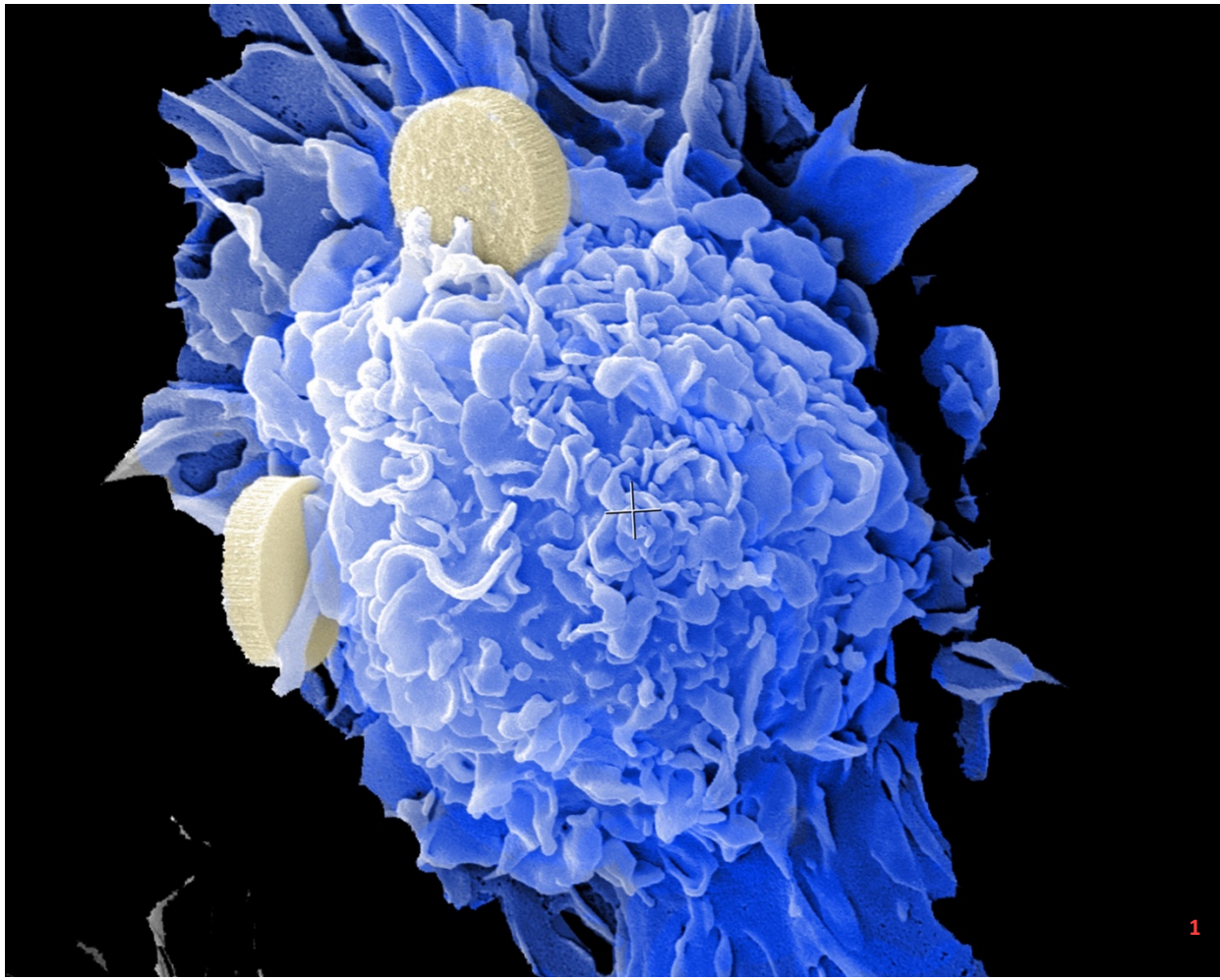
Heat Biologics

Analyst and Investor Day
February 28, 2018



Forward Looking Statements

This presentation includes statements that are, or may be deemed, ‘‘forward-looking statements’’ within the meaning of the Private Securities Litigation Reform Act of 1995, as amended. In some cases, these forward-looking statements can be identified by the use of forward-looking terminology, including the terms “believes,” “estimates,” “anticipates,” “expects,” “plans,” “intends,” “may,” “could,” “might,” “will,” “should,” “approximately” or, in each case, their negative or other variations thereon or comparable terminology, although not all forward-looking statements contain these words. They appear in a number of places throughout this presentation and include statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things, future trial results being consistent with interim results, our ongoing and planned discovery and development of drugs targeting cancer, the strength and breadth of our intellectual property, our ongoing and planned preclinical studies and clinical trials, the timing of and our ability to make regulatory filings and obtain and maintain regulatory approvals for our product candidates, our ability to partner our product development, the degree of clinical utility of our products, particularly in specific patient populations, expectations regarding clinical trial data, our results of operations, financial condition, liquidity, prospects, growth and strategies, the length of time that we will be able to continue to fund our operating expenses and capital expenditures, our expected financing needs and sources of financing, the industry in which we operate and the trends that may affect the industry or us.

By their nature, forward-looking statements involve risks and uncertainties because they relate to events, competitive dynamics, and healthcare, regulatory and scientific developments and depend on the economic circumstances that may or may not occur in the future or may occur on longer or shorter timelines than anticipated. Although we believe that we have a reasonable basis for each forward-looking statement contained in this presentation, we caution you that forward-looking statements are not guarantees of future performance and that our actual results of operations, financial condition and liquidity, and the development of the industry in which we operate may differ materially from the forward-looking statements contained in this presentation as a result of, among other factors, the factors referenced in the “Risk Factors” section of our most recent Annual Report on Form 10-K and our quarterly report on Form 10-Q for the subsequent quarters (collectively, our “SEC Filings”). In addition, even if our results of operations, financial condition and liquidity, and the development of the industry in which we operate are consistent with the forward-looking statements contained in this presentation, they may not be predictive of results or developments in future periods. Any forward-looking statements that we make in this presentation speak only as of the date of such statement, and we undertake no obligation to update such statements to reflect events or circumstances after the date of this presentation, except as required by law.

You should read carefully the factors described in the “Risk Factors” sections of our SEC Filings to better understand the risks and uncertainties inherent in our business.

