EVALUESERVE

ESMO 2022 Post-Conference Summary

September 2022

ESMO'22 highlights from five broad themes

Breakthrough early assets

Early-stage assets that vouch for an accelerating innovation in oncology

- 754P: initial efficacy signals of AFM24 in difficult-to-treat EGFR cancer patients
- 728O: encouraging response rate for the first and only off-the-shelf TCE bispecific protein, IMC-F106C in solid tumors
- LBA56: doubled DoR & extended survival could position MEDI5752 as next-gen bispecific immunotherapy

Revolutionizing precision oncology

Tailored therapies gaining lot of traction around pathologic findings, clinical staging & molecular profiling

- LBA10: Sotorasib emerges as SoC in $KRAS^{G12Cm}$ NSCLC by outperforming chemo (reduced risk of progression & improved QoL)
- LBA24: strengthens adagrasib's position as front-runner in KRASm CRC

Practice informing readouts

Data exhibition with potentially significant impact on current Tx practices

- LBA7: exceptional pathological response strongly positions neoadjuvant nivolumab + ipilimumab as a potential SOC in dMMR CRC
- LBA2: encouraging clinical outcomes of nirogacestat in small niche segment of desmoid tumors

Traction gaining ADCs

ADCs development continues a positive trajectory, driven by deeper understanding of MoAs and technological advancements

- LBA76: notable improvement in efficacy and delayed deterioration in health status with sacituzumab govitecan in HR+/HER2 mBC
- LBA73: readout reinforces ADCs role in bladder cancer treatment, especially in combo with checkpoint inhibitors

Out of the box findings

Elevated insights around diagnostic and treatment infrastructure

- LBA1: Mechanistic basis for particulate matter driven lung cancer in absence of classical carcinogen-driven mutagenesis
- 909P: Early cancer detection approach utilizing next-gen sequencing and machine learning

For detailed analysis slides please click on abstract numbers

Twitter intelligence of key ESMO'22 readouts

Positive Sentiments

Adagrasib maintains lead in CRC data vs competitors

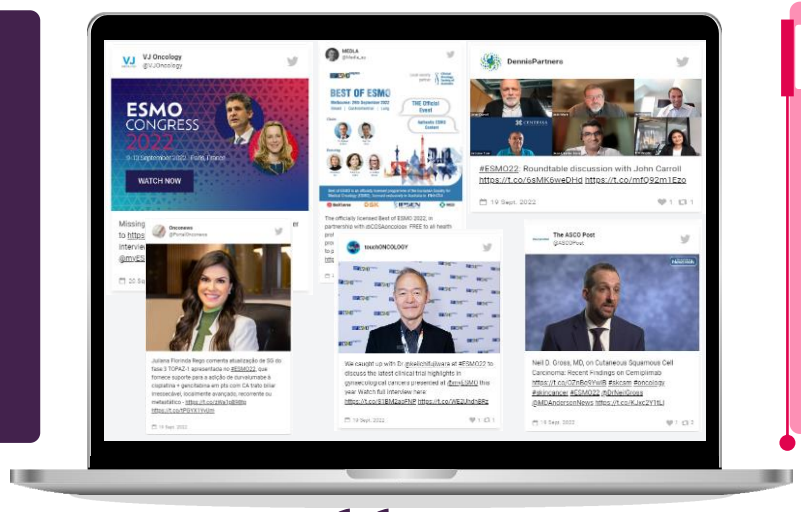
Air pollution cancer breakthrough to rewrite rules

Fantastic NICHE-2 data

PATHFINDER: doubled traditional cancer screening number

Promising results of adagrasib + cetuximab

TROPiCS-02: evolving era of ADCs in breast cancer continues



Negative Sentiments

CodeBreaK 200

hepatotoxicity concerns are disappointing

Competitor AL102 presents cheaper option in desmoid tumors

CodeBreaK 200: mPFS of at least 6mos was expected

MEDI5752: 70% Gr3 TRAEs at 1500mg & 70% discontinuation

AFM24 mono not effective..

