Immunotherapy in Breast Cancer: Recent Updates

New Orleans, Nov 2020

Edith A. Perez, M.D.

Professor of Medicine

Hematology/Oncology and Cancer Biology

Director, Breast Cancer Translational Genomics Program

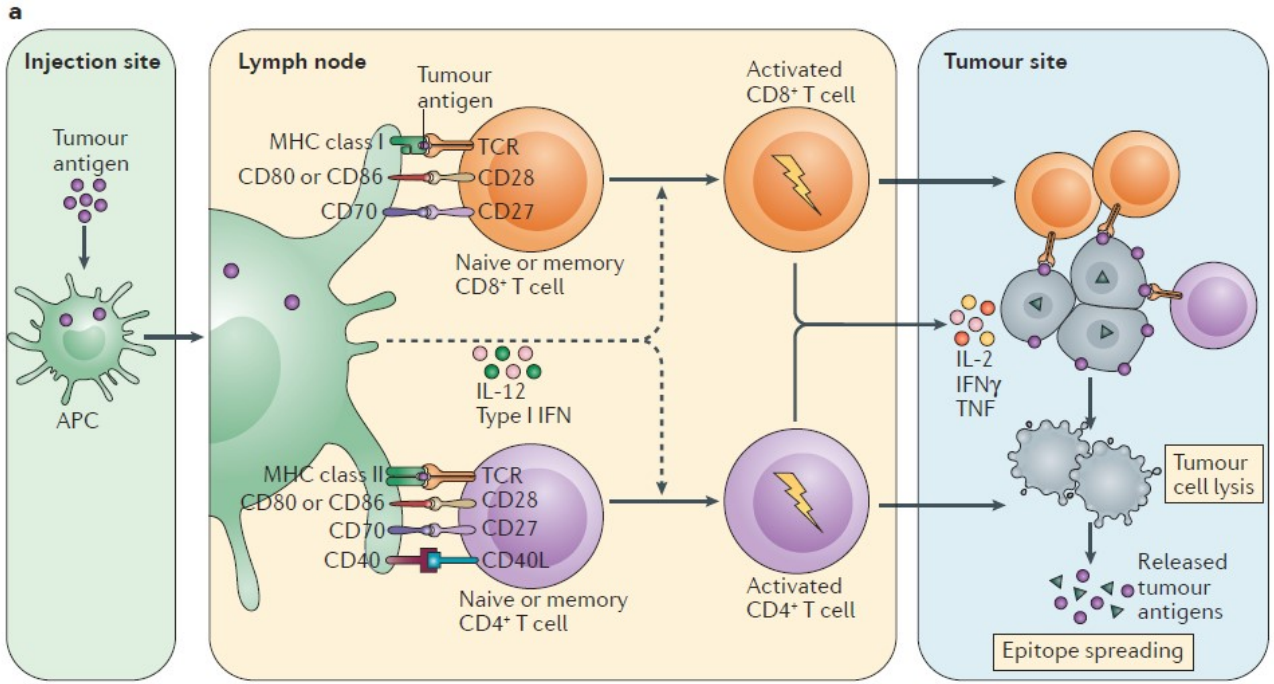
Mayo Clinic, Jacksonville, FL

Topics

- General concepts
- Highlights of recent data of immune therapies for TNBC
- Recent data of novel immune approaches for HER2+ BC
- Biomarkers, now and the future

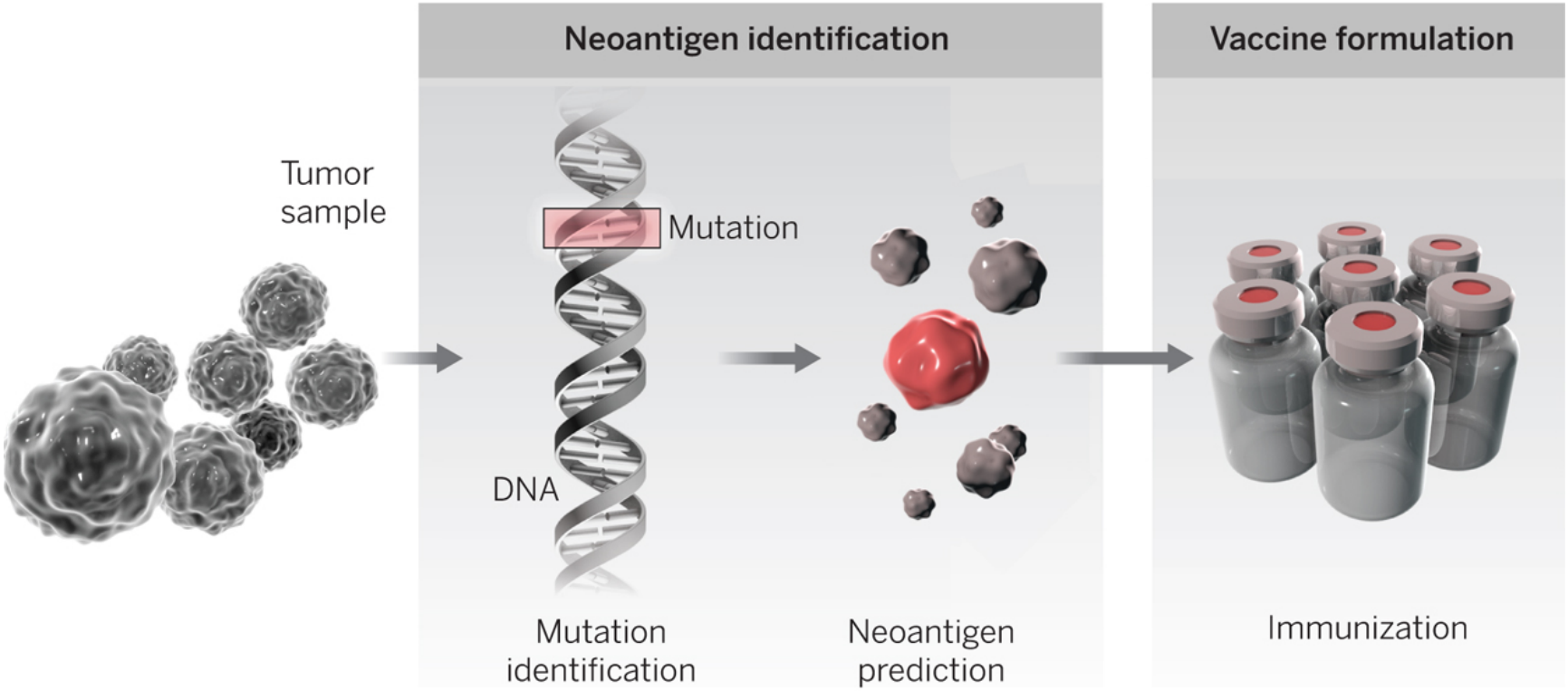
Rationale for Cancer Vaccines

- Providing a target antigen/antigens to dendritic cells
- Immunostimulatory molecules (adjuvants) activate dendritic cells and facilitate migration to a lymph node