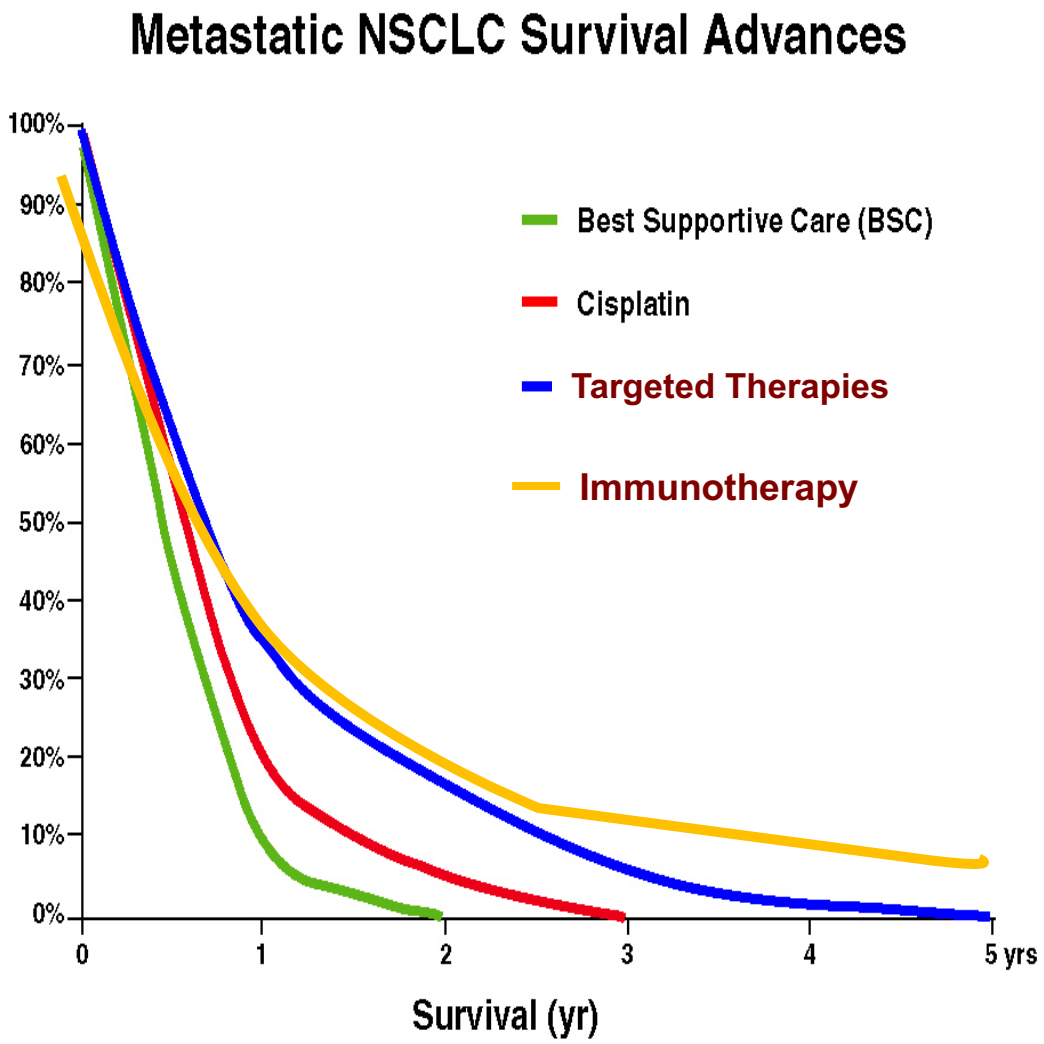
Penn Medicine

Roger B. Cohen

Professor of Medicine
University of Pennsylvania
Associate Director Clinical Research Abramson Cancer Center
Chief Clinical Research Officer Abramson Cancer Center
Co-Director, Head and Neck Cancer Research Center

