What's coming up at ESMO 2021?

Multi-Omics for Cancer Care Coming of Age?

Multi-omics, such as genomics, epigenomics, transcriptomics, proteomics, and metabolomics, is fast emerging in the clinic as a reliable tool to diagnose cancer or determine a patient's prognosis or likelihood of response to specific therapeutic intervention. However, its utility is limited by the uneven maturity of different omics approaches.[1,2]

Epigenomics and Artificial Intelligence (AI) based diagnostic approaches are currently the most attractive areas of diagnostic pursuit.

Epigenomics, a study of epigenetic changes such as DNA methylation, chromatin modifications, has emerged as a crucial and alternative diagnostic approach to the genomic analysis. Screening diagnostic tests, detecting altered DNA methylation, are able to differentiate normal vs malignant tissue and identify 'suspected' cancer patients.[3]

Some epigenomic screening markers to detect cancer are:

Colorectal cancer	**Promoter methylation of MGMT, TMEF2, SEPT9, Vimentin, MLH1 etc. and microRNA profiling.[4]**
Lung cancer	**Promoter hypermethylation of CDKN2A, PTPRN2, RASSF1A, CDH13, MGMT and microRNA (hsa-miR-let-7) profiling.[5]**
HCC	**Promoter hypermethylation of RASSF1, GATA4, CDKL2, MYOCD, PANX2, LHX9, MTA1 etc and microRNA (miR-300, miR-630 etc.)[6]**

However, the need to analyze and interpret this 'Big' data from a multi-omics approach, at a clinically meaningful level, has led to the introduction of AI.[7] Image analysis is the most effective area in which AI provides the advantage of processing large screening samples, with speed and accurate data interpretation, combined with reduced radiation exposure and manual labor. Often hidden patterns and abnormalities are extracted from images, that could otherwise have been missed/misinterpreted by a pathologist/operator.[8]

Some examples of innovative AI approaches, especially for screening of 'at risk' populations are:

- An AI based p16/Ki-67 dual stain test in cervical cancer with higher screening efficacy and reduced false positives as compared to the routine Pap procedure for screening.[9]
- Data driven AI methodology which combines tissue histology with quantitative analysis of gene expression has been used to understand prostate cancer heterogeneity, that serves as a validation tool and a standardization option of the pathological grading process to ensure consistency and application across regions.[10]

For broad utility and adoption of these above mentioned diagnostic approaches, generation of robust evidence will be the key to maximize impact as exemplified in AI-based screening for breast cancer vs. radiologist interpretations.[11]

References:

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12. A DNA methylation markers panel for prediction of luminal B breast cancer neoadjuvant chemotherapy response by quantitative PCR [Abs #70P]. In: ESMO 2021; Sept 16-21.
13. Identifying the origin of lung-specific cancer of unknown primary based on comprehensive genomic profiling optimized with DNA methylation [Abs #93]. In: ESMO 2021; Sept 16-21.
14. Circulating tumor DNA (ctDNA) from patients (pts) with advanced colorectal cancer (CRC) is enriched for EGFR extracellular domain (ECD) mutations [Abs #457]. In: ESMO 2021; Sept 16-21.
15. A multi-analyte liquid biopsy assay integrating cfDNA methylation and protein biomarkers for liver cancer diagnosis. [Abs #956]. In: ESMO 2021; Sept 16-21.

At ESMO 2021, over 75 presentations are on diagnostics, with more than half on multi-omics including a few on AI.[12-15] SmartAnalyst will be closely monitoring them to assess emerging trends and how multi-omics may redefine cancer care.

Advent of Next-Generation Antibody Drug Conjugate (ADCs)

Technologic advances in conjugation chemistry and an expanding range of druggable targets are key innovation drivers for the next wave of ADCs. Advances in exploiting new and emerging TAA targets through carrier mAb development are being explored.