"A paradigm shift to the way we need to look at tumour development. Air pollution, not as mutation-causing carcinogen, but tumour-promoting on a background of oncogenic driver mutations…" **Onco KOL, EU**

"@X detected more cancers than all US PSTF-recommended standard single cancer screenings combined, doubling the number of cancers detected compared to standard screening" **Genome expert, US**

"Promising results of adagrasib plus cetuximab in heavily pretreated pts with KRAS G12mCRC. Dual blockade of the pathway seems the way to go!" **Onco HCP, EU**

"Following the fantastic #NICHE-2 data, presented during #ESMO22 would we be able in the future to cure stageII/III CRC-MSI-H just with ICIs and without a morbid surgery for our patients? **Onco HCP, EU**

"Hopes to Defi expectations in desmoid tumors, but $AYLA represents a cheaper bet on gamma secretase inhibition" Biopharma publication editor, EU

"Sotorasib may squeak by with significant PFS benefit, but lack of OS benefit & hepatotoxicity concerns are disappointing for the cost difference of sotorasib vs docetaxel. Leaves it plenty vulnerable to challenges here" **HCP, US**

"Why the world are we still waiting for a AFm24-NK PDL1 combo is beyond me...clearly AFM24 does not work on its own..." **KOL, US**

Clearly a step forward and we must advocate for regulatory agencies to rapidly approve this for our patients. But no doubt I was hoping for a bit more. Maybe sotorasib is the sprinter in the 10K race, and others will overtake" **Medical Oncologist, US**

Optimism for scoring supplemental approval of sacituzumab in HR+/HER2 mBC has further strengthened, with this positive trend of improved OS

GILEAD Creating Possible

LBA76 - OS results from Ph3 TROPiCS-02 study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in pts with HR+/HER2 mBC

ESMO'22 data spotlight

- Second interim OS analysis for Ph3 trial (**TROPiCS-02**) evaluating SG vs. chemo (treatment of physician's choice/TPC) in pts with previously treated hormone receptor–positive/HER2-negative locally recurrent inoperable or mBC
- Total treated pts: 543 [SG (n=272) vs TPC (n=271)]

Safety:

- SG arm consistent with prior results, no new safety signals were observed

Efficacy:

- mOS (mos): 14.4 (SG) 11.2 (TPC)
- 12mos OS (%): 61 (SG) 47 (TPC)
- ORR (%): 21 (SG) 14 (TPC)
- mDoR (mos): 8.1 (SG) 5.6 (TPC)

QoL analysis:

- Median time-to-deterioration (mTTD) of global health status (mos): 4.3 (SG) 3 (TPC)
- mTTD of fatigue (mos): 2.2 (SG) 1.4 (TPC)
- mTTD of pain (mos): 3.8 (SG) 3.5 (TPC)

Industry Perception

- With this updated data, SG now holds **survival benefit in both pre-treated HR+/HER2-ve mBC and 2L mTNBC** – two difficult-to-treat forms of Breast cancer
- Experts opine this largest late-line trial hormone receptor–positive/HER2-ve mBC population run trial defines the evolving era of ADCs in breast cancer continues
- Along with significant improvement in efficacy, **delayed deterioration in global health status** was also highlighted as noteworthy
- Few KOLs are comparing this data with "practice-changing results" of "DESTINY-Breast04" of trastuzumab deruxtecan in previously treated HER2-low disease pts
  - ✓ Before any 1:1 comparison it should be considered that DESTINY had median of 1 prior chemo lines compared to 3 for TROPiCS-02

EV-103 study outcomes appear highly promising; provides stronghold to enfortumab for unlocking 1L potential in locally advanced mUC

LBA73 - Study EV-103 Cohort K: Antitumor activity of EV mono or in combo with Pembro (P) in previously untreated cisplatin-ineligible pts with locally advanced or metastatic urothelial cancer (la/mUC)

ESMO'22 data spotlight

- Ph1/2 trial (**EV-103**) cohort K aimed to evaluate Enfortumab vedotin (EV) as monotherapy or in combination with Pembro for treating urothelial cancer
- Total treated pts till Jun'22: 149 (EV/mono: n=73, EV+P/combo: n=76)
- Tumor inclusion: la/mUC

Safety:

- Majority TRAEs were Grade ≤2 | Serious TRAEs: mono 15.1%, combo 23.7%
- TRAEs of special interest are:
  - Skin reactions (%): mono 45.2 (33/73) | combo 67.1 (51/76)
  - Peripheral neuropathy (%): mono 54.8 (40/73) | combo 60.5 (46/76)
  - Ocular disorders (e.g., dry eye and blurred vision) (%): mono 28.8 (21/73) | combo 26.3 (20/76)
  - Hyperglycemia (%): mono 11 (8/73) | combo 14.5 (11/76)