the cure is within
ABRAMSON CANCER CENTER

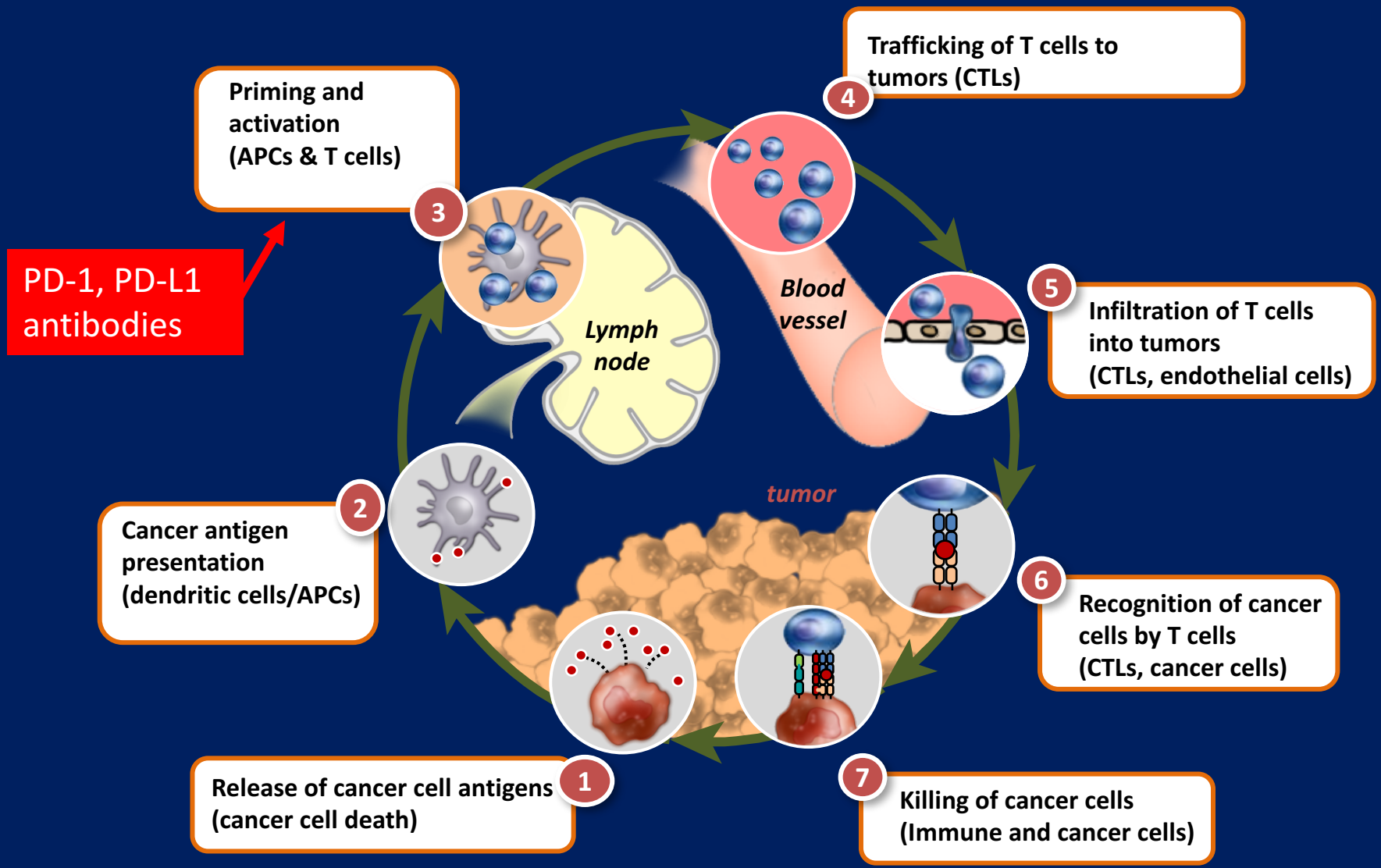
Therapy for Advanced Lung Cancer



There have been some modest gains since 1980

Are we doing better with immunotherapy?

Cancer-Immunity Cycle



APCs = antigen-presenting cells; CTLs = cytotoxic T lymphocytes.

Chen DS, Mellman I. *Immunity.* 2013;39:1-10.

Immune Checkpoints

Immune checkpoints are normal ‘brakes’ on the activity of the immune system; checkpoint proteins turn off activated T cells when they are no longer needed

Immune checkpoints have been ‘hijacked’ by the cancer to evade the immune system

Checkpoint Inhibitors remove the checkpoint and “take the brakes off the immune system”

Now the immune system can ‘see’ the tumor and kill it

1st Line NSCLC Treatment Landscape

Incurable NSCLC (adenocarcinoma) without activating EGFR, ALK, etc. mutations:

- If PD-L1 is ≥ 50%, consider Keytruda as monotherapy
- If PD-L1 <50%, consider Keytruda in combination with chemotherapy
- Platinum doublet chemotherapy

Incurable NSCLC (squamous cell):

- If PD-L1 is ≥ 50%, consider Keytruda as monotherapy
- If PD-L1 <50%, platinum doublet chemotherapy

