Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

WEST CANCER CENTER & RESEARCH INSTITUTE

# What's Next for Cancer Immunotherapy?

Daniel A. Vaena, MD

*West Cancer Center & Research Institute*

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

sitc Society for Immunotherapy of Cancer



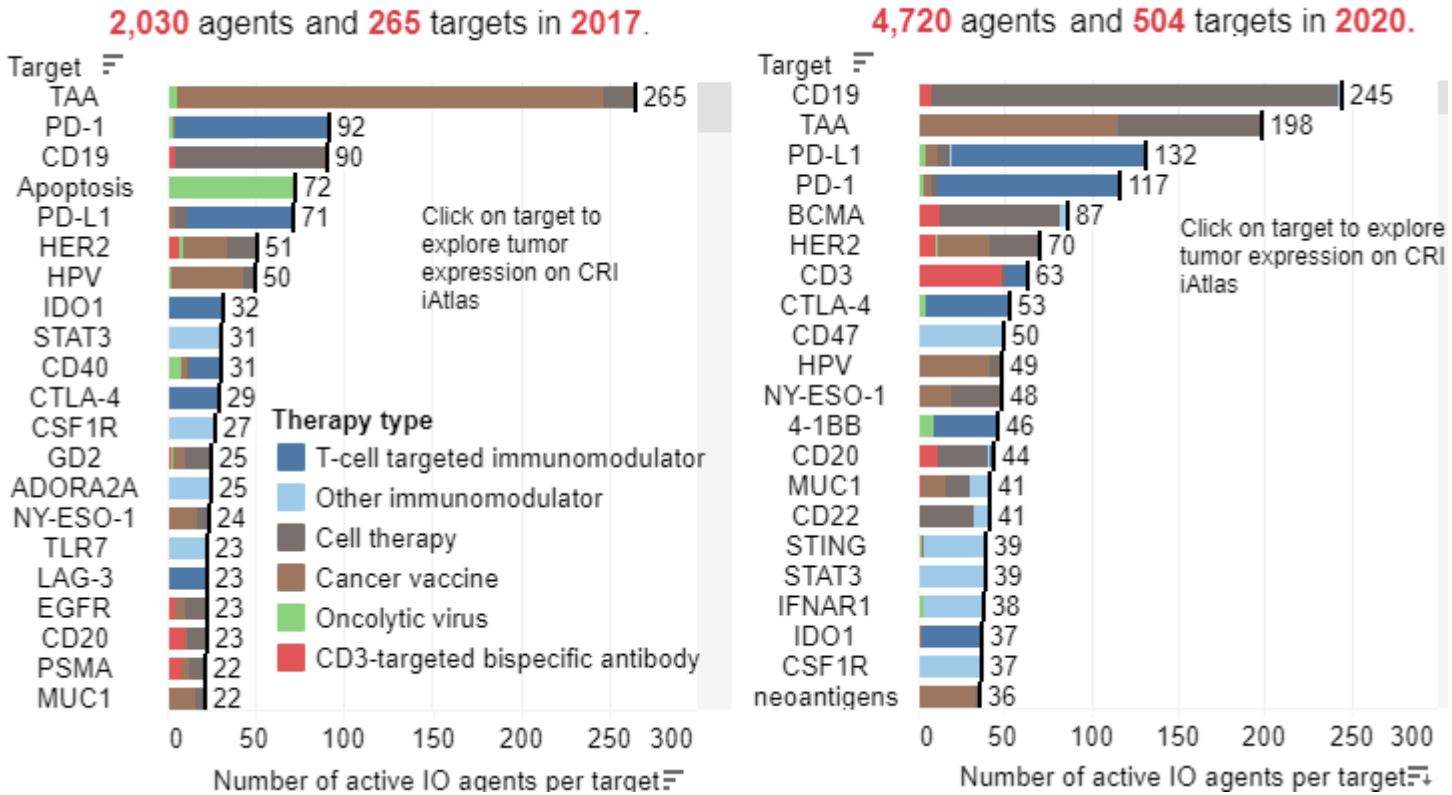
#LearnACI

# Disclosures: Vaena

- Consulting Fees: HMP Global, Bayer, Bristol Myers Squibb, Seattle Genetics, Exelixis, EMD Serono, Immunomedics, Eisai
- I will be discussing non-FDA approved indications during my presentation

