Exosome Diagnostics for Cancer Patients on Immunotherapy

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Yale Life Sciences

PITCHFEST

December 5, 2024

Team behind exosome diagnostics for precision oncology

We are innovators in exosome diagnostics

Transplant health

Heart

BLAVATNIK FUND FOR INNOVATION *FY2024*

Lung

Kidney

Oncology

Patient response to immunotherapy

Focus for today

Co-inventors

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Immune checkpoint inhibitor “tsunami” in cancer therapeutics

Since 2011 when ICI was first introduced …

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11 new ICI drugs on the market

Examples

KEYTRUDA® (pembrolizumab) Injection 100 mg

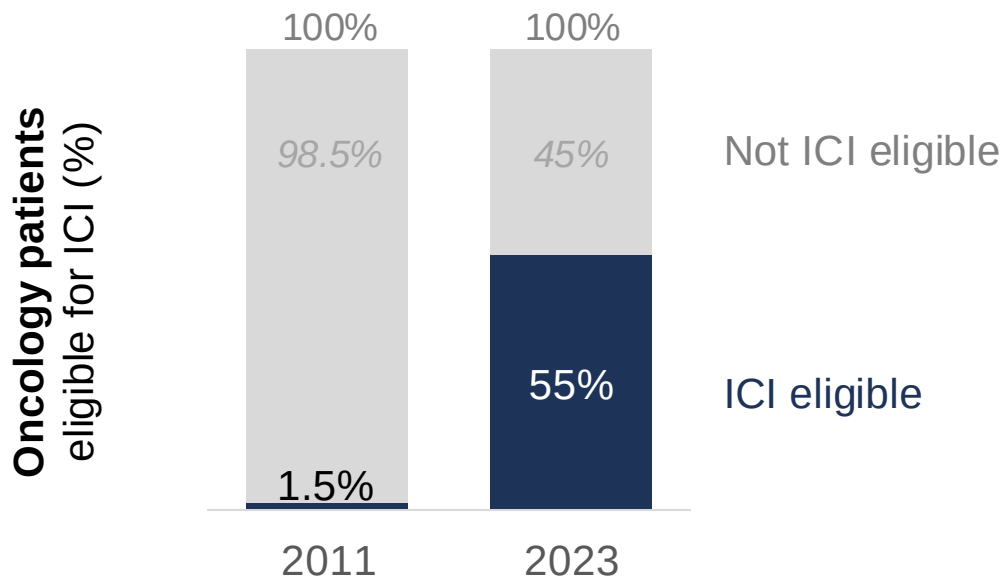
TECENTRIQ® atezolizumab

OPDIVO™ (nivolumab)

Approval in **20 general tumor types**

- 88 indications in cancer patients

… today, of the >2M new cancer patients per year in the United States, 55% have an indication for which ICI treatment is approved



But there are significant limitations to consider…

ICI treatment adoption has experienced big obstacles

Low response rates

≤ 20%
of patients
have cancer remission

Inability to identify responders prior to treatment selection

High risk of adverse events

As high as **70% of patients** experience complications (grade 3-5)

Inability to noninvasively monitor ICI response

The need for noninvasive biomarkers in this field is so critical that an entire Task Force for Immunotherapy Biomarkers was convened in 2014 (still active)

There is a critical gap in diagnostics for ICI treatment today

FDA approved biomarkers are all based on biopsy of tumor tissue…

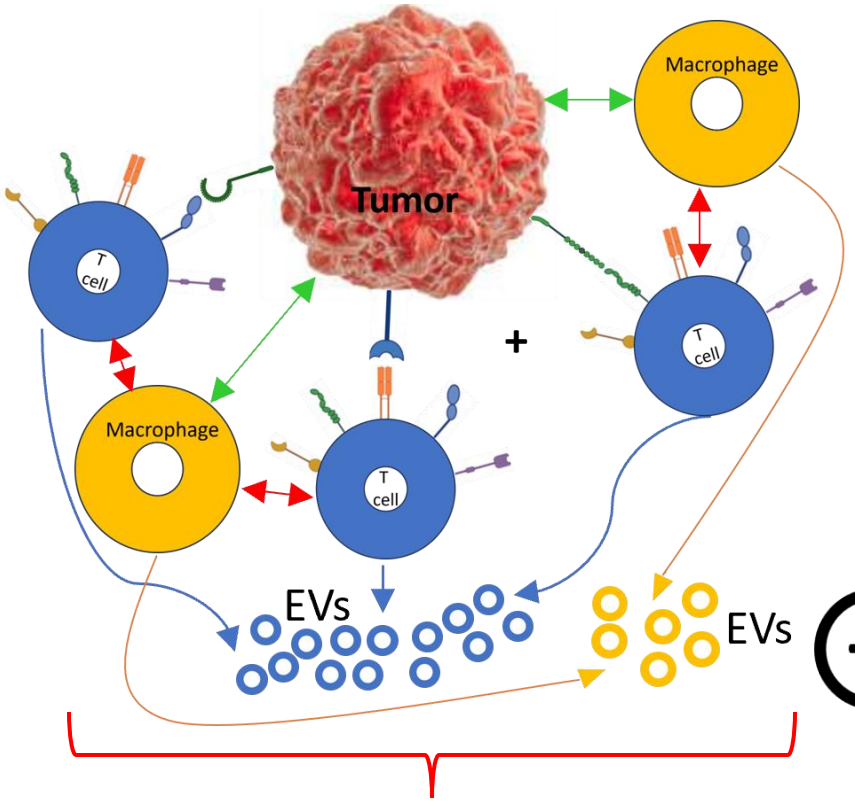
PDL1	MSI-H	TMB
Tumor protein expression	Tumor microsatellite instability	Tumor DNA mutational burden
Nonsmall cell lung cancer	Small subset of tumors have MSI (3.8%)	Pembrolizumab candidacy