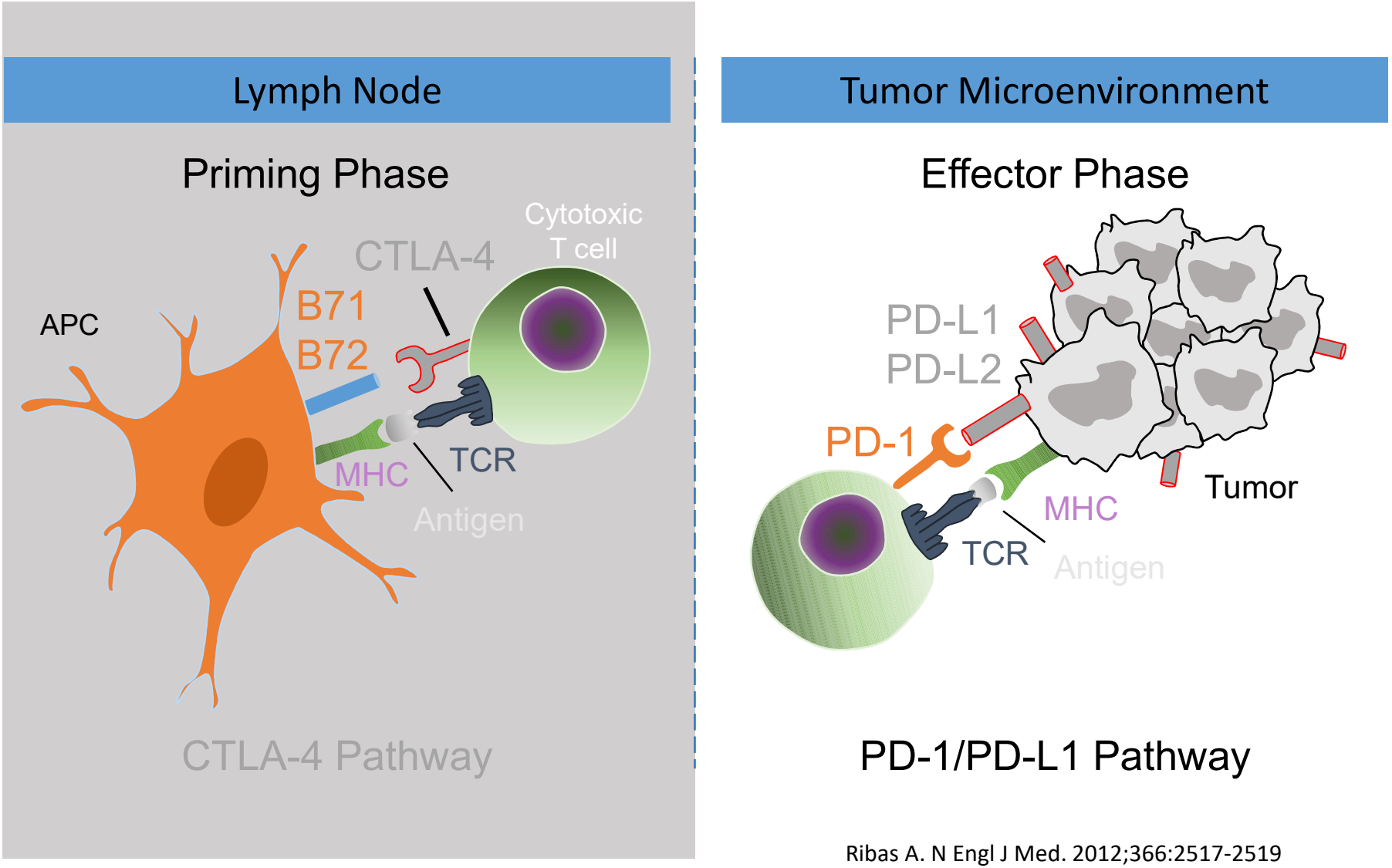
Hu et al. Nature Review Immunology 2018

Personalized cancer vaccines: high interest, but no clinical effectiveness data in breast cancer



1 vaccine – 1 person?
1 vaccine – many persons?

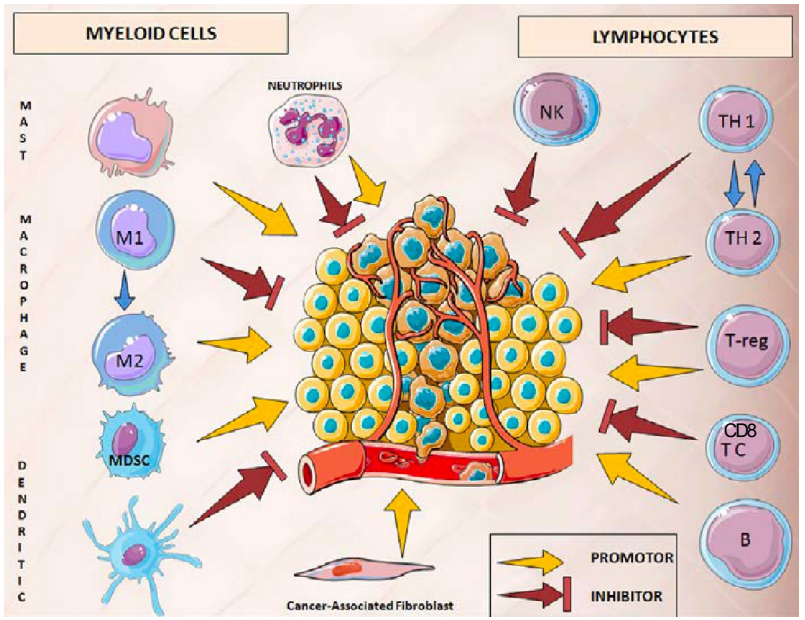
Two Actionable Immune Synapses – checkpoint inhibitors



Ribas A. N Engl J Med. 2012;366:2517-2519
Spranger S, et al. J Immunother Cancer. 2013;1:16

Tumor Microenvironment and Antigen Presenting Cells

- The presence of immunosuppressive factors in the tumor microenvironment limits the potential activity of immune therapies
  - PGE2 – suppresses M1 cytokine secretion and recruits myeloid-derived stem cells
  - IL10 – Inhibits MHCII expression and M1 cytokine secretion
  - TGFb – Inhibits T cell priming and infiltration
- Antigen presenting cells in the tumor microenvironment are often tumor-supportive rather than tumor-destructive



Goubran et al. *Cancer Growth & Metastasis* (2014)

- Co-treatment of tumor-targeting mAbs and APC immune stimulation (CD40 + TNF) required to eradicate tumors from mice (Carmi et al. *Nature* 2015)

- Reawakening/enhancing antigen presentation capability of suppressed APCs can unleash the full power of the immune system

Modified from Dornan D. 2nd Annual Advances in Immuno-Oncology USA Congress, Oct 2019

Pattern Recognition Receptors (PRRs) Play Key Roles in the Activation of the Innate Immune Response

