A nomogram may predict the likelihood of axillary lymph node metastasis in patients with breast cancer

Jianquo Lai of the Breast Tumor Centre, Sun Yat-sen Memorial Hospital, Sun Yat-sen University in Guangzhou, China and colleagues used ultrasonographic-pathologic features to formulate a nomogram to predict the likelihood of metastasis to axillary lymph nodes prior to surgery in patients with breast cancer. They collected data from January 2012 to March 2017 from 1,273 patients with histologically proven breast cancer who were divided into the training set and the validation set. Multivariate logistic regression analysis identified statistically significant independent predictors and a receiver operating characteristic curve was implemented to evaluate the discriminative ability of the nomogram. A calibration plot was also executed to compare actual versus predicted probability and the utility of the nomogram was evaluated using decision curve analysis.

The multivariate logistic regression analysis revealed that axillary lymph node status was associated with clinical tumour size, the histological grade, longitudinal diameter, cortical thickness, and hilum status. The area under the receiver operating characteristic curve was 0.876 (95% confidence interval [CI] 0.830, 0.923) in the validation set, which compared favourably to 0.873 (95% CI 0.851, 0.896) in the training set. The decision curve suggested the nomogram had clinical utility. NCT02992769. Lai *et al.* Abstract 57O

Practice point and future research opportunities

The investigators have constructed a user-friendly tool that uses clinical variables that are preoperatively available to clinicians to predict the risk of axillary lymph node metastasis in individual patients based on ultrasonographic-pathologic features. This interesting tool warrants further validation.

Pembrolizumab has comparable safety and efficacy in a Japanese subgroup and in the overall population of patients with metastatic TNBC in KEYNOTE 086

Lead author Masaya Hattori of the Department of Breast Oncology, Aichi Cancer Centre Hospital in Nagoya, Japan presented a subgroup analysis of Japanese patients with metastatic triple negative breast cancer (TNBC) in cohorts A and B of the KEYNOTE 086 trial evaluating the safety and anti-tumour activity of pembrolizumab. Cohort A enrolled Japanese patients regardless of PD-L1 expression with centrally confirmed metastatic TNBC who had received at least one systemic treatment or no prior systemic therapy, whereas cohort B comprised Japanese patients with metastatic disease, ECOG performance status 0-1, and having tumour PD-L1 expression of combined positive score (CPS) ≥1%. Both cohorts received pembrolizumab at 200 mg i.v. every 3 weeks for 24 months or until disease progression, intolerable toxicity, or investigator or patient decision. Clinically stable patients experiencing progressive disease (PD) could remain on pembrolizumab until PD was confirmed by the next assessment; tumour imaging was performed every 9 weeks over the course of one year and every 12 weeks thereafter. The primary endpoints of KEYNOTE 086 were the objective response rate (ORR) according to RECIST by central review in cohort A and safety in both cohorts. The secondary endpoints

included ORR in cohort B, disease control rate (DCR; complete response [CR] + partial response [PR] + stable disease [SD] lasting ≥ 24 weeks), progression-free survival (PFS) and overall survival (OS) in both cohorts. Data cut-off for this analysis was 10 November, 2016.

Cohort A had 20 Japanese patients with a median age of 53 years. Of these, 12 patients' tumours were positive and 8 were negative for PD-L1 expression. Eleven patients had elevated LDH and 13 patients had visceral metastases. One patient demonstrated CR and one had PR, and 2 patients had SD as the best overall response. Median PFS was 2.0 months (95% confidence interval [CI] 1.7, 2.1) in cohort A, and median OS was 8.3 months (95% CI 4.6, 10.3).

Cohort B consisted of 9 Japanese patients with a median age of 38.0 years; of these, one patient had elevated LDH, and 5 had visceral metastases. One patient achieved CR, 2 had PR, and 2 patients showed SD. Median PFS was 2.1 months (95% CI 1.6, 4.2) and median OS was not reached in this cohort.

Drug-related adverse events (DRAEs) occurred in 20 (67.0%) patients in both cohorts. The most commonly reported DRAEs were pruritus in 4 patients, while 3 patients each reported fatigue, pyrexia, anaemia, rash, and diarrhoea. All grade 3/4 DRAEs occurred in cohort A, including diarrhoea, nausea, and bacteraemia, which each occurred in one patient. Immune related adverse events included grade 2 infusion reaction in one patient, grade 1 interstitial lung disease, grade 2 hypersensitivity in one patient, and one patient experienced grade 1 hyperthyroidism. No deaths or treatment discontinuation due to an AE occurred. NCT02447003. Hattori *et al.* Abstract 93O

Practice point and future research opportunities

Data from 29 Japanese patients participating in the KEYNOTE 086 trial showed similar responses to pembrolizumab to those observed in the overall population. Pembrolizumab monotherapy was well tolerated and demonstrated anti-tumour activity in Japanese patients.

Palbociclib added to endocrine therapy improves PFS over endocrine therapy in women with HR-positive/HER2-negative ABC in the Asia-Pacific region

An analysis of data from a subgroup of women from the Asia-Pacific region who participated in the PALOMA-2 and -3 trials of palbociclib in advanced breast cancer (ABC) were presented by Seock-Ah Im, Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea. The trials demonstrated the efficacy and tolerability of palbociclib administered in combination with endocrine therapy in the overall population of patients with hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative ABC. PALOMA-2 enrolled postmenopausal women who were untreated for HR-positive/HER2-negative ABC and were randomised 2:1 to palbociclib at 125 mg/day plus letrozole at 2.5 mg/day or placebo plus letrozole. PALOMA-3 enrolled women of any menopausal status with disease progression after previous endocrine therapy. These women were randomised 2:1 to the same schedule of palbociclib plus fulvestrant at 500 mg or placebo plus fulvestrant.

In the PALOMA-2 study, 92 (14%) patients were from the Asia-Pacific region, which was defined as Australia, Japan, Korea, and Taiwan. These patients were younger than the overall population with a median age of 61 years; 79% of these patients were Asian and 20% were white. The majority (70%) of patients had ≥2 disease sites, 59% displayed visceral disease and 64% had received prior (neo)adjuvant endocrine therapy. Sixty-four percent of patients had a disease-free interval (DFI) longer than 12 months and 58% of these patients showed a DFI longer than 6 months following prior (neo)adjuvant therapy. Palbociclib/letrozole was administered to 64 patients and 28 received placebo/letrozole. Median progression-free survival (PFS) was 22 months (95% confidence interval [CI] 19, 26) with palbociclib/letrozole versus 14 months (95% CI 7, 22) for placebo/letrozole (hazard ratio [HR] 0.49; 1-sided p = 0.007). Treatment-emergent adverse events (TEAEs) of any grade with palbociclib occurred in 100% of patients compared to 96% of patients on placebo. The most common AE with palbociclib was neutropenia, which was reported in 91% of patients and 55% of patients receiving palbociclib required a dose reduction due to AEs.

The PALOMA-3 trial had 114 (22%) patients from the Asia-Pacific region; similarly, these patients were also younger than the overall population with a median age of 53 years. Due to this younger age, more (38%) patients were premenopausal. Seventy-five percent of these patients were Asian and 23% were white. All patients had received prior endocrine therapy, 70% had received prior chemotherapy for ABC, 66% of patients had ≥2 disease sites, and 57% had visceral disease.

Palbociclib plus fulvestrant was given to 78 and placebo plus fulvestrant was given to 36 patients from the Asia-Pacific region in PALOMA-3. The median PFS was 13 months (95% CI 9, 16) with palbociclib/fulvestrant compared to 6 months (95% CI 4, 9) with placebo/fulvestrant (HR 0.51; 1-sided p = 0.002). TEAEs of any grade occurred in 100% versus 92% of patients on palbociclib/fulvestrant versus placebo/fulvestrant. With palbociclib, 95% of patients reported neutropenia and 51% of patients on palbociclib required a dose reduction due to AEs. NCT01740427; NCT01942135. Im *et al.* Abstract 95O

Practice point and future research opportunities

Palbociclib plus endocrine therapy showed similar clinical benefit in Asian and white patients recruited from the Asian-Pacific region compared to the overall population in two randomised, clinical trials. In both trials, the patients in the Asian-Pacific cohorts were younger than the overall population. PALOMA-2 only enrolled postmenopausal patients, whereas PALOMA-3 enrolled both pre- and postmenopausal women, the proportion of premenopausal patients was higher in PALOMA-3. Palbociclib plus endocrine therapy in the first-line and later-lines of therapy, showed clinically meaningful improvement in PFS over placebo plus endocrine therapy and demonstrated a tolerable safety profile in patients with HR-positive/HER2-negative advanced breast cancer from the Asian-Pacific region. This benefit was regardless of menopausal status.

Abemaciclib in combination with fulvestrant improves PFS in Asian women with HR-positive/HER2-negative ABC that progressed on endocrine therapy

Masakazu Toi of Kyoto University in Kyodai, Japan presented the primary endpoint data, investigator-assessed progression-free survival (PFS), as well as secondary efficacy and safety endpoints from a cohort of Asian patients participating in the phase III MONARCH 2

trial. This study evaluated abemaciclib, a third-generation CDK4 and CDK6 inhibitor, plus fulvestrant in women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer (ABC) who had progressed within 12 months from the end of (neo)adjuvant endocrine therapy, or were on first-line endocrine therapy administered for metastatic breast cancer but had not received chemotherapy for metastatic disease; pre/perimenopausal patients also received a gonadotropin-releasing hormone agonist.

Previously reported findings from the overall intent-to-treat (ITT) population of MONARCH 2 showed that median PFS was significantly improved with abemaciclib plus fulvestrant over placebo plus fulvestrant (hazard ratio [HR] 0.553; $p < 0.0000001$). The objective response rate (ORR) among patients with measurable disease was 48.1% with the abemaciclib combination and 21.3% with placebo/fulvestrant ($p < 0.001$).

The patients were stratified by metastatic site (visceral, bone only, or other) and the demonstration of primary or secondary resistance to prior endocrine therapy and randomised in a 2:1 ratio to receive abemaciclib plus fulvestrant (n=446) or placebo plus fulvestrant (n=223). Abemaciclib was initially given at a dose of 200 mg twice daily; following a protocol amendment, all patients received abemaciclib at 150 mg twice daily and fulvestrant at 500 mg was provided as per label.

In all, 214 Asian patients had been randomised; 149 patients to the abemaciclib/ fulvestrant arm and 65 to the placebo/fulvestrant arm. The data from this cohort of Asian women were in accord with findings in the overall population. The median PFS was 22.8 months with the abemaciclib combination versus 11.6 m with placebo/fulvestrant, HR 0.515; 95% confidence interval [CI] 0.359, 0.740 (log-rank $p < 0.001$). In the 170 (70.4%) Asian patients with measurable disease, the ORR was 48% with abemaciclib and fulvestrant versus 23.4% with placebo/fulvestrant. With abemaciclib, 2.4% of patients achieved complete response (CR) versus 0% of patients treated with placebo/fulvestrant ($p = 0.004$).

Adverse events were more frequently reported for abemaciclib/fulvestrant versus placebo/fulvestrant, including diarrhoea (90.5% versus 20.0%), neutropenia (68.2% versus 4.6%), nausea (37.8% versus 16.9%), and fatigue (53.8% versus 30.9%). NCT02107703. Toi *et al.* Abstract 96O

Practice point and future research opportunities

The abemaciclib/fulvestrant combination constituted an effective treatment in Asian patients with HR-positive/HER2-negative advanced breast cancer who progressed on endocrine therapy. Significantly improved PFS and ORR were demonstrated in this cohort that were consistent with the ITT population in MONARCH 2.

CNS MALIGNANCIES

Mismatch repair deficiency and PD-L1 expression in high grade glioma tumours

Dianna Patricia, Faculty of Medicine Department of Anatomic Pathology, Universitas Pelita Harapan, Tangerang, Indonesia discussed how loss of expression of the mismatch repair (MMR) proteins, MLH1 and MSH2, leads to mismatch repair deficiency (MMRD), which may contribute to the high tumour mutational burden (TMB) that is characteristic of high grade glioma. Dr. Patricia and colleagues have focused their research on the interaction between MMRD, the programmed death-ligand 1 (PD-L1), which mediates immune evasion by tumour cells, and the apoptotic factor, TP53, in patients with high grade glioma in Siloam Hospital in Indonesia.

In this study, the investigators performed immunohistochemistry assays on 43 formalin-fixed paraffin-imbedded high grade glioma samples to detect the levels of MLH1, MSH2, TP53, and PD-L1 protein expression. E1L3N antibody was used to detect PD-L1 expression. MMR deficiency was defined as loss of expression of at least one of the MMR proteins.

Four samples were omitted from the analysis. In the 39 remaining samples, MMRD was determined in 13 (33%) patient samples that was associated with negative expression of TP53 ($p = 0.0161$), suggesting the TP53 independent pathway of genetic instability. In MMRD samples, the PD-L1 positive rate tended to be higher at 38% than in MMR proficient samples, where the PD-L1 expression rate was 11% ($p = 0.0896$). There was also no significant relationship between MMRD and age, or between MMRD and histological status. An analysis of overall survival showed MMRD was significantly associated with poorer prognosis ($p = 0.005$). Patricia *et al.* Abstract 119O

Practice point and future research opportunities

This study confirms that the presence of MMRD in the tumour associates with poor survival, and that MMRD may serve as useful prognostic biomarker. High grade glioma tumours with MMRD may also express PD-L1.

DEVELOPMENTAL THERAPEUTICS

Oral combination of paclitaxel shows similar bioavailability as i.v. paclitaxel in patients with solid tumours

Christopher Jackson of the Department of Medicine at the University of Otago in Dunedin, New Zealand presented preliminary bio-equivalence data from a scheduled interim analysis of the first 6 patients in a randomised crossover study, ACTRN 12615000894594, that compared Oraxol, which is oral paclitaxel in combination with HM30181, to i.v. paclitaxel in patients with advanced solid tumours. Dr. Jackson explained that HM30181 was designed to resolve the poor oral bioavailability seen with paclitaxel that is due to active excretion by Pgp, which is expressed on intestinal epithelial cells. Furthermore, oral administration is preferable to i.v. administration to minimize i.v. site-specific adverse events, and also avoids allergic reactions to cremaphor, the vehicle used for i.v. delivery of paclitaxel and other drugs having poor water-solubility.

The patients received HM30181 at 15 mg plus oral paclitaxel at 205 mg/m2 once daily for 3 consecutive days and also crossed over to receive a single dose of i.v. paclitaxel at 80 mg/m2. Blood samples for pharmacokinetics analysis were taken up to day 9 for the combination and to day 5 for i.v. paclitaxel.

Patients with advanced solid tumours treated with combined oral paclitaxel plus novel HM30181 demonstrated bioavailability that was equivalent to i.v. paclitaxel. Comparison of HM30181/paclitaxel versus i.v. paclitaxel by area under the curve measurements (AUC0-∞) revealed that the geometric mean ratio (GMR) was 87.09% (90% confidence interval [CI] 74.61-101.66%) and the intra-subject coefficients of variation (CV) were 12.62%. The time over minimum effective concentration was increased five-fold with the oral combination to 30 hours, compared to 6 hours for i.v. paclitaxel.