Soon, many patients will get a checkpoint inhibitor in the first line of therapy

2nd Line NSCLC Treatment Landscape

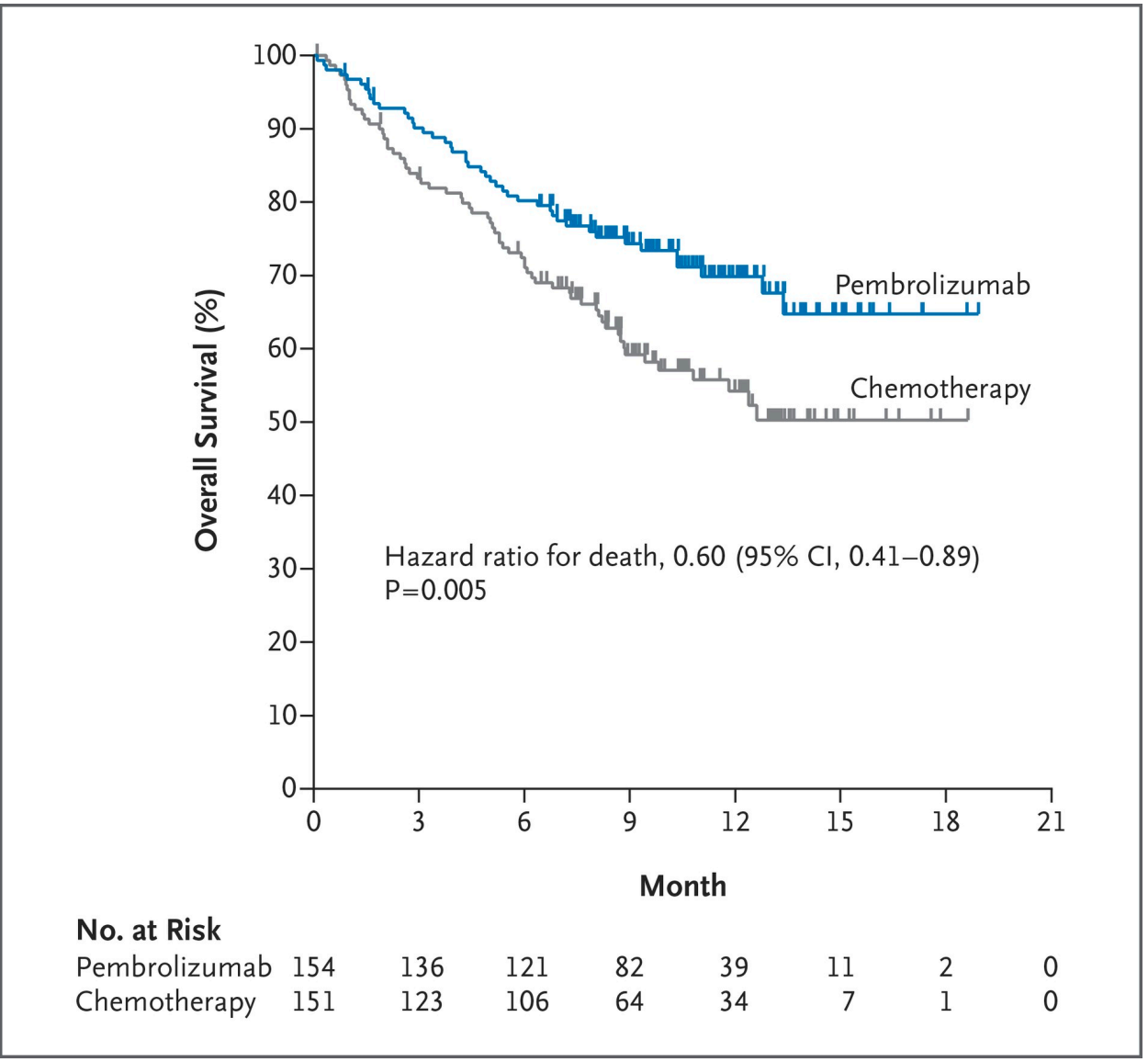
- Adenocarcinoma: chemotherapy (taxanes) or checkpoint inhibitor if not given previously
- Squamous Cell: chemotherapy (taxanes) or checkpoint inhibitor (Keytruda, Opdivo, Tecentriq) if not given previously

What if the patient already received a checkpoint inhibitor and wants more immunotherapy?