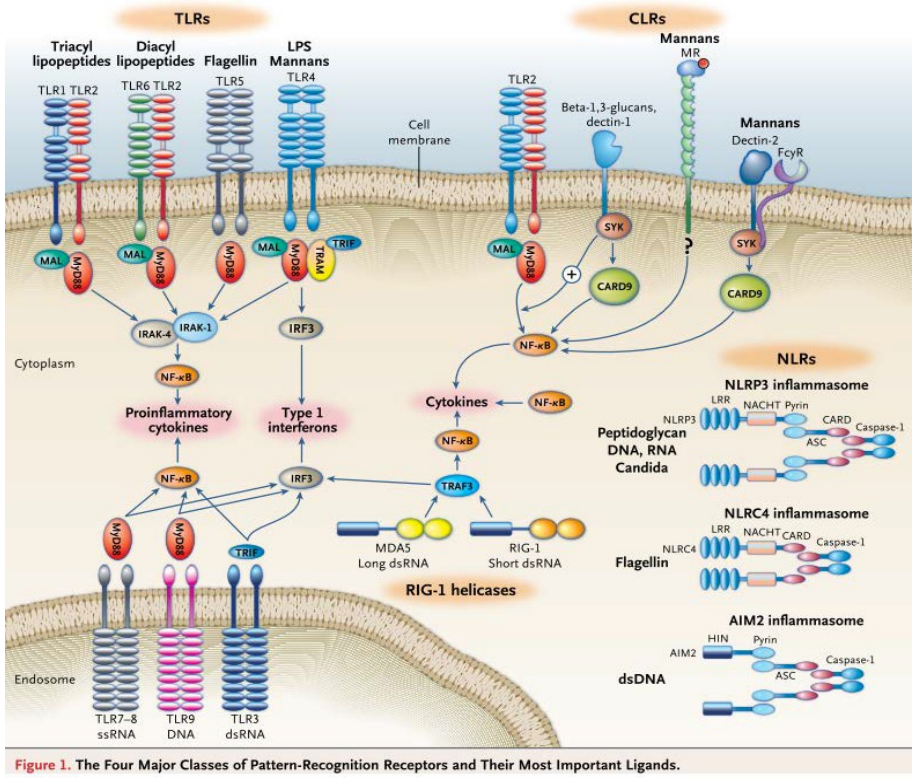


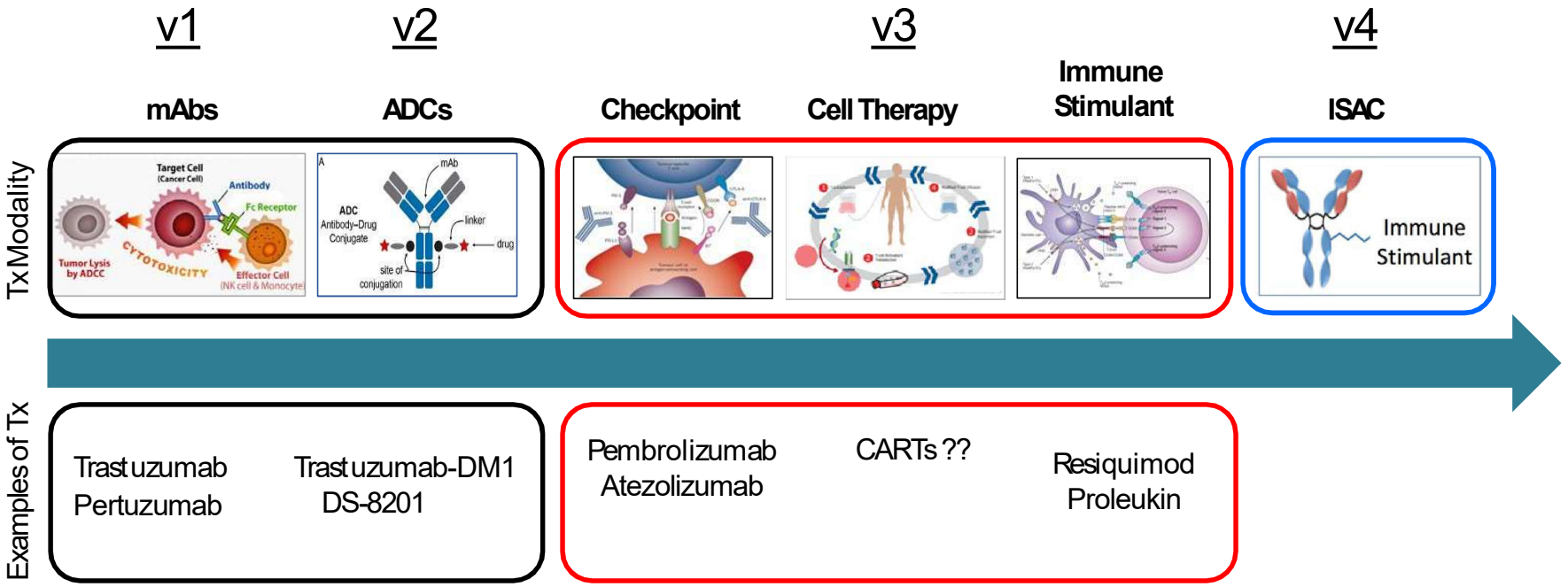
Figure 1. The Four Major Classes of Pattern-Recognition Receptors and Their Most Important Ligands.

Netea et al. *N Engl JMed* (2011)

- PRRs agonists are a validated targeting modality in cancer
- PRR agonists (e.g. TLR7/8/9, STING, and NLRP3) create an immune microenvironment poised for an anti-tumor immune response
  - Enhanced antigen presentation for T cell- mediated killing
  - Reducing function of immunosuppressive cells (Treg, M2, MDSC)
  - Activation of innate cell-mediate tumor killing (NK, M1)
- PRR agonists therapies have been largely restricted to intratumoral administration; until 2020

Immune-stimulation

Therapeutic Evolution From Tumor Targeting to Immune Targeting and Beyond in BC



Investigational Immune Stimulating Antibody Conjugates (ISACs) and STING ADCs

Key Features: Systemic Delivery, Local Effect

- Systemically delivered, tumor-targeting, innate immune-stimulating therapeutic
- Antibody against a tumor antigen directs ISCAs to the tumor microenvironment
- Proprietary TLR7/8 agonists conjugated to the antibody activates tumor-infiltrating myeloid cells
- STING agonists (as part of ADCs) also under investigation

- Addressing difficult-to-treat tumors resistant to current therapies
- Potential for improved clinical durability via immunological memory and epitope spreading to tumor neoantigens

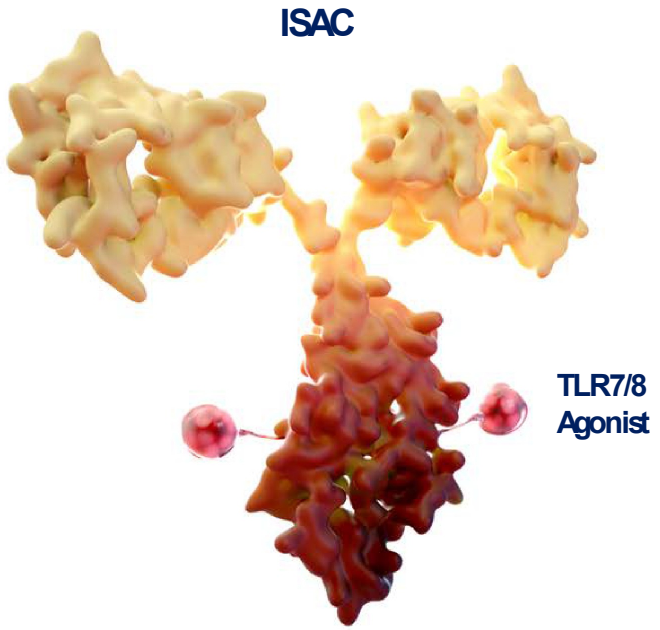
Ackerman, SE, et al. AACR 2019; Ackerman SE, et al. SITC 202;, LeBlanc H, et al. SITC 2020; Emmens L, et al. SITC 2020

