

What's coming up at ASCO 2021?

Will Innovations in Oncolytic Viruses and Therapeutic Cancer Vaccines Disrupt the Oncology Landscape?

ASCO 2021

Oncolytic viruses (OVs) have been explored since the early 2000s. Recently, there has been a surge in unique innovations and the number of OVs entering early phase clinical trials. These innovations are driven by:

- New payloads (increased efficacy compared to the conventional payloads such as GM-CSF)
- Engineered viral capsids (to overcome neutralization, increase selectivity)
- Alternate RoA-i.v. (to reach tumors that are not easily accessible for an intratumoral route)

Along with OVs, there is also a renewed interest in “therapeutic cancer vaccines” (TCVs), which are used to train a patient’s immune system before killing the cancer cells. They have the benefit of eliciting immune responses specific to tumor antigens (shared or neoantigens); however, there remain several challenges to achieve better efficacy. Innovations have resulted in:

- New vaccine platforms (mRNA/DNA)
- Novel tumor-associated antigens/tumor-specific antigens (TAAs/TSAs)
- Novel combinations with other OVs, vaccines, and targeted therapies

ASCO 2021 is expected to provide insights on a stimulating array of advancements, which will provide direction on how the OVs/TCVs are evolving. We will closely follow the impactful presentations, and will focus on:

- Newer platforms such as a) those delivering multiple novel payloads (e.g., CARG-2020), and b) highly selective and potent OV targeting p16-CDK-RB-E2F
- Clinical outcomes from novel approaches
 - Intravenously delivered OVs (e.g., VSV-IFN β -NIS)
 - Vaccine combinations (GX-188E, a DNA vaccine, with pembrolizumab in HPV16/18+ cervical cancers)

We will be back soon with our point of view based on the news at ASCO.

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CAR-T Cell Therapy – Eyeing Opportunities in Solid Tumors

ASCO 2021

CAR-T cell therapy has been transformational in the treatment of B-cell lymphoma and multiple myeloma. Translating these results to solid tumors is challenging because of several barriers such as lack of appropriate therapeutic targets, tumor heterogeneity, and a suppressive solid tumor microenvironment (TME). AACR 2021 highlighted innovative CAR-T strategies tested in pre-clinical models to overcome some of these challenges.¹⁻³

The clinical relevance of these preclinical findings is explored in first-in-human studies which are being reported in ASCO 2021. Some interesting abstracts we will be following are:

- **CART-TnMUC1-cells for the treatment of MUC-1 expressing solid tumors (resistant ovarian cancer, pancreatic cancer, TNBC, or NSCLC)⁴**
 - By Jan 2021, 6 patients were treated in 2 cohorts [cohort 1: no lymphodepletion; dose = $1-2 \times 10^7$ TDN CAR-T cells; cohort 2: fludarabine/cyclophosphamide lymphodepletion; dose = $1-2 \times 10^7$ TDN CAR-T cells. The trial is currently enrolling in cohort 3 (flu/cyclo lymphodepletion, $5-6 \times 10^7$ TDN). CAR-T expansion in all patients; SD in all patients in cohort 2
- **Adoptively transferred autologous T cells genetically modified to express huMNC2-CAR44** in patients with metastatic MUC-1 star positive breast cancer. Lymphodepletion with cyclophosphamide and fludarabine is followed by infusion of huMNC2-CAR44 CAR-T cells in escalating doses (3.3×10^5 CAR+ T cells/kg – 1×10^7 CAR+ T cells/kg). Enrollment target is 69 patients in dose escalation and expansion cohorts.⁵ Data is awaited.
- **CAR macrophage product CT-0508 expressing an anti-HER2 CAR.** The study will enroll ~18 patients in heavily pretreated locally advanced (unresectable) or metastatic solid tumors overexpressing HER2. Patients will be enrolled in two groups (Group 1: split dosing between D1, 3 and 5; Group 2: Full dose on D1).⁶ Data is awaited.

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Are Two Targets Better Than One?

ASCO 2021

A promising approach to improve upon monoclonal antibodies (mAbs) is through the dual binding mechanism of bispecific antibodies (BsAbs). This is premised on the fact that BsAbs attach to two different antigens/epitopes simultaneously, are constructed to provide higher binding specificity and avidity, have enhanced cytotoxic effects, and less resistance. The mechanism of action for BsAbs includes the induction of CDC, ADCC, ADCP, apoptosis, and recruitment of cell surface receptors, as well as activation or inhibition of signaling pathways.

With the promise also come some challenges. While conceptually simple, BsAbs are mechanically complex, and optimal constructs are still evolving: packing two activities in one molecule is cost-effective but also less flexible. Additionally, the evolving competitive landscape of ADCs and cell therapies sets a high bar in order for BsAbs to succeed.

Does the Evolving Data Provide Some Direction?

There are >150 BsAbs in various stages of clinical development: ~30 abstracts are covered in ASCO 2021 with targets including PD-1/L1, CTLA4, HER2, VEGF, LAG-3, EGFR, MET, NRG1, LGR5, IL15, and CD47. Some of the programs we'll be watching include:

- **PD-1(L) 1xCTLA4 targeting BsAbs, AK104 and KN046**, demonstrate **favorable safety and efficacy in advanced solid tumors including gastric, pancreatic, esophageal, and hepatocellular Ca**¹⁻⁶
- **HER2 targeting BsAbs, zanidatamab and KN026**, have shown **durable anti-tumor activity in heavily pretreated patients in gastric and biliary tract Ca**⁷⁻¹¹
- **Amivantamab, an EGFRxMET BsAb**, has demonstrated **promising overall survival (OS) in Exon20ins aNSCLC**^{12,13}
- **AK112, a PD-1xVEGF BsAb**, has shown **encouraging objective response rate (ORR) in solid tumors resistant to standard therapies**¹⁴
- **Zenocutuzumab, a HER2xHER3 BsAb**, has induced **major radiologic tumor regression and biomarker responses in heavily pretreated NRG1+ cancers**¹⁵

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Versatile ctDNA Put to the Test

ASCO 2021

Circulating tumor DNA (ctDNA) addresses issues of tissue availability, serial testing, turnaround time and patient convenience, with the promise of utility across key intervention points in a patient's journey to support:

- Early diagnosis and detection
- Prediction of outcomes
- Precision treatment
- Monitoring disease progression

However, key issues that still need to be addressed include improving sensitivity and establishing concordance with tissue biopsies. More than 20 presentations on ctDNA are being presented at ASCO 2021, with evidence addressing some of these issues, generated from clinical trials, single institution studies, and real-world data:

- **More sensitive assays** to better detect high-risk patients with ctDNA (e.g., RaDaR™ assay in LUCID study tested in early stage NSCLC, that has earlier received a breakthrough designation¹; minimal residual disease (MRD) in NSCLC and bladder cancer)²
- **Confirms that presence of co-mutations** defines patient outcomes (e.g., TP53 or KEAP/STK11 co-mutations with KRASG12C)³
- **Validation of ctDNA-based patient selection for precision treatments** (e.g., METex14 skipping mu in NSCLC)⁴
- **Validation of IO biomarkers** in ctDNA (e.g., sensitivity and concordance for TMB-high)⁵
- Use of **ultra-sensitive ctDNA panels** for molecular profiling of patients for precision treatment and monitoring (e.g., amplicon-based NGS in pan cancers)⁶

We believe ASCO 2021 will be a significant milestone for validating the broad utility of ctDNA.

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SmartAnalyst is helping clients interpret the data presented at ASCO 2021 (June 4-8) focusing on key developments in cancer research. Contact us to learn more.

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