Abstract Highlights

The following highlights spotlight selected abstracts presented at the European Society for Medical Oncology (ESMO) Annual Congress 2023. They cover key topics, including the importance of nutrients in lung cancer survival rates; a new, minimally invasive therapy which targets endometrial cancer stem cells; and new potential for identifying bladder cancer using genomic sequencing.

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Alternative to Chemotherapy for Locally Advanced Metastatic Urothelial Carcinoma

FOR the first time, there is an alternative to chemotherapy for patients with advanced or metastatic urothelial carcinoma. The results of a randomised Phase III study of enfortumab vedotin in combination with pembrolizumab (EV+P) compared to chemotherapy for the treatment of locally advanced metastatic urothelial carcinoma (la/mUC) received a standing ovation at the ESMO Congress 2023. Platinum-based chemotherapy is the standard of care for la/mUC, but long-term outcomes are poor.

The global, Phase III, open-label, randomised study evaluated EV+P in patients with previously untreated la/mUC who were eligible for cisplatin or carboplatin-containing chemotherapy. The participants were randomised 1:1 to receive 3-week cycles of EV (1.25 mg/kg intravenously) on Days 1 and 8, and P (200 mg; IV) on Day 1, or gemcitabine with cisplatin or carboplatin. Primary endpoints investigated were progression-free survival and overall survival, while secondary endpoints included overall response rate and safety.

Overall, 886 participants were included in the study with a median follow-up of 17.2 months. Progression-free survival was significantly higher in the EV+P group, yielding median values of 12.5 months compared to 6.3 months in the chemotherapy group (hazard ratio: 0.45; 95% confidence interval: 0.38–0.54; P<0.00001), thus reducing the risk of progression or death by 55%. Overall survival was also significantly prolonged, increasing from 16.1 months in the chemotherapy group to 31.5 months in the EV+P group (hazard ratio: 0.47; 95% CI: 0.38–0.58; P<0.00001), with the risk of death reducing by 53%. Furthermore, confirmed objective response rate was 67.7% and 44.4% in the EV+P and chemo arms, respectively (P<0.00001).

> **"The results of a randomised Phase III study received a standing ovation at ESMO 2023."**

Overall, the research team report significantly improved outcomes in participants with previously untreated la/mUC receiving EV+P, with progression-free survival and overall survival significantly increasing in these treatment groups, compared to those receiving chemotherapy. Furthermore, the safety profile was generally manageable, with no new safety signals reported. ●