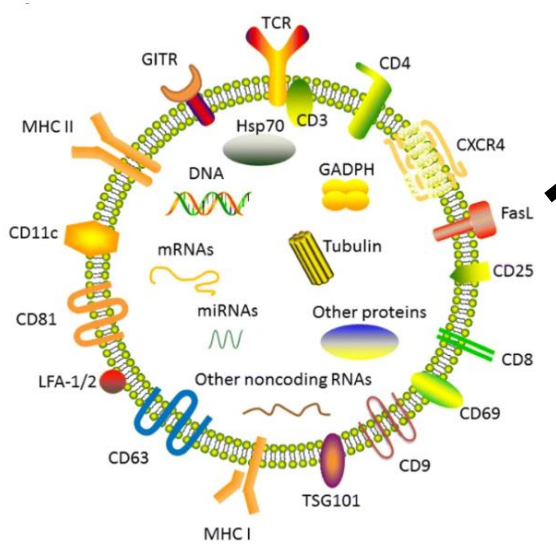
… and current solutions are lacking on multiple fronts

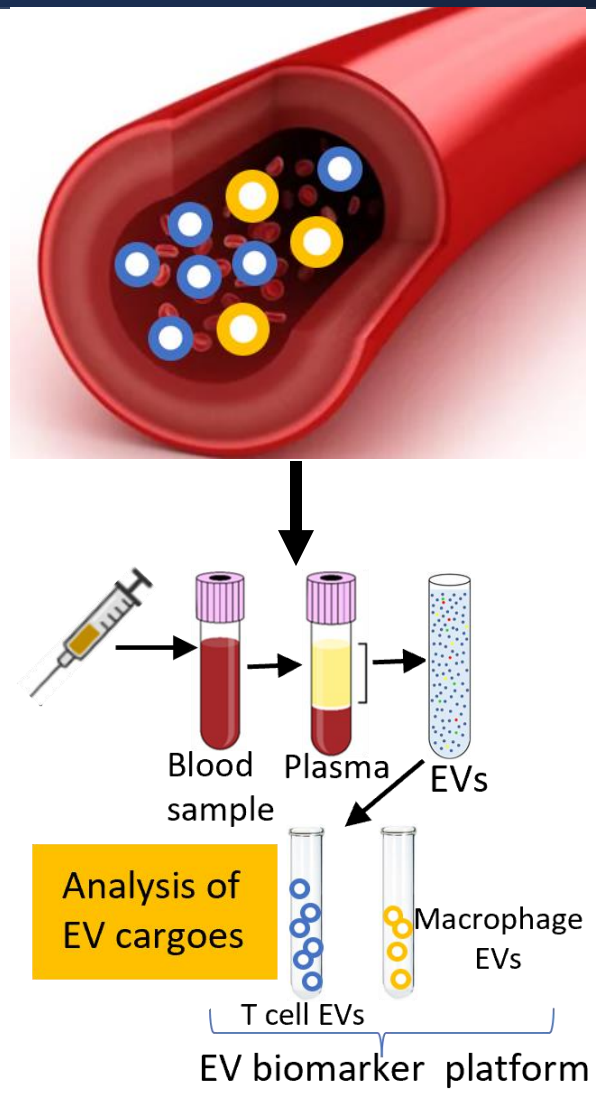
- **Static** | One-time readout of tumor
- **Not repeatable**
- **No molecular window** into the patient's immune response
- **Narrow application** | Approved for only a few tumor types
- **Inadequate sensitivity** and **specificity**
- **Invasive** | Requires biopsy of the tumor