The combination was well tolerated; no grade 3/4 toxicities were seen with combined HM30181 and oral paclitaxel. The investigators noted that a sample size of 30 subjects is required to formally demonstrate bioequivalence between the combination and i.v. paclitaxel and additional patients are being enrolled to achieve this. Based on these findings the combination has been taken further to a phase III trial assessing the efficacy of oral paclitaxel plus HM30181 compared to three weekly doses of i.v. paclitaxel in advanced breast cancer. Jackson *et al.* Abstract 133O

Practice point and future research opportunities

HM30181 plus oral paclitaxel administered to patients with solid tumours achieved AUC levels of paclitaxel that were comparable to paclitaxel delivered by i.v. The oral combination of paclitaxel plus HM30181 was well tolerated and provided advantages to patients over traditional i.v. weekly paclitaxel. The combination also removed the need for steroid pre-treatment, injection site specific adverse events, and the possibility of allergic reactions to the i.v. vehicle, since it is administered orally.

GASTROINTESTINAL CANCERS, COLORECTAL

mXELIRI is non-inferior to FOLFIRI in second-line metastatic colorectal cancer

Tae Won Kim, Department of Oncology, Asan Medical Centre in Seoul, Korea presented data from a randomised trial designed to demonstrate the non-inferiority of a modified formulation of XELIRI (mXELIRI) that contains reduced doses of irinotecan (200 mg/m2 on day 1) and capecitabine (1600 mg/m2 on days 1–14).

Dr. Kim and colleagues conducted the multicentre, open-label, randomised phase III Asian XELIRI ProjecT (AXEPT) trial to evaluate the efficacy and safety of mXELIRI versus FOLFIRI, with or without bevacizumab, as second line treatment of patients with metastatic colorectal cancer. AXEPT was designed to demonstrate non-inferiority of the capecitabine-containing regimen in terms of overall survival (OS); a total of 464 events were estimated as necessary to show OS non-inferiority with a power of 80% at a one-sided α of 0.025, requiring a target sample size of 600 patients. The 95% confidence interval upper limit of the hazard ratio was pre-specified as less than 1.3.

AXEPT enrolled 650 adult patients with histologically confirmed metastatic colorectal cancer, and ECOG performance status (PS) 0–2, who experienced disease progression or intolerance of the first-line regimen. The patients were randomised equally to the mXELIRI or FOLFIRI arms; 326 patients received mXELIRI and 324 received FOLFIRI, with both regimens delivered with and without bevacizumab. Patients were also stratified according to country, ECOG PS, number of metastatic sites, prior oxaliplatin treatment, and the receipt of concomitant bevacizumab.

After a median follow-up of 15.8 months, patients in the mXELIRI and FOLFIRI arms demonstrated median OS of 16.8 and 15.4 months, respectively, (hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.71, 1.02; non-inferiority test $p < 0.0001$). Comparable median progression-free survival (PFS) was also observed between the treatment arms; median PFS was 8.4 months (95% CI 7.1, 9.1) with mXELIRI versus 7.2 months (95% CI 6.6, 8.5) with FOLFIRI (HR 0.95, 95% CI 0.81, 1.11; $p = 0.5078$).

The incidence of grade 3/4 adverse events (AEs) was significantly lower in the mXELIRI arm than the FOLFIRI arm; 167 (53.9%) patients on mXELIRI compared to 224 (72.3%) patients on FOLFIRI reported grade 3/4 AEs ($p < 0.0001$). The most common grade 3/4 AE was neutropaenia, which was reported by 52 (16.8%) and 133 (42.9%) patients in the mXELIRI and FOLFIRI arms, respectively ($p < 0.0001$). NCT01996306; UMIN000012263. Kim *et al.* Abstract LBA3_PR

Practice point and future research opportunities

The AXEPT trial demonstrates that modified XELIRI with or without bevacizumab is non-inferior to FOLFIRI with or without bevacizumab in terms of overall survival and was well tolerated. The modified XELIRI regimen could be an alternative to the standard FOLFIRI regimen as a standard second-line backbone therapy for metastatic colorectal cancer. An additional advantage is that capecitabine is given orally and is more convenient for patients.

Oral trifluridine/tipiracil hydrochloride may be a new treatment option in the third-line and higher setting for metastatic colorectal cancer in Asia

Virote Sriuranpong, Medicine, Chulalongkorn University Faculty of Medicine, Bangkok, Thailand, discussed findings from an analysis of data that was done according to 3 Asian country-based subgroups included in the TERRA study. TERRA assessed a tablet formulation of the anticancer agents trifluridine and tipiracil hydrochloride (trifluridine/tipiracil) that can be taken orally, by comparing the efficacy and safety of trifluridine/tipiracil with placebo in Asian patients with metastatic colorectal cancer (mCRC). Trifluridine is a nucleoside analogue and tipiracil hydrochloride inhibits thymidine phosphorylase.

The TERRA study enrolled patients from centres in China, the Republic of Korea, and Thailand who had received at least 2 prior standard regimens for mCRC including fluoropyrimidines, oxaliplatin and irinotecan. Eligible patients were randomised 2:1 to receive oral tablets of trifluridine/tipiracil hydrochloride at 35 mg/m2 twice daily for a 5 days on and 2 days off schedule for 2 weeks, followed by 14 days off per cycle, or placebo in each country. Of the 406 randomised patients, 305 (75.1%) were from China, 81 (20.0%) from the Republic of Korea, and 20 (4.9%) patients comprised the Thailand subgroup.

Oral trifluridine/tipiracil hydrochloride demonstrated significant improvements in overall survival (OS) and progression-free survival (PFS) in patients with mCRC; improved survival was observed in patients overall and across all 3 subgroups.

In the Chinese subgroup, improved OS and PFS, hazard ratio [HR] 0.82 (95% confidence interval 0.62,1.08), and HR 0.41 (95% CI 0.31, 0.54) were observed in the 204 patients receiving trifluridine/tipiracil compared to 101 patients on placebo, respectively.

The subgroup of 55 patients treated with trifluridine/tipiracil from the Republic of Korea also showed improved OS and PFS compared to the 26 patients on placebo, HR 0.77 (95% CI 0.48, 1.26) and HR 0.56 (95% CI 0.34, 0.93), respectively.

The 12 patients in the Thailand subgroup on trifluridine/tipiracil showed improved OS and PFS compared to the 8 patients on placebo, HR 0.54 (95% CI 0.19, 1.53) and HR 0.54 (95% CI 0.20, 1.42), respectively.

Overview of OS and PFS by Country

	China		Republic of Korea		Thailand	
ITT	FTD/TPI (n=204)	Placebo (n=101)	FTD/TPI (n=55)	Placebo (n=26)	FTD/TPI (n=12)	Placebo (n=8)
Median OS, months	7.9	7.2	8.1	5.9	7.3	7.3
OS HR (95% CI), P value	0.82 (0.62-1.08), P=0.144		0.77(0.48-1.26), P=0.196		0.54 (0.19-1.53), P=0.279	
Median PFS, month	2.0	1.8	1.9	1.7	3.7	2.1
HR (95% CI), P value	0.41 (0.31-0.54), P<0.001		0.56 (0.34-0.93), P=0.056		0.54 (0.20-1.42), P=0.178	

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The most commonly reported grade ≥3 adverse events according to NCI-CTCAE version 4.0 across all 3 countries were haematological adverse events; more than 30% of patients in each country receiving trifluridine/tipiracil hydrochloride reported grade 3 or higher neutropenia. No cases of febrile neutropenia were reported and the incidence was less than 2% of grade ≥3 treatment emergent adverse events per country, including nausea, vomiting, and diarrhoea in patients receiving trifluridine/tipiracil. NCT01955837. Sriuranpong *et al.* Abstract 142O

Practice point and future research opportunities

The safety profile of trifluridine/tipiracil in the TERRA trial was similar to previously reported safety profiles overall. Taken together with the progression-free survival benefits observed with trifluridine/tipiracil in each Asian country analysed, these findings support the potential of this oral agent as a new option for third-line or later treatments for patients with mCRC in Asia.

Fewer surgery-related complications reported with robotic assisted surgery in simultaneous resection of colorectal cancer and liver metastases

Jianmin Xu, Department of General Surgery, Zhongshan Hospital, Fudan University, Shanghai, China and colleagues conducted a study comparing a robot-assisted procedure with open surgery, and identifying the patients with colorectal cancer and liver metastasis that were most likely to benefit from each method. Patients with confirmed colorectal cancer and liver metastasis were randomised equally into a robotic arm or an open arm of 60 patients each. The primary endpoint was disease-free survival (DFS) at 3 years and the secondary endpoints were short-term surgical outcomes, complications, and safety. The study findings were presented by Ren Li.

Of the 60 patients undergoing robotic surgery, one patient converted to open surgery due to a drop of blood pressure induced by oppressing the inferior vena cava during hepatectomy. The remaining patients in the robotic arm demonstrated more favourable

short-term outcomes and fewer complications than patients in the open surgery arm. Despite longer operating times in the robotic arm, these patients experienced significantly less blood loss of 99.3 ml compared to 205.1 ml in patients receiving open surgery ($p < 0.001$). Patients in the robotic arm also had a shorter time to pass first flatus of mean (standard deviation) 63.0 (±28.2) hours compared to 93.6 (±35.5) hours in the open surgery arm ($p < 0.001$), and were able to return to a fluid diet sooner, at 83.2 (±34.1) hours versus 113.2 (±64.5) hours, respectively ($p = 0.002$). Patients in the robotic arm had shorter hospital stays of 8.1 (±2.1) days compared to 10.6 (±4.9) days with open surgery. Urinary function was improved and faster recovery of stress response, as indicated by lower C-reactive protein levels, and better liver function, indicated by lower ALT/AST levels, were observed. Dindo grade III/IV complication was decreased with robotic surgery to 6.7% compared to 20.0% with open surgery ($p = 0.032$). The research team headed by Dr. Xu identified patients with colorectal cancer that had fewer than 3 liver metastases, with a lesion maximal size of less than 5 cm as the patients most likely to benefit from robot-assisted surgery, which was found to offer improved short-term post surgical outcomes in these patients. Xu *et al.* Abstract 143O

Practice point and future research opportunities

Robotic surgical platforms are currently used for treatment of several cancer types, including resections of colorectal cancer and liver metastasis, sphincter-preservation in rectal cancer, surgery of endometrial cancer, and of head and neck cancer resections. Data from this study demonstrated improved short and long-term patient outcomes following robot assisted surgical platforms used for simultaneous resection of colorectal cancer and liver metastasis as compared with conventional surgical approaches in patients with colorectal cancer and liver metastasis.

Validated nCounter platform used to stratify colorectal cancer into Consensus Molecular Subtypes and CRCassigner subtypes in an Asian population

Elisa Fontana of the department of Molecular Pathology, the Institute of Cancer Research/Royal Marsden NHS Foundation Trust in Sutton, UK, discussed this study that aimed to characterise a sample of the Asian colorectal cancer (CRC) population according to five distinctive subtypes (CRCassigner) that were consolidated into four consensus subtypes (CMS), which these investigators previously developed based on microarray/RNAseq data. They developed a low-cost, easy-to-use clinically-deployable assay, the NanoCRC, NanoString Technologies, that could be used on fresh-frozen and formalin-fixed paraffin-embedded samples to characterise tumours into CMS and CRCassigner subtypes. In this study, they also associated the subtypes with clinical and genomic covariates. Dr. Fontana pointed out that, while the prognostic role of subtypes was confirmed in multiple trials conducted in the West, subtype classification of the Asian population had not been done.

Primary CRC samples from 190 Chinese, Malay and Indian patients were prospectively collected in Singapore. Of these, NanoCRC has been successfully performed on 23 of these samples to date and 17 were further validated with RNAseq. The samples were classified into all of the 4 CMS or 5 CRCAssigner subtypes across different disease stages. The subtypes derived from the Asian population were similar to the Caucasian population. Of patients with early stage at diagnosis, 7 were classified as CMS2 microsatellite stable, one patient as CMS1 microsatellite unstable and BRAF mutant, and 3 patients each were mixed

subtypes. Of the patients having stage IV disease at diagnosis, one was classified as CMS4, 2 as CMS2, and one patient as CMS3 KRAS mutant. Both the CMS and CRCassigner were concordant for all non-mixed cases. Correlation with gender, age, stage, grade, sidedness, genomic data, and survival outcomes are ongoing. Fontana *et al.* Abstract 145O

Practice point and future research opportunities

This study represents the first Asian colorectal cancer cohort to be classified according to molecular subtypes using the NanoCRC assay. The nCounter platform was successful in classifying both the Caucasian and Asian populations, and may be suitable for the stratification of patients in worldwide clinical trials.

GASTROINTESTINAL CANCERS, NON-COLORECTAL

Prognostic gene expression signature in chemotherapy treated patients from the MAGIC trial

Elizabeth C. Smyth, Gastrointestinal Oncology, Royal Marsden Hospital NHS Foundation Trust, London, UK reported data from a study using post-chemotherapy resection specimens from patients with gastro-oesophageal cancer (GC) treated in the MAGIC trial. The investigators determined the molecular subgroups of GC from gene expression data derived from patient FFPE resections that were analysed with the NanoString Technologies' nCounter system. The gene panel included 200 genes associated with different GC characteristics. Penalised Cox regression was used to identify genes that could impact overall survival (OS) followed by computing risk scores (GC-Assigner) for each patient using standard Cox regression. Finally, unsupervised analysis was used to cluster patients into GC-Assigner risk groups associated with OS and the classified subgroups were evaluated as prognostic markers of survival outcomes following chemotherapy for GC.

Gene expression data from 82 patients who were treated with chemotherapy in the MAGIC trial were used to generate a 7-gene signature that could be predictive of OS. Three risk groups were defined according to the GC-Assigner scores and OS was assessed accordingly. Following surgery, 3-year OS was 0% (95% confidence interval [CI] 0, 0%) for high risk patients, 3-year OS was 40% (95% CI 27.0%, 64.0%) for intermediate risk patients, and 80% (95% CI 63.8%, 99.8%) for low risk patients ($p < 0.000001$). By multivariate analysis, GC-Assigner risk groups were found to be independent of lymph node metastasis in predicting OS (lymph node positive, hazard ratio [HR] 3.46, $p = 0.025$), intermediate risk GC-Assigner HR 0.18 ($p = 1.00E-05$), and low risk GC-Assigner HR 0.072 ($p = 5.23E-06$). GC-Assigner group status was not prognostic in 117 patients treated with surgery alone ($p > 0.05$). ISRCTN93793971. Smyth *et al.* Abstract 193O

Practice point and future research opportunities

These data suggest that risk score and GC-Assigner groups are independent predictors of overall survival in patients with gastro-oesophageal cancer treated with neoadjuvant chemotherapy in the MAGIC trial, but not for patients treated with surgery alone. As risk was assigned using post-treatment resection tissue, which is less limited than diagnostic biopsies, validation of this signature and these risk groups, GC-Assigner could be useful in stratification of future clinical trials evaluating personalised post-chemotherapy and resection treatment approaches for patients with gastro-oesophageal cancer.

