Abstract Highlights

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The following abstracts showcase the top cutting-edge research presented at the European Society for Medical Oncology (ESMO) Congress 2024. Topics covered include the use of AI in breast cancer screening, racial disparities in clinical trial enrollment, and germline variants associated with non-small cell lung cancer, amongst others.

Genetic Variants in RNA Modification Genes Impact Non-small Cell Lung Cancer Prognosis

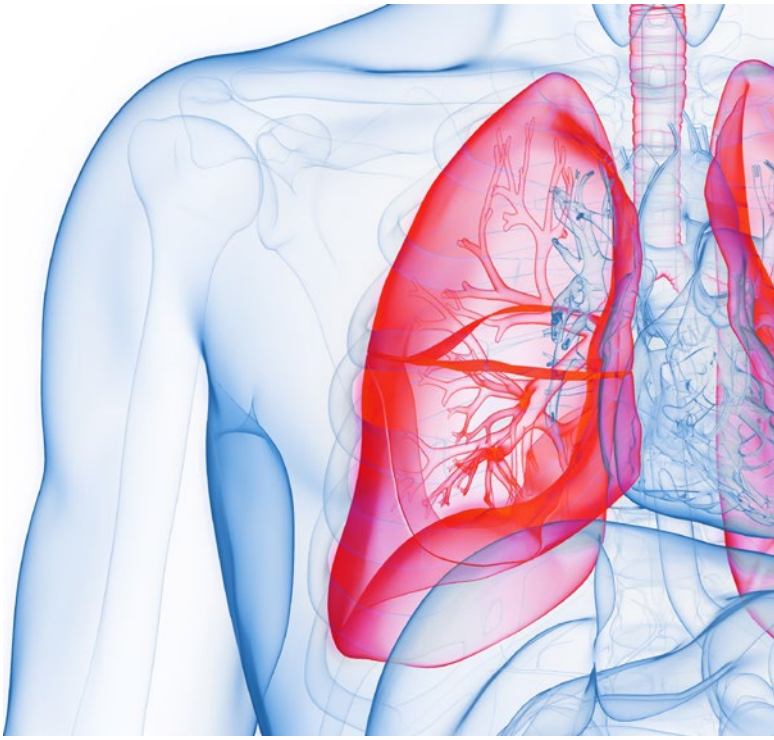
RNA modifications are crucial in regulating gene expression and cellular functions, with their dysregulation linked to cancer progression. This study, presented at ESMO Congress 2024, investigated the association between genetic variants in 25 RNA modification regulatory genes and the prognosis of 744 patients with non-small cell lung cancer (NSCLC). Among the 21 single nucleotide polymorphisms (SNP) analysed, three were significantly linked to overall survival (OS) outcomes.

The SNP rs10877013T>C in the *METTL1* gene was associated with improved OS. Specifically, patients with the variant allele had a 33% lower risk of death (adjusted hazard ratio [aHR]: 0.67; 95% CI: 0.48–0.93; p=0.02). This SNP is located in the intronic region, and a linked variant, rs703842G>A, located in *METTL1*'s 3' untranslated region, was identified. Functional assays demonstrated that the rs703842 A allele significantly increased promoter activity in lung cancer cells, suggesting a regulatory role in gene expression. Additionally, knocking down *METTL1* using specific siRNA resulted in reduced cancer cell proliferation, invasion, and migration, while inducing apoptosis.

Conversely, two SNPs in the *ADAR2* gene, rs3788152A>C and rs414743G>A, were associated with worse OS as patients with these variants had a higher risk of death (aHR: 1.46; 95% CI: 1.05–2.03; p=0.03 and aHR: 1.40; 95% CI: 1.02–1.93; p=0.04, respectively).

In conclusion, genetic variations in RNA modification regulatory genes, particularly *METTL1* rs10877013T>C and *ADAR2* rs3788152A>C and rs414743G>A, play a significant role in the prognosis of NSCLC patients, highlighting their potential as prognostic biomarkers.

> **Genetic variations in RNA modification regulatory genes play a significant role in the prognosis of NSCLC patients**



Pathogenic Germline Variants Associated with Non-small Cell Lung Cancer

RESULTS from the INHERITY LC study have demonstrated the prevalence of pathogenic germline variants (PGV) in patients with non-small cell lung cancer (NSCLC), primarily affecting DNA damage repair pathway genes.