We propose a blood test that can improve on all these limitations

SOLUTION: Immune cell-specific extracellular vesicle (EV) profiling







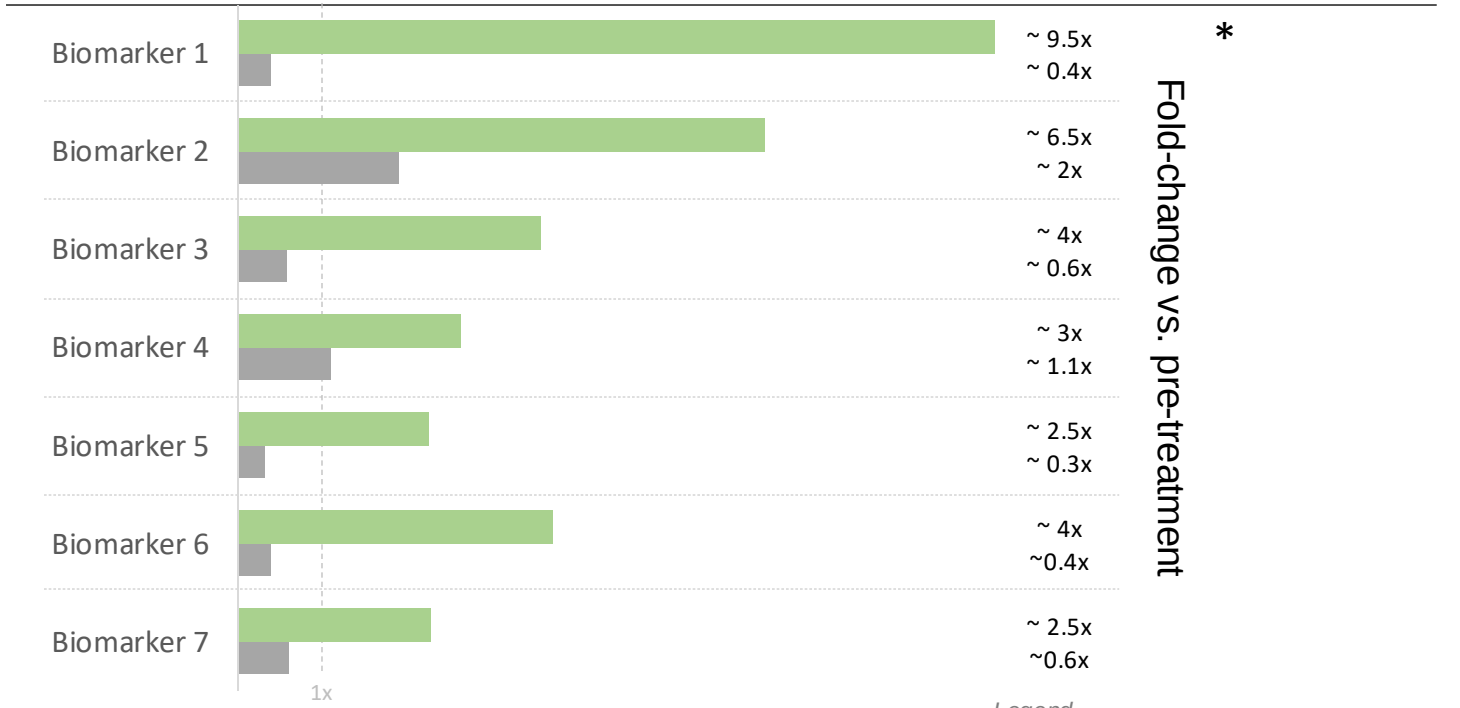
Clinical pilot study in melanoma patients shows predictive value of biomarker assay

Biomarker Assay

Panel of 7 markers
in T cell EVs that reflect ICI mediated changes in the T cells in the tumor microenvironment

- Noninvasive
- Repeatable
- Dynamic
- Wide application | Tumor agnostic, for any ICI
- Molecular window into tumor immune microenvironment

T cell EV biomarkers show distinct profile changes to ICI therapy in responders



Preliminary results based on 20 patients with melanoma stage III receiving anti-PD1 antibody ICI therapy

* All biomarkers were statistically significant in responders

A diagnostic that reliably distinguishes responders from non-responders would disrupt the treatment paradigm

The global ICI market is already a $50B market …

ICIs approved by FDA for over 20 cancer types

USD 50 B Market
(expected USD 150B by 2030)

~ 80%	**~20%**
spent on non-responders	improves patient's lives

70% of these patients have ICI-associated adverse complications

… with strong reasons for <u>HCPs</u> to use the Dx

- Minimize risk of adverse events in non-responders
  - *80% of non-responsive patients are exposed to adverse events*
- Help HCPs determine the appropriate treatment (if predictive)

… and for <u>Payers</u> to reimburse

- Reduce healthcare burden in terms of cost and resource utilization

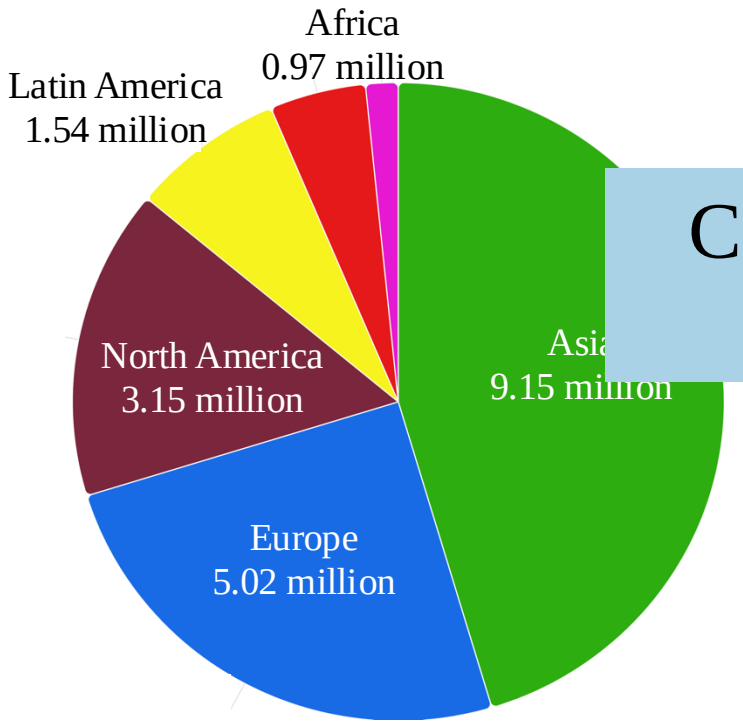
Blavatnik Fund support will be critical for the next important stage of biomarker development

	Clinical pilot	Extended validation study		
When	**Summer – Fall 2024**	**Stage 1** *(2 months)*	**Stage 2** *(2 months)*	**Stage 3** *(8 months)*
Steps	**Pilot study of approach** 20 patients with melanoma receiving ICI therapy Cross validated for other cancer types – head and neck cancer	• **Validate clinical correlation** Study 30 patients to achieve robust statistical confidence and clinical correlation	• **Optimization of biomarker panel.** Explore additional biomarkers to improve accuracy and sensitivity (in 30 patients)	• **External validation of the optimized biomarker panel** - analyze 100 pts • **Correlate EV biomarkers to tumor immuno-histology** - analyze 20 pts
		Yale Melanoma SPORE – **258 melanoma patients** treated with ICIs with pre- and post-treatment blood samples.		
Outcomes	POC T cell EV biomarker panel distinguishes responders versus non-responders	• Validated diagnostic accuracy of EV platform	• Finalized set of biomarkers for full scale study	• Validated T cell EV profiles reflect tumor immune microenvironment • FDA pre-submission
	Completed	*$50k*	*$50k*	*$200k*
		$300k total funding		