# Acknowledgments and Disclosures of Slide Creator

- Some slides courtesy of Terence Rhodes, MD, PhD of Intermountain Healthcare
- Consulting Fees: AstraZeneca, BMS
- Fees for Non-CE Services Received Directly from an Ineligible Entity or their Agents : BMS




https://www.cancerresearch.org/scientists/immuno-oncology-landscape

Slide courtesy of Dr. Rhodes

# Current immunotherapy challenges

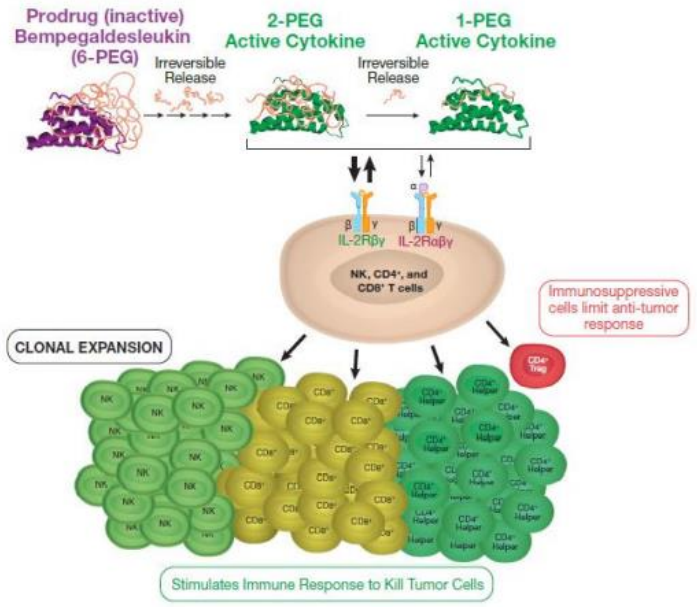
- Average single agent responses across tumor types range 10-50%
- Minority of patients are long term responders; varies with tumor type as well
- Minority of patients have severe toxicity; early recognition is key; but how much workup?
- Lack of reliable biomarkers for most tumor type indications
- Depending on tumor types, biomarker associations (“molecular tumor boards”) often take into account MSI status, PD-L1, TMB and other molecular profile results; reliability level of predicting outcomes is often low
- Most novel agents in development are initially tested in PD-1 relapsed refractory patients and for cancers which are progressing slowly; long development timeline for combinations
- Unclear which tumor types truly exhibit pseudo-progression phenomenon

# Mechanistic approaches to cancer immunotherapy

- Checkpoint inhibition and checkpoint combinations
- Immunomodulators
  - Immunometabolism; immune agonists; IL2 agonists; etc
- Adoptive T cell transfer (CAR-T)
- Combinations with non-immunotherapy agents
  - PARP inhibitors; XRT; chemotherapy; TKIs
- Therapeutic vaccines
- Antibodies and antibody drug conjugates
- Oncolytic viruses

# IL-2 analog example: bempegaldesleukin

## Background: Bempegaldesleukin Preferential Signaling Through the IL-2 Receptor Pathway




- Bempegaldesleukin (BEMPEG; NKTR-214): is a CD122-preferential IL-2 pathway agonist shown to increase tumor-infiltrating lymphocytes, T cell clonality and PD-1 expression[1,2]
- BEMPEG plus checkpoint inhibitor (CPI) nivolumab (NIVO) has been shown to convert baseline tumors from PD-L1(-) to PD-L1(+)[3-6]
- Low levels of baseline tumor-infiltrating lymphocytes (TILs)[7-9] and T cell–inflammation[10] is predictive of a poor response to CPIs

1. Charych D, et al. *PLoS One*. 2017; 12: e0179431; 2. Bentebibel SE, et al. *Cancer Discov*. 2019;9:711-721; 3. Diab A, et al. SITC 2018. Abstract O4; 4. Siefker-Radtke, et al. ASCO GU 2019. Abstract 388; 5. Hurwitz M, et al. ASCO 2019. Abstract 2623; 6. Tolaney S, et al. CICON 2019. Poster A001; 7. Daud AI, et al. *J Clin Oncol*. 2016;34:4102-09; 8. Daud AI, et al. *J Clin Invest*. 2016;126:3447-52; 9. Tumeh PC, et al. *Nature*. 2014;515:568-71; 10. Ayers M, et al. *J Clin Invest*. 2017;127:2930-2940.