Efficacy:

- ORR (%): mono 45.2 (33/73) | combo 64.5 (49/76)
- CR (%): mono 4.1 (3/73) | combo 10.5 (8/76)
- PR (%): mono 41.1 (30/73) | combo 53.9 (41/76)
- SD (%): mono 34.2 (25/73) | combo 22.4 (17/76)
- PD (%): mono 9.6 (7/73) | combo 7.9 (6/76)
- mDoR (mos): mono 13.2 | combo (not reached)
- Median time to ORR (mos): mono 2.1 | combo 2.1
- Median treatment duration (mos): mono 5.5 | combo 9
- Median follow-up (mos): mono 15 | combo 14.8

Industry Perception

- Experts clarify that latest data showed EV+P combo holds **better efficacy as compared to EV mono,** further result of trials in different cohorts awaited
- Several other experts remained optimistic regarding the **potential of the combo to become the 1L treatment for bladder cancer**
- Analyst are optimistic about Astellas target to see **Padcev peak sales reaching ¥300–400bn**, as they believe results from **EV-103 cohort K have put the drug well on the road toward this target**
- Analyst are optimistic about the ongoing Ph3 study (EV-302) in bladder cancer as results of EV-103 are supportive, encouraging and **forms basis for 1L EV-302 trial**

Latest Ph3 readout holds potential to convert existing accelerated approval of sotorasib to full-fledged FDA approval in KRAS^{G12Cm} NSCLC

AMGEN **LBA10 - Sotorasib versus docetaxel for previously treated NSCLC with KRAS^{G12C}m: CodeBreaK 200 phase III study**

ESMO'22 data spotlight

- Ph3 trial (**CodeBreak 200**) comparing efficacy, safety and patient-related outcomes for sotorasib vs. docetaxel in KRAS G12Cm NSCLC pts
- Total treated pts: 345 (initially planned to enroll 650 pts but amended based on FDA guidance)

Safety: (S arm: n=169 | D arm: n=151)

- Gr≥ 3 TRAEs (%): 33.1 (S); 40.4 (D)
- Serious TRAEs (%): 10.7 (S); 22.5 (D)
- TRAEs discontinuation (%): 9.5 (S); 11.3 (D)
- Fatal TRAE: 1 (S); 2 (D)

Efficacy:

- 1-yr PFS (%): 24.8 (S); 10.1 (D)
- ORR (%): 28.1 (S); 13.2 (D)
- DCR (%): 82.5 (S); 60.3 (D)
- OS indicated not being statistically different between arms, though study wasn't powered for OS

QoL:

- Common Side effect: ALT and AST increase (both indicative of liver damage)- 10.1% (S); 0% (D)
- Risk of QoL and delayed physical functioning deterioration: 31% reduction (S) each
- At one year, 24.8% (S) were alive and didn't show any disease worsening, versus 10.1% (D)

Industry Perception

- Sotorasib is considered as new SoC for KRAS^{G12C} NSCLC, as it **outperformed chemo in reducing the risk of progression or death and improving QoL**
- On the contrary, lack of OS benefit & **hepatotoxicity concerns are considered disappointing for cost difference of S vs D ($18,000 vs ~$2,000/month, respectively)**
  - ✓ Higher rate of Gr3+ ALT elevation reported vs earlier Codebreak-100 trial data
- **mPFS was extended by just over a month, few experts hoped at least six mos**
- This first randomized study of KRASi holds potential to block Mirati's adagrasib AA path (PDUFA date: Dec 14, 2022)
  - ✓ If Amgen scores full approval before Dec'22, adagrasib's approval pathway based on its surrogate endpoint of ORR will be difficult

Adagrasib emerges as a front-runner in KRAS^{G12C}m CRC; supersedes sotorasib driven by stronger clinical profile

MIRATI THERAPEUTICS

LBA24 - KRYSTAL-1: Updated efficacy and safety of adagrasib (MRTX849) with or without cetuximab in patients with advanced colorectal cancer (CRC) harboring a KRASG12C mutation