Genomic data may expand therapeutic options in advanced hepatocellular carcinoma

James Suh of the Pathology Department, Foundation Medicine in Morrisville, USA and colleagues used comprehensive genomic profiling (CGP), a hybrid capture-based next-generation sequencing (NGS) technique, to determine the tumour mutational burden (TMB) and microsatellite instability (MSI) in samples from patients with HCC. Both TMB and MSI serve as biomarkers for response to immune checkpoint inhibitors and may offer information

allowing the determination of optimal therapy in patients with advanced stage hepatocellular carcinoma (HCC).

The investigators performed CGP of up to 315 cancer-related genes from 614 consecutive patients with HCC from 2012 to 2016. Of the 614 patients providing samples, 70% were male and their median age was 61 years, which was similar to the overall population of the CheckMate 040 trial. No information on the HBV/HCV infection status was available.

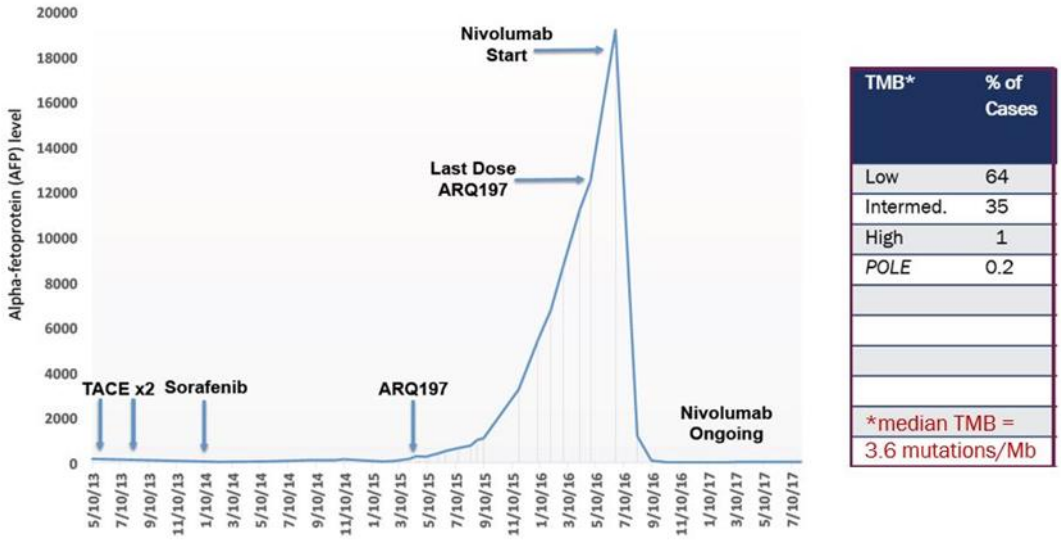
The MSI status was determined in 378 patients; one HCC sample was MSI-High.

The investigators used a hybrid-capture, adaptor ligation based NGS assay to detect genomic alterations, including point mutations, small indels, copy number changes and rearrangements. TMB was calculated from up to 1.1 megabase (Mb) of the cancer genome and was defined as the number of somatic, coding point mutations and indels per Mb. The cut-off for low TMB was <6, intermediate was from 6 to 19, and high TMB was defined as ≥20 mutations/Mb. TMB was low in 394 (64%) tumour samples, intermediate in 214 (35%), and high in 6 (1.0%) patients' tumours. The median TMB was 3.6 mutations/Mb.

Genomic alterations were most often observed in the *TERT,* TP53 and *CTNNB1* genes; genomic alterations were detected in 51% of *TERT,* 34% of *TP53*, and 32% of *CTNNB1* genes. Genomic alterations occurred less frequently in 14% of *MALT1*, *PASK*, and CD36 genes, followed by 13% of *MYC*, 12% of *ARID1A*, 8.5% of *CDKN2A*, and 7.6% of RB1 genes. Genomic alterations were also detected in 0.4% of *MLH1*, and *MSH2* genes, 1.1% of *MSH6*, and 0.2 % of *POLE* genes. Genomic alterations that were potentially targetable with approved agents involved *CCND1* (5.5%), *FGF19* (5.1%), *FGF3/4* (4.2%), *MET* (2.0%), *ERBB2* (1.1%), *EGFR* (0.7%), *BRAF* (0.5%) and *ALK* (0.4%) genes.

An 82-year old Asian-American male with untreated hepatitis C presented with HCC in 2013. Following TACE, sorafenib and tivantinib, CGP of 2015 liver biopsy detected TMB of 15 mutations/Mb. Nivolumab was started in mid-2016 with rapid symptomatic improvement and concurrent decline in serum AFP, now 15 months on therapy with only mild pruritis.

The image below shows serum AFP in responder to nivolumab (left) and study TMB data (right).



TMB*	% of Cases
Low	64
Intermed.	35
High	1
POLE	0.2

*median TMB = 3.6 mutations/Mb

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Su *et al.* Abstract 194O

Practice point and future research opportunities

Hepatocellular carcinoma is the third leading cause of cancer mortality worldwide but limited response to existing chemotherapies has been reported, creating a high unmet need for new therapies. Comprehensive genomic profiling detected genetic alterations in the tumours of patients with hepatocellular carcinoma that may be targetable with already approved drugs.

TMB (36% intermediate or high) and MSI assessed by CGP rather than PD-L1 immunohistochemistry status may predict benefit from nivolumab, which showed ~20% response rate in the overall population of CheckMate 040. CGP of hepatocellular carcinoma also reveals rarer genomic alterations involving understudied, recurrently altered genes such as *PASK* and *MALT1* that may open new avenues of medical treatment, suggesting a role in the management of advanced-stage hepatocellular carcinoma.

Subanalysis of CheckMate 040 data demonstrates nivolumab is safe and provides durable responses in Asian patients with advanced hepatocellular carcinoma

Choo Su Pin, Medical Oncology, National Cancer Centre Singapore, in Singapore, presented findings from a subgroup analysis of nivolumab in Asian patients with advanced hepatocellular carcinoma (HCC) on behalf of the CheckMate 040 investigators. Previously reported results from the dose-expansion portion of the phase I/II CheckMate 040 study demonstrated an objective response rate (ORR) of 20%, a median duration of response (DOR) of 9.9 months, and a 9-month overall survival (OS) rate of 74% in patients with advanced HCC in the overall trial population.1 Based on data from the CheckMate 040 trial, nivolumab was granted accelerated approval by the FDA in September 2017 for the treatment of HCC in patients who have been previously treated with sorafenib.

The study administered nivolumab to patients who were naive to or previously treated with sorafenib at 0.1 to 10 mg/kg during the dose-escalation phase (n=48) and at 3 mg/kg to the expansion cohort (n= 214) every 2 weeks regardless of PD-L1 status. The primary endpoints of the escalation phase were safety and tolerability and ORR by blinded independent central review according to RECIST v1.1 in the expansion phase. Secondary endpoints for both phases included DOR, disease control rate (DCR), and OS.

The analysis was done on data from 107 Asian patients, including 25 from Hong Kong, 32 from Japan, 13 from Korea, 15 from Singapore, and 22 patients from Taiwan (n=22); median follow-up was 19.2 months. The median age of the patients was 62 years, and 99% had Child-Pugh scores of 5 or 6. Overall, 18% and 50% of patients were positive for hepatitis C virus (HCV) or HBV, respectively, and the remaining 32% of patients were uninfected.

In the Asian subgroup, 22 sorafenib-naive patients had an ORR of 14%, which consisted of 3 (14%) partial responses (PR) and the DCR was 41%. In 85 sorafenib-experienced patients, the ORR was 15% with 2 (2%) complete responses (CR) and 11 (13%) PR, and the DCR was 49%. Across both cohorts, the median DOR was 13.8 months and 6 of the 16 (38%) responses were ongoing at data cut-off. The 12- and 18-month OS rates in both cohorts were 62% (95% confidence interval [CI] 51.6, 70.2) and 44% (95% CI 34.1, 53.5), respectively.

The adverse event (AE) profile was consistent with the known safety profile of nivolumab and with the overall population. Any grade treatment-related AEs (TRAEs) occurred in 75% of patients and grade 3/4 TRAEs occurred in 11% of patients. The rates of grade 3/4 ALT and AST elevations were 1% and 2%, respectively. NCT01658878. Pin *et al.* Abstract 195O

Citation: 1. El-Khoueiry *et al.* Lancet 2017; 389(10088):2492-2502.

Practice point and future research opportunities

Nivolumab demonstrated durable responses and a manageable safety profile in Asian patients that were comparable to the overall CheckMate 040 population of patients with advancedHCC, with or without chronic viral hepatitis. A randomised phase III study of nivolumab versus sorafenib in the first-line setting for patients with advanced HCC is currently ongoing (CheckMate 459; NCT02576509).

GENITOURINARY CANCERS

Neoadjuvant chemotherapy may improve cancer specific PFS in patients with locally advanced upper tract urothelial carcinoma

Shingoh Hatakeyama and colleagues from the Hirosaki University School of Medicine in Hirosaki, Japan investigated the outcomes of platinum-based neoadjuvant chemotherapy (NAC) in patients with locally advanced upper tract urothelial carcinoma (UTUC). Their retrospective study reviewed the data of 426 patients who underwent radical nephroureterectomy at five medical centres between January 1995 and April 2017. Of these, 234 patients were treated as having high-risk disease (cT3–4 or cN+) with or without NAC based upon the eligibility of cisplatin. The investigators assessed tumour response, post-therapy pathological downstaging, lymphovascular invasion (LVI), and prognosis stratified by NAC exposure.

Of 234 patients treated for high-risk disease, 101 patients received NAC whereas 133 patients did not and served as controls. The regimens in the NAC group included gemcitabine plus carboplatin for 75% of patients, and gemcitabine together with cisplatin in 21% of patients. Patients receiving NAC experienced significantly more pathological downstaging of the primary tumour than control patients and NAC for locally advanced UTUC significantly prolonged progression-free, cancer-specific survival. According to multivariate Cox regression analysis using an inverse probability of treatment weighted method, NAC emerged as an independent predictor for prolonged progression-free, cancer-specific survival. However, the influence of NAC on overall survival was not statistically significant. UMIN000027611. Hatakeyama *et al.* Abstract 272O

Practice point and future research opportunities

The clinical impact of neoadjuvant chemotherapy on oncological outcomes remains unclear. This retrospective analysis provided data suggesting that platinum-based neoadjuvant chemotherapy for locally advanced UTUC potentially improves oncological outcomes. Further prospective studies are needed to demonstrate whether there is a clinical benefit with neoadjuvant chemotherapy in locally advanced UTUC.

Cost benefit analysis decides against adding abiraterone plus prednisone to ADT in metastatic hormone sensitive prostate cancer in the Hong Kong setting

Androgen deprivation therapy (ADT) may remain the standard of care in Hong Kong for patients with metastatic hormone sensitive prostate cancer despite the well documented survival benefit seen in these patients by adding abiraterone and prednisone to ADT, due to a cost-effectiveness analysis conducted by Chi-Leung Chiang, Department of Clinical Oncology, the University of Hong Kong and Horace Choi, the University of Hong Kong – Shenzhen Hospital, Hong Kong, Hong Kong Province. Professor Chiang, Doctor Choi and a team of investigators evaluated whether this combination treatment would be cost effective for institutions in Hong Kong, in addition to providing clinical benefit. Their cost/benefit analysis contained data from the 1,199 patients with metastatic, castration-sensitive prostate cancer participating in the randomised LATITUDE clinical trial. LATITUDE demonstrated that abiraterone plus prednisolone in combination with ADT significantly improved the overall survival of patients with hormone sensitive metastatic prostate cancer.

The investigators used a deterministic Markov model with probabilistic sensitivity analysis for accounting parameter uncertainty to compare abiraterone plus prednisolone in combination with ADT to ADT alone in patients with metastases across a 20-year time horizon. The primary outcomes of the analysis were the quality-adjusted life-year (QALY) and incremental cost-effectiveness ratio (ICER). The analysis used Hong Kong's societal perspective and the 3 times the local gross domestic product (GDP) per capita (USD 43,530 / HKD 339,531 in 2016) was used as the threshold of cost-effectiveness.

It was determined that adding abiraterone/prednisone to ADP would result in an ICER of median 183,003 in US dollars (95% central range [CR] 148,780 to 235,632) or, in Hong Kong dollars, approximately HKD 1,427,425 (95% CR 1,160,480 to 1,837,926) per QALY gained. Such ICER was more than 4 times of the local GDP per capita. As such, abiraterone/prednisone plus ADT was not evaluated to be a cost-effective strategy compared with the ADT standard care strategy currently employed in Hong Kong institutions.

However, the authors pointed out that the combined strategy of abiraterone/prednisone plus ADT would become more cost-effective with ICER less than 3 times of the GDP per capita should the cost of abiraterone be reduced to approximately 72% of the current price in a Hong Kong public hospital, or to 3,116 in US dollars (approximately a median of 24,304 in Hong Kong currency) per cycle. Chiang, Choi *et al.* Abstract 261O

Practice point and future research opportunities

Although abiraterone and prednisone added to ADT has demonstrated significant clinical benefit in patients with metastatic hormone sensitive prostate cancer, this regimen cannot be recommended since is not a cost-effective treatment in the Hong Kong setting. The high cost of abiraterone in Hong Kong precludes its addition to standard ADT in patients with metastatic hormone sensitive prostate cancer in the Hong Kong even though Hong Kong has a high global ranking in GDP per capita.

GYNAECOLOGICAL CANCERS

Attempt to mainstream genetic counselling for genetic testing of *BRCA1* and *BRCA2* in ovarian cancer patients in Malaysia evaluated

Sook-Yee Yoon, genetic counsellor, Cancer Research Malaysia, Subang Jaya, Malaysia explained that, while the importance of identifying germline *BRCA* mutations in ovarian cancer patients for medical management of patients and risk management for relatives is well-known, genetic services remain relatively inaccessible in Asia. She noted that mainstreaming improved access to cancer genetic testing in United Kingdom, leading to the MaGiC Study, which aimed to determine the prevalence of germline *BRCA1*/*BRCA2* mutations in a population-based cohort, to assess the feasibility of mainstreaming genetic counselling and testing, and to examine the psychosocial impact of genetic testing in Malaysia.

The prospective observational study aims to recruit 800 ovarian cancer patients over a two-year period. Basic genetic counselling workshops have been held for 70 non-genetic clinicians from 29 hospitals across Malaysia so that they may provide patients with counselling in their local hospital, while other patients received counselling from a genetic counsellor or clinical geneticist. Blood samples were obtained from the patients and analysed for *BRCA* mutations and the patients were informed of the results. All patients receiving both pre- and post-test counselling, followed by a telephone interview by a researcher, who evaluated the study feasibility and psychosocial impact using the Genetic Counselling Satisfaction Scale (GCSS), Decisional Conflict Scale (DCS), Psychosocial Aspect of Hereditary Cancer (PAHC), and Cancer Worry Scale (CWS).