The successful development of an ADC depends on the selection of an appropriate tumor associated antigen [TAA] for the binding of the antibody. Besides high tumor-specificity to minimize on-target toxicity of ADCs, the antigens engaged by ADCs need to be endocytosed upon antibody binding. The next wave of ADCs with novel targets is expected to reenergize ADC development. ESMO 2021 will see updates on novel tumor associated antigens such as integrin beta 6, CDH6, AFP and STn.[1-5] Two interesting novel targets (AFP and STn) are discussed here:

AFP-Maytansine Conjugate (in Solid and Heme Malignancies)

Alpha fetoprotein (AFP) is a human protein produced by embryonic cells during fetal development. Cancer cells and immune suppressor cells express AFP receptors while normal cells do not.

Recombinant human Alpha fetoprotein platform uses a recombinant human AFP to deliver Maytansine payload to cancer cells and immune suppressor cells (Myeloid Derived Suppressor Cells). Preclinical data for ACT-903 (Alpha Cancer Technologies) demonstrated that it directly targets cancer cells expressing AFP receptors as well as MDSCs while bypassing normal cells. The dual action results in increased efficacy and reduced toxicity. A biodistribution study reported that ACT-903 was stable in blood and released the toxin once it entered the tumor while bone marrow toxin levels were below detection levels. A Phase Ib study is planned to be initiated in 2022.[1,2]

Sialyl-Thomsen Nouveau (STn) Targeting ADC

SGN-STNV (Seagen) is an investigational ADC targeting Monomethyl auristatin E (MMAE) to STn expressing tumor cells with the clinically validated vedotin linker technology. High STn expression is reported in mucinous subtypes of ovarian, pancreatic, colorectal, and lung adenocarcinomas. ESMO 2021 will highlight the study design of a Phase I study of SGN-STNV, a novel ADC targeting STn, in adults with advanced solid tumors (SGNSTNV-001).[3,4]

References:

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At ESMO2021, apart from these novel targets, ~25 ADC presentations will include data from first-in-human studies, results reported from LCM trials and next generation HER2 targeting ADCs. SmartAnalyst will be following this emerging science.

Synthetic Immune Receptors- Novel Designs

Opportunities to fine tune and develop next-level immune cell therapies with CAR-Ts, TCR and NK cells are being actively pursued through basic, translational, and clinical research resulting in fast advancement of synthetic biology. A few approaches that have continued to be the focus of innovation include:

- Enhancing T-cell functions, overcoming T-cell suppression in the TME, improved safety, conferring resistance to lympho depletion, mitigating risk of rejection (reduce alloreactivity), novel NK cell design, engineered TCR cell therapies and improvement in manufacturing process.

ESMO 2021 will highlight ongoing development and novel T and NK cell synthetic immune receptors pursued by global pharma and biotech innovators.

TCR² Therapeutics

Will present efficacy outcomes of Gavocabtagene autoleucel (gavo-cel, TC-210) from the dose escalation portion of the Phase I/II trial in patients with treatment refractory mesothelin-expressing solid tumors.[1] Gavo-cel is based on proprietary TCR fusion construct T-cells (truc2-T cells) comprising an antibody-based binding domain fused to TCR that directs anti-tumor response by harnessing signaling from the entire TCR independent of HLA. Recently, Gavo-cel received FDA orphan drug designation for the treatment of cholangiocarcinoma.

Adaptimmune

Will provide updates of their "next-generation" SPEAR T-cell as they continue to advance ADP-A2M4CD8 SPEAR T-cells[2] that incorporate a CD8α co-receptor and an affinity optimized TCR targeting cancer testis antigen MAGE-A4. Co-expression of CD8α is expected to broaden the immune response against solid tumors and increase anti-tumor activity.