Improving Nutritional Interventions Could Increase Lung Cancer Survival Rates

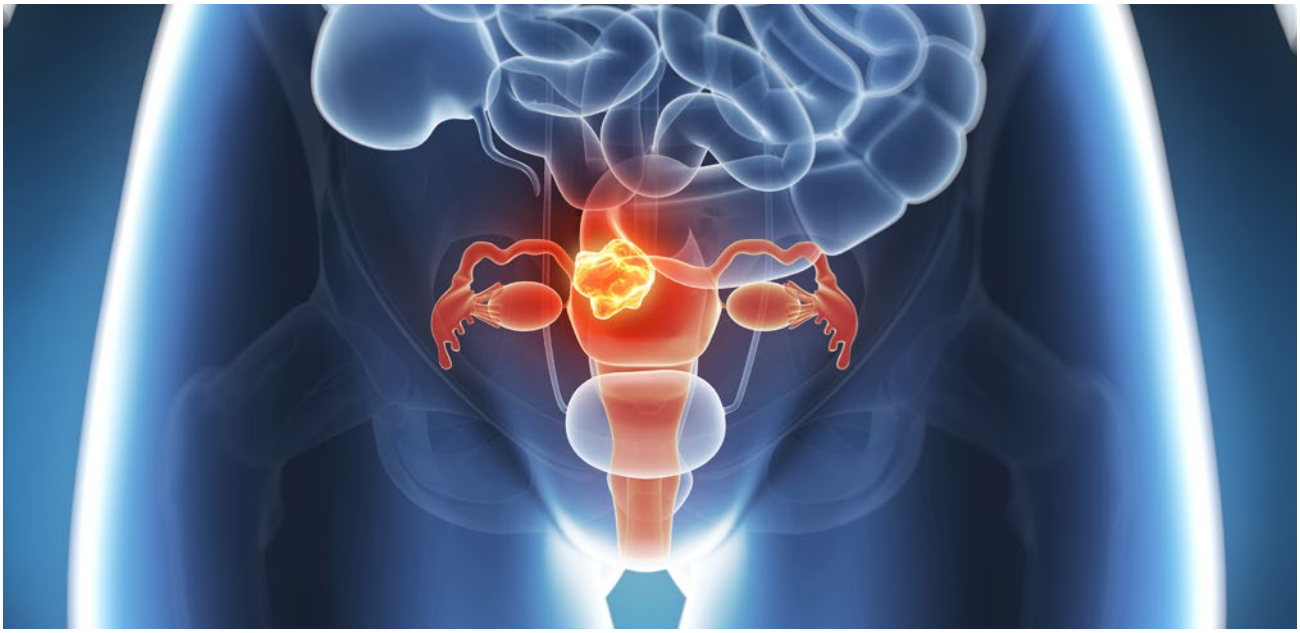
IDENTIFYING an early food consumption deficit may improve preservation of muscle mass in patients with lung cancer, as low muscle mass is often associated with this disease, according to new research presented at the ESMO Annual Congress 2023, held from 20th–24th October in Madrid, Spain.

The provision of nutrients in an adequate quantity and of a suitable quality is essential in treating low muscle mass. In a prospective, observational study, carried out by Imanuely Borchardt, Universidade Federal do Rio de Janeiro, Brazil, and colleagues, data were collected at the first nutritional consultation of patients with cancer between January–December 2019. Patients' height, body weight, weight loss, calf circumference, and handgrip strength were measured in order to estimate average food and macronutrient intake. Survival curves to analyse the association between caloric and protein intake and 3-year mortality were created.

In total, 50 patients with lung cancer were included in the study, 62% of whom were female, 94% elderly, 88% diagnosed with non-small cell lung cancer, 88% diagnosed with disease Stages III and IV, and 64% were smokers. The weight-adjusted mean daily intake of energy was 18.6 kcal/kg/day, while for protein it was 0.94 g/kg/day. The results showed that those with a consumption greater than 1 g/kg/day had a significantly longer overall survival rate than those with consumption lower than the recommended amount for patients with cancer (35.2 months versus 21.9 months, respectively; p=0.03). The differences in caloric intake of the patients showed no significant difference in length of survival (p=0.2).

The team concluded that lower protein intake was associated with shorter survival time in patients with lung cancer. They added that nutritional interventions would be low-cost, and would not be difficult to implement as a strategy to improve the survival rates for these patients. ●

"Provision of nutrients in an adequate quantity is essential in treating low muscle mass."



Photodynamic Therapy Strategy to Target Endometrial Cancer Stem Cells

A MINIMALLY invasive anticancer strategy, photodynamic therapy, is a promising targeted therapy for cancer stem cells in endometrial cancer, according to new research presented at the ESMO Congress 2023. Researchers from Portugal aimed to investigate photodynamic therapy through 4,5,6,7-tetrahydropyrazolo[1,5-*a*] pyridine-fused chlorins, which were modulated to target cancer stem cells in endometrial cancer by incorporating aldehyde substituents.

The researchers synthesised a mono-aldehyde derivative of a 4,5,6,7-tetrahydropyrazolo[1,5-*a*] pyridine-fused chlorin (A-PX) by mixing a monoester/mono-alcohol derivative chlorin with a Dess–Martin periodinane and dichloromethane solution. Proton nuclear magnetic resonance confirmed the presence of aldehyde. Aldehyde dehydrogenase 1A1 oxidation of the A-PX was followed by reverse-phase high-performance liquid chromatography through a reaction, which was stopped every 30' with acetonitrile. The researchers performed a resazurin assay to evaluate A-PX-based photodynamic therapy.