One year into the study, 208 of the recruited 248 patients had received genetic testing/counselling. The incidence of *BRCA* mutations was determined at 13%, which is similar to the prevalence in other populations. In addition, 16% of tests revealed variants of uncertain significance and 71% of tests were negative for *BRCA* mutation.

Analysis of 160 patient reported outcomes showed that most patients were satisfied with their counselling experience, not conflicted in making decision, and felt informed about their choices. Preliminary findings showed that the answers to the psychosocial surveys were similar between the two groups indicating that most patients were satisfied with their counselling experience, regardless of whether they were counselled by non-genetic clinicians or a traditional genetics counsellor. The PAHC results showed that 79% of patients at pre- and 69% at post-test expressed concerns regarding ‘living with cancer’. The Distress Thermometer revealed that 26% of patients may require psychosocial support at pre-test, which was reduced to 17% after result disclosure. Frequent concerns about cancer recurrence were raised by 41% of patients at both the pre- and post-test evaluation by CWS. Yoon *et al.* Abstract LBA4_PR

Practice point and future research opportunities

BRCA1 or *BRCA2* mutation is carried by one of 9 breast cancer patients and 4 of 10 of these carriers do not have a family history of breast or ovarian cancer. Knowing the BRCA status may inform treatment decisions and the level of risk of developing metastases. Mainstreaming may improve access to cancer genetic testing regionally. The MaGiC study

showed the feasibility of mainstreaming genetic testing and counselling to local hospitals, and that most patients were satisfied with the counselling experience.

Molecular characterisation of a panel of ovarian clear cell carcinoma cell lines determines different molecular subtypes

Ruby Huang, Gynaecologic Oncology, National University Cancer Institute, Singapore, Singapore and colleagues undertook characterisation of ovarian clear cell carcinoma (OCCC) cell lines due to the limited availability of pre-clinical models for drug screening and biomarker discovery in OCCC. A preclinical model is needed since OCCC commonly occurs in Asia and is linked to chemoresistence to standard treatment. The investigators profiled and authenticated 6 OCCC cell lines (JHOC9, TAYA, RMG2, KOC7C, OVTOKO, RMG5) using short tandem repeat (STR) profiling. Extracted DNA was used for next generation sequencing (NGS) with ACT Genomics ACTOnco and ACTBRCA™ and mutations were identified using the Torrent Variant Caller. Only non-synonymous mutations with coverage ≥25 and variant frequency ≥5% that were not found in common variant database were included in the analysis. Extracted RNA was used for gene expression microarray profiling with Affymetrix U133A2. Epithelial ovarian cancer gene expression molecular subtypes (GEMS) and epithelial-mesenchymal transition (EMT) scores were determined from this microarray analysis.

Three OCCC lines, JHOC9, TAYA, and RMG2, were determined as “epithelial” according to low EMT scores of -0.71, -0.69, and -0.53, respectively; all of these epithelial lines were characterised as Epi-A. Three other OCCC lines, KOC7C, OVTOKO, RMG5, were identified as “mesenchymal” due to high EMT scores of 0.23, 0.28, and 0.4), respectively; two mesenchymal lines, KOC7C and RMG5, were characterised as Stem-A, and OVTOKO was Mes when characterised by GEMS.

Of the epithelial types, the JHOC9 and TAYA cell lines harboured *ARID1A* and *PIK3CA* mutations, whereas *MLH1* mutation was detected in the RMG2 line. TP53 mutation was also found in the TAYA cells.

The mesenchymal lines OVTOKO and RMG5 also harboured *ARID1A* mutation. *BRCA1* mutation was detected in 2 mesenchymal lines, KOC7C and RMG5 while a *BRCA2* mutation was detected in the RMG5 cell line.

The investigators also observed that the percentage of apoptotic cells significantly increased in the epithelial compared to the mesenchymal lines when the cells were cultured under anchorage independent conditions. Huang *et al.* Abstract 289O

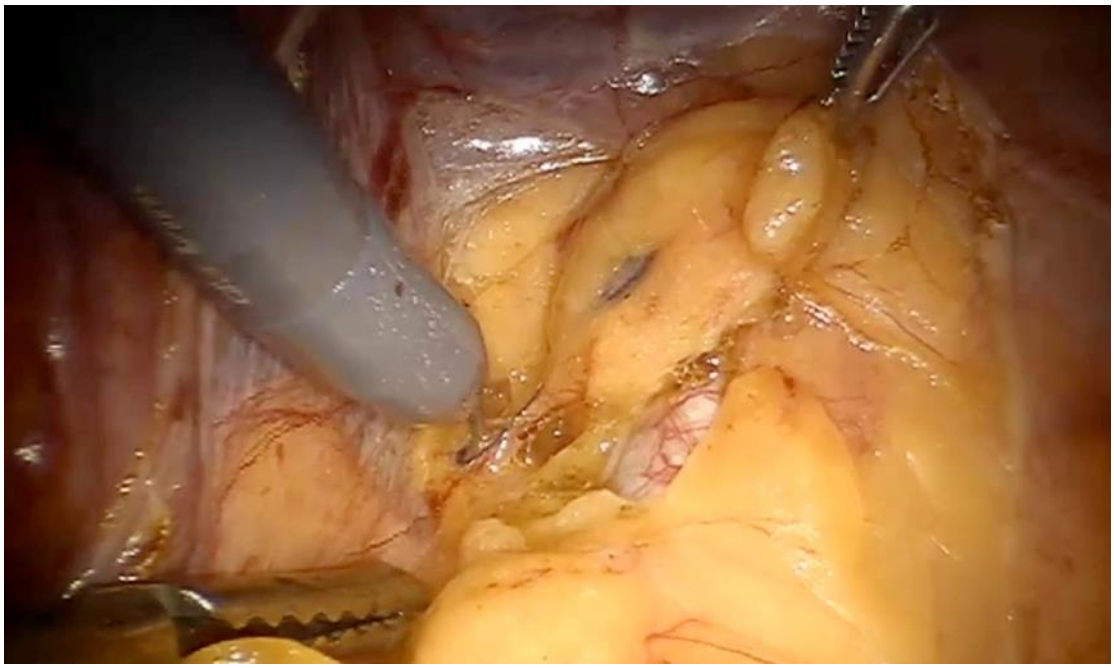
Practice point and future research opportunities

The data from these OCCC lines will be useful to investigate possible therapeutic options. The information that existing OCCC cell lines have certain molecular features that are common in OCCC such as *ARID1A* and PIK3CA mutations is useful, as is knowing that uncommon mutations such as *BRCA1*/2 may also be present.

Sentinel lymph node mapping shows an association with improved detection of nodal metastasis following robotic assisted techniques in endometrial cancer

Tien Le of the Division of Gynaecologic Oncology, The Ottawa Hospital Regional Cancer Centre, Ottawa, Ontario, Canada discussed how sentinel lymph node (SLN) mapping strategies can improve the detection of nodal metastasis following robotic-assisted surgical staging for early stage endometrial cancer and provided his team's local SLN mapping experience using blue dye, as compared to full lymphadenectomy under the robotic DaVinci platform.

The image below shows sentinel node dissection in endometrial cancer done using the robotic platform.



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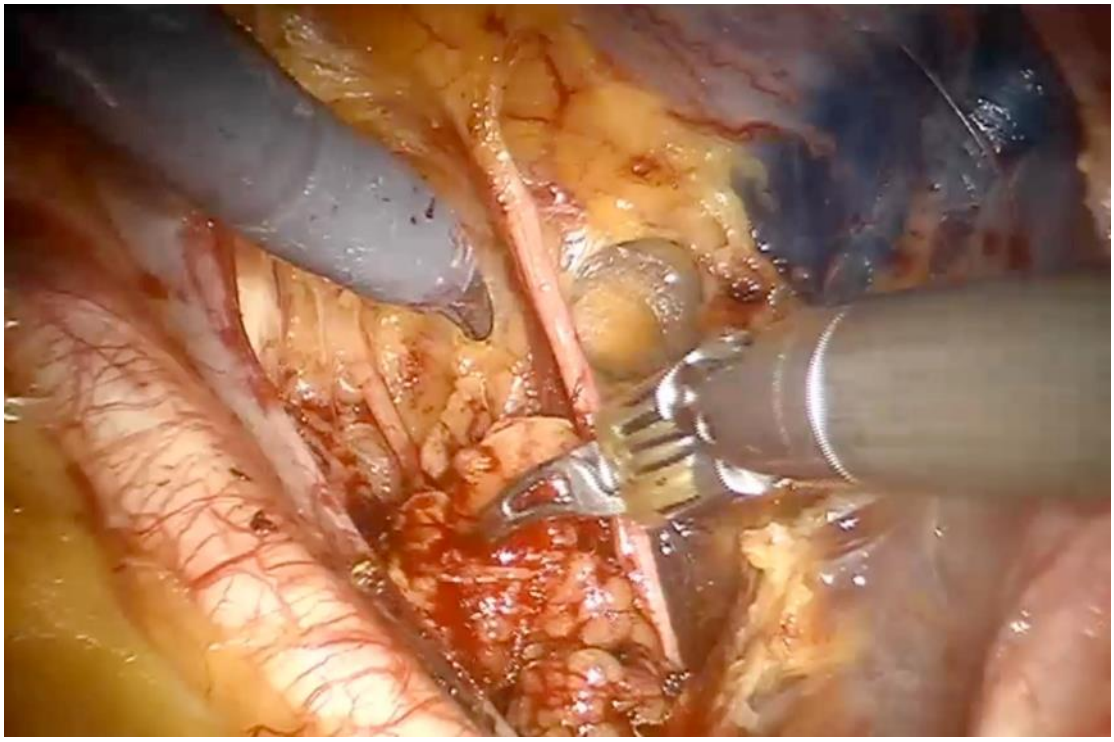
This retrospective analysis reviewed data from all patients with clinical stage I endometrial carcinoma from November 2011 to May 2016. Robotic assisted staging was done in 469 patients. Staging full lymphadenectomy was done in 409 patients, with SLN mapping performed in 60 patients. No significant association was apparent between the use of SLN mapping and tumour grade, depth of invasion, lymph-vascular space invasion (LVSI), or cervical stromal invasion. Grade 1 tumour was documented in preoperative biopsy for 372 (79%) patients, while 290 (78%) patients had confirmed grade 1 based on the hysterectomy pathology.

Nodal metastases were detected in 5 (1.2%) patients treated with full lymphadenectomy versus 5 (8.3%) of the 60 patients that underwent SLN mapping ($p < 0.001$).

Image below shows full pelvic lymphadenectomy in endometrial cancer done using the robotic platform.



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A logistic regression model that included grade (1 versus 2/3), histology (endometroids versus non-endometroids), cervix stromal involvement (yes versus no), myometrial invasion (none versus less than 50% versus more than 50%), and SLN mapping application showed two significant predicting factors of nodal metastasis: the final non-endometroids histology, odds ratio [OR] 5.02; 95% confidence interval [CI] 1.26, 19.96 (p = 0.02) and the use of SLN mapping, OR 7.80; 95% CI 2.06, 29.58 (p = 0.002). In patients with endometroids histology and negative SLN, application of SLN mapping protocol did not result in a significant increased risk for recurrence. Le *et al.* Abstract 290O

Practice point and future research opportunities

SLN mapping can improve the sensitivity of detection of nodal metastasis with no increased risk for recurrence in patients with low risk endometrial cancer.

HEAD AND NECK CANCER

Plasma EBV DNA used to identify patients at higher risk of relapse after radiotherapy or chemoradiation for nasopharyngeal cancer

Lead author Edwin Pun Hui, Department of Clinical Oncology, The Chinese University of Hong Kong, Shatin, Hong Kong PRC, discussed the results of a randomised controlled trial evaluating adjuvant chemotherapy in high and low risk patients with nasopharyngeal cancer. The trial was biomarker guided with the aim of selecting high-risk patients that could benefit from adjuvant chemotherapy while sparing low risk patients from unnecessary toxicity. Eligible patients had nasopharyngeal cancer AJCC (6th Ed) stage IIB-IVB, ECOG performance status 0-1, adequate organ function, and no locoregional disease or distant metastasis after receiving radiotherapy or chemotherapy. From September 2006 to July 2015, a total of 789 patients were screened for the presence of Epstein-Barr virus (EBV) DNA in plasma at 6 to 8 weeks post-radiotherapy. The patients having EBV DNA >0 copies/ml underwent work-up and were randomised to receive 6 cycles of adjuvant cisplatin-gemcitabine (arm A) or arm B (observation). Patients with no EBV DNA were observed. The trial's primary endpoint was relapse-free survival (RFS).

Screening of plasma EBV DNA indicated that 573 (72.6%) patients had EBV DNA = 0, whereas 216 (27.4%) patients had EBV DNA >0. Of the EBV positive patients, 104 (13.2%) were randomised equally; each arm contained 52 patients and clinical characteristics and significant biomarkers were evenly balanced in the two arms. The median follow-up was 6.6 years. There was no significant difference in RFS or overall survival (OS) between the two arms in the intent-to-treat and per protocol population, nor by subgroup analysis defined by EBV DNA level and PET-CT.

The investigators used recursive partitioning analysis (RPA) and data from the overall population of 789 patients to identify 3 prognostic groups: the low risk group had EBV DNA <50 and stage II/III disease (n=518), the intermediate risk group had EBV DNA <50 and stage IV disease (n=155), and the high risk group had EBV DNA ≥50 (n=116). The 3-year OS rates were 94.2%, 87.6%, and 55.9% ($p < 0.0001$) and the 5-year OS rates were 89.2%, 78.3%, and 42.2% ($p < 0.001$). The investigators observed that low risk group comprised 66% of the patients who could potentially be spared the toxicity of adjuvant chemotherapy. In addition, 5-year OS rates were comparable in the low and intermediate risk groups ($p = 0.069$). NCT00370890. Hui *et al.* Abstract 336O

Practice point and future research opportunities

Adjuvant chemotherapy with cisplatin-gemcitabine did not improve overall survival in patients with nasopharyngeal cancer with detectable post-radiotherapy plasma EBV DNA who were at high risk of relapse. However, using EBV DNA levels as a biomarker, the authors were able to identify low risk patients that may potentially be followed-up with observation only and spared the toxicity of adjuvant chemotherapy.

Intensification of treatment by transoral robotic surgery in HPV-negative stage IV oropharyngeal cancer yields high survival rates

Karan Gupta, Department of Head-Neck and Thoracic Surgical Oncology, Fortis Memorial Research Institute in Gurgaon, India reported patient outcomes following treatment intensification using transoral robotic surgery (TORS) in addition to adjuvant radiotherapy/chemoradiotherapy in 86 patients with stage IV (cT1-3N2) HPV-negative oropharyngeal carcinoma. TORS neck dissection was performed using *daVinci*® surgical system and patients received adjuvant radiation (60-64 Gy) or chemoradiation at the same dose with weekly cisplatin following this procedure.