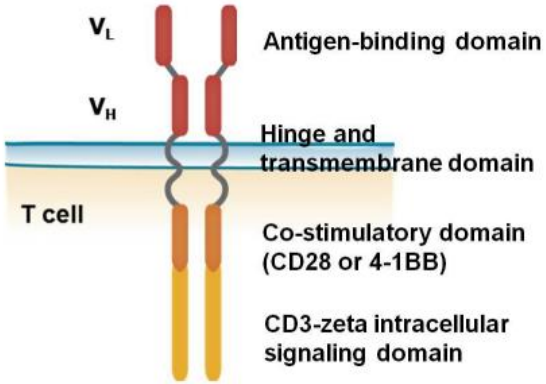
# CAR-T in solid tumors

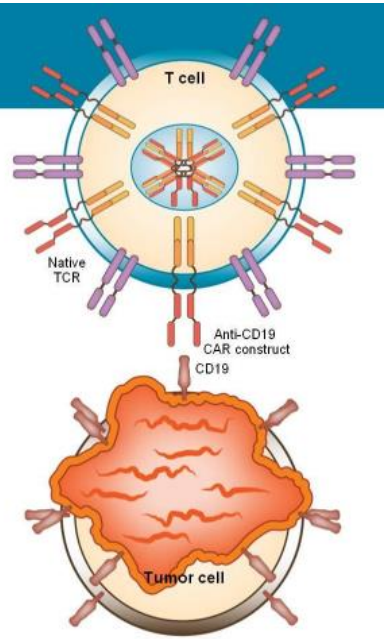
## Genetically modified autologous T-cells

Direct autologous T-cells against cancer antigen

No risk of GVHD or need for immune suppression

Living drug, single infusion



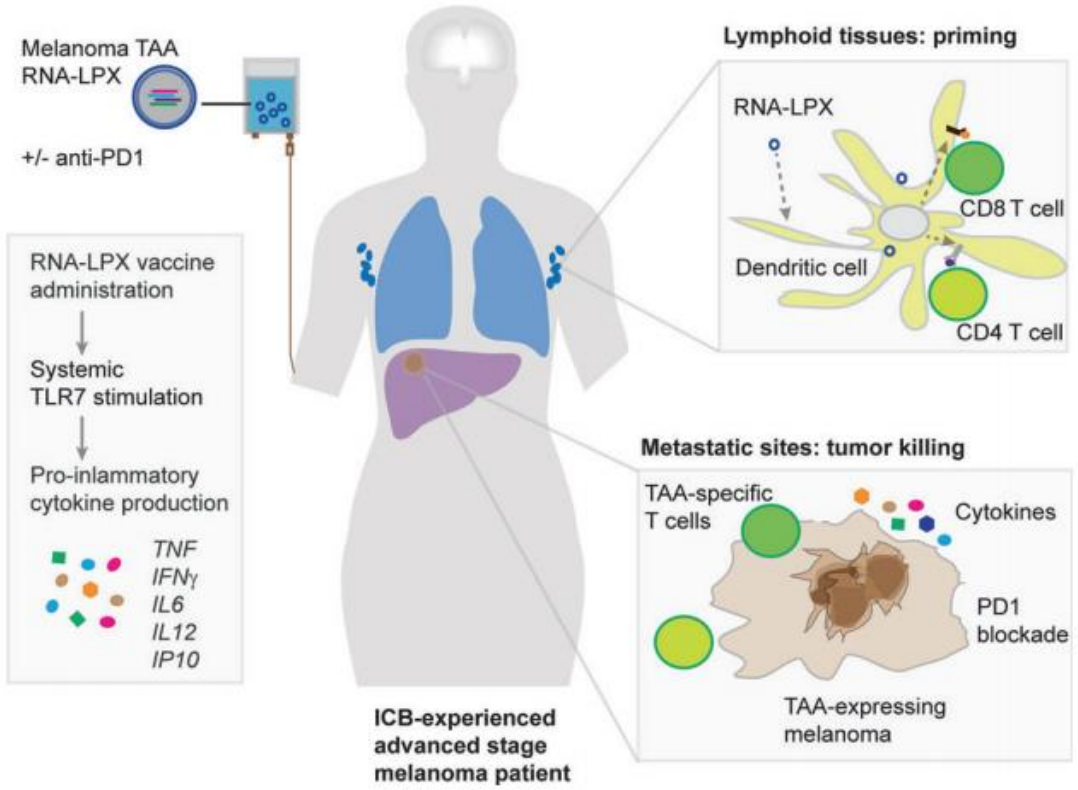




## Potential mechanisms of resistance to anti-CD19 CAR T-cells

- Antigen escape
- Poor proliferation or persistence of CAR T-cells
- Poor T-cell function/exhaustion
- Immune escape, microenvironment