- They will need a 'rescue' strategy: a checkpoint inhibitor "plus *something* to make the checkpoint inhibitor work or work again"
- *Something* =
  - Radiation ("RadVax")
  - Addition of a 2nd immune modulating drug: IDO inhibitor, IFNγ, or antibodies against CTLA-4, OX40, B7H3, CSFR1, LAG-3, TIGIT, TIM-3, etc.
  - **A vaccine (ex: HS-110) that induces CD8+ T cells to infiltrate the tumors**

The Big Challenge:

Most patients with NSCLC don't respond to checkpoint inhibition



Even the "ideal" pts (PD-L1 ≥ 50%) don't all respond to checkpoint inhibitors

Reck M et al. N Engl J Med 2016;375:1823-1833

Penn Medicine

The NEW ENGLAND JOURNAL of MEDICINE

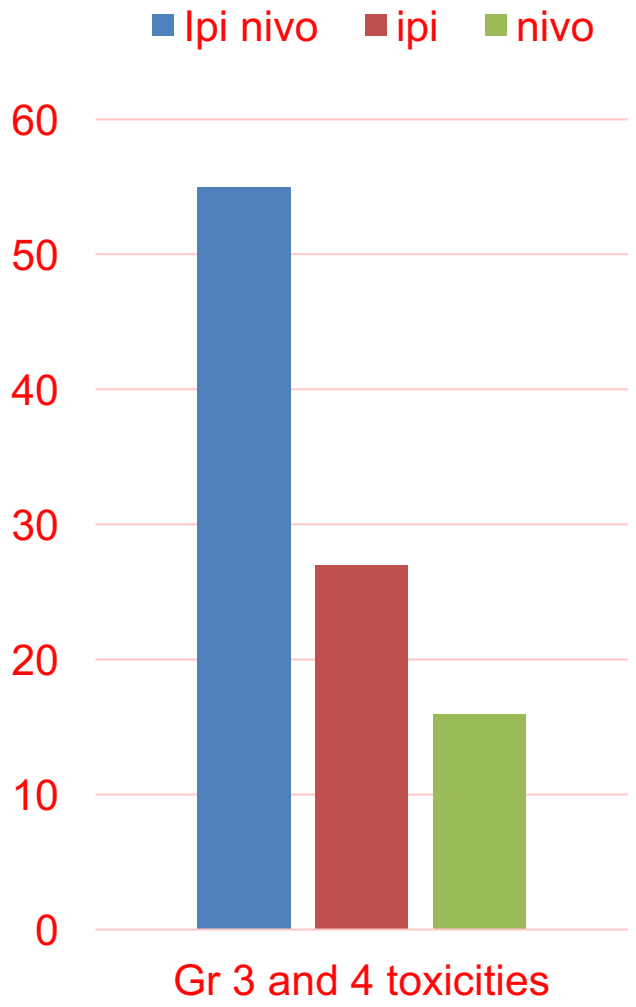
the cure is within
ABRAMSON CANCER CENTER

Considerable Unmet Need in All Lines of Therapy

- In the PDL-1 intermediate (1-50%) patients the response rate is lower: ~20-25%
- In the PDL-1 negative (<1%) patients the response rates are < 10%
- And patients who do respond are not cured
  - They eventually get worse and die from NSCLC
- Reasons for failure of checkpoint inhibition likely include:
  - There are no T-cells in the tumor (the tumors are ‘cold’)
  - There are other white blood cells in the tumors that block the T-cells from doing their job
  - The cancer is using checkpoints other than PD-1/PD-L1
  - The cancer substitutes new checkpoints when we block PD-1/ PD-L1
  - Unknown mechanisms of immune evasion