The overall cohort in this prospective trial included 69 males and 17 females who were evaluated for disease-free survival (DFS) and overall survival (OS). The patients' mean age at presentation was 57.4 years (range 32 to 83 years). All patients were treated with TORS. After mean follow-up of 34 months (range 21 to 51 months), DFS was 76.7% and OS was 88.4% in the overall cohort.

The investigators also determined patient outcome according to disease stage. In 12 patients with T1-3N2a disease, 7 patients received subsequent radiotherapy and 5 patients received chemoradiotherapy. At an average follow-up of 29 months, all patients were alive; 10 patients remained disease free but 2 patients developed nodal recurrence and received salvage surgery. In the 56 patients with T1-3N2b stage disease, 16 patients received subsequent radiotherapy and 40 patients received chemoradiotherapy subsequent to TORS. In this cohort, 46 (82.1%) patients were alive and disease free, 4 patients died due to metastasis. Of the 6 patients who developed loco-regional recurrence, 4 patients received salvage surgery and remain disease free. Of the 18 patients with 3N2c status, 5 received radiotherapy subsequent to TORS and 13 patients received adjuvant chemoradiotherapy; of these, 3 patients died due to disease progression. Of the 15 patients alive at data cut-off, 10 (55.6%) patients remained disease free. Seven patients developed locoregional recurrence; of these, 4 patients remained disease free after salvage surgery. The Gupta team recommended TORS as a good option for cure in relatively radio-resistant HPV-negative resectable oropharyngeal malignancies. Gupta *et al.* Abstract 338O

Practice point and future research opportunities

This prospective trial demonstrated that TORS was successfully used to intensify treatment of stage IV oropharyngeal carcinoma and allowed the achievement of better oncological outcome, while avoiding early and late toxicities due to higher doses of radiotherapy or chemoradiotherapy.

Close clinical monitoring advised after definitive radiotherapy treatment of nasopharyngeal carcinoma

Chung Hang James Chung Chow, Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong, and a team of researchers determined the incidence of second primary tumour (SPT) and the risk of developing cancer in patients with nasopharyngeal carcinoma following intensity-modulated radiotherapy (IMRT) by reviewing the records of 759 patients with non-metastatic nasopharyngeal carcinoma who underwent definitive IMRT between February 2003 and September 2011. The cumulative SPT incidence and overall

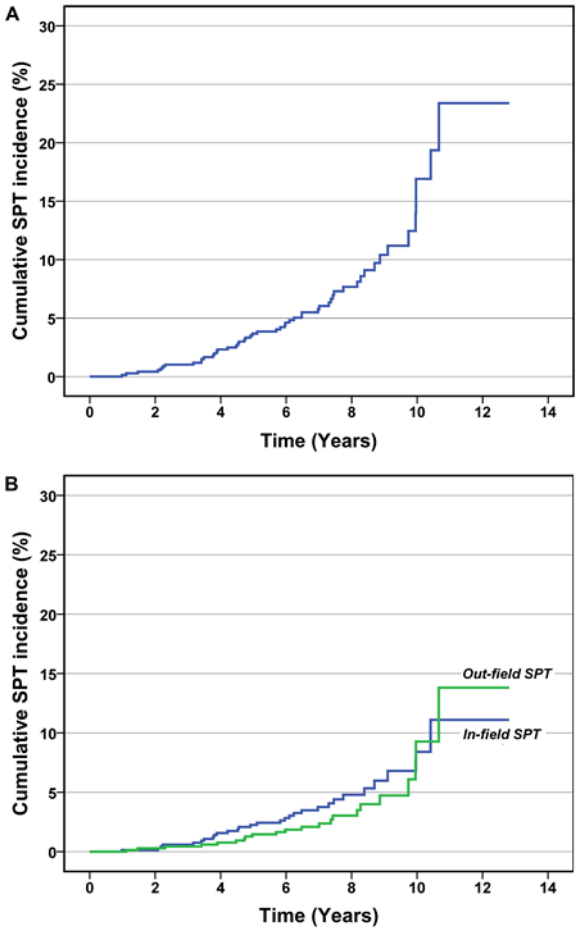
survival (OS) after SPT diagnosis were estimated. Standardised incidence ratios (SIR) were calculated using age, gender and calendar-year specific incidence rates from the Hong Kong Cancer Registry to quantify excess cancer risks in patients with nasopharyngeal carcinoma compared with the general population.

At a median follow-up of 7.5 years, 51 (6.7%) cases of SPT had occurred; of these, 22 (43.1%) cases were located within the previous radiotherapy fields. The in-field SPTs most commonly reported were tongue cancers in 31.8%, and sarcomas in 31.8% of patients. The cumulative SPT incidence was 1.0% at 3 years. The cumulative incidence of SPT at 5- and 8-years was 3.7% and 7.7%, respectively. Median OS after diagnosis of a SPT was 2.9 years.

Patients undergoing IMRT were found to have an elevated risk of 84% for developing a second cancer (SIR 1.84; 95% confidence interval [CI] 1.37-2.42). Significant excess risk was determined for specific cancers, including sarcoma (SIR 38.10; 95% CI 16.41-75.06), tongue (SIR 33.33; 95% CI 13.36-68.67), oropharyngeal (SIR 25.00; 95% CI 2.81-90.25), prostate (SIR 3.19; 95% CI 1.17-6.95), and liver cancer (SIR 2.80; 95% CI 1.02-6.10).

The excess risks of developing cancer in general and each for specific cancer all were higher beyond 5 years of follow-up.

Cumulative incidence of all SPTs (A) and SPTs within/outside radiotherapy fields (B) is shown on graphs below.



Analysis using a Cox proportional hazard model revealed the only independent variable that was associated with SPT development was age, hazard ratio [HR] 1.061; 95% confidence interval [CI] 1.029-1.094 ($p < 0.001$). Chow *et al.* Abstract 340O

Practice point and future research opportunities

Patients have a high risk of developing a SPT, particularly for a SPT located within the radiotherapy field, following definitive IMRT for nasopharyngeal carcinoma, warranting close clinical follow-up. The occurrence of a SPT severely limits the longevity of nasopharyngeal carcinoma survivors, necessitating that clinicians have high awareness for this lethal late complication in clinical follow-up.

IMMUNOTHERAPY OF CANCER

A review of autoimmune colitis following single agent and combination immunotherapy in patients treated for cancer at a tertiary referral centre in Australia

Arthur Mulvey, Medical Oncology, The Crown Princess Mary Cancer Centre, Westmead, Australia reported findings from a retrospective review of a case series of patients experiencing colitis following immunotherapy. Immunotherapy-induced autoimmune colitis is a known immune adverse event that occurs with ipilimumab used as single agent or in combination, and with other programmed death-1 (PD-1) or PD-1 ligand (PD-L1) inhibitors, but the clinical course has not yet been clearly described. The review included data from all patients with autoimmune colitis presenting at a tertiary referral centre, Westmead Hospital, beginning in 2011 who were identified from the melanoma database, clinical trials databases, and medical records coding. The data were stratified according to whether treatment with single agent ipilimumab, another single agent PD-1/PD-L1 inhibitor, or a combination of both was received and these 3 cohorts each contained 6 patients.

In all, 18 cases of immunotherapy-induced colitis were identified that occurred in 12 male and 6 female patients. Fourteen of these patients had been treated for melanoma, 2 for renal cell carcinoma, and 2 for non-small cell lung cancer. The group treated with combination therapy experienced more episodes of grade 3 colitis; 5 cases occurred with combination therapy versus 2 cases with each single agent. Hospital admission was also higher with combination therapy; 5 hospital admissions were reported with combined therapy versus 3 with PD-1 treatment, and 2 with ipilimumab.

PD1-associated colitis showed a slower onset of symptoms of a median of 14.8 weeks from the start of treatment, compared to 6 weeks for ipilimumab alone, and 8 weeks for combination therapies. The median time to resolution of symptoms was 60 days in the ipilimumab group, 65 days in the PD-1 group, and 34 days in the combination group. Endoscopy revealed no statistically significant difference in the severity and distribution of colitis between the treatment groups.

Only one patient in the PD-1 inhibitor-associated colitis group had a raised white cell count (WCC) on presentation; the median WCC was 9.4 and median C-reactive protein (CRP) was 47.5 in the ipilimumab cohort versus median WCC of 6.4 and CRP 5.1 with PD-1 inhibitors, versus WCC of 11.25 and CRP of 35 with combination treatment. Three patients in the combination group, 2 in the PD-1-colitis group and one patient in the ipilimumab group required infliximab and 5 patients experienced relapse during steroid wean.

There was no recurrence of colitis in 3 patients in the ipilimumab cohort and one patient in the combination group who were re-challenged with a PD-1 inhibitor. The disease control rate was 58% and the median survival was 11 months in patients with progressive disease. Mulvey *et al.* Abstract 374P

Practice point and future research opportunities

The study provides an important start to understanding the clinical characteristics of colitis that is associated with 3 different immunotherapy treatments in 3 cancer types. While

combination immunotherapy resulted in more severe colitis, that required more hospital admissions and infliximab therapy. PD-1 inhibitors resulted in an indolent sub-acute phenotype. Relapse during steroid wean was common, highlighting the need for a slow and cautious steroid dose reduction. Patients with ipilimumab- and combination-associated colitis were safely re-challenged with PD-1 inhibitors.

MELANOMA

Subgroup analysis of patients with unresectable or metastatic melanoma patients in a phase II trial of HF10 oncolytic virus immunotherapy plus ipilimumab

Robert H.I. Andtbacka of the Huntsman Cancer Institute, University of Utah in Salt Lake City, USA described HF10 as a bioselected replication-competent oncolytic virus derived from HSV-1. Together with colleagues, he conducted a subgroup analysis of patients with unresectable or metastatic melanoma in a phase II trial evaluating the safety and efficacy of HF10 combined with ipilimumab. The analysis was done on data from 46 ipilimumab-naive patients with stage IIIB-IV unresectable melanoma who initially received four HF10 injections (1x107 TCID50/mL, up to 5mL/dose) per week directly into single or multiple dermal, subcutaneous, or lymph node tumours followed by up to 15 injections every 3 weeks. Ipilimumab was administered i.v. at 3 mg/kg every 3 weeks for a total of 4 doses. Tumour responses were assessed at 12, 18, 24, 36, and 48 weeks; the primary endpoint was best overall response rate (BORR) at 24 weeks.

The patient population comprised 59% men, with a median age of 67 years (range 28 to 91). Disease stage was IIIB in 20% of patients, IIIC in 43%, and IV in 37% of patients. Fifty-seven percent of patients were therapy naive and 43% had received ≥1 prior cancer therapy, including 2 patients that had received prior immune checkpoint inhibitors.

Of the 44 patients evaluable for efficacy the BORR at 24 weeks was 41%, including 18% of patients with an immune-related complete response (irCR), 23% of patients achieved immune-related partial response (irPR), and 17% showed immune-related stable disease (irSD) making the disease control rate (DCR) of 68%.

The BORR at 48 weeks was 45%, which consisted of 18% irCR and 27% irPR. Median progression-free survival (PFS) was 19 months and the 1-year overall survival (OS) rate was 85%. HF10 plus ipilimumab provided a decrease in lesion size of 50% or greater in 57% of injected lesions (N=148), 39% of never injected non-visceral lesions (N=41), and in 14% of never injected visceral lesions (N=22). Complete lesion resolution occurred in 30% of injected lesions and 20% of never injected non-visceral lesions.

The BORR according to patient characteristics was also determined; in treatment-naive patients, the BORR at 24 weeks was 50%, consisted of 17% irCR and 33% irPR, and BORR in patients with ≥1 prior therapies was 30%, comprising 20% irCR and 10% irPR. Median PFS in treatment-naive and in patients with ≥1 prior therapies was 19 and 22 months, respectively; 1-year OS rates were 87% and 82%, respectively. According to disease stage at baseline, BORR in 34 patients with stages IIIB/IIIC/IVM1a was 47%, with 21% irCR and 26% irPR, whereas 10 patients with stage IVM1b/IVM1c had BORR of 20% consisting of 10% irCR and 10% irPR.

Most ipilimumab plus HF10-related adverse events (AEs) were grade 2 or lower and similar to HF10 monotherapy. AEs ≥grade3 occurred in 37% of patients and the majority were due to ipilimumab. Three HF10-related ≥grade 3 AEs occurred, including embolism,

lymphoedema, diarrhoea, hypoglycaemia, and groin pain. NCT02272855. Andtbacka *et al.* Abstract 378O

Practice point and future research opportunities

The combination of HF10 and ipilimumab as treatment for non-resectable or metastatic melanoma demonstrated a favourable benefit/risk profile and showed encouraging antitumour activity.

Phase Ic trial of intralesional OrienX010 oncolytic viral therapy into liver metastases occurring in melanoma patients

Chuanliang Cui, Department of renal cell carcinoma and melanoma, Peking University Cancer Hospital-Beijing Cancer Hospital in Beijing, China explained that OrienX010 is an oncolytic immunotherapy that is derived from herpes simplex virus type 1 and contains expression of a gene encoding human GM-CSF. OrienX010 previously demonstrated efficacy in intra-lymphatic diseases, and has been tested for safety and efficacy in a phase Ic trial of intralesional injection into liver metastases. The liver is a common metastatic site in melanoma that carries a poor prognosis and limited efficacy for liver metastases has been shown with systemic therapy.

In this trial, OrienX010 (8×107 pfu/ml, 10ml per injection) was given intralesionally by ultrasound guide every 2 weeks; the dose was distributed into 1 to 2 liver lesions according to tumour size. Tumour assessment by computed tomography (CT) scan was done every 8 weeks. The primary endpoint was toxicity, while secondary endpoints included objective response rate (ORR), disease control rate (DCR) and progression-free survival (PFS).

Beginning in May 2016, nineteen patients were enrolled; 57.9% were men with a median age of 47 (range: 32 to 61) years. The mean size of injectable lesions was 30.4 mm (range: 10.0 to 59.0 mm). One tumour showed c-Kit mutation (exon 9) but no BRAF mutations were observed. All patients had received at least one prior therapy, most (68.4%) were transcatheter hepatic arterial chemoembolization. Multiple liver metastases were reported in 79% of patients, and 57.9% of patients had extrahepatic metastases including lung, bone, abdominal, and distant lymph node.

As of January 2017, twelve patients were evaluable with a median follow-up of 6.0 months. At this time, the ORR was 8.3%, including one partial response and 4 patients with stable disease for a DCR of 41.7%. The time to response was 8 to 16 weeks. Median PFS was 13.3 weeks (95% confidence interval [CI] 8.3, 18.4) and median OS was not reached.

Mean injection times were 6 (range 4 to 18). Serum LDH was elevated in 57.9% of patients. Reported adverse events (AEs) were all grade 1, including pyrexia in 84.2% of patients, fatigue in 31.6%, injection site pain in 26.3%, nausea/vomiting in 21.0%, hepatotoxicity in 21.0%, and leucopoenia in 10.5% of patients. NCT03048253. Cui *et al.* Abstract 379O

Practice point and future research opportunities

This is the first trial to evaluate the clinical benefit of an intralesional oncolytic virus injection into liver metastases among melanoma patients, which showed that OrienX010 was

tolerable and had a potentially beneficial effect. The pending phase II and combination trials are warranted.