Presented By Jeremy Abramson at 2019 ASCO Annual Meeting

# Therapeutic Cancer Vaccines




**Same technology used in two COVID-19 vaccines**

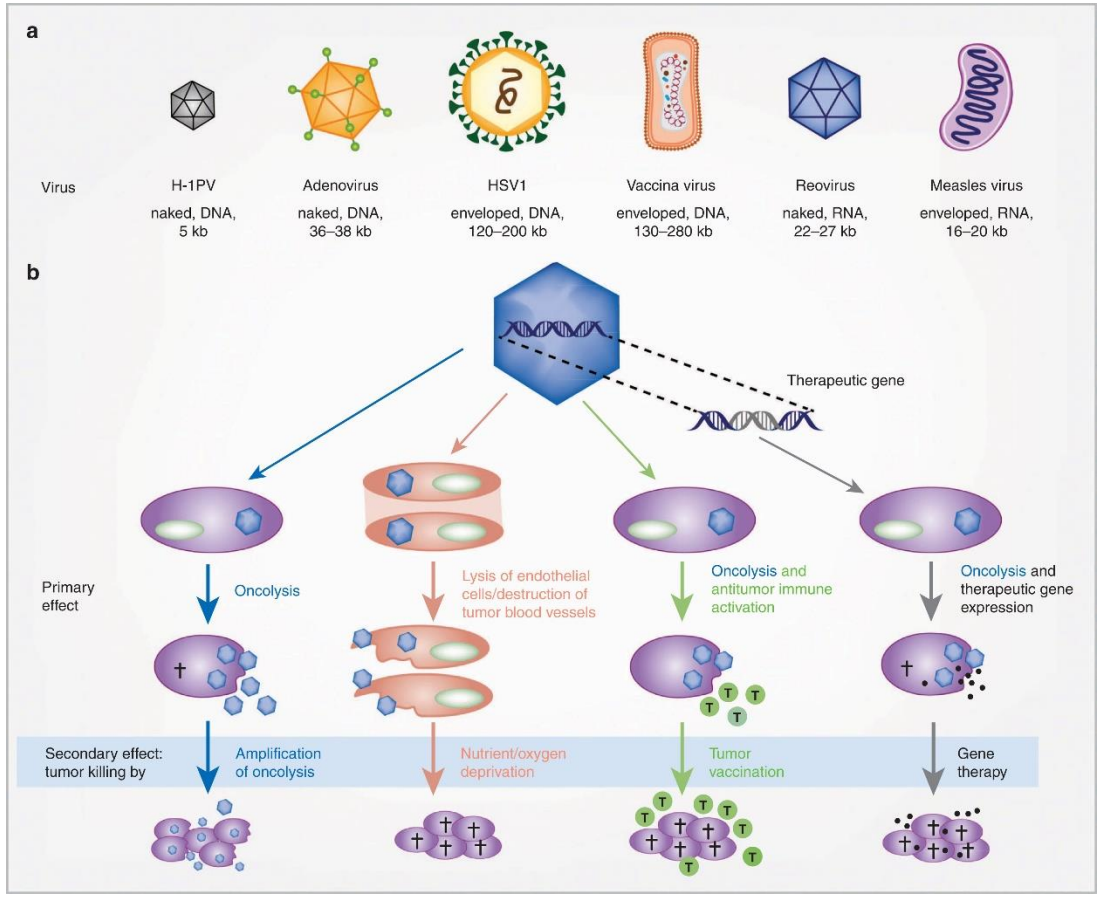
Cancer vaccines: shared tumor antigens return to the spotlight

Lijin Li[1], S. Peter Goedegebuure[1,2] and William Gillanders[1,2]

*Signal Transduction and Targeted Therapy* (2020)5:251 ; https://doi.org/10.1038/s41392-020-00364-8