Investigational Immune Stimulating Antibody Conjugate (ISAC)

Efficacy in Preclinical Models as Monotherapy

Complete, durable regression of established tumors in preclinical models demonstrating:

- Activity on resistant tumors
- Immunological memory
- Epitope spread
- Neoantigen recognition

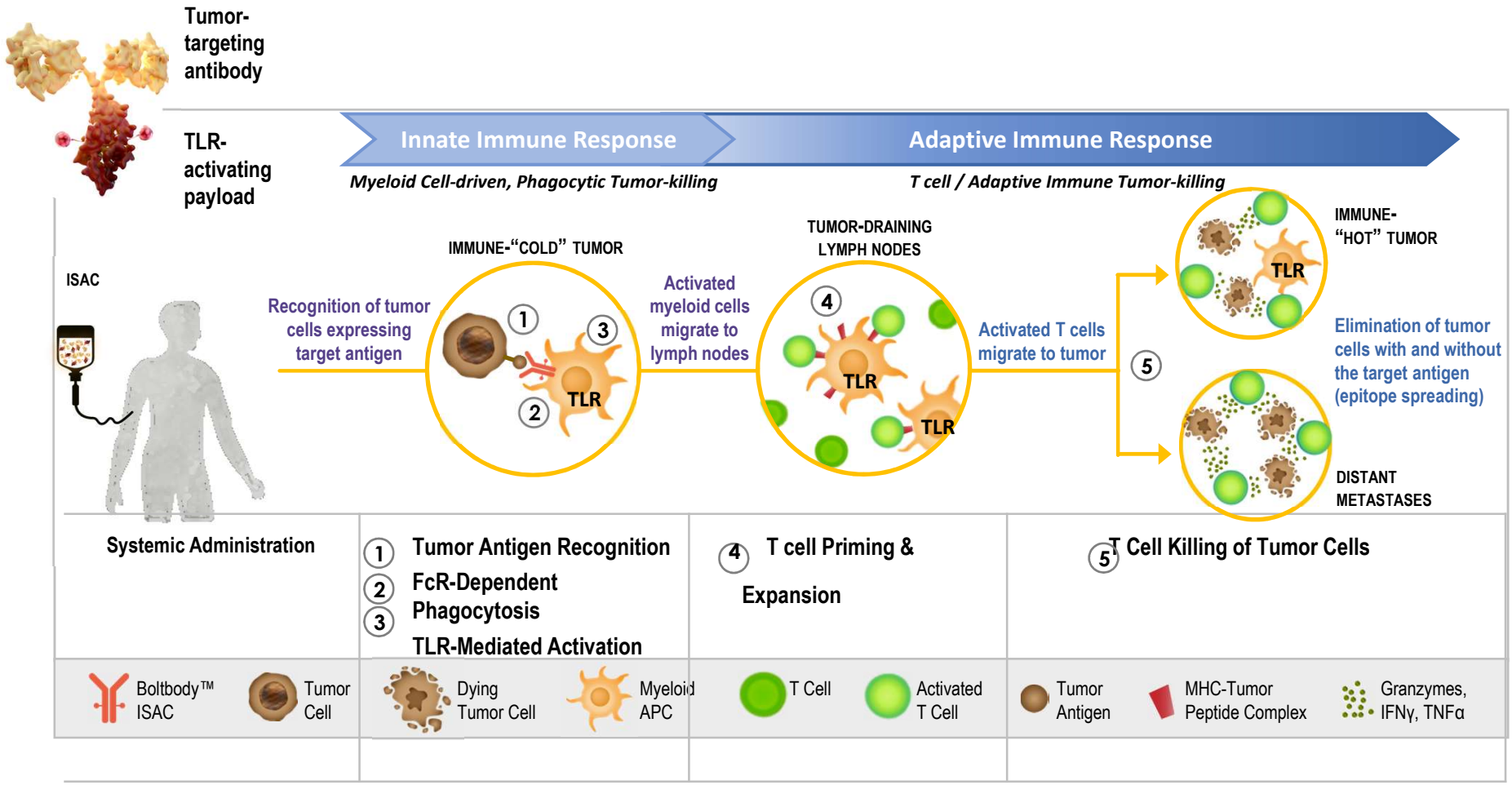


Status: November 2020

- Investigational off the shelf product
  - Designed to drive presentation of all available tumor neoantigens (vs. personalized vaccine)
- First in human clinical trials in 2020

Ackerman SE, et al. AACR 2019; SITC Nov 2020. Personal communication 2020; Le Blanc H, et al. SITC Nov 2020; Emens L, et al. SITC 2020; Sharma et al. SITC Nov 2020

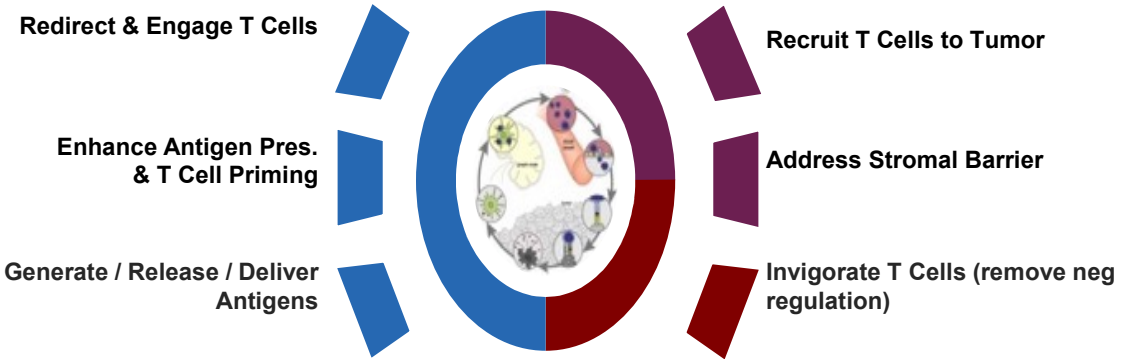
ISAC Mechanism of Action: Systemic Delivery Leads to Activation of Myeloid Cells and Subsequent Eradication of Tumor Cells



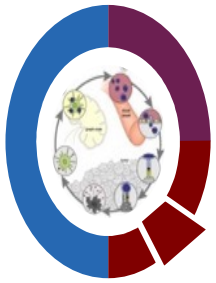
Ackerman SE, et al. AACR 2019; SITC Nov 2020. Personal communication 2020; Le Blanc H, et al. SITC Nov 2020; Sharma et al. SITC Nov 2020