Medigene

Will report in vitro and in vivo activity of their transgenic TCR-lead candidate which is specific for an HLA-A2-restricted PRAME-epitope (TCR-4) and also incorporates chimeric PD1-41BB co-stimulatory receptor.[3]

NK cells are important effectors of anti-tumor immunity. Strategies are being actively pursued to improve NK cell activity, function and persistence

- Innate Pharma will showcase their versatile, fit-for-purpose technology called 'ANKET' (Antibody-based NK cell Engager Therapeutics).[4] ANKETs are next-gen multi-specific NK cell engagers. Tetra-specific ANKET engages activating receptors (NKp46 and CD16), a tumor antigen and a cytokine (IL-2v) via a single molecule to harnessing NK cell effector functions.
- Another multi-specific approach to engage NK cells is being developed by GT Biopharma.[5] Their proprietary NK cell engager GTB-3550 trike is a single-chain, trispecific scFv recombinant fusion protein conjugate of anti-CD16 and anti-CD33 antibodies and a modified form of IL-15. It provides a self-sustaining signal that activates NK cells and enhances their ability to kill. The potential of the methodology is being tested in immune-suppressed patients with advanced myeloid malignancies; the novel paradigm is also being explored in solid tumors expressing HER2 or B7H3.
- Advancing the NK cell-based developments a step further, Acepodia will report pre-clinical and early clinical activity of their first-in-class, off-the-shelf, selected natural killer cell product ACE1702 in HER2 < 3+ tumors.[6] These are trastuzumab-armed selected natural killer cell based on antibody-cell conjugation platform.

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We will be back soon with our point of view derived from focused Sessions/Presentation/Abstracts and News on synthetic Immune receptors at ESMO 2021.

Emerging Role of Immunotherapies in Early-Stage Solid Tumors

Immunotherapies are expected to become a part of the standard preoperative and adjuvant treatment settings in various solid cancers.[1] In the early stages, the immune microenvironment is robust and healthier, and with broader response to immunotherapies, more patients could be drawn into long-term remission or downstaging of the tumors. This has been supported by recent approval of immunotherapies in early stages such as pembrolizumab in non-muscle invasive bladder cancer and high-risk TNBC and durvalumab in Stage III unresectable NSCLC. In addition, recent data readouts demonstrated tumor downstaging in >70% of the patients with neoadjuvant nivolumab in early-stage mismatch repair unselected, resectable (T3-T4) colon cancer and increase in disease-free survival (22.4 months vs. 11 months) following neoadjuvant chemoradiation and resection in early-stage esophageal/gastroesophageal junction cancer patients.

At ESMO 2021, we expect to see continued momentum with new data being read out in early-stage solid tumors.

Neo-Adjuvant Therapies

- Effect of addition of atezolizumab and ipatasertib to neoadjuvant chemotherapy in early-stage TNBC patients[2]
- Effect of toripalimab and chemotherapy in patients with potentially resectable NSCLC[3]
- Efficacy of penpulimab-based combination neoadjuvant/adjuvant therapy for patients with resectable locally advanced NSCLC[4]

Adjuvant therapies

- Efficacy of adjuvant tislelizumab in resected high-risk esophageal squamous cell carcinoma patients[5]
- Effect of camrelizumab and apatinib after resection of hepatocellular carcinoma[6]
- Neo-adjuvant nivolumab, regorafenib combined with short-course radiotherapy (SCRT) in intermediate-risk, Stage II-III rectal cancer (RC)[7]

References:

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SmartAnalyst will be reviewing the emerging data to understand how immunotherapies will shape the future treatment landscape for early-stage solid tumors.

Please contact:
John.L'Ecuyer@smartanalyst.com

GLOBAL HEADQUARTERS
(New York, USA)
285 Madison Ave
22nd Floor, New York
NY 10017
Mobile: +1 (646) 852-5097

EUROPE
(London, UK)
1.04 Power Road Studios
114 Power Road, Chiswick
London W3 5PY
Mobile.: +44-(0)-752-163-8242
Mobile.: +44-(0)-772-574-4296

ASIA PACIFIC
(Gurgaon, INDIA)
First Floor, DLF Plaza Tower
DLF Qutub Enclave, DLF City
Phase-I, Gurgaon 122002
Haryana, India
Tel.: 91-124-4313800