Slide courtesy of Dr. Rhodes

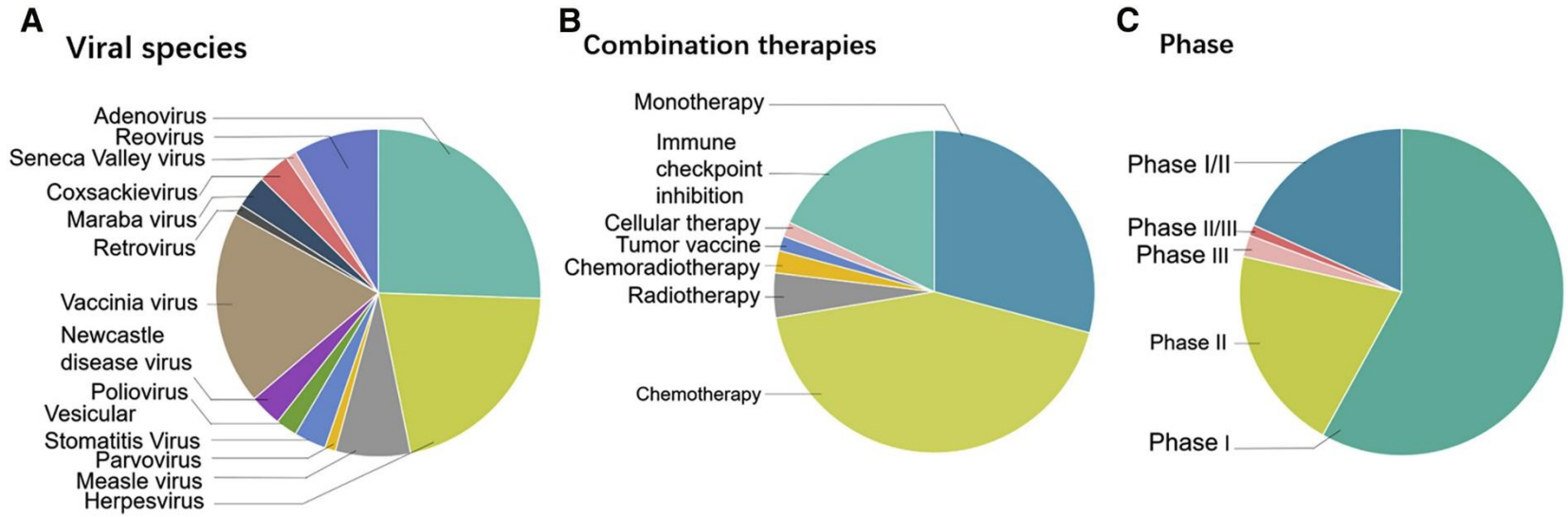
# Oncolytic viruses




*Molecular Therapy - Methods & Clinical Development* 2016 3DOI: (10.1038/mtm.2016.18)

Slide courtesy of Dr. Rhodes

# Oncolytic viruses




*Molecular Therapy - Oncolytics* 2019 15234-247DOI: (10.1016/j.omto.2019.10.007)

Slide courtesy of Dr. Rhodes

# Oncolytic viruses: the challenge of determining responses

- Responses in injected site?
- Abscopal responses?
- What are the lesions being measured in the study? How is RECIST criteria to be used?