The results show a A-PX proton nuclear magnetic resonance peak of 10.28 ppm with the aldehyde. Furthermore, overexpression of aldehyde dehydrogenase is associated with cancer stem cells in endometrial cancer. The high-performance liquid chromatography and the kinetics of the enzymatic reaction illustrated a decreased relative area of the aldehyde peak, which was paralleled with the increase of carboxylic acid, which was formed by aldehyde dehydrogenase 1A1-promoted oxidation.

A-PX did not show toxicity, according to the preliminary results, and the A-PX cytotoxicity on cancer stem cells in endometrial cancer showed a decreased proliferation.

> **"Overexpression of aldehyde dehydrogenase is associated with cancer stem cells."**

The researchers concluded that it is possible to create chlorins that can interact with aldehyde dehydrogenase 1A1, which allows for the modification of the hydrophilicity of the photosensitiser *in situ*. Therefore, A-PX appears to be effective in treating cancer stem cells in endometrial cancer. However promising these results, more studies are needed to confirm this. ●

Bladder Cancer: Could Genomic Sequencing of Urine Aid Diagnosis and Identify Treatment Targets?

"*TP53* and *ERBB2* mutations were found to be significantly higher in those with MIBC compared to those with NMIBC."

NEXT-GENERATION sequencing (NGS) assays have the potential to identify tumour-derived variants of non-muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC) to aid diagnosis, and identify targets for personalised treatment, according to novel research presented at the ESMO Annual Congress 2023.

Researchers from Renji Hospital, affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China, and Hui (Shanghai) Medical Technology Company Ltd, Shanghai, China, performed a prospective study to determine whether evaluation of urinary tumour DNA led to identification of actionable mutations.

The study included 154 patients, some of whom were treatment naïve, and others had received treatment and were at risk of recurrence. Of the total cohort, 65 had a diagnosis of NMIBC and 89 had a diagnosis of MIBC. Using the PredicineCARE™ (Hayward, California, USA) NGS liquid biopsy assay, urine samples from each patient were analysed for somatic mutations in urinary tumour DNA.

In patients with MIBC, 485 somatic mutations and 43 copy number variants were identified, and the genes most frequently mutated were *TP53* (57%), *TERT* (39%), *ERBB2* (24%), *ARID1A* (20%), and *PIK3CA* (20%). For those with NMIBC, 368 somatic mutations and 14 copy number variants were identified, and the most frequently mutated genes were *TP53* (38%), *TERT* (37%), *ARID1A* (22%), and *BRCA2* (20%).

TP53 and *ERBB2* mutations were found to be significantly higher in those with MIBC compared to those with NMIBC (*TP53*: 51/89 versus 25/65, respectively; $p<0.05$; and *ERBB2*: 21/89 versus 4/65, respectively; $p<0.01$). In contrast, there was significantly higher prevalence ($p<0.05$) of *RARA* variations in those with NMIBC (5/65) than those with MIBC (0/89). The authors additionally found that FGFR2/3 variations were prevalent in 13% and 15% of all patients with MIBC and NMBIC, respectively. However, when looking at only patients who were treatment-naïve, the prevalence of FGFR2/3 variations was 26.3% for MIBC and 38.5% for NMIBC.

From these findings, the authors were able to discuss the identified mutational landscape of MIBC and NMIBC by performing NGS of urine samples in a real-world setting. They concluded that their study highlights the potential use for urine-based NGS assays in bladder cancer diagnosis and personalised treatment. ●

Does Analgesia Affect Survival in Patients with Lung Cancer Receiving Immune Checkpoint Inhibitors?

CANCER-RELATED pain, when unrelieved, is associated with worse survival, and non-opioid analgesics are frequently used to manage pain in patients with cancer. New research presented at the ESMO Annual Congress 2023, in Madrid, Spain, explored whether non-opioid analgesics affect survival in patients with lung cancer who receive immune checkpoint inhibitor (ICI) therapy.