EXTRA SLIDES

Precision Oncology: Novel Biomarker for Cancer Immunotherapy

- Immune checkpoint inhibitors (ICIs), a class of drugs that promote patient's own immune cells to fight cancer, have revolutionized the care of cancer patients over the past decade



World Health Organization estimated

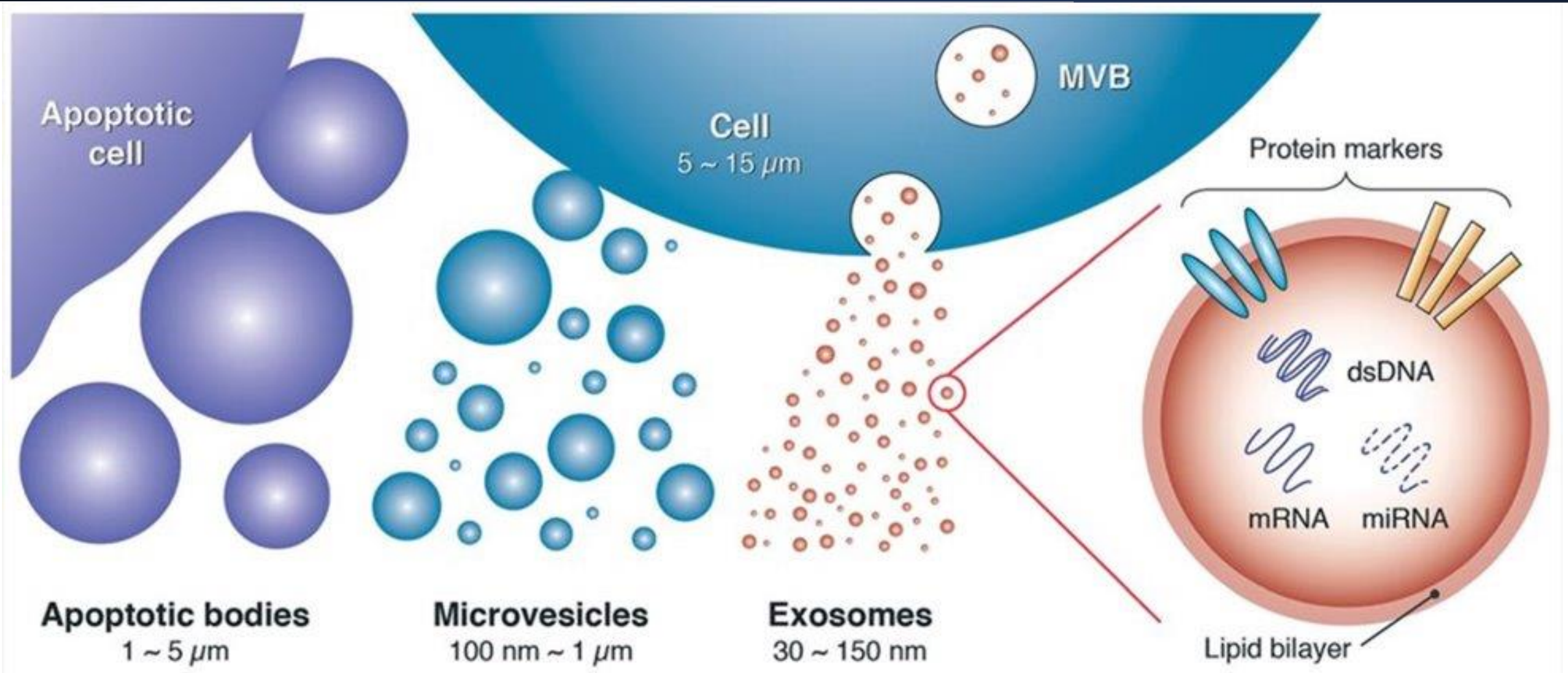
CRITICAL NEED FOR BIOMARKERS

2 million new cases in the United States

>50% eligible for ICI therapies

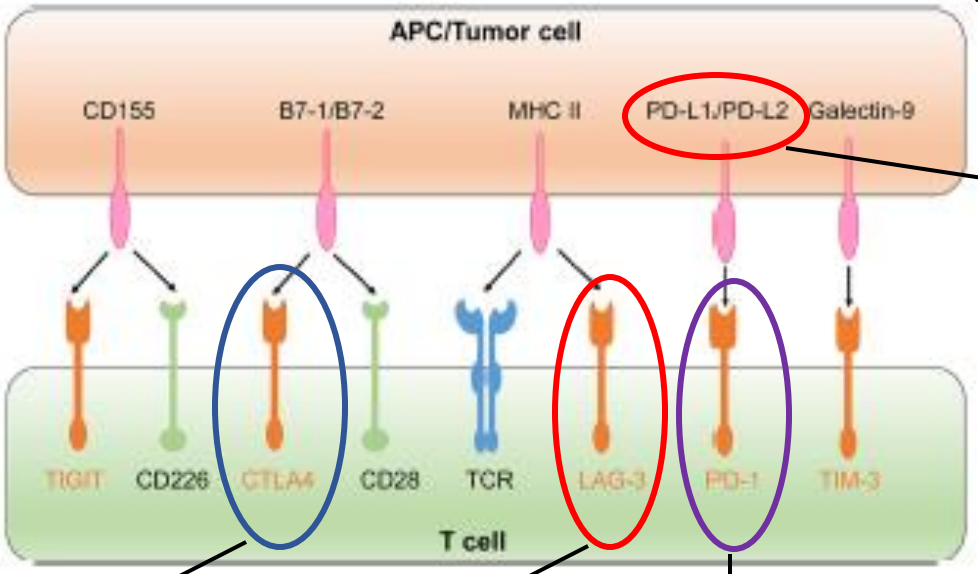
Novel biomarker in the field of cancer immunotherapy to enable precision oncology