The INHERITY LC study, presented at ESMO Congress 2024, was a prospective, multicentre investigation designed to explore the presence of germline mutations in a cohort of patients with NSCLC, and to assess the genetic factors influencing lung cancer development. Historically, inherited predisposition to lung cancer has not been a routine consideration in clinical evaluations, and genetic testing has not been routinely established. However, preliminary studies have shown that the prevalence of PGVs in NSCLC ranges from 2.3–14.9%, prompting researchers to focus on a selected group of patients who might be at higher risk due to specific clinical or familial factors.

From May 2021–April 2023, 145 patients with NSCLC were enrolled in the study based on three selection criteria: a family history of lung cancer, diagnosis at an early age or with minimal tobacco exposure, and the presence of actionable somatic mutations in their tumour biopsies. Genetic testing was conducted using next-generation sequencing (NGS) with a 74-gene panel. The study identified 15 patients (10.3%) with germline mutations classified as pathogenic or likely pathogenic, with most of the genes involved in the DNA damage repair pathway: *BRCA2* (one patient), *CHEK2* (two), *ATM* (two), *PALB2* (one), *BARD1* (one), *XRCC2* (one), *MRE11*(one), *NBN* (three), *FAN1* (one), *MLH1* (one), and *TP53* (one). Among the PVG carriers, 67% were women; 73% had adenocarcinoma, a common subtype of NSCLC; and they typically had low tobacco exposure, with a median of 9 pack-years. The analysis also revealed that patients who met all three selection criteria had a higher prevalence of PGVs (22%), highlighting the importance of comprehensive patient selection for genetic testing.

These findings suggest that whilst inherited predisposition has not traditionally been considered a significant risk factor for lung cancer, patients with specific clinical criteria may benefit from genetic testing to improve early detection and prevention, by identifying individuals at higher risk for lung cancer.

> **Patients with specific clinical criteria may benefit from genetic testing to improve early detection and prevention**

Racial Disparities in Cholangiocarcinoma Clinical Trials

A STUDY presented at ESMO Congress 2024 has revealed that clinical trials have significant racial disparities in participant enrolment, particularly a decline in the representation of Black patients over the past decade.

The study's authors identified 57 clinical trials focused on cholangiocarcinoma, with 91.2% conducted in Europe or the USA. The majority of these trials (59.6%) were Phase II studies. Data on racial distribution was publicly available for 63.4% of the trials, and enrolment varied across phases, with 100% of Phase IV trials reporting race distribution, compared to 50% of Phase I trials.

The study analysed 1,946 participants across 52 clinical trials. The results revealed that 76% were White, 8.9% were Asian, 7.1% were Black, 3.8% were of other races, and 4.1% had unreported race. The results also revealed an enrolment factor of 0.87 for Black participants, 1.48 for Asians, and 0.97 for White, showing a stark underrepresentation of Black individuals compared to the prevalence of cholangiocarcinoma in the broader population.

Notable trends from 2009–2022 indicated a sharp decline in Black participant representation, dropping from 16% to 5.4%, while Asian enrolment increased significantly from 4% to 23%. This trend

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suggests that while efforts may have been made to include Asian participants, the representation of Black patients has not only remained insufficient but has worsened over time.

The study concludes that urgent action is needed to address these disparities and implement strategies that promote equitable representation in cholangiocarcinoma clinical trials. Ensuring diverse participation is essential for developing treatment strategies that are effective across different populations and for improving health outcomes in minority communities.

K-index Could Predict Treatment Outcomes in Urologic Cancers

DESPITE the increased popularity of immune checkpoint inhibitor therapies, biomarkers utilising peripheral blood are not yet established. CD62LlowCD4+ T cells are thought to enhance the functions of cytotoxic CD8+ cells, and it is reported that the K-index (X2/Y; X: CD62LlowCD4+T cell %, Y: Treg % in peripheral blood CD4+ T cell population) could be augmented immune-reactive status and predict outcomes for anti-PD-1 therapy against non-small cell lung cancer.