# Combination x plus immunotherapy

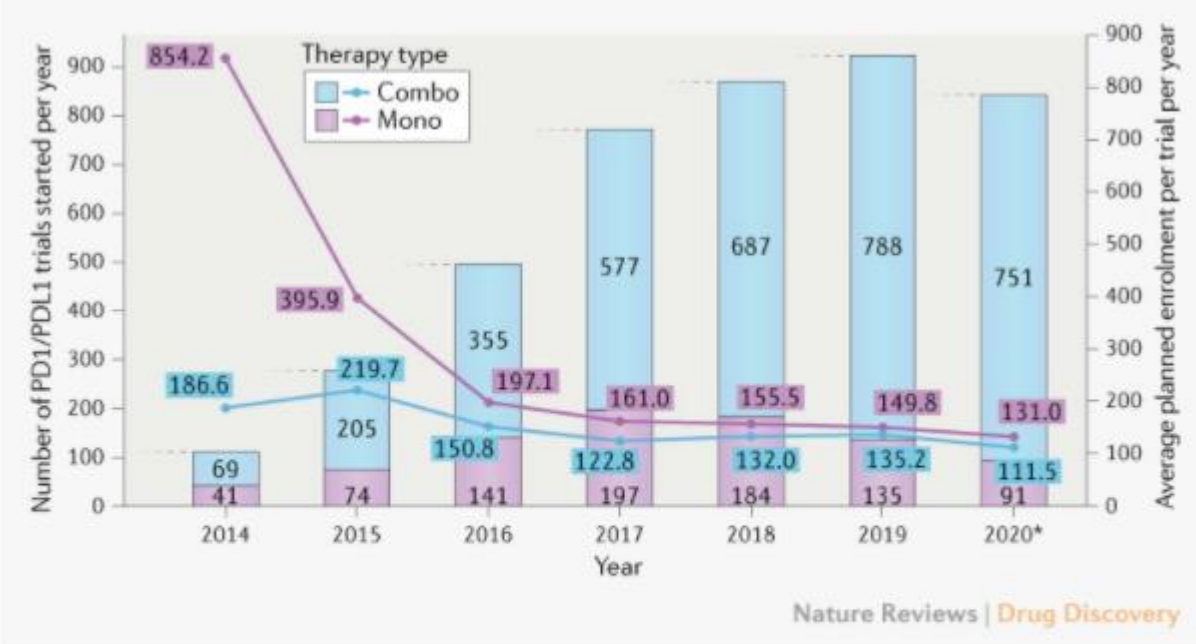



**Fig. 2 | Comparison of monotherapy and combination trials.** Most new trials since 2014 have been combination trials (bar graphs). The average planned patient enrolment (line graph) has decreased since 2014 for monotherapy trials more than for combination trials. *Only data from the first three quarters of 2020 were used to generate the analysis.

Upadhaya et al. Nature Reviews Drug Discovery. November 2020.

**Continuous FDA approvals of combination therapies.**

Slide courtesy of Dr. Rhodes

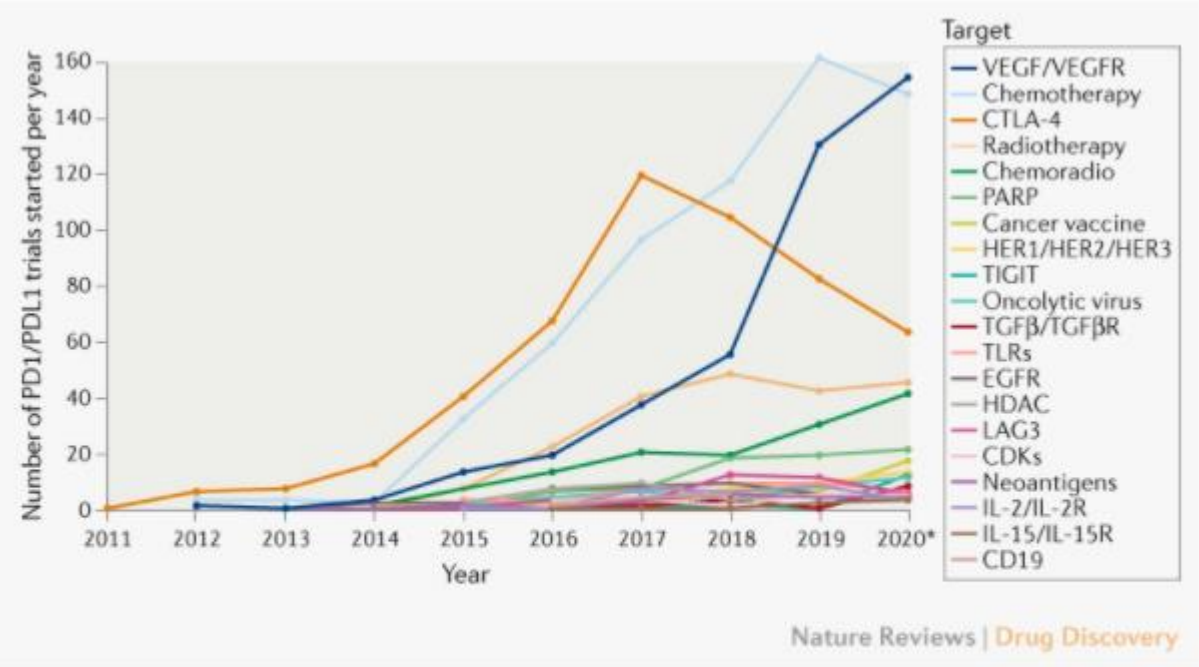



**Fig. 3 | Main targets assessed in combination with anti-PD1/PDL1 mAbs.** The graph shows the number of combination trials starting each year since 2011. The main 20 targets assessed in combination are shown in descending order according to the number of trials started in 2020. *Only data from the first three quarters of 2020 were used to generate the analysis.

Upadhaya et al. Nature Reviews Drug Discovery. November 2020.