SOLUTION: Immune cell-specific extracellular vesicle (EV) profiling



Contreras-Naranjo JC, Wu HJ, Ugaz VM 2017

Scientific foundation for ICI therapy is based on releasing the blockade of immune cells called T cells by tumor cells



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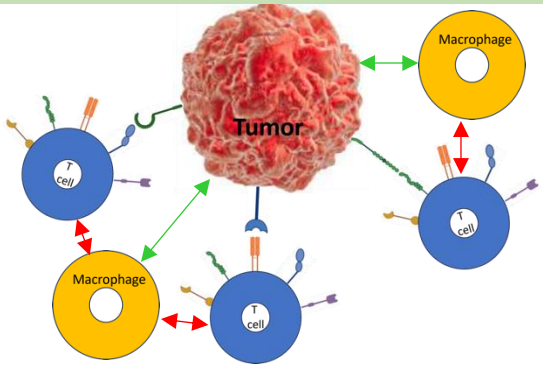
ICIs
Atezolizumab
Avelumab
Durvalumab

Ipilimumab
Tremelimumab
ICIs

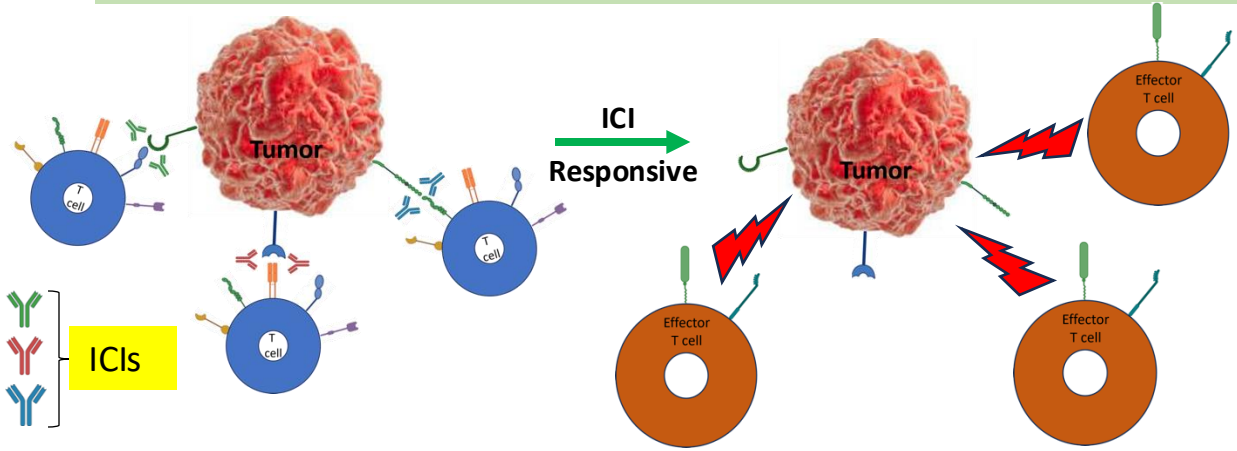
Relatlimab
ICI

Cemiplimab
Dostarlimab
Nivolumab
Pembrolizumab
Retifanlimab
tislelizumab
ICIs

Tumor interactions with checkpoint inhibitors on T cells leads to their exhaustion/ inability to fight cancer cells