ESMO'22 data spotlight

- Multicohort Ph1/2 trial (**KRYSTAL-1**) evaluating efficacy and, safety for adagrasib ± cetuximab in KRAS G12Cm advanced STs (here results for previously treated CRC in Ph 2 and 1b cohorts reported)
- Total analysis evaluable pts (n): adagrasib mono arm 44 | adagrasib plus cetuximab combo arm 28

Safety:

Mono arm

- Any grade TRAEs (%): 93 | Gr3: 30 - diarrhea (7), fatigue (5), anemia (9), and QT prolongation (5)
- Gr5: None
- TRAEs discontinuation: none
- TRAE leading to dose reductions and interruptions (%) : 39 and 46, respectively

Combo arm

- Any grade TRAEs (%): 100 | Gr3: 9 diarrhea (3), dermatitis acneiform (3), and stomatitis (3)
- Gr5: None
- TRAEs discontinuation: 16% due to cetuximab | none due to adagrasib
- TRAE leading to dose reductions and interruptions (%) : 31 and 44, respectively

Efficacy:

- ORR (%): mono 19 (8/43) | combo 46 (12/28)
- DCR (%): mono 86 (37/43) | combo 100 (28/28)
- mDoR (mos): mono 4.6 | combo 7.3
- mPFS (mos): mono 5.6 | combo 6.9

Industry Perception

- Mirati reported strong ORR, durability and PFS recently in heavily pretreated CRC, an indication where prime competitor Amgen's Lumakras has struggled
  - ✓ Results appear even better considering pts in this trial tried median 3 prior LoT compared to Amgen's trial with only 2 prior LoT
- Although, few experts recommend cautious evaluation of these early-stage data given small pts subset [Combo arm (n): Codebreak-101 40 | KRYSTAL-1 28]
- Mirati to provide clarity on CRC regulatory strategy later this year**, full approval likely to be supported by the 2L** KRYSTAL-10 trial, testing adagrasib+erbitux vs. chemo
- Approaching competition from Roche's GDC-6036 was also highlighted, given similar mono data (ORR 20%) from Ph1

IMC-F106C, PRAME targeted bispecific TCR therapy, spurs early promise in advanced solid tumors

IMMUNOCORE 728O - Ph1 dose escalation data of IMC-F106C, the first PRAME × CD3 ImmTAC bispecific protein in solid tumors

ESMO'22 data spotlight

- Ph1/2 trial aimed to determine safety, preliminary efficacy and RP2D in HLA-A*02:01-+ve ST pts
- Total treated pts till Jul'22: 55
- Tumor inclusion: uveal melanoma (47%), ovarian carcinoma (18%), cutaneous melanoma (15%), NSCLC (7%), endometrial cancer (7%) and TNBC (5%)

Safety:

- Most frequent related AE: Gr 1/2 CRS (consistent with proposed mechanism)
  - CRS events were all manageable: Majority (77%) within first 3 doses | 71% Gr1 | 29% Gr2 | No Gr≥3 CRS
- No treatment-related discontinuation or Gr 5 AEs or deaths

Efficacy:

- PR: Observed across multiple tumor types
  - Uveal melanoma: 3/6 (50%) | Cutaneous melanoma: 2/6 (33%) | Serous ovarian: 2/4 (50%)
- Among 20 pts eligible for ctDNA analysis, 90% showed evidence of ctDNA reduction
  - 13 (65%) had >50% ctDNA reduction, including 5 with ctDNA clearance (common in melanoma)

PD: Strong and consistent pharmacodynamic activity at ≥20 mcg

MTD: Not reached

Trial to move in dose-expansion phases for pts with cutaneous melanoma, NSCLC, endometrial cancer and ovarian carcinoma

Industry Perception

- **Interesting prelim response rates** observed in multiple STs in a group of heavily pretreated pts who have exhausted all standard treatment options
- Few stakeholders remain apprehensive as nearly half (49%) pts experienced cytokine release syndrome (CRS)
  - ✓ Although company re-iterated that mostly these CRS were Gr1 (none Gr ≥3) and occurred predominantly during the initial 3 doses
- Higher hopes with the next set of plans including trial **expansion into combination therapy cohorts**, including combination with chemotherapy and IC inhibitor

Initial data of MEDI5752 in NSCLC is set to advance the science of bispecific antibodies as a next-gen immunotherapy

AstraZeneca **LBA56 - A phase 1b/2 trial evaluating MEDI5752 (Bi-antiPD1-CTLA4 antibody) + chemotherapy vs Pembrolizumab + chemotherapy in 1L NSCLC**