**Continuous FDA approvals of combination therapies.**

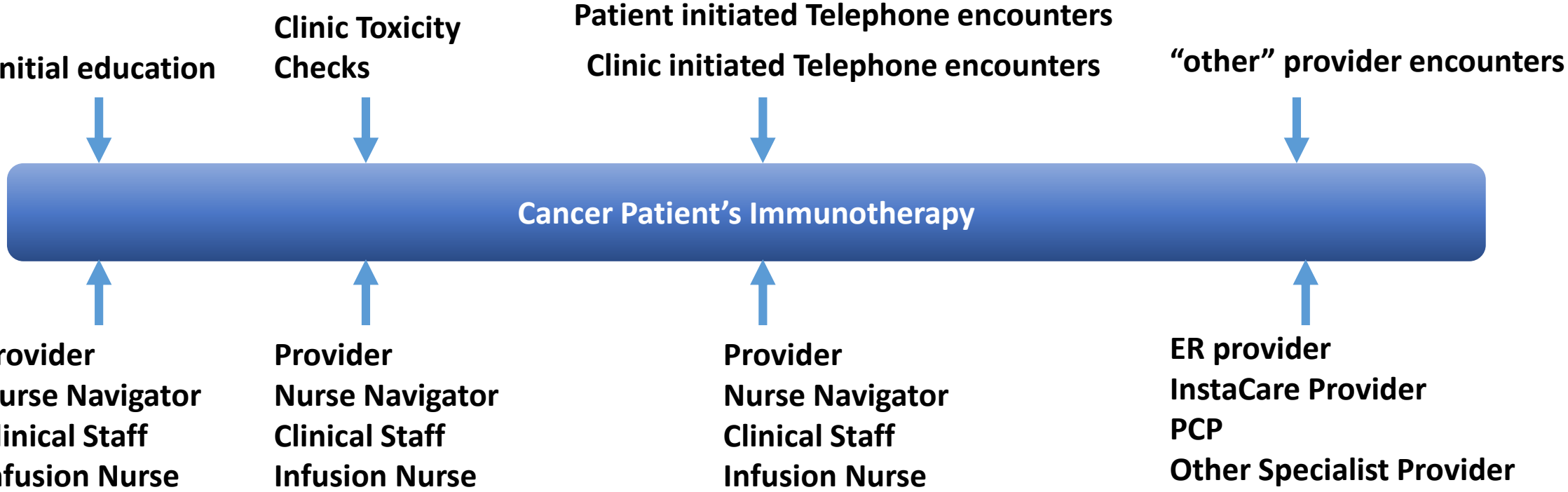
Slide courtesy of Dr. Rhodes

# Combination immunotherapy drug development: timeline considerations

- Novel immunotherapy agents typically tested initially in single agent dose escalation phase 1 trials
- However, mechanism of action is often expected/hoped to be synergistic with current anti PD1/L1 therapy, therefore responses with novel single agent immunotherapy are generally rare; PFS often used as “signal” for activity
- Subsequent combination dose escalation cohorts typically follow
- Initial development in phase 1 trials might take 2-3 years, followed by subsequent ph 2/3
- Most patients are relapsed or refractory to prior checkpoint inhibitors, but what does this really mean?

# Enhanced Clinical Response to toxicity

**Multiple touch points**




Slide courtesy of Dr. Rhodes

# Biomarkers

- Evolving biomarkers for response: getting beyond anti PD1 IHC, MSI, TMB
  - Rest of the comprehensive molecular profile: other mutations predictive of outcome? (examples: STK11 in NSCLC; PBRM1 in RCC; POLE; DNA repair alterations; etc)
  - For particular combinations with different MOAs (example: IO + VEGF in RCC: immunotherapy vs angiogenesis signatures)
- Biomarkers for toxicity prediction: cytokine panels?
- Which pre-existing conditions should be exclusionary for cancer immunotherapy?