"This cohort of patients had shorter survival than their counterparts who did not use non-opioid analgesics."

Sichao Wang, The University of Hong Kong – Li Ka Shing Faculty of Medicine, Hong Kong, and colleagues, reviewed the records of 910 patients with lung cancer who had a minimum of two cycles of ICI prescription±non-opioid analgesic prescription between 2018–2020. Data were obtained from the Clinical Data Analysis and Reporting System of Hong Kong, and patients were followed up for a median duration of 35.9 months.

Using Kaplan–Meier curves and Cox proportional hazards regression analysis, the team compared the overall survival of patients with lung cancer receiving ICI with (n=765) and without (145) non-opioid analgesics.

The findings showed that overall survival was significantly shorter in patients with lung cancer receiving ICI who had records of non-opioid analgesic prescriptions (13.4 months), when compared to those without (40.5 months; $p<0.0001$). Significantly worse prognosis was also seen in patients with lung cancer receiving ICI and non-opioid analgesic prescriptions upon the Cox regression analysis (hazard ratio: 2.42; 95% confidence interval: 1.86–3.10; $p<0.001$).

Wang and colleagues concluded that patients with lung cancer receiving ICI and using non-opioids are likely to have suboptimal tumour control and cancer-related pain, which were associated with poorer prognosis, and that overall, this cohort of patients had shorter survival than their counterparts who did not use non-opioid analgesics. ●

Does BMI Influence Breast Cancer Survival Outcomes?

PREVIOUSLY, the relationship between BMI and survival outcomes had not been investigated in patients with breast cancer who have undergone adjuvant chemotherapy. Researchers set out to investigate the effect of baseline BMI, BMI after adjuvant therapy, and change in BMI from baseline to post-adjuvant chemotherapy on disease-free survival (DFS) and overall survival (OS). Their findings were presented at the ESMO Congress 2023, held in October in Madrid, Spain.

Data were collected from 2,394 patients who had taken part in two randomised Phase III clinical trials that investigated adjuvant chemotherapy in breast cancer, accessed through Project Data Sphere. Restricted cubic splines, adjusting for confounding factors, were used to examine potential non-linear associations between BMI value and survival. Stratified analyses involved chemotherapy regimens used.

Results showed that patients who were severely obese (BMI ≥40.0 kg/m^2 at baseline) were associated with poorer DFS (hazard ratio [HR]: 1.48; 95% confidence interval [CI]: 1.02–2.16; p=0.04) and OS (HR: 1.79; 95% CI: 1.17–2.74; p=0.007) when compared with those who had a normal BMI (≤24.9 kg/m^2). Adverse OS was also associated with a BMI loss of more than 10% (HR: 2.14; 95% CI: 1.17–3.93; p=0.014).

When taking into account chemotherapy regimens, multivariate analysis showed that severe obesity had detrimental effects on DFS (HR: 2.38; 95% CI: 1.26–4.34; p=0.007) and OS (HR: 2.90; 95% CI: 1.46–5.76; p=0.002) in the docetaxel group. This was not observed in the non-docetaxel group. Restricted cubic splines demonstrated an association between baseline BMI and risk of recurrence (p for non-linearity: 0.111) or all-cause death (p for non-linearity: 0.008). This was more pronounced in the docetaxel-based group for DFS (p for non-linearity: 0.011) and OS (p for non-linearity: <0.001).

Overall, baseline severe obesity was associated with worse DFS and OS in patients with breast cancer treated with adjuvant chemotherapy. Significant BMI loss (>10%) from baseline to post-adjuvant chemotherapy was also associated with poorer OS. Lastly, the diagnostic ability of BMI may be altered depending on chemotherapy regimens, as observed in the docetaxel-based and non-docetaxel-groups.

"Data were collected from 2,394 patients who had taken part in two randomised Phase III clinical trials."