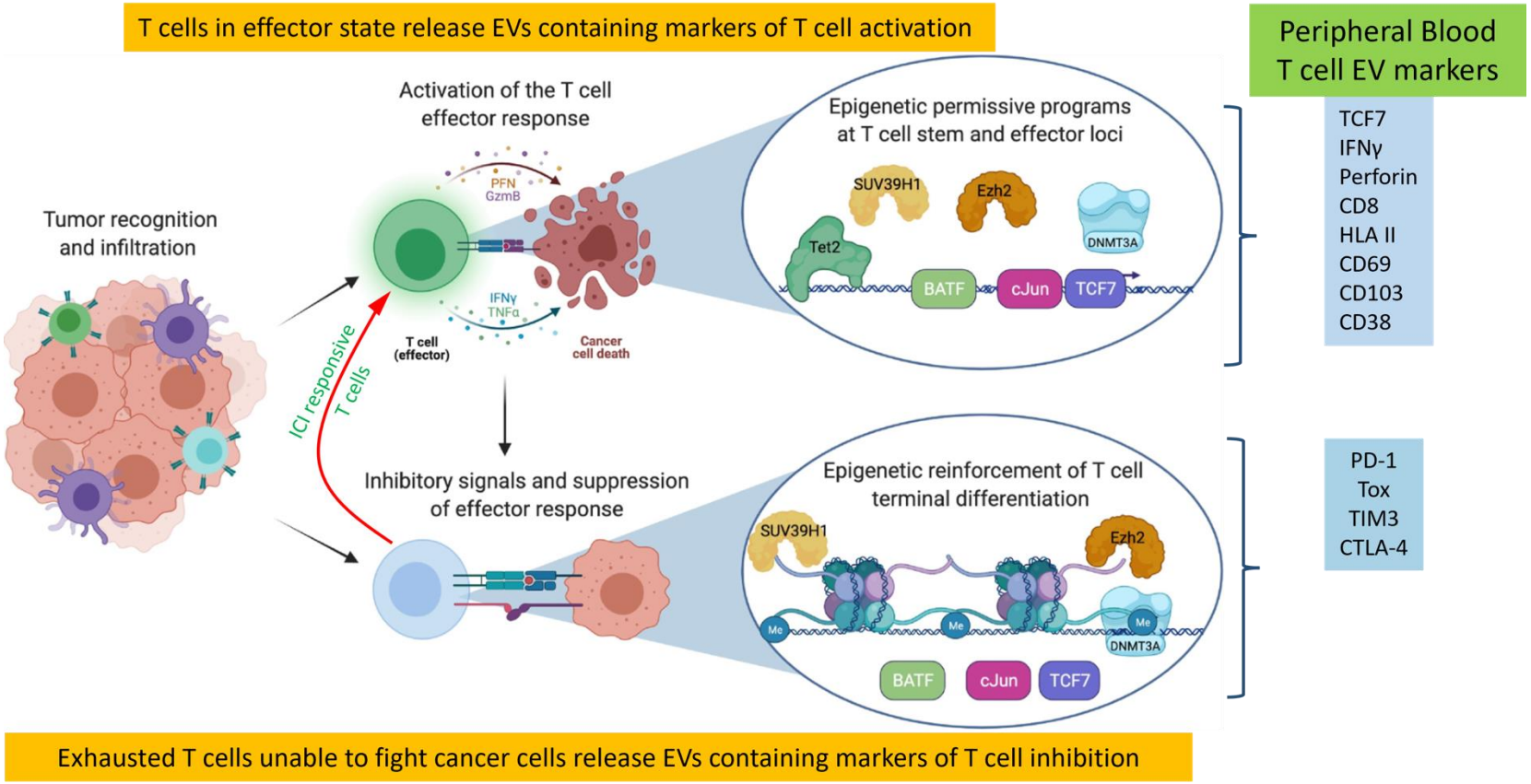
ICIs block these inhibitory interactions, leading to activation of T cells that target tumor cells



*Yamaguchi et al. Cell Reports Medicine 5, 101621, July 16,2024

Biomarker Development : T cell activation versus T cell exhaustion markers reflecting tumor infiltrating T cell phenotypes

- Most solid tumors contain immune cells, including T cells, along with the cancer cells. But these T cells are not active – they are in an exhausted state, unable to attack and kill cancer cells.
- ICIs work by altering the functional phenotype of the tumor infiltrating T cells from an exhausted state into effector T cells that actively kill tumor cells – ICI RESPONSIVE CANCER
- These different functional states of T cells in the tumor microenvironment can be defined by expression of specific markers
- Our laboratory has validated that these same markers defining the functional phenotypes of T cells in the tumor microenvironment are also expressed in the cargoes of T cell EVs enriched from peripheral blood of cancer patients



Zebley, Youngblood. Trends in Cancer. 2022. 8(9): 726-734

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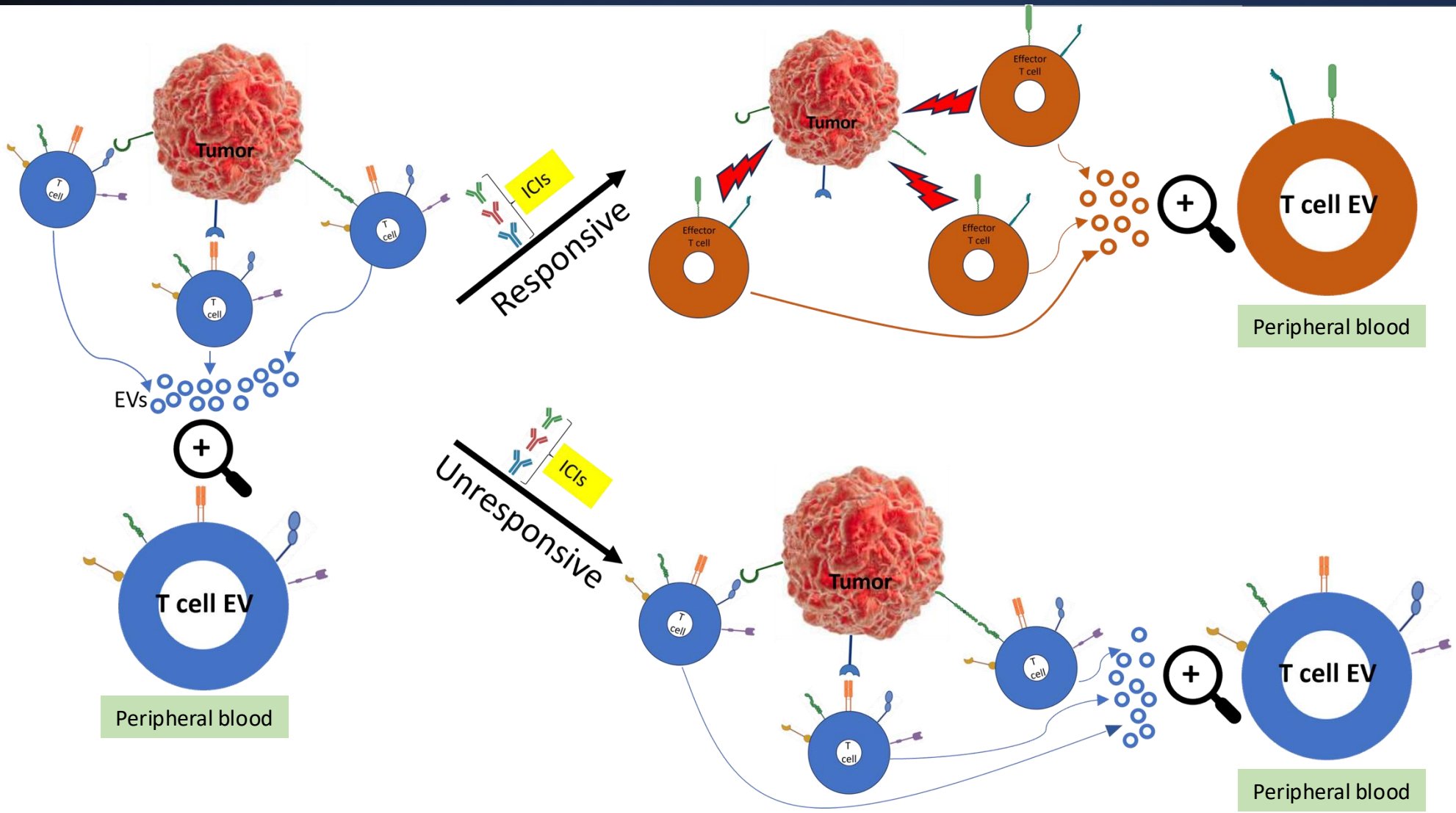
Biomarker Assay: Panel of T cell EV Markers