# SITC 2018 Immuno-Oncology Biomarkers Meeting

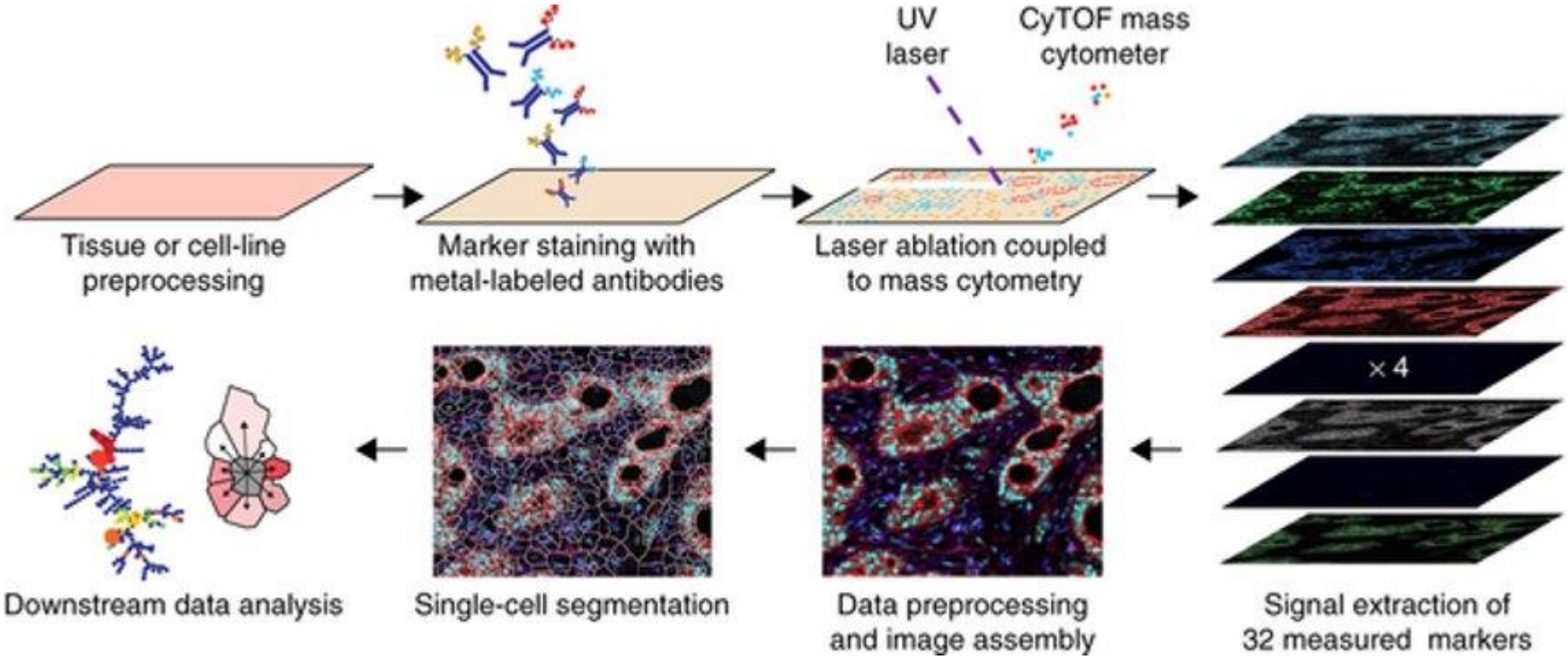
## Developing Markers for Immunotherapy

| Category | Assay | Specimen |
|---|---|---|
| Immune cells characterization | Immunohistochemistry*/** (image analysis) | Tissue |
| | Immunofluorescence (multiplex; image analysis)** | Tissue |
| | Flow cytometry** (panels) | Tissue and blood |
| | MIBI and CyTOF (panels) | Tissue and blood |
| Functional assessments | Flow cytometry detection of T cell activation** | Tissue and blood |
| | ELISPOT | Blood |
| | Neo-antigen prediction (from WES and RNA-seq) | Tissue |
| | TCR** and BCR** sequencing | Tissue and blood |
| Host factors | Cytokine analyses (MSD**, Luminex**, ELISA**) | Blood |
| | Microbiome (16S deep sequencing) | Stool (others) |
| Tumor and malignant cells genomics | Next generation sequencing (WES, RNA-seq, targeted*/**) | Tissue |
| | Low-input gene expression signatures (Nanostring**, HTG-Edge Seq**, Affymetrix arrays) | Tissue (FFPE) |
| | Liquid biopsy (cfDNA*/**, exosomes, CTC) | Blood |

*Assays/platforms available at CLIA-certified laboratories*
*** Analytical validation (non-CLIA).*

# Biomarkers to evaluate response

- Multiplex imaging




Slide courtesy of Dr. Rhodes

C. Giesen, et al., Nat Meth. 11:417-422

# Take home points

- Major advances last several years, however only a fraction of cancer patients benefit
- Major opportunities to improve outcomes with immunotherapy remain
- Due to the huge complexity (“targets”) and dynamic aspects of the immune system, drug development and biomarker development is a slow process and often incremental
- Exact MOA, exact tumor type (and subtype!), and therapeutic sequence matters; this will continue to challenge the regulatory system in terms of the best framework for future drug approval indications