Findings from a retrospective review suggest Asian patients with metastatic uveal melanoma are refractory to first-line nivolumab monotherapy

Kenjiro Namikawa Dermatologic Oncology, National Cancer Center Hospital, Tokyo, Japan, reported findings from a retrospective study of immunotherapy for patients with uveal melanoma, which is a distinct subtype of melanoma that has demonstrated limited response to immunotherapy thus far. Dr. Namikawa and colleagues conducted this retrospective study to evaluate the efficacy of nivolumab for Asian patients with metastatic uveal melanoma who were previously untreated with ipilimumab.

The investigators reviewed the database of National Cancer Centre Hospital in Tokyo, Japan, in which nivolumab was approved one year earlier than ipilimumab for cases of uveal melanoma. They assessed the best overall response (BORR) by RECIST v1.1, progression-free survival (PFS), and overall survival (OS) following treatment in 14 patients with metastatic uveal melanoma who received nivolumab at 3 mg/kg every 2 weeks or 2 mg/kg every 3 weeks. The patients' median age was 59.5 (range 42 to 74) years, and 11 patients were male. Performance status was 0 in 9 patients and 1 in 5 patients. At baseline, all of the patients had liver metastases, and 9 patients had additional extrahepatic metastases. Also serum lactate dehydrogenase was elevated in 8 patients. Transarterial chemoembolization had previously been administered to 8 patients but none of the 14 patients had received any prior systemic therapies including ipilimumab.

Findings from 12 evaluable patients revealed one patient had an objective tumour response yielding an ORR of 8.3%, and 5 patients achieved stable disease. The median PFS was 10 weeks (range 4 to 94 weeks), and the median OS was 58 weeks (range 5 to 105 weeks). Namikawa *et al.* Abstract 381O

Practice point and future research opportunities

Unlike cutaneous melanoma, metastatic uveal melanoma seems to be refractory to nivolumab monotherapy. However, since one patient in this analysis achieved a partial response, treatment strategies containing nivolumab as monotherapy and in combination with anti-PD1 antibody should be further investigated in uveal melanoma.

HF10 oncolytic virus immunotherapy is safe and well tolerated in Japanese patients with refractory superficial cancers

Naoya Yamazaki, Dermatologic Oncology, National Cancer Centre Hospital in Tokyo, Japan presented findings from a study of HF10, an oncolytic viral immunotherapy derived from an attenuated, replication-competent mutant strain of Herpes Simplex Virus type 1 (HSV 1). HF10 is delivered as an intratumoral injection that has shown promising activity in both injected lesions and uninjected lesions.

This phase I open label, non-randomised, dose escalation trial evaluated safety and tolerability of HF10 in Japanese patients with refractory solid tumours with cutaneous and/or superficial lesions. Six patients with melanoma or other skin cancers were initially administered 2 dose levels of HF10 (1 x 106 and 1 x 107 TCID50/dose); thereafter, dose escalation proceeded according to a “3+3” design. Adverse events (AEs) were evaluated according to NCI CTCAE v4.0. Evaluation criteria at sequential time-points included overall and injected tumor response per mWHO criteria, safety, and detection of the virus by qPCR.

A maximum of 4 injections of HF10 were injected into single lesions. Injections were given more than 2 weeks apart. All 6 treated patients were evaluable for safety. No dose limiting toxicities were reported. The AEs related to treatment with HF10 were all grade 1 and easily managed by the investigators. The AEs included malaise in 2 patients, and one patient each had headache and lower abdominal pain. No HF10-related serious AEs were reported.

All 6 patients were also evaluated for efficacy; of these, 4 patients achieved stable disease (SD) and 2 patients experienced disease progression. One patient with vaginal melanoma showed fading of the pigmented-lesion during the HF10 treatment, and achieved SD, and also had a 16.7% decrease in lesion by the end of the study. Thereafter, the patient began PD-1 immunotherapy, and achieved complete response. The investigators compared the results from the phase I trial that was carried out in the US, and determined that there was no significant difference in the safety profile between the US and Japanese patients. NCT02428036. Yamazaki *et al.* Abstract 382O

Practice point and future research opportunities

Multiple intratumoral injections of HF10 in superficial tumours were well tolerated and appeared to be safe in Japanese patients with melanoma or other skin cancers. HF10 provided stabilisation of the injected tumour. This interesting approach warrants further study.

NSCLC, EARLY

The clinical impact of PD-L1 protein expression in NSCLC

Naoki Yanagawa, Diagnostic Pathology, Yamagata Prefectural Central Hospital in Yamagata, Japan and colleagues addressed the controversy surrounding whether programmed cell death ligand 1 (PD-L1) is prognostic for response to immunotherapy by determining the levels of PD-L1 protein expression in non-small cell lung cancer (NSCLC) types and the association of expression levels with clinicopathological variables, including patient outcome.

The study included 899 NSCLC tumour samples. Most (550) patients were male with a mean age of 68.9 (range 32 to 89) years. Histopathology revealed 657 tumours were adenocarcinoma, 209 were squamous cell carcinoma, and 43 were other. PD-L1 expression was analysed using immunohistochemistry (VENTANA clone SP263) in stages I-IV NSCLC using tissue microarray. The percent of PD-L1 staining in tumour cells was scored as: 0 = 0%, 1 = 1 to 24%, 2 = 25 to 49%, and 3 = ≥ 50%.

PD-L1 tumour staining showed that 739 (82.2%) samples were 0, or negative for PD-L1 expression, score 1 was recorded for 47 (5.2%), score 2 in 26 (2.9%), and score 3 was determined in 87 (9.7%) samples. PD-L1 expression was associated with sex, smoking history, histology, tumour size, stage, pleural invasion, p53 protein expression, MIB-1 labelling index and EGFR mutation.

For the investigation of patient outcome, the mean duration of follow-up was 62.2 months and cut-off values of ≥1%, ≥25%, ≥50% were used for PD-L1 expression levels. Patients with adenocarcinoma having any levels of PD-L1 positive staining (≥1%) demonstrated a trend towards worse 5-year overall survival (OS) than those with negative staining; 5-years OS rates were 73.5% in patients with positive PD-L1 staining and 79% in patients with negative PD-L1 staining (p = 0.096). In multivariate analysis, PD-L1 expression was not an independent prognostic factor in adenocarcinoma. In squamous cell carcinoma, PD-L1 expression was not prognostic using these cut off values. Yanagawa *et al.* Abstract 395O

Practice point and future research opportunities

Findings from this study support other evidence showing that PD-L1 protein expression is not a prognostic factor in NSCLC.

PD-L1 expression is heterogeneous among the different histological components and metastatic lymph nodes in patients with resected lung adenosquamous carcinoma

Yiwei Liu, Department of oncology, Shanghai Pulmonary Hospital, Tongji University in Shanghai, China and colleagues investigated levels of programmed cell death ligand 1 (PD-L1) expression by immunohistochemistry (IHC) in 72 consecutive patients with pulmonary adeno-squamous carcinoma who underwent primary lung cancer resection. PD-L1 expression levels were assessed by IHC using PD-L1: Clone E1L3N (Cell Signaling #13684) in different histological components of primary and lymph node tissues.

Setting the staining level cut-off at 5%, the levels of PD-L1 expression were 20.8% in adenomatous and 33.3% squamous cell tissues. When other cut-off values were used, including 0.01, 0.05, and 0.10 the PD-L1 expression was discrepant between adenomatous and squamous histology in 26.4%, 19.4%, and 12.5% of cases, respectively. The investigators then evaluated a combination of the expression in tumour cells (TC) plus tumour-infiltrating lymphocytes (TILs), discrepancies between the two histological components were observed in 13.9%, 22.2%, and 30.6% cases, using cut-off values of 0.01, 0.05, and 0.10, respectively.

Evaluation of 38 patients with lymphatic metastasis revealed 4 types of lymphatic node histology: adenocarcinoma, squamous cell, adenosquamous, and a mixture. Analysis of different histological component using cut-off values of 0.01, 0.05, and 0.10, the concordances of PD-L1 expression were 74.1%, 80.0%, and 88.9% for the adenomatous cell component and 90.0%, 80.0%, and 85.0% for the squamous cell component, respectively. The authors noted that the discrepancy of adenocarcinoma histological subtype accounts for the lower concordant rate in the adenomatous component. Lui *et al.* Abstract 396O

Practice point and future research opportunities

This analysis shows the high level of discrepancy in PD-L1 expression between adenomatous and squamous cell components. In contrast, PD-L1 expression was highly consistent between paired histological types of lymph node and the primary lesion.

Low molecular weight heparin does not improve survival in patients with localised lung cancer

Benjamin Besse, Head of the thoracic cancer unit, Department of Medicine, Institut Gustave Roussy in Villejuif, France and colleagues addressed the controversy surrounding whether low molecular-weight heparins, specifically tinzaparin, impact the survival of cancer patients.

This phase III, controlled study enrolled patients with completely resected stage I, II or IIIA non-small cell lung cancer (NSCLC) who were randomised within 8 weeks of surgery to receive standard care with or without tinzaparin. The primary outcome was overall survival (OS). All clinical outcomes were centrally and blindly adjudicated. From August 2007 to June 2013, 269 patients were randomised to tinzaparin at 100 IU/kg daily for 12 weeks and 280 to control. Of these patients, 359 (65.4%) had stage I disease and 190 (34.6%) patients had stage II-III disease. A total of 220 (40.1%) patients received adjuvant chemotherapy.

After a median follow-up of 5.7 years, no significant difference was observed in OS between the treatment groups (hazard ratio [HR] 1.24; 95% confidence interval [CI] 0.92, 1.68; p = 0.17). Five-year OS rates were 68.2% (95% CI 62.5%, 74.4%) with tinzaparin compared to 74.2% (95% CI 68.9%, 79.9%) in the control arm. There was no difference in the cumulative incidence of recurrence between groups (subdistribution HR 0.94; 95% CI 0.68, 1.30; p = 0.70). However, a negative effect with tinzaparin was observed in the patients receiving adjuvant chemotherapy where OS was shorter in the tinzaparin group (HR 1.78; 95%CI 1.13, 2.81; p = 0.013). Two patients receiving tinzaparin experienced serious bleeding during the treatment period. NCT00475098. Besse *et al.* Abstract 397O

Practice point and future research opportunities

Findings from this study do not support a survival benefit with tinzaparin in patients with NSCLC. Adjuvant tinzaparin at a dose of 100 IU/kg/d for 12 weeks had no detectable impact on overall and recurrence-free survival in patients with completely resected stage I-IIIA NSCLC.

NSCLC, METASTATIC

Osimertinib is poised to become the standard of care in Asian patients with EGFR-TKI sensitising mutation-positive advanced NSCLC

Byoung Chul Cho, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea and colleagues conducted this analysis of a subset of Asian patients that were enrolled in the FLAURA trial at Asian sites. FLAURA is a phase III, double-blind, randomised study that evaluated the efficacy and safety of first-line osimertinib, a third generation, epidermal growth factor receptor - tyrosine kinase inhibitor (EGFR-TKI) that potently and selectively inhibits both EGFR mutations and EGFR T790M resistance mutations, compared to a standard of care (SoC) EGFR-TKI in patients with EGFR mutation-positive, advanced non-small cell lung cancer (NSCLC). This analysis was pre-planned to examine the clinical benefit in Asian patients, where EGFR mutations occur in 30 to 40% of NSCLC cases compared to 10 to 15% of Western NSCLC patients.

Patients who had not received prior EGFR-TKI systemic anti-cancer therapy for advanced disease, with Ex19del/L858R EGFR-mutated advanced NSCLC that were ≥18 years or ≥20 years in Japan were enrolled. Patients with neurologically stable central nervous system metastases were also eligible, provided definitive treatment/steroids had been completed for ≥2 weeks. The patients were randomised 1:1 to oral osimertinib at 80 mg once daily or to SoC EGFR-TKI (either 250 mg gefitinib or 150 mg erlotinib, each administered orally once daily), and stratified by mutation status (Ex19del/L858R) and race (Asian/non-Asian). The primary endpoint was investigator assessed progression-free survival (PFS) by RECIST v1.1. The Asian subgroup included 322 patients, of whom 46 were Chinese, 120 were Japanese, and 156 patients were from other Asian countries. Baseline patient characteristics were balanced.

A consistent PFS benefit was observed across predefined subgroups, with hazard ratios [HR] ranging from 0.48–0.68 with osimertinib versus SoC. Median total treatment duration was 15.5 (range 0.5 to 25.5) months with osimertinib and 11.7 (range 0 to 26.2) with SoC. The median PFS was 16.5 months with osimertinib compared to 11.0 months with SoC, HR 0.54; 95% confidence interval [CI] 0.41, 0.72 ($p < 0.0001$).

The median duration of response was doubled at 17.6 months with osimertinib versus 8.7 months with SoC. The objective response rate was 80% versus 75% with osimertinib versus SoC and median overall survival was not reached with either treatment.

Overall, 33 (20%) and 44 (28%) deaths occurred in the respective osimertinib and SoC arms. Adverse events (AEs) of any grade occurred in 99% of patients in both arms. Grade ≥ 3 AEs were reported for 40% of patients on osimertinib versus 48% with SoC. AEs leading to discontinuation occurred in 15% of osimertinib patients versus 21% of patients on SoC. The most commonly reported AEs with osimertinib were diarrhoea in 54%, and paronychia in 40% of patients. Grade ≥ 3 AEs included diarrhoea in 2% and paronychia in 1% of patients receiving osimertinib. NCT02296125. Cho *et al.* Abstract LBA6_PR

Complete findings from the FLAURA trial have been published in The New England *Journal of Medicine* (Soria *et al.* NEJM 2018;378:113-125).

Practice point and future research opportunities

The results of this subset analysis are quite compatible with the findings in the overall population where first-line osimertinib demonstrated superior efficacy over SoC EGFR-TKI. Osimertinib may be considered as the SoC for the first-line treatment of Asian patients with advanced NSCLC and EGFR mutations.

Robust CNS response observed with first-line osimertinib in patients with EGFR-TKI sensitising mutation-positive advanced NSCLC

Johan Vansteenkiste, of the University Hospitals Leuven in Leuven, Belgium explained that central nervous system (CNS) metastases frequently occur in patients with epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) sensitising mutation positive advanced non-small cell lung cancer (NSCLC), prompting this prespecified subgroup analysis of FLAURA trial data. The analysis evaluated CNS activity following osimertinib treatment in patients with CNS metastasis. Osimertinib is a third-generation, EGFR-TKI that selectively inhibits both EGFR sensitising mutations and EGFR T790M resistance mutations and has demonstrated CNS penetration and CNS activity in patients with T790M-positive advanced NSCLC.