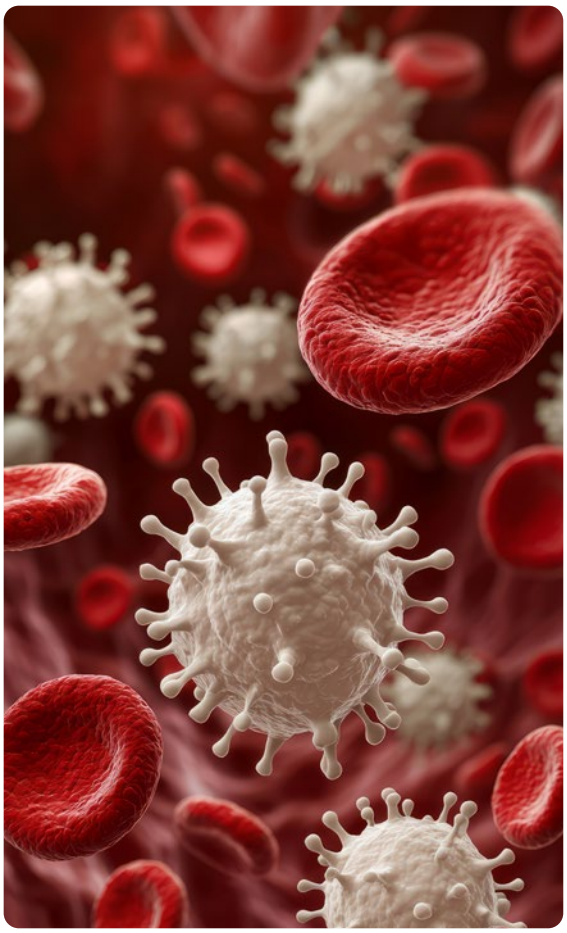
Thus, research presented at ESMO Congress 2024 examined the clinical significance of the CD4+ T cell subsets in peripheral blood for anti-PD-1/PD-L1 therapy against other cancers except lung cancer.

Lead author, Yoshimichi Haruna, Osaka General Medical Center, Japan, utilised flow cytometry analysis analysed peripheral blood mononuclear cells obtained from patients with urological cancers or hepatocellular carcinoma before anti-PD-1/PD-L1 therapy. The correlation between K-index and therapy outcomes was assessed.

> **The objective response rate was significantly higher in patients with a high K-index**

In total, 35 patients with urologic cancers (16 renal cell carcinoma, eight ureteral cancer, 11 bladder cancer) and 28 patients with hepatocellular carcinoma (HCC) participated in the study. Specifically considering urological cancers, the objective response rate (ORR) was significantly higher in patients with a high K-index (K-index ≥300, 75% versus K-index <300, 30.4%; P=0.012). On the other hand, patients with immune-related adverse events (irAE) often had a high K-index before treatment (P=0.017). In contrast, in patients with HCC, no relevant relationship was seen between the K-index and treatment outcome. Finally, the ORR of patients with a high Treg population (≥3% of CD4+ T cells) was significantly higher than that of patients with low Treg (<3%; P=0.019).

Overall, the researcher suggests that the K-index could predict treatment outcomes and the possibility of irAE in urological cancers, and it is considered a valuable biomarker to select the anti-cancer regimens. Further study would be valuable to assess whether the K-marker could act as a predictive biomarker in other cancers. Alternatively, in patients with HCC, the Treg population could be a valuable biomarker.



AI for Ki67 Scoring in Breast Cancer

AI COULD limit inter-pathologist variability in Ki67 scoring for breast cancer, according to novel research presented at ESMO Congress 2024.

Whilst guidance to reduce the variability in breast cancer Ki67 immunohistochemistry scoring has been provided by working groups, no universal scoring method has yet been agreed upon.

Researchers sought to evaluate the potential impact that AI could have on Ki67 immunohistochemistry scoring by comparing results achieved by an AI deep learning image analysis platform, image analysis supervised software, and two independent pathologists, across a population of patients with breast cancer.

The authors stained a total of 114 breast tumours for Ki67. The deep learning image platform was trained for breast cancer and the Ki67 clone; the two independent pathologists were trained in accordance with the international Ki67 Working Group guidelines; and the image analysis supervised software was used to separate the image into tumour, non-tumour, and background, with pathologist approval. Ki67 positivity was assessed via threshing and the time to complete each analysis was recorded for each method.

The results showed that whilst there was high reproducibility at the intra-pathologist level (r^2=0.95), matched pair analysis between the two pathologists was lower (r^2=0.86). There was consistency between the AI deep learning model and Pathologist 1 (r^2=0.92), Pathologist 2 (r^2=0.90), and the image analysis supervised software (r^2=0.93). Whilst within an acceptable range, the consistency between the image analysis supervised software and Pathologist 1 and 2 was lower (r^2=0.79 and r^2=0.84, respectively). The fastest approach was the AI deep learning model, followed by pathologists and then the image analysis supervised software.

The research concluded that the approaches to Ki67 tumour analysis yielded similar results, highlighting that AI could prove to be useful in aiding Ki67 scoring and could reduce inter-pathologist variability in scoring.

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