Rational combinations: Building blocks to assemble Effective Immunity

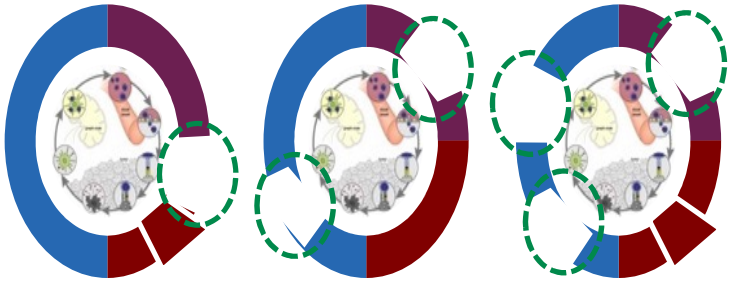
Each individual patient may require 1, 2, 3, 4, etc., of these molecules in combination (or sequentially) to restore cancer immunity



Some patients may only require targeting of negative regulator (aPD-L1 monotherapy), or a targeted activator of the innate and adaptive immunity to enable cancer immunity



Some patients will need two or more therapies to enable cancer immunity (to drive infiltration, boost MHC expression, activity, etc)



Topics

- General concepts
- Highlights of recent data of immune therapies for TNBC
- Recent data of novel immune approaches for HER2+ BC
- Biomarkers, now and the future

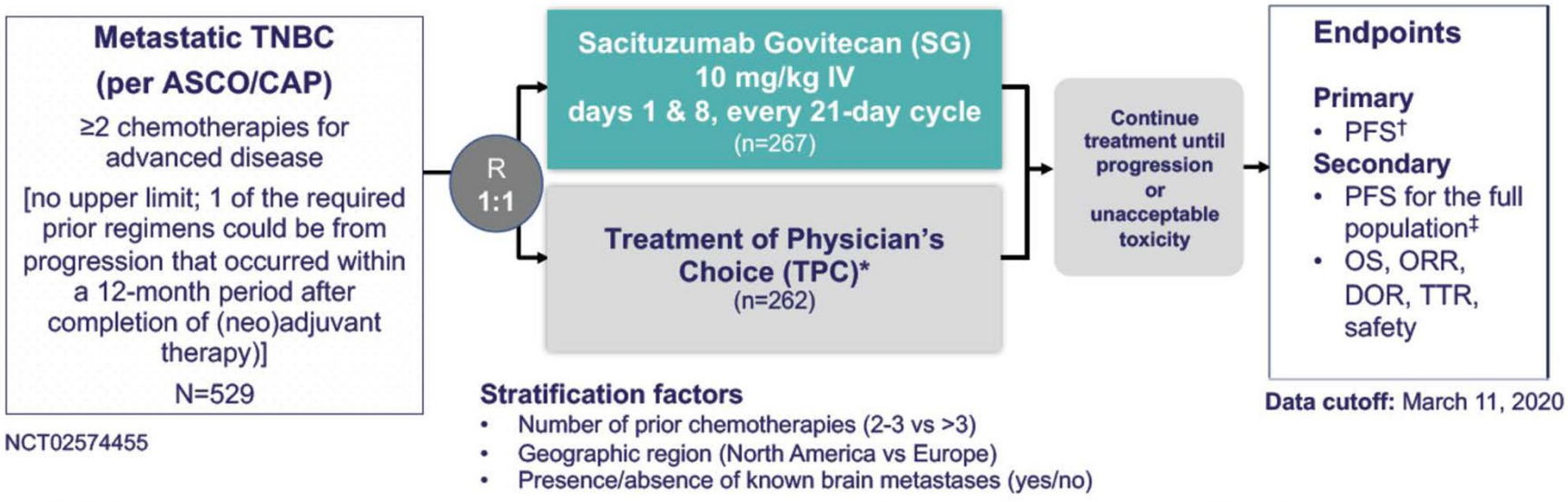
Novel immune approaches for TNBC

- Checkpoint inhibitors in combination with chemotherapy
  - Metastatic disease
  - Neoadjuvant/adjuvant therapy
- Drug antibody conjugates
  - Metastatic disease
    - Sacituzumab Govitecan (Trop2 + SN-38)
- Combinations of chemotherapy, vaccines, PARP inhibitors, and other targeted agents with checkpoint inhibitors

CPIs = checkpoint inhibitors

Bardia et al. JCO 2018; NEJM 2019; clinicaltrials.gov 2020

ASCENT: Randomized Phase III Sacituzumab vs. TPC chemotherapy

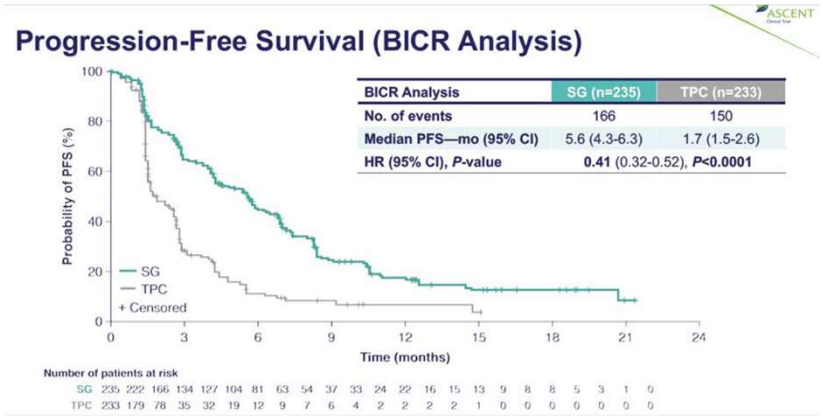


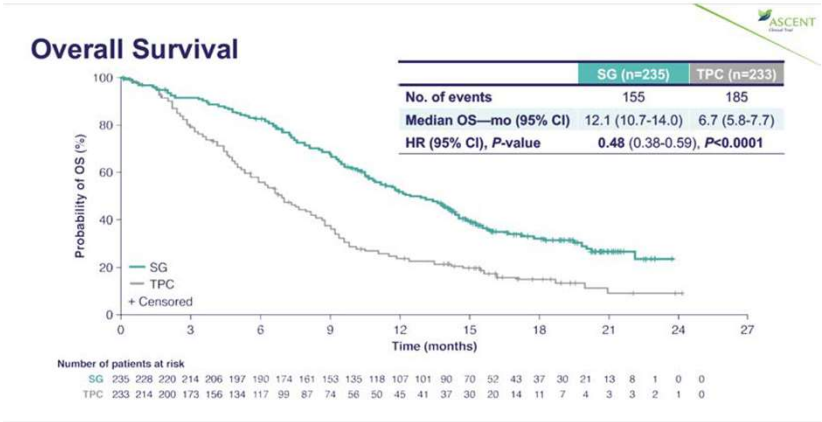
Bardia A, et al .ESMO2020 LBA17

Sacituzumab vs TPC chemo for mTNBC

Patient population and response data:

- gBRCAm - appox 7%, unknown 37%, neg 57%
- Approx 30% prior CPI
- Median # of prior regimens 4 (2-17)
- ORR: 35% vs 5%





mPFS 5.6 mo vs. 1.7 mo
HR 0.41; p<0.0001

mOS 12.1 mo vs. 6.7 mo
HR 0.48; p<0.0001

Bardia A, et al. ESMO 2020 LBA17

Sacituzumab is associated with higher toxicity than chosen TPC chemotherapy

Treatment related discontinuation rates: Sacituzumab 4.7%, TPC5.4%

ASCENT Clinical Trial

TRAEs (All Grade, >20%; Grade 3/4, >5% of Patients)