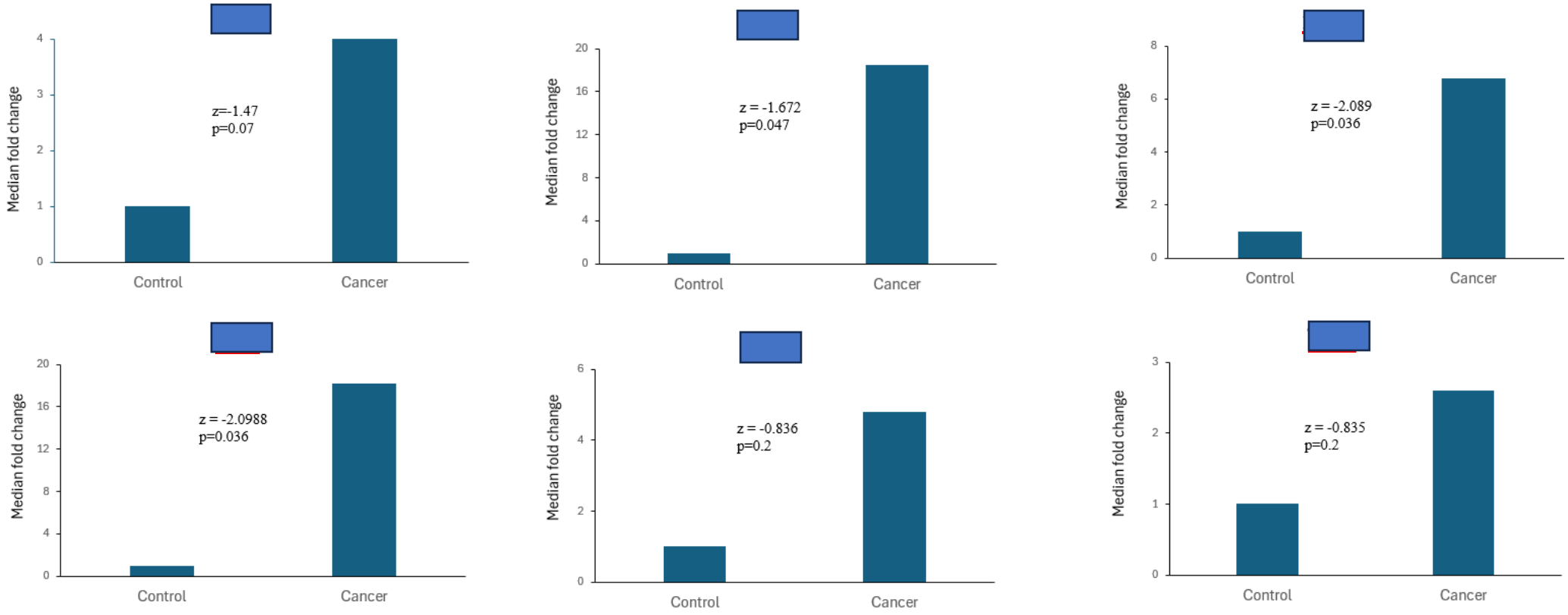
EV Biomarker Potential

- Noninvasive
- Repeatable
- Dynamic
- Wide application for all cancer types (tumor agnostic)
- Wide application for all classes of ICIs
- Molecular window into tumor immune microenvironment

Detection of T cell EV markers in head and neck cancer patients

In a small pilot study, markers of exhausted versus effector T cells were assessed in peripheral blood samples from 5 patients with head and neck cancer versus 5 matched control subjects

Peripheral blood T cell EV mRNA cargo analysis : RT-qPCR



Mann Whitney U test

Similar preliminary analysis was performed in 3 patients with recurrent respiratory papillomatosis receiving pembrolizumab (anti-PD1 antibody) therapy and EV biomarkers correlated with ICI response