ESMO'22 data spotlight

- Ph1/2 dose-escalation and dose-expansion study evaluating safety, tolerability, efficacy, PK and immunogenicity of MEDI5752 + chemo combo in adv. STs (here results from 1L NSq NSCLC discussed)
- Total treated pts till Jul'22: 105 [Evaluable pts 91: Cohort R MEDI5752 (1500mg) + chemo vs pembro + chemo (n=41) | Cohort S MEDI5752 (750mg) + chemo (n=50)]

Safety:

- Gr3/4 TRAEs (%): 80 vs. 61.9 (Cohort R) | 50% (Cohort S)
- Treatment discontinuation (%): 70 vs. 28.6 (Cohort R) | 20% (Cohort S)

Efficacy:

- **ORR** (%): 50 (mFU ~22.8mos) vs. 47.6 (Cohort R) | 44 (mFU ~3.9mos) (Cohort S)
- **mOS** (mos) - NR vs. 16.5 (Cohort R)
- PD-L1<1%: **mDOR** (mos) - 13.8 vs. NR (Cohort R) | **ORR** (%): 55.6% vs. 30% (Cohort R); 48% (Cohort S) | **mPFS** (mos) - 13.4 vs. 9 (Cohort R)

Industry Perception

- Higher dose in experimental arm **doubled the DoR and extended survival** compared with pembro, but at the cost of **very high toxicities and discontinuations**
  - ✓ Few KOLs even cited this as one of the worst toxicity/discontinuation data ever observed
  - ✓ Latest data reinforce high toxicity trends witnessed with long-plagued CTLA-4-targeting medicines
- Results with **750mg dose led to better safety profile than 1500mg**, but experts did highlight that longer-term data will inform future dose selection
- AZ also disclosed, T-cell proliferation at 750mg dose and even smaller 500mg dose that the company has begun testing, are found higher than other approved drugs

PARIS 2022 ESMO congress

AFM24's early data induces some confidence to benefit broad EGFR-expressing cancer patients; advanced data will define further potential

AFFIMED **754P - A Phase 1/2a dose escalation study of AFM24 in patients with EGFR solid tumors: Results from Ph1**

ESMO'22 data spotlight

- Ph1/2 trial (**AFM24-101**) aimed at evaluating safety, immunogenicity, PK and PD of AFM24 in metastatic/refractory pts with EGFR+ tumors
- Total treated pts till Mar'22: 34
- Tumor inclusion: Colorectal (18/34; 12 KRASm) NSCLC (8/34; 7 EGFRm)

Safety:

- General TEAEs- Infusion-related reactions (IRRs): 25/34 | nausea: 8/34 | acneiform dermatitis (AD): 7/34
- Gr 3-4 TEAEs- G3 – IRRs (2/34) | Hypertension (1/34) | AD (1/34) | ≥G3 Lymphocytopenia
- Treatment-related death- None
- DLT: 1 at 40 mg (G3 IRR)

Efficacy:

- SD: 10/27 evaluable pts; (4 pts had SD for ≥4 mos)

PK:

- Dose proportional increase in PK- doses ≥320 mg

The trial findings led RP2D to be **480 mg** (Treatment is ongoing in 4 pts)

Industry Perception

- Some experts opine that latest data clarifies **mono cetuximab being better than mono AFM24** (considering similar side effects), thus presenting lesser chances of commercial success for AFM24
- Few others remained optimistic, indicating the asset holds **potential for an upside surprise in future readouts**
- **Although latest data covers** limited pts, but experts highlight that it do indicate **early signs of efficacy** in heavily pretreated pts in very difficult to treat disease
- In a recent twitter survey, (~120 responses) **31% participants anticipated some SDs to turn into PRs** whereas another **14% were expecting >5% ORR**

Nivo+Ipi & nirogacestat present game-changing capabilities in dMMR CRC & desmoid tumors respectively

Bristol Myers Squibb — LBA7 - Neoadjuvant immune checkpoint inhibition in locally advanced MMR-deficient colon cancer: the NICHE-2

ESMO'22 data spotlight

- NICHE-2 trial evaluating nivolumab + ipilimumab (EudraCT 016-002940-17) was initiated post successful NICHE-1 trial results (100% pathologic responses to an immune checkpoint blockade in dMMR colon cancer)