		SG (n=258)			TPC (n=224)		
	TRAE*	All grade %	Grade 3, %	Grade 4, %	All grade, %	Grade 3, %	Grade 4, %
Hematologic	**Neutropenia†**	**63**	**46**	**17**	**43**	**27**	**13**
	Anemia‡	**34**	**8**	**0**	**24**	**5**	**0**
	Leukopenia§	16	10	1	11	5	1
	Febrile neutropenia	6	5	1	2	2	<1
Gastrointestinal	**Diarrhea**	**59**	**10**	**0**	12	<1	0
	Nausea	**57**	**2**	**<1**	**26**	**<1**	**0**
	Vomiting	29	1	<1	10	<1	0
Other	**Fatigue**	**45**	**3**	**0**	**30**	**5**	**0**
	Alopecia	**46**	**0**	**0**	**16**	**0**	**0**

Bardia A, et al. ESMO2020, LBA17

Immunotherapy take-aways for mTNBC

- Recent data are consistent with the concept that inhibition of PD1/PD-L1 is important for a subset of patients with TNBC
  - Atezolizumab with nab-paclitaxel associated with improved PFS and non-statistically assessed ~7mo longer mOS in pts with tumors PDL1+ (>=1) tumors used in the 1st line setting – 2yr survival: 51%
    - BUT…..Atezolizumab with paclitaxel did not meet pre-specified study endpoint for PFS in PDL1+ mTNBC
  - Pembrolizumab prolongs PFS when added to taxane or gemcitabine/carboplatin in patients with PDL1+ tumors when used in the 1st line setting
    - PFS improved from 5.6mo to 9.6 mo in pts with tumors CPS>=10
    - FDA accelerated approval Nov 13, 2020
    - OS data are not yet mature from KEYNOTE-355

Immunotherapy take-aways for mTNBC: Questions

- What will be the FDA's decision (and other regulatory agencies) related to the accelerated approval of nab-paclitaxel + atezo as 1st-line now that the confirmatory study (with paclitaxel) did not show benefit?
- Will physicians move to using pembrolizumab with their choice of chemotherapy?
  - Or, await data of response and PFS based on chemo backbone?
- Can we select the best patient for CPI in the 1st line setting? Would a multiparametric biomarker further enrich those likely to benefit?
- Will physicians need to continue ordering various tests for PD-L1 to decide which agent to use?
  - Cost-effectiveness and time for pathologists and practitioners
- Which is the ideal partner for anti-PD1/PD-L1 therapy?
  - Chemotherapy? If so, which agent?
  - Other IO combinations?
  - Targeted therapy?
  - How to improve beyond CPIs and sacituzumab govitecan?

Checkpoint inhibition in early stage TNBC

- Promising evidence that pembrolizumab (Keynote-522) and atezolizumab (IMpassion031) increase pCR when added to neoadjuvant chemotherapy.
- Meaningful endpoint is EFS in early stage disease.
  - Pembrolizumab associated with 37% improvement in EFS (HR 0.67 (0.43-0.93); 91.3% v 85.3%)
  - Atezolizumab data are not yet mature
- FDA has accepted for standard review a new sBLA for pembrolizumab for treatment of patients with high-risk, early stage TNBC in combination with chemotherapy as neoadjuvant treatment and then as single agent adjuvant treatment. PDUFA date is March 29, 2021.
- Questions remain:
  - Which patients will benefit most? PDL1 "+" vs. all TNBC? Is PDL1 less predictive in eTNBC vs. mTNBC?
  - Optimal chemotherapy partner in (neo)adjuvant setting? Is platinum necessary?
  - Implication for adjuvant trials? And post-neo management?
  - Will there be a place for de-escalation?

Topics

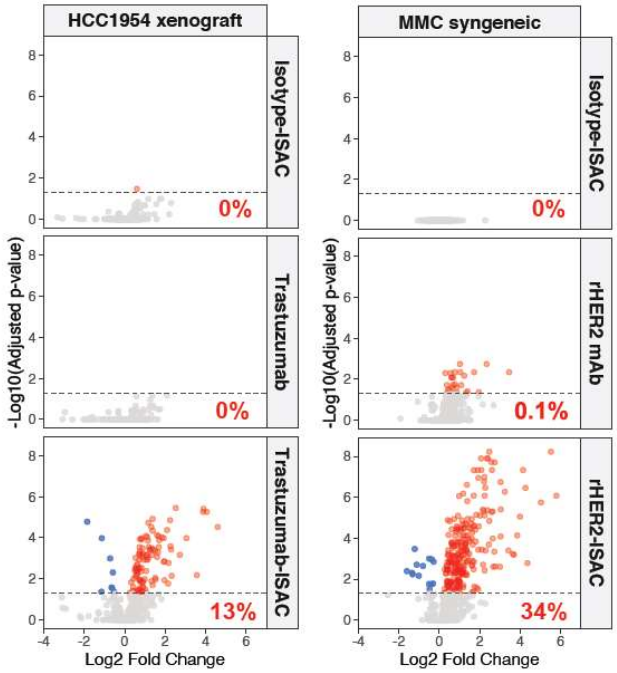
- General concepts
- Highlights of recent data of immune therapies for TNBC
- Recent data of novel immune approaches for HER2+ BC
- Biomarkers, now and the future

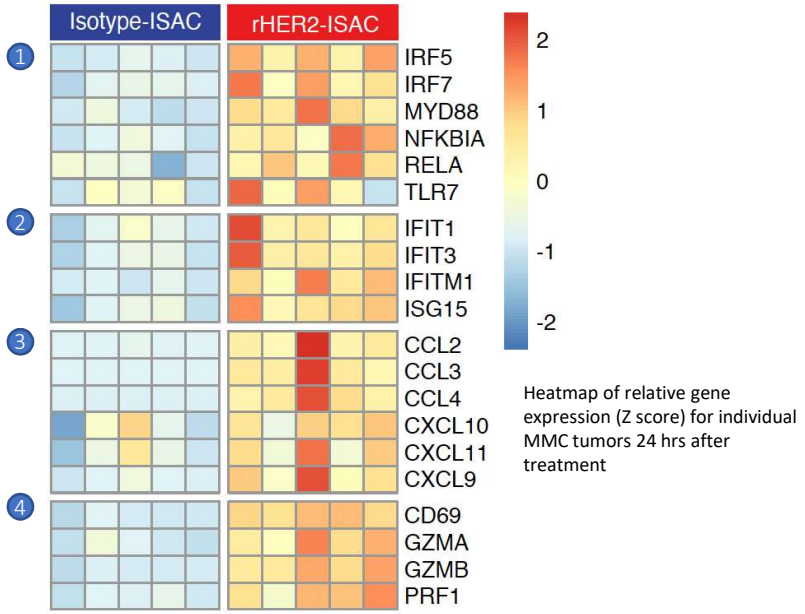
Immune therapies for HER2+ BC

- Monoclonal antibodies have had a major impact on advanced and early stage breast cancer management
  - Trastuzumab, pertuzumab
    - Mostly given with chemotherapy
- Drug antibody conjugates
- T-DM1, DS-8201
- Lots of research
  - Other DACs
  - Modulation of Fc receptor
  - ISACs with trastuzumab, trastuzumab biosimilar, or pertuzumab as antibody
    - TLR 7/8 agonism
    - Separate TLR 7, or TLR8, or TLR, or STING agonists also in clinical research

HER2-directed ISACs Induced Rapid, Robust Target-dependent Activation of the Immune System

% upregulated genes vs isotype mAb in tumors 24 hrs after treatment





Heatmap of relative gene expression (Z score) for individual MMC tumors 24 hrs after treatment

- HER2-targeted ISACs dramatically upregulated immune-related genes in both HCC1954 xenograft and MMC syngeneic tumors.
- In the absence of tumor targeting (Isotype-ISAC) or TLR agonism (HER2 mAbs) changes in gene expression were minimal.

