Conclusions: The IPMS is a reliable epigenome prognostic tool in clinical tumor immunophenotyping. It has the potential to guide immunotherapeutic strategies and may facilitate the development of personalized epigenetic anticancer approaches for different HNSC subgroups.

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89P Novel resistance mechanisms to second-generation EGFR tyrosine kinase inhibitor afatinib in non-small cell lung cancer

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Background: Afatinib, an irreversible pan-ErbB family inhibitor, has demonstrated promising efficacy in non-small cell lung cancer (NSCLC) patients with uncommon *EGFR* activating mutations. However, besides the acquisition of secondary T790M mutation, other resistance mechanisms to afatinib remained to be explored.

Methods: This study retrospectively included 40 NSCLC patients harboring either *EGFR* or *ERBB2* activating mutations, who had received afatinib as first-line treatment. Targeted next-generation sequencing (NGS) data on the baseline and post-treatment samples were subjected to analysis. Comparative analyses of genetic features and clinical parameters were performed.

Results: Overall, the progression-free survival (PFS) of the *EGFR*-positive patients on first-line afatinib was longer than that of the *ERBB2*-positive patients (P=0.01). In the *EGFR*-positive subgroup, primary resistance was associated with the presence of *EGFR* exon 20 insertion mutation (P=0.02), higher tumor mutational burden (TMB, P=0.02), higher proportion of APOBEC signature (P=0.001) and higher tumor heterogeneity (P=0.01). Secondary resistance mainly involved *EGFR* T790M and *MET* amplification. Patients with 19del were more likely to acquire T790M mutation compared with those harboring L858R or other *EGFR* mutations (57.1%, 33.3% and 0%, respectively). On the other hand, no significant difference was observed in the distribution of *MET* amplification among different *EGFR* subgroups. In the *ERBB2*-positive subgroup, patients with the p.Y772_A775dup mutation tended to have a longer PFS than those harboring *ERBB2* mutations (HR=0.19, 95%CI, 0.02-1.56, P=0.09). In addition, alterations in *PIK3CA* or genes in the cell cycle pathway were associated with primary resistance to afatinib in the *ERBB2*-positive patients. Secondary resistance mechanisms included alterations in *ERBB4*, *EGFR*, *TSC2*, *NF1* and *CDKN2A* that participate in the bypass or downstream pathway of ERBB2 and the cell cycle pathway.

Conclusions: This study identified multiple genetic factors associated with afatinib efficacy and resistance. In addition, genomic characteristics such as TMB, tumor heterogeneity and APOBEC signature might serve as biomarkers for afatinib response.

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90P Infrared molecular fingerprinting: A new in vitro diagnostic platform technology for cancer detection in blood-based liquid biopsies

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Background: The levels, chemical modifications, and relative ratios of biomolecules circulating in systemic bioliquids, like blood plasma, are indicators of various physiological and pathological states. Capitalizing on broadband optics, ultrafast laser sources, and precision femtosecond-attosecond field-resolving technologies, we recently developed electric-field molecular fingerprinting (EMF) to detect changes in molecular composition of bioliquids, establishing EMF as a new *in vitro* diagnostic analytical technique to uncover characteristic molecular traces of diseases in blood samples.

Methods: EMF, as advanced infrared spectroscopy, has the inherent capacity to sensitively and robustly probe across different types of chemical bonds and molecular classes within one measurement, providing deep cross-molecular description of physiological states. Here, we present data from our multi-centric multi-cancer study in which we analyzed infrared molecular fingerprints of plasma and serum from several thousands of individuals, involving cancer patients with different solid tumors and matched reference individuals. Focusing on four common cancers - breast, bladder, prostate, and lung cancer - we find that infrared molecular fingerprinting is capable of detecting therapy-naïve malignant conditions.

Results: Employing machine learning data analytics, we obtain binary classification performances in the range of 0.78—0.89 (area under the receiver operating characteristic curve [AUC]), and additionally demonstrate correlation between AUC and tumor load. Intriguingly, we find that the spectral signatures differ between different cancer types, thus allowing to distinguish between different cancers in a single measurement.

Conclusions: Our studies lay the foundation for using EMF in health monitoring, in particular for onco-infrared-fingerprinting, providing a novel high-throughput, cost-effective technology platform that can be used as a complementary analytical tool for cancer detection and screening.

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91P Liquid biopsy, a tool to detect genetic alterations with therapeutic impact in international patients: Prospective data on 47 patients from Gustave Roussy

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Background: Liquid biopsy (LB), or cell-free DNA analysis (cfDNA), is a novel non-invasive approach to detect molecular alterations (MAs) in cancer patients (pts) allowing personalized therapy. It has been validated in clinical trials, however, the real-world evidence is still in its initial steps. The aim is to evaluate the outcomes of LB in ICP (International cancer pts) with the intention of offering novel treatment options.

Methods: We included in this prospective real-world study pts with advanced solid cancers admitted to the international department of Gustave Roussy starting December 2021. cfDNA was extracted from peripheral blood using streck tubes which were sent to FoundationOne® Liquid CDx for sequencing.

Results: 47 pts were included with a median age of 60.5 years. 46.8% (22 pts) were males. Gastrointestinal cancers were the most common neoplasms in 20 (42.5%) followed by thoracic tumors in 9 (19.1%). Pts were from 7 nationalities (29 from Kuwait (61.7%), 11 from Algeria (23.4%), and 7 from other countries (14.9%). 17 were treatment-naïve (36.2%), 34 were previously treated with chemotherapy (73.3%), and 16 (34%) with immunotherapy. On the day of LB, 43 had distant metastases (91.5%) while 24 had an ECOG score of 0-1 (51.1%). Among the 47 pts, 2 (4.2%) had insufficient cfDNA to perform the LB. Median number of MA detected was 5. Tumor mutational burden (TMB) $\geq$ 10 was found in 7 (14.9%) pertaining an option for immunotherapy. Beyond TMB, 10 MAs were detected with available therapeutic options in 9 (19.1%). The following MAs were confirmed: KRAS G12C (2, lung and pancreatic), EGFR (1, lung), IDH1 (1, cholangiocarcinoma), BRAF (2, angiosarcoma and colon), BRCA2 (1, pancreatic), PIK3CA (2, breast) and FGFR3 (1, bladder). In total, 15 pts with 17 MAs were offered an innovative approach based on LB (31.9%). Also, an additional 22 MAs were detected in 16 pts with available phase I or II clinical trials. A JAK2 mutation was detected in a pt which necessitated hematology referral.

Conclusions: LB proved to be an easy and attractive tool to pinpoint MAs with a significant diagnostic and therapeutic impact. It is an alternative mean to carefully spot MAs in ICP with 31.9% of pts offering them additional therapeutic options.

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