Efficacy: (107 evaluable pts)

- 106 pts (99%) showed pathologic response
- MPR: 102 (95%) | pCR: 72 (67%) |Partial pathologic response: 4 (4%)

Safety: (112 evaluable pts)

- iAEs: 61% | ≥Gr3 iAEs: 4% | AEs leading to surgery delay: 2%
- Surgery related AEs: 21% | ≥Gr3 surgery related AEs: 13%

Industry Perception

- Widely neoadjuvant nivo + ipi being anticipated as a new emerging SoC for pts with dMMR CRC, **as historical data involving neoadjuvant chemo have shown pathologic response rates in range of only 5-7%**
- Experts also opine that ctDNA dynamics coupled with novel imaging techniques should be explored to likely aid in achieving organ preservation moving forward with dMMR CRC

SpringWorks Therapeutics — LBA2 - DeFi: A Ph3, randomized controlled trial of nirogacestat vs placebo for progressing desmoid tumors (DT)

ESMO'22 data spotlight

- Ph3 trial (**DeFi**) evaluating efficacy, safety and tolerability of nirogacestat (investigational oral gamma secretase inhibitor) in adult pts with progressing desmoid tumors

Efficacy:

- 71% reduction in the risk of disease progression with N arm vs placebo
- ORR (CR+PR): niro arm 41% | placebo arm 8%
- CR: niro arm 7% | placebo arm 0%

Safety:

- AEs: N arm 95% Gr1/2 | Ovarian dysfunction: 75% (27/36)
- Dose reduction & discontinuation due to TEAEs: N (42%, 20%) | P (0%, 1%)

Industry Perception

- Encouraging data from the largest and most robust Ph3 trial conducted to date in pts with DTs evokes hope of being the first approved therapy for this niche segment
- SpringWorks plans to **file to FDA in H2'22**, but investors seem dicey about the prospect of a solo launch for this small subset being profitable

Patho-physio findings in NSCLC and multi-cancer screening liquid biopsy, embraces the capacity to mold future in oncology

Multiple Cancer Research Centres*

LBA1 - MoA & an actionable inflammatory axis for air pollution induced NSCLC: Towards molecular cancer prevention

ESMO'22 data spotlight

- Evaluation of mechanism and cause of NSCLC initiation in never smokers due to air pollutants, particulate matter (PM)
- Findings basis: human and laboratory research on mutations

Data snapshot:

- Increased risk of EGFRm NSCLC was linked to rising PM2.5 levels, although it's noteworthy that neither pollution or EGFRm alone are sufficient to augment a stem cell state, activation of both is required
- EGFR and KRAS driver mutations found to in normal lung tissue (18% & 33%, respectively) as a likely consequence of aging

Industry Perception

- Findings considered as 'wake-up' call on danger of air pollution and at same time unlocks possibilities for molecular targeted cancer prevention
- Latest analysis also **propels investigations around why some lung cells with mutations become cancerous when exposed to pollutants while others don't**
- Also highlights need to have a strong mandate for tackling long persistent air-pollution issues – for both environmental and health reasons

*Lung Cancer Research Foundation Grant, ERC Advanced Grant, MarkFoundation ASPIRE I Award, ERC Advanced Grant, CRUK TRACERx grant and Rosetrees Out-of-round Award

燃石医学 Burning Rock Dx

909P - Multi-cancer early detection model based on liquid biopsy of multi-omics biomarkers: A POC study (PROMISE)

ESMO'22 data spotlight

- Evaluation of (**PROMISE**) performance of 3 prototype assays of cfDNAm, cfDNA methylation and miRNA expression in early detection of multi-cancer
- Test set evaluated pts: 492

Data snapshot:

- Test specificity: 99.1%
- Positive prediction value: 38% (71% pts with +ve results have no routine screening test available currently)
- False positives: <1%
- Tumor location confirmation: 97.1%
- Diagnosed cancers: 19 solid tumors, 17 hematological cancers

Industry Perception

- Most exciting aspect around this new paradigm, in concept, is that many of the cancers detected lack any standard screening available as of now
- This revolutionary data is being considered as "important first step" in evaluating how multi-cancer early detection test could fit into real-world care
- Combining different cancer biomarkers **visibly improves cancer detection, especially in stages I/II, when treatment may be more effective for pts**

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