Anti-HER2 ISAC treatment led to activation of pathways indicative of TLR7/8 agonism and FcγR engagement.

1. TLR7/8 transcription pathway
2. Type 1 interferon-inducible genes
3. Markers of myeloid cell activation
4. Markers of effector cells, including T cells

LeBlanc H, et al. SITC Nov 2020

Topics

- General concepts
- Highlights of recent data of immune therapies for TNBC
- Recent data of novel immune approaches for HER2+ BC
- Biomarkers, now and the future

Biomarkers of Response to Immunotherapy

- Biomarker team
  - Dendritic cell migration and activation
  - “cold” vs “hot” tumor
  - Immune cell infiltration
    - Digital spatial profiling (DSP)
  - PD-L1 expression (what test?)
  - Interferon and other gene expression signature profiles
  - High mutation burden/neoantigens
  - Gut microbiome
  - T cell clonality

Maleki Vareki. Crit Rev Oncol Hematol. 2017;116:116; Personal communication , EAPerez Nov 2020

Biomarker Testing for and Beyond Translational Phase I-II Studies of Novel CIT

- Biological rationale for test being performed
- Real-time patient management
- Analytic validity standards for molecular diagnostic testing
- Criteria for assessment
- Clinical utility testing
- Prognostic is not helpful if not predictive
- Does therapy change result in better outcome?

Patient Impact of Immune System Modulation with Checkpoint Inhibitors and Beyond

- Advanced setting
  - Can we increase the number of patients who benefit?
    - In those who benefit, how to prevent resistance?
- Early stage setting
  - Whether cancer recurrence will be prevented
  - Will it be better to start with neoadjuvant Rx?
  - Whether recurrent tumors will retain responsiveness to PD-1/PD-L1 or other blockade
  - Whether challenging molecular resistance pathways will emerge among recurrent tumors
- Prevention setting
  - Whether overall patient survival will be improved.
  - Placing immunotherapy on the front line of cancer treatment

Gajewski TF. NEJM 2018; Forde PM, et al.. NEJM 2018; Perez EA 2020

THANK YOU

Collaborators including colleagues, biopharma, foundations, patients

As part of our ongoing commitment to health, wellness and survivorship, The DONNA Foundation produces athletic events throughout the year including The National Marathon to Finish Breast Cancer, hosting nearly 10,000 athletes from all 50 States and many countries.

www.breastcancermarathon.com

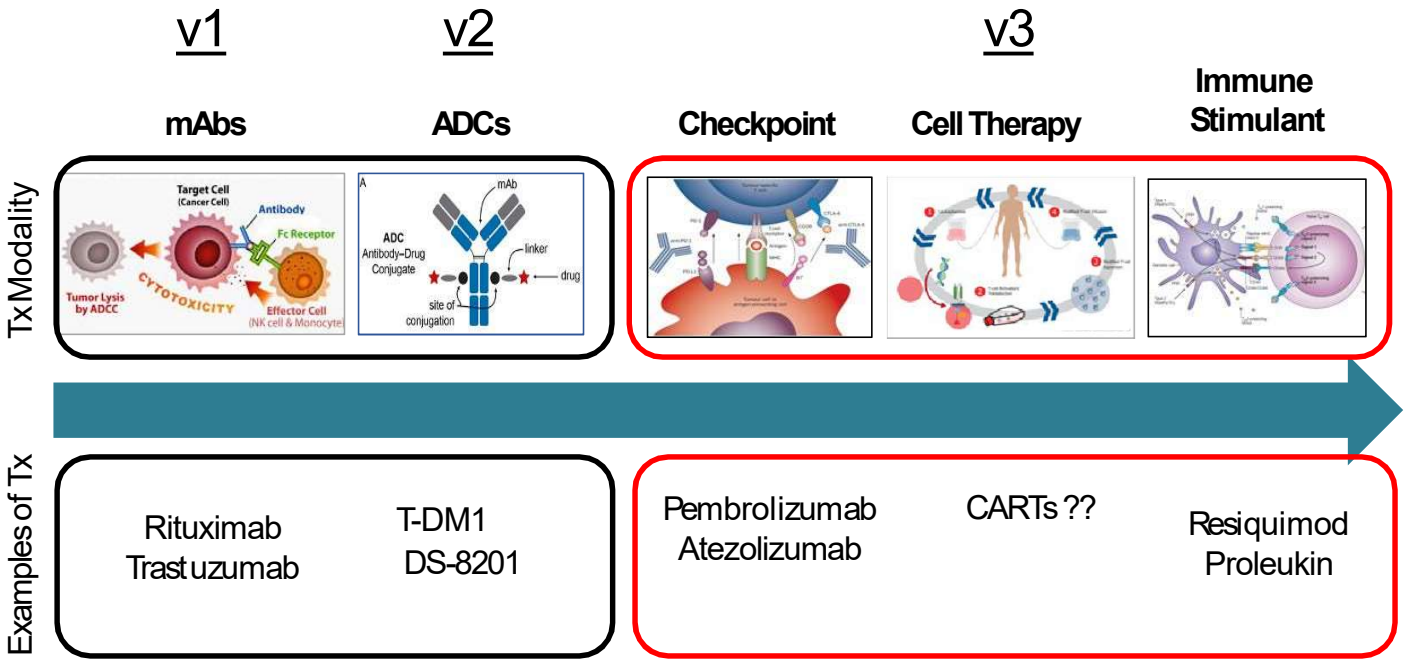
Extras

TNBC: Adjuvant Folate Receptor-α Vaccine in High-risk early stage TNBC

- FOLR1 mRNA higher in TNBC/Basal tumors
- Vaccine development: membrane-bound protein with high affinity for binding and transporting folate
  - Multi-epitope: 5 degenerate peptides from FRα (FR30, FR56, FR76, FR113 and FR238)
- Phase I (22 patients with breast or ovarian cancer) - FRα-specific T cell responses observed in 20 of 21 patients
- Accruing: Randomized phase II trial in patients with stage II-III TNBC (after neoadjuvant and/or adjuvant therapy)
  - Mayo Clinic, Univ of Miami, Univ of Chicago, Mass General, Dana Farber, City of Hope