The phase III FLAURA trial enrolled previously untreated patients with EGFR mutated advanced NSCLC, including those with neurologically stable CNS disease, if definitive treatment/steroids had been completed for ≥2 weeks. The patients were randomised 1:1 to oral osimertinib at 80 mg once daily or to a standard of care (SoC) EGFR-TKI (either 250 mg gefitinib or 150 mg erlotinib, each administered orally once daily). This prespecified subgroup analysis included patients with CNS metastasis that was present on baseline brain scan, as assessed by blinded independent central neuroradiology review (BICR). The CNS full analysis set (cFAS) included patients with ≥1 measurable and/or non-measurable CNS lesion present on baseline brain scan by BICR; the CNS evaluable for response set (cEFR) included only patients with ≥1 measurable CNS lesion. The endpoints in all cohorts included CNS progression-free survival (CNS PFS) by RECIST v1.1, CNS objective response rate (CNS ORR), and duration of CNS response (CNS DoR).

The cFAS cohort included 128 (23%) patients; of these 61 patients received osimertinib and 67 received SoC. In the respective cohorts, 62% versus 61% of patients were female, 66% versus 55% were Asian, and 25% versus 24% had received prior brain radiotherapy. In this overall cFAS population, 18 CNS PFS events, including death, occurred with osimertinib compared to 30 events with SoC. The median CNS PFS was not reached (NR; 95% confidence interval [CI] 16.5, NC) with osimertinib compared to 13.9 months (95% CI 8.3, NC) with SoC, CNS PFS hazard ratio [HR] 0.48. The confirmed CNS ORR was 57% versus 40% with osimertinib versus SoC, respectively, odds ratio [OR] 2.0 (p = 0.053), and the median DoR was NR (95% CI 11.9, NC) versus 14.4 (95% CI 8.3, 18.7) months, respectively.

In the cEFR cohort of patients having measurable CNS lesions at baseline, 22 patients had been treated with osimertinib and 19 had been given SoC. Confirmed CNS ORR in these patients was 77% (95% CI 55, 92) compared to 63% (95% CI 38, 84) with osimertinib and SoC, respectively, OR 2.0 (p = 0.322). The median CNS DoR was NR (95% CI 8.5, NC)

versus 18.7 (95% CI 4.2, 18.7) months, respectively. NCT02296125. Vansteenkiste *et al.* Abstract LBA5

Practice point and future research opportunities

New treatment options are needed for CNS metastases, which are common in patients with EGFR-mutated advanced NSCLC. This prespecified subgroup analysis of data from the FLAURA trial demonstrated superior CNS PFS with osimertinib compared to SoC in patients with CNS metastases documented by neuroradiology BICR. The patient benefits with osimertinib were similar to that reported in the overall population, including a CNS response rate that was higher and more durable with osimertinib than with SoC EGFR-TKI.

First-line alectinib and crizotinib show comparable efficacy and safety in Asian and non-Asian patients with ALK-positive advanced NSCLC

First author Tony S. Mok, professor in the Department of Clinical Oncology at the Chinese University of Hong Kong in Prince of Wales Hospital in Hong Kong presented findings from a comparison of safety and the response to alectinib versus crizotinib in Asian and non-Asian patients with treatment-naive advanced ALK-positive non-small cell lung cancer (NSCLC).

This subgroup analysis of the phase III ALEX study included 303 patients aged ≥18 years. In the ALEX trial, patients were stratified by race and randomised 1:1; 152 patients to receive alectinib at 600 mg twice daily and 151 to crizotinib at 250 mg twice daily until progression, toxicity, withdrawal or death. In the alectinib arm, 69 patients were Asian and 82 were non-Asian and in the crizotinib arm, 69 patients were Asian and 82 were non-Asian. Baseline characteristics were consistent between Asian and non-Asian subgroups, excepting the median weight. The trial's primary endpoint was investigator-assessed progression-free survival (PFS). Secondary endpoints included Independent Review Committee(IRC) assessed PFS, time to central nervous system (CNS) progression, objective response rate (ORR) by investigator, overall survival (OS), and safety.

The analysis showed that efficacy and safety data were similar between the Asian and non-Asian subgroups. With alectinib, investigator-assessed PFS (primary endpoint) was longer than with crizotinib (hazard ratio [HR] 1.24) in Asian, and in non-Asian (HR 0.49) patients. Median PFS with alectinib was NE (95% confidence interval [CI] 14.7, NE) versus 10.9 months (95% CI 8.6, 16.4) with crizotinib in Asian patients, and median PFS was NE (95% CI 14.9, NE) versus 11.1 months (95% CI 8.8, 14.6) with alectinib versus crizotinib, respectively, in non-Asian patients.

The OS data were not yet mature but showed that median OS had not yet been reached in either alectinib subgroup compared to crizotinib: Asian HR 0.68, non-Asian HR 0.82.

Alectinib reduced the time to CNS progression compared to crizotinib in the Asian and non-Asian groups, with cause-specific HRs of 0.21 and 0.16, respectively. Fewer patients experienced CNS progression with alectinib; the 12 month cumulative incidence was 9.0% versus 44.9%, respectively, with alectinib versus crizotinib in Asian patients, and 9.6% versus 38.4% with alectinib versus crizotinib in non-Asian patients.

In the Asian subgroup the ORR was 81.2% versus 76.8% and in the non-Asian subgroup the ORR was 84.3% versus 74.4% with alectinib versus crizotinib, respectively.

Treatment discontinuation due to adverse events (AEs) occurred in 13.0% of Asian and 9.6% of non-Asian patients on alectinib compared to 11.6% of Asian and 13.4% of non-Asian patients receiving crizotinib. The AE profiles of Asian and non-Asian subgroups were consistent with the intention-to-treat population. Diarrhoea was more common with crizotinib; diarrhoea occurred in 15% of Asian and 10.0% of non-Asian alectinib patients versus 39.1% of Asian and 50% of non-Asian crizotinib patients. Nausea also more commonly occurred with crizotinib and was reported in 10.1% of Asian and 17.0% of non-Asian versus 42.0% of Asian and 52.4% of non-Asian patients receiving alectinib versus crizotinib, respectively. NCT02075840. Mok *et al.* Abstract 410O_PR

Practice point and future research opportunities

This subgroup analysis demonstrated that efficacy and safety data were similar between Asian and non-Asian patients who showed comparable responses to alectinib versus crizotinib. These findings confirm that alectinib is more effective than crizotinib in treatment naive Asian and non-Asian patients with advanced NSCLC. Demonstrating the CNS activity with alectinib was important since approximately 50% of patients with NSCLC and ALK mutations eventually develop brain metastases. Furthermore, alectinib demonstrated an acceptable safety profile in Asian patients. Alectinib at 600 mg twice daily was similarly effective in Asian and non-Asian patients and rates of toxicities were also comparable. The findings suggest that 600 mg should be the standard dose of alectinib across Asia.

A global phase II study of olmutinib (HM61713) in patients with T790M-positive NSCLC after failure of first-line EGFR-TKI

Keunchil Park, Division of Hematology & Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Sungkyunkwan, South Korea reported findings from a global phase II study investigating the safety and efficacy of olmutinib (HM61713), a novel third-generation epidermal growth factor receptor (EGFR) mutation-specific tyrosine kinase inhibitor (TKI). The trial enrolled patients with EGFR T790M mutation-positive non-small cell lung cancer (NSCLC), who developed resistance to initial EGFR TKI therapy. All 162 enrolled patients were treated with 800 mg of olmutinib once daily in 21-day cycles. The patients' median age was 63 years and they were enrolled from 68 sites in 10 Asian, European, and North American countries. The primary endpoint of the study was centrally confirmed objective response rate (ORR) and secondary endpoints included progression-free survival (PFS), disease control rate (DCR), and safety.

After a median 5.9 months of follow-up, and median a treatment duration of 5.3 months (range 0.03 to 13.01) 115 patients were evaluable for independent reviewer response assessment. Over half of the patients (51.3%) had a confirmed objective response by independent review, including 51 (44.4%) patients with a confirmed response. The DCR was 87.8%, which indicated that 101 of 115 patients had a response or stable disease. Median PFS was 6.9 months (95% CI 5.8, not reached).

The ORR was 43.3% (95% confidence interval [CI] 30.6, 56.8) in patients with brain metastases and 45.5% (95% CI 32.0, 59.5) in patients without brain metastases at baseline.

Median PFS in patients with brain metastases was 6.8 months (95% CI 5.4, not reached) and was similar to the PFS in patients without brain metastases, where median PFS was 9.5 months (95% CI 5.8, not reached).

The most common treatment-related adverse events (AEs) were diarrhoea, which occurred in 37.7% of patients, hyperkeratosis, nausea, and rash, which each occurred in 25.3% of patients. Grade 3 treatment-related AEs were reported in 45.1% of patients and 9 (5.6%) patients discontinued treatment. One case of toxic epidermal necrolysis with fatal outcome was reported.

Dose reductions to 600 mg were reported in 54 (33.3%) patients and to 400 mg in 7 (4.3%) patients. Professor Park commented that the optimal dose of olmutinib is being determined by additional translational studies, to produce more improved therapeutic outcome in phase III clinical trials. NCT02485652. Park *et al.* Abstract 412O

Practice point and future research opportunities

Olmutinib showed robust activity with a tolerable safety profile in patients with T790M-positive NSCLC who had previously received an EGFR TKI. These data demonstrate the potential efficacy of olmutinib for EGFR T790M mutation-positive patients with NSCLC. These findings warrant further evaluation.

Rare *NTRK* gene fusion detected in Japanese patient with lung cancer

Atsushi Nakamura, Department of Pulmonary Medicine, Sendai Kousei Hospital, Sendai, Japan, noted that several differences exist between East Asian and Caucasian patients with lung cancer in the frequency of actionable gene alterations, such as EGFR and *KRAS* mutations. Specifically, *NTRK* fusions have been recently identified as a therapeutic target in 3.3% of Caucasian patients with lung adenocarcinoma, but whether they occur and at what frequency in East Asian patients was unknown.

Professor Nakamura and colleagues evaluated data collected in a nationwide lung cancer genomic screening project in Japan (LC-SCRUM-Japan) that was initiated in February 2013, with 4118 lung cancer patients enrolled by April 2017. Of these patients, 2088 patients with non-squamous lung cancer, 275 with squamous, and 305 patients with small-cell lung cancer were screened using a next generation sequencing (NGS) platform, Oncomine™ Focus Assay (OFA) specific for *NTRK1/2/3* fusions or Oncomine™ Comprehensive Assay (OCA) for detecting *NTRK1/3* fusions.

Of this entire cohort shown on graph below, just one (0.04%) patient was identified with an *ETV6-NTRK3* fusion. This patient was a 60-year-old man with a 35 pack-year smoking history, who was diagnosed with lung adenocarcinoma.

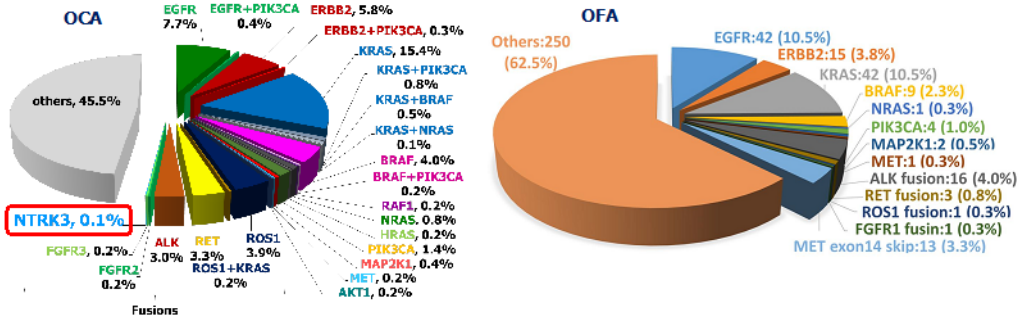
Screened Results of *NTRK* fusion

LC SCRUM

<Non-Sq cohort (N=2088)>

- Only one patient with *ETV6-NTRK3* fusion was detected in non-Sq cohort.

<Frequencies of gene mutations and fusions detected by OCA (N=1688, left) and OFA (N=400, right)>



<Sq cohort (N=275) and SCLC cohort (N=305)>

- No *NTRK1/2/3* fusion was detected by OCA in the patients with Sq and SCLC.

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*ETV6-NTRK*3 fusions have been detected in tumours having mesenchymal origin and have been identified in secretory carcinoma of the breast and in infantile fibrosarcoma and mesoblastic nephroma. The frequency of *NTRK* fusions in Japanese patients with lung cancer is rare, with the investigators estimating the incidence as 0.04%.

The investigators also evaluated *NTRK1* gene fusion–induced imbalances in the expression of the 5' and 3' regions of the transcripts using the OFA sequencing data, but found no case of 5'/3' expression imbalances of *NTRK1* gene transcripts. Nakamura *et al.* Abstract 415OO

Practice point and future research opportunities

NTRK fusion, which occurs only rarely in Caucasian patients with lung adenocarcinoma, has been detected in one Japanese man with lung cancer who participated in a large genomic screening project. The *NTRK* is a potentially targetable gene alteration and ROS1, ALK, and *NTRK* fusions may be sensitive to Trk inhibition. The STARTRK (NCT02568267) basket study is currently investigating whether entrectinib (RXDX-101) is active in patients with solid tumours harbouring *NTRK 1/2/3*, ROS1, or ALK fusions.

SARCOMA

Tumour histology and primary site but not *MDM2* amplification levels are prognostic for poorer PFS in well differentiated and dedifferentiated liposarcoma

Winston Chew, Division of Medical Oncology, National Cancer Centre Singapore in Singapore and colleagues investigated whether amplification of the oncogene, *MDM2*, may serve as a prognostic factor in well-differentiated (WD) and dedifferentiated (DD) liposarcomas (LPS).

They conducted a retrospective review of clinical records to identify patients with primary LPS who underwent curative resection and were also assessed for *MDM2* using fluorescent in situ hybridization (FISH). Dual color *MDM2*/CEP 12 probes were applied to FFPE tissue sections and the signals from 60 non–overlapping nuclei were counted to determine the copy numbers of *MDM2* and CEP 12. *MDM2* gene amplification was defined as the ratio of *MDM2* signals to CEP 12 signals. Using receiver operating curve analysis, a cut-off value of >9.1 was determined as high *MDM2* ratio. Survival analysis was done using Kaplan-Meier and multivariable cox models and progression-free survival (PFS) was assessed as the time from resection to relapse or death.

Data from 55 patients, 20 with DDLPS and 35 with WDLPS were used in this analysis. Higher levels of *MDM2* ratio were found to associate with retroperitoneal tumour site (8.1 versus 5.4, Mann-Whitney p = 0.023) but no statistical difference in *MDM2* ratio was seen regarding other clinical features, including age of diagnosis, performance status, resection margins, tumour histology, and tumour size. On univariate survival analysis, *MDM2* amplification level was not prognostic for PFS (hazard ratio [HR] 2.191; 95% confidence interval [CI] 0.599-8.016; p = 0.130). However, DDLPS (HR 11.163; 95% CI 3.935, 31.663; p < 0.001), positive resection margins (HR 3.138; 95%CI 1.21, 8.110; p = 0.034), and retroperitoneal primary tumour (HR 6.884; 95%CI 2.324, 20.387; p < 0.001) were predictive of poorer PFS. Multivariable analysis did not confirm this finding and only retroperitoneal primary (HR 3.400; 95%CI 1.015, 11.388; p = 0.047) and DDLPS (HR 6.993; 95%CI 1.762, 27.757, p = 0.006) remained prognostic for worse outcomes. Chew *et al.* Abstract 487O

Practice point and future research opportunities

In this cohort of patients with well-differentiated and dedifferentiated liposarcoma, the *MDM2* amplification level did not associate with clinical outcome; however, tumour histology and primary tumour site were prognostic for poorer PFS.