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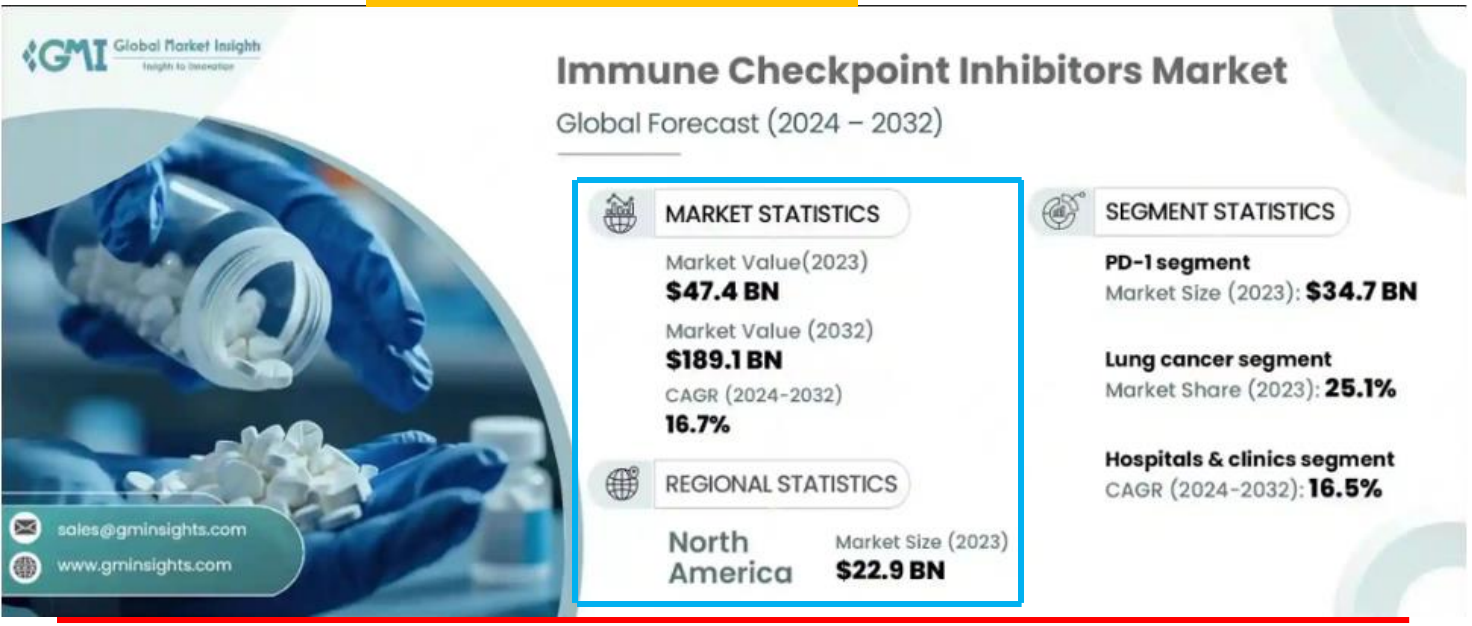
Market Opportunity: Global Market Insights, Grand View Research

Global Market Insights



Growth Drivers:	• Rising cancer incidence across the world • Ongoing research and development in immunotherapy • Favourable regulatory environment • Increasing investments and partnerships
Pitfalls & Challenges:	• High cost of treatment • Adverse side effects

Immune Checkpoint Inhibitors Market - By Type (PD-1, PD-L1, CTLA-4), Application Report ID: GMI10860

Grand View Research

Immune Checkpoint Inhibitors Market Report Scope

Report Attribute	Details
Market size value in 2024	USD 57.43 billion
Revenue forecast in 2030	USD 154.25 billion
Growth rate	CAGR of 17.9% from 2024 to 2030
Base year for estimation	2023
Regional scope	North America; Europe; Asia Pacific; Latin America; Middle East and Africa
Country scope	U.S.; Canada; UK; Germany; France; Italy; Spain; Denmark; Sweden; Norway; Japan; China; India; South Korea; Australia; Thailand; Brazil; Mexico; Argentina; South Africa; Saudi Arabia; UAE; Kuwait
Key companies profiled	Sanofi; F. Hoffmann-La Roche Ltd.; Merck & Co.; Bristol-Myers Squibb Company; Eli Lilly and Company; Regeneron Pharmaceuticals Inc.; AstraZeneca PLC; Shanghai Jhunsi Biosciences Ltd; Immutep Ltd; BeiGene Ltd/ GlaxoSmithKline PLC

Immune Checkpoint Inhibitors Market Size, Share & Trends Analysis Report By Type (PD-1, PD-L1, CTLA-4), By Application (Lung Cancer, Breast Cancer, Melanoma), By Distribution Channel, By Region, And Segment Forecasts, 2024 - 2030

Report ID: GVR-4-68040-257-4 | Number of Report Pages: 150 |

Competitive Landscape for ICI therapy biomarkers

FDA approved biomarkers in ICI diagnostics space

	Approach	Nature	Application – cancer types	Notable differences
PD-L1 expression	Immunohistochemistry of tumor biopsy	Invasive Static – one time biopsy of tumor	Multiple tumor types	Predicts ICI response chance. One time only. Not repeatable. No information of tumor immune microenvironment.
Tumor mutational burden	Exome sequencing of tumor tissue to assess for mutational changes	Invasive Static- one time biopsy of tumor	Melanoma, Bladder cancer, Non small cell lung cancer	Predicts ICI response chance. One time only. Not repeatable. No information of tumor immune microenvironment.
Tumor microsatellite instability	Sequencing of tumor tissue	Invasive Static – one time biopsy of tumor	<4% of cancers	Predicts ICI response chance. One time only. Not repeatable. No information of tumor immune microenvironment.
Proposed Immune cell EV biomarker	Peripheral blood	Non-invasive Dynamic – easily repeatable	Potentially for all cancer types with indication for ICI therapies	Unlike FDA-approved biomarkers, this looks at the immune cell biology of the tumor microenvironment. It is a composite read-out of immune cell specific markers implicated in T cell-mediated attack of cancer cells