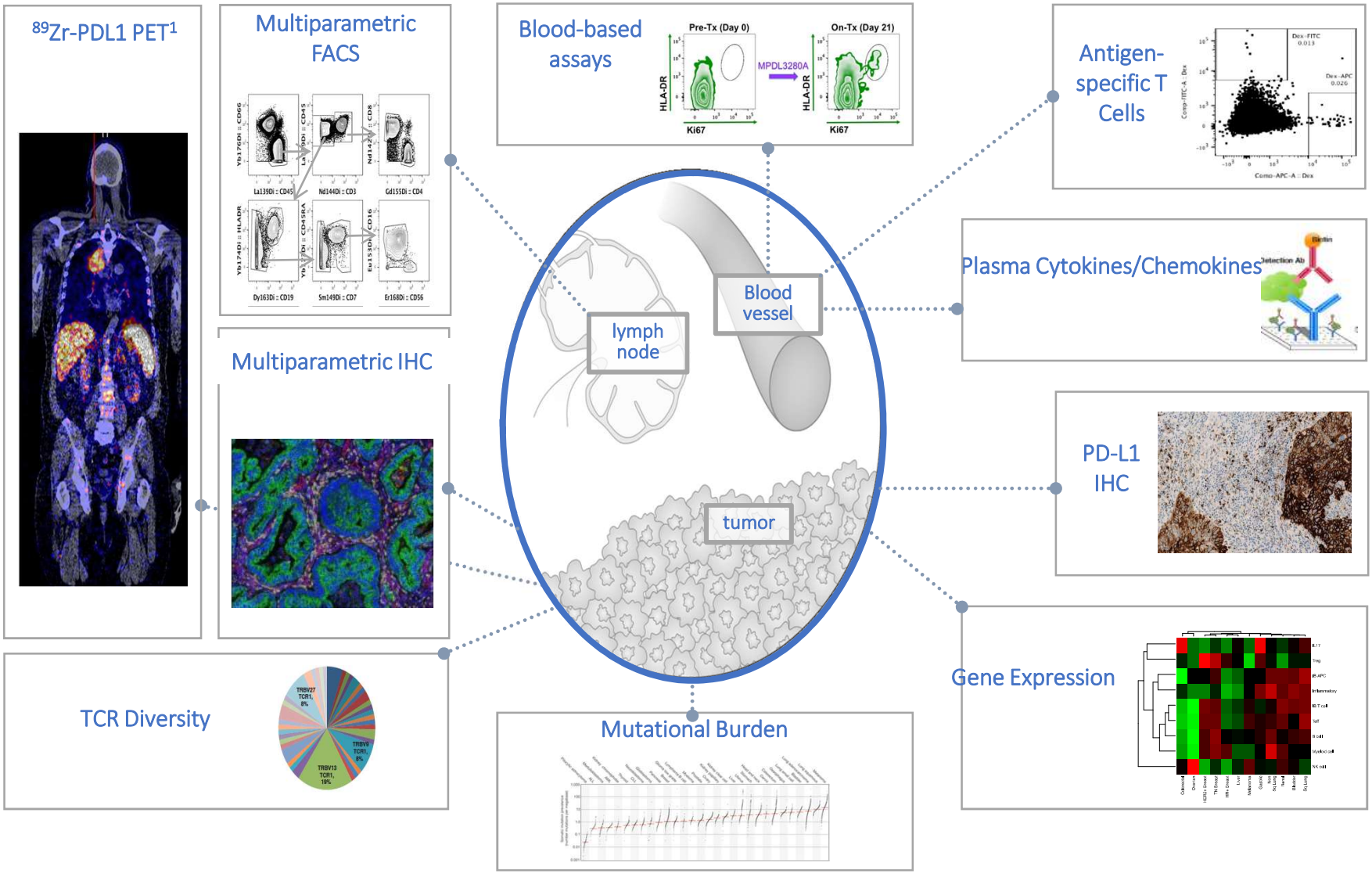
Necela et al. PLoS One 2015; Kasi JCO.2015.33.15_suppl.e14028;Norton N et al, 2020. PIs. EA Perez, K Knutson

Therapeutic Evolution From Tumor Targeting to Immune Targeting in Breast Cancer



Modified from Dornan D. 2nd Annual Advances in Immuno-Oncology USA Congress, Oct 2019

Comprehensive CIT Biomarker Platform

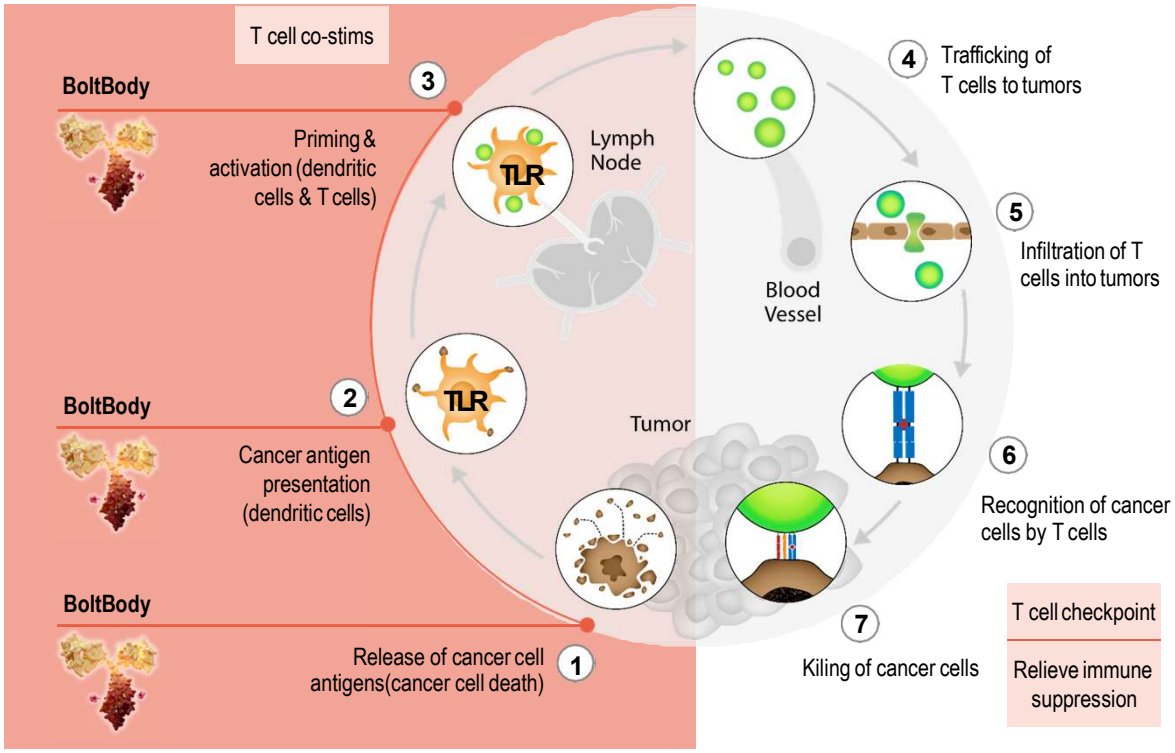


Modified from Chen DS SITC 2015

[1]De Vries, NIH workshop 2016

ISACs and other stimulators of the innate immune system such as STING agonists Act at Different Steps of the Cancer Immune Cycle vs. Checkpoint Inhibitors

Initiation of new immune response



Adapted from Chen & Mellman, *Immunity* (2013)

ISACs and STING-ADCs act to initiate an entirely new immune response and avoids shortcomings of other IO approaches

Engagement of biology encompassing multiple IO approaches within a single therapeutic

Neoantigen recognition: enhancing or antigen presentation capability of immunosuppressed APCs drives a robust new anti-tumor immune response