Serum miRNA can discriminate between treatment-naive patients with localised synovial sarcoma patients from those in follow-up after radical combined therapy

Hanna Kosela-Paterczyk of the Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology in Warsaw, Poland reported next-generation sequencing (NGS) data from patients who were treated

according to a uniform protocol consisting of preoperative chemotherapy and radiotherapy for locally advanced synovial sarcoma.

Serum samples were collected from 28 patients with synovial sarcoma prior to preoperative therapy, following two courses of neoadjuvant chemotherapy (n = 23), and during follow-up after radical radiotherapy and surgery (n = 18), and also from 30 healthy donors. The investigators evaluated circulating miRNA in the blood as response markers of treatment. MiRNAs were isolated from serum using the MirVANA miRNA Isolation Kit and analysed using deep sequencing on Ion Torrent PGM. Reads were mapped to miRBase miRNA collection with miRDeep2. Differential expression was evaluated with edgeR and compared in the samples taken prior to during, as after treatment, as well as with the samples of healthy donors.

The investigators detected 1370 miRNAs by deep sequencing; of these, 47 miRNAs were found that could differentiate between post-treatment samples or observation samples and samples taken prior to chemotherapy and/or surgery (adjusted p-value < 0.05). Two miRNAs were present in both comparisons and were found to have good discriminative properties: hsa-miR-31-5p, and hsa-miR-127-5p (area under the curve [AUCs] ranging from 0.75 to 0.87). In addition, 49 miRNAs could be used to differentiate between patients prior to treatment from healthy controls. Eight of these (hsa-miR-423-5p, hsa-miR-320a, hsa-miR-339-5p, hsa-miR-214-3p, hsa-miR-486-3p, hsa-miR-150-5p, hsa-miR-214-5p, hsa-miR-769-5p) were also present in previous comparisons; however, none of these miRNAs reached AUCs above 0.8. Kosela-Paterczyk *et al.* Abstract 488O

Practice point and future research opportunities

This study used an NGS-based approach to identify circulating blood-based miRNAs having high to good discriminative properties that could differentiate between treatment-naive patients and post- treatment patients with synovial sarcoma or patients in observation following surgery. Further evaluation in an independent group of patients is warranted to confirm the value of these miRNAs as biomarkers for the diagnosis of synovial sarcoma recurrence or metastasis.

SUPPORTIVE CARE

A single oral dose of NEPA is comparable to a 3-day regimen of aprepitant/granisetron for the prevention of chemotherapy-induced nausea and vomiting in Chinese patients

Li Zhang, of the State Key Laboratory of Oncology in South China, Collaborative Innovation Centre for Cancer Medicine, Cancer Centre Sun Yat-Sen University in Guangzhou, China pointed out that guidelines for the use of antiemetic therapy recommend the combination of an Neurokinin-1 receptor antagonist (NK-1 RA), a serotonin 5-HT3 receptor antagonist (5-HT3 RA), and dexamethasone for patients receiving highly emetogenic chemotherapy (HEC), prompting this evaluation of NEPA, a fixed combination of netupitant (NK1 RA) and palonosetron (5-HT3 RA) that can be administered orally and has been approved in the United States and Europe. Dr. Zhang and colleagues conducted this pre-planned data subgroup analysis of Chinese patients participating in the head-to-head comparison of NEPA versus an aprepitant/granisetron regimen, wherein comparable efficacy and safety with both treatments was demonstrated in the full analysis set (FAS).

The randomised double-blind, parallel group trial enrolled 828 chemotherapy-naive patients with solid tumours who received either a single oral dose of NEPA prior to cisplatin-based HEC or a 3-day regimen of aprepitant/granisetron. Both regimens were administered with oral dexamethasone on days 1 through 4. The efficacy endpoint was complete response (CR) defined as no emesis/no rescue medication during the acute (0-24h), delayed (25-120h) and overall (0-120h) phases post-chemotherapy for the FAS.

The subgroup analysis used the Cochran-Mantel-Haenszel test to determine the risk difference (RD) and associated 95% confidence intervals (CI) in the 667 (81%) patients in the Chinese subgroup of the FAS population. Patient characteristics were comparable between treatment groups in the subgroup; the majority (69.0/69.5%) were male with a mean age of 54.4/54.9 years, ECOG performance status was 0-1 in 98.2/97.6% of patients who predominately had lung cancer (70.9/67.4%) in the NEPA and aprepitant/granisetron treatments arms, respectively. Confirming the response in the FAS, the response rates in Chinese patients were similar for both treatment groups. The CR during the acute phase was 84.8% versus 87.8%, RD -3.4% (95% CI -8.6%, 1.8%) and in the delayed phase, CR rates were 78.8% versus 75.3%; RD 3.5% (95% CI -82.8%, 9.9%). In the overall phase, CR rates were 74.0% versus 73.8%, RD 0.3% (95% CI -6.3%, 7.0%), with NEPA versus aprepitant /granisetron, respectively. Zhang *et al.* Abstract 501O

Practice point and future research opportunities

These findings demonstrated that oral NEPA administered as a single dose on day 1 provided comparable efficacy to a 3-day aprepitant/granisetron regimen in Chinese patients receiving HEC. NEPA offers patients a convenient effective prophylactic antiemetic that is administered orally and need only be taken once. This convenience may also yield cost benefits.

Rapid cachexia improvement seen with appetite stimulants

Manit Sae-Teaw, Pharmacy Practice, Ubon Ratchathani University, Ubon Ratchathani, Thailand presented findings from network-meta-analysis assessing the relative efficacy and safety of 12 pharmacologic interventions for cachexia. The author explained that comparative information on the efficacy and safety of agents used in recent clinical trials was not available, leading Prof. Sae-Teaw and colleagues to compare the weight and appetite improvement provided by several pharmacologic interventions for cachexia in this meta-analysis. The investigators first performed a systematic review of PubMed, EmBase, Cochrane, and ClincalTrials.gov databases for randomised clinical trials (RCTs) reporting key outcomes of total body weight (TBW) improvement, and improved appetite (APP) scores, as well as serious adverse events. The meta-analysis included data from 9,615 patients participating in 73 RCTs; of these patients, 6,335 were cancer patients and 2,324 were HIV patients.

The data were reviewed and the risk of bias of all RCTs was assessed by two independent researchers. The meta-analysis estimated relative magnitude of weight gain and appetite score increase within 8 weeks of administration of all interventions, which were reported as mean difference (MD) or standardized mean difference with 95% confidence interval (CI). To rank the intervention hierarchy in the network meta-analysis, the rankograms, surface under the cumulative ranking (SUCRA) curves, and mean ranks were estimated. Twelve therapeutic cachexia interventions were evaluated and compared.

Although improved weight gain was seen with corticosteroids, appetite stimulants showed the quickest improvement in appetite scores

Regarding improved total body weight, corticosteroids, megace-H-com, megace-H, and androgen were significantly associated with mean differences of 6.23 (95% CI 1.91, 10.56), 3.73 (95% CI 1.58, 5.88), 2.80 (95% CI 1.46, 4.13), and 1.47 (95%CI 0.31, 2.63) kilograms compared to placebo, respectively.

Regarding appetite improvement, significantly improved standardized APP scores were observed with megace-L, megace-H, medroxyprogesterone, androgen, megace-H-com, and ghrelin mimetics, compared to placebo. These score improvements were reported earlier than 8 weeks with the appetite stimulants ghrelin, megace-L, megace-H, and medroxyprogesterone.

No significant difference in serious adverse drug reactions was observed with any of these agents compared to the placebo. Sae-Teaw *et al.* Abstract 502O

Practice point and future research opportunities

Findings from this network meta-analysis suggest that appetite stimulants may offer superior benefits in the treatment of cachexia. However, comparative studies that directly compare safety and efficacy are warranted to optimise cachexia management.

Evaluation of the impact of a topical lotion, CG428, on permanent chemotherapy-induced hair and scalp disorders in breast cancer survivors

Chemotherapy-induced alopecia remains one of the most distressing side effects of breast cancer treatment, prompting Juhee Cho, Department of Clinical Research Design and Evaluation, SAIHST, Samsung Medical Centre Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, and a team of investigators to conduct the double-blind randomised controlled pilot VOLUME trial. This study evaluated whether a topical lotion, CG428, could improve hair thickness and density among breast cancer survivors who had permanent chemotherapy-induced alopecia (PCIA).

Investigators randomised 35 patients with PCIA to receive CG428 or placebo, which the patients self-administered twice-daily, mornings and evenings, for 6 months. Change of hair density and thickness was assessed using a non-invasive bioengineering device, and the level of distress and body image were assessed at 3 and 6 months after randomisation using standardised questionnaires. All analyses were conducted by the intention-to-treat principle.

The 18 patients in the CG428, study product group were older with a mean (standard deviation) age of 52.1 (6.8) years compared to the 17 placebo patients, who had a mean age of 41.6 (7.8) years ($p < 0.001$). Mean hair thickness at baseline was similar at 49.9 (12.7) in the placebo arm and 48.1 (8.4) µm in the CG428 arm ($p = 0.64$), and the corresponding values for hair density were 97.6 (6.4) and 126.8 (30.3) hairs/cm2 in the placebo and intervention groups, respectively. After the 6-month intervention, hair thickness had increased by 19.8% in the control arm and by 35.6% with CG428 compared to baseline. Hair density was increased by 34.7% with placebo and 24.9%, with CG428 ($p = 0.37$). These findings remained similar following after adjusting for the patients' age. NCT02605629. Cho *et al.* Abstract 503O

Practice point and future research opportunities

This pilot study demonstrated the feasibility of using a self-administered topical lotion, CG428, to increase hair thickness and density among breast cancer survivors with PCIA and showed longitudinal changes in patients' hair that associated with this use. Patients self-administering placebo also showed an effect.

TRANSLATIONAL RESEARCH

The Drug Rediscovery Protocol expands the use of commercially available drugs

Emile Voest of the Molecular Oncology department, Netherlands Cancer Institute in Amsterdam, Netherlands, explained the underlying premise of the programme as that once a drug receives approval from a regulatory organisation, the use of this drug could be expanded by identifying signals of activity in cancer subsets outside the approved indication, which would be beneficial to both patients and pharma.

Whole Genome Sequencing (WGS) allows the detection of a spectrum of potentially actionable genetic aberrations across all cancer types and is offered by the Netherlands' precision oncology-network to systemically treated cancer patients, leading Dr. Voest and colleagues to conduct this study. Adult patients were recruited who currently had no standard treatment options for solid tumours, including glioblastoma, lymphoma or multiple myeloma. Patients were required to have a fresh tumour biopsy for biomarker research and they were enrolled in multiple parallel cohorts, each defined by one tumour type, one tumour profile and one treatment. Efficacy was analysed per cohort using a Simon-2-stage approach, aimed at achieving one or more clinical benefit of complete (CR) or partial response (PR) or stable disease (SD) lasting ≥ 16 weeks) per every 8 patients in stage I, and ≥5 per 24 in stage II (85% power, α error rate 7.8%). Currently, 23 hospitals are participating and 10 pharmaceutical companies have supplied 19 study drugs.

Since the study launch in September 2016, approximately 250 cases were submitted for review and about one-third of these patients began treatment. Clinical benefit was observed in 37% of the study patients, including 6% of patients who achieved CR and 14% of patients with PR. In addition, SD ≥ 16 weeks was achieved by 17% of patients. All CRs and approximately 66.6% of PRs were ongoing at data cut-off and awaiting ≥30 days' confirmation.

Approximately two-thirds of case submissions were not taken forward; 18% of these were due to general protocol ineligibility, 17% were due to current unavailability of matching study drugs, in 15% of cases there was no detection of actionable target, 13% showed negative evidence for target-drug-match, 12% of patients were eligible for standard treatment 11% were eligible for competing trials, 10% of cases were lost to follow-up, and the genetic tumour profile had not yet been assessed in 4% of cases. NCT02925234; EudraCT 2015-004398-33. Voest *et al.* Abstract 2O

Practice point and future research opportunities

This study demonstrated that execution of a national multi-drug and multi-tumour precision oncology trial is feasible and that whole genome sequencing in many different cancer types can identify subgroups of patients that may benefit from existing drugs outside of their registered indication. This study not only accelerates translation of new findings to the clinic but also highlights how patients may benefit from increasing the yield of existing therapies.

Concordance study demonstrates high levels of concordance between IBM Watson for Oncology and clinical practice for breast and lung cancer patients in China

Lead author Xiao Chun Zhang of the Department of Medical Oncology, The Affiliated Hospital of Qingdao University in Qingdao, China reported findings regarding the degree of concordance between treatment recommendation provided by Watson for Oncology (WFO) and the multidisciplinary tumour board in The Affiliated Hospital of Qingdao University. WFO was developed by IBM in collaboration with Memorial Sloan Kettering Cancer Center, and is a computing system that can extract and assess large amounts of structured and unstructured data from medical records through natural language processing and machine-learning. WFO provides physicians with evidence-based treatment options and ranks them into three categories for oncology treatment decision support.

Dr Zhang and colleagues retrospectively studied the cases of 152 cancer patients who had been treated from August 2015 to July 2017. They entered the cases into the WFO system, then analyzed the degree of concordance between WFO's recommendations and those of the tumour board. WFO's recommendations were delivered in three categories: recommended standard treatment, for consideration, and not recommended. WFO achieved a high degree of concordance with the recommendations from the tumour board. Overall, 79% of WFO's treatment recommendations for breast cancer and 96.9% of lung cancer recommendations were concordant with those of the tumour board. Further analysis attributed the concordance difference between breast and lung cancer to the payment capacity in targeted therapy, which was explained by the inability of some HER2-positive breast cancer patients to afford trastuzumab therapy, which is regarded as standard in guidelines and WFO. When data from HER2-negative and Her-2-positive patients were reviewed, the concordance was 90.3% and 61.7%, respectively. Zhang *et al.* Abstract 544P

Practice point and future research opportunities

These retrospective data demonstrated that treatment recommendations made by WFO were highly concordant with clinical practice by the affiliated hospital of Qingdao University in different types of carcinoma. These findings indicate that the WFO cognitive system may be very useful in providing support for decision making by a multidisciplinary tumour board.

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Affiliations and Disclosure

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Disclosure

No conflicts of interest to disclose.

Acknowledgment

ESMO would like to thank you Virginia Powers, PhD for editorial assistance in preparation of this report.

ESMO would like to thank you Drs Michael Davidson, Virote Sriuranpong, James Suh, Tien Le, Chung Hang James Chung Chow, and Hibiki Udagawa for giving their permission to publish the images from the studies presented during the ESMO Asia 2017 Congress in the ESMO Scientific report

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