Immunotherapy Combinations

- Improving response rates and response duration will require IO combinations
- Existing combinations, such as Opdivo-Yervoy are significantly more toxic than Opdivo monotherapy
- Immune-related toxicities include pneumonitis, colitis, rashes, hepatitis, nephritis, encephalitis and others
- Additive immune therapies that don't add significant toxicity are needed



Larkin et al, N Engl J Med 2015; 373:23-34

Cancer Immunity Cycle (continued)

HS-110

3 Priming & activation

CD28/B7.1
CD137/CD137L
OX40/OX40L
CD27/CD70
HVEM
GITR
IL-2
IL-12

CTLA-4/B7.1
PD-L1/PD-1
PD-L1/B7.1
prostaglandins

HS-110

2 Cancer antigen presentation

TNF-a
IL-1
IFN-a
CD40L/CD40
CDN
ATP
HMGB1
TLR

IL-10
IL-4
IL-13

■ Stimulatory factors
■ Inhibitors

1 Release of cancer cell antigens

Immunogenic cell death
Tolerogenic cell death

4 Trafficking of T cells to tumors

CX3CL1
CXCL9
CXCL10
CCL5

5 Infiltration of T cells into tumors

LFA1/1CAM1
Selectins

VEGF
Endothelin B receptor

6 Recognition of cancer cells by T cells

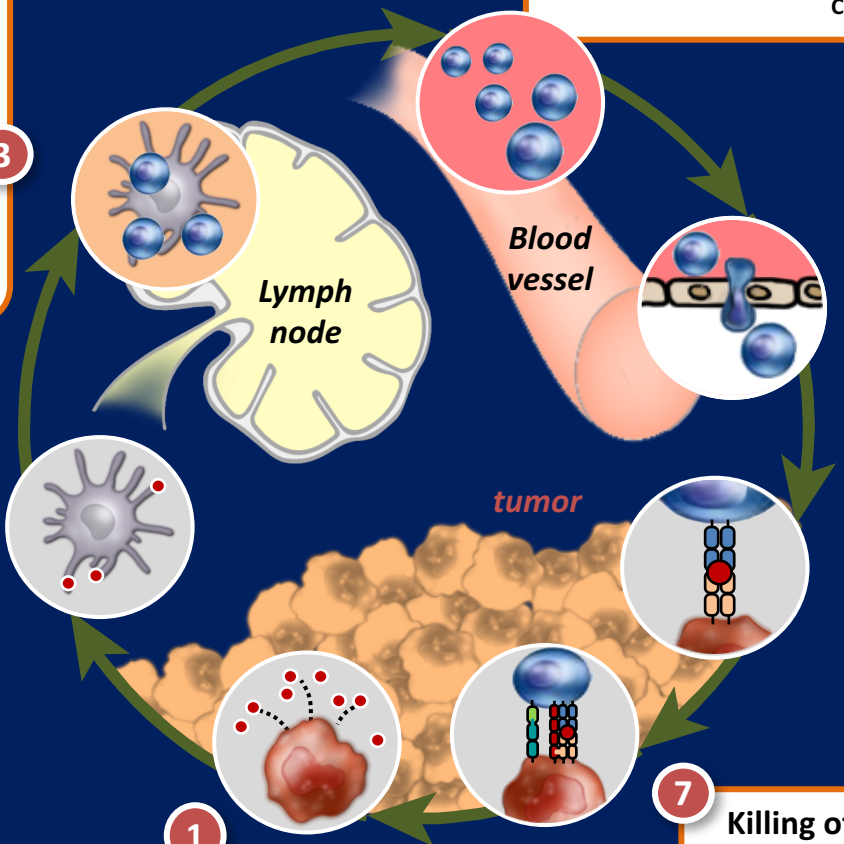
T cell receptor

Reduced pMHC on cancer cells

7 Killing of cancer cells IFN-γ

T cell granule content

PD-L1/PD-1
PD-L1/B7.1
IDO
TGF-β
BTLA
VISTA
LAG3
Arginase
MICA/MICB
B7-H4
TIM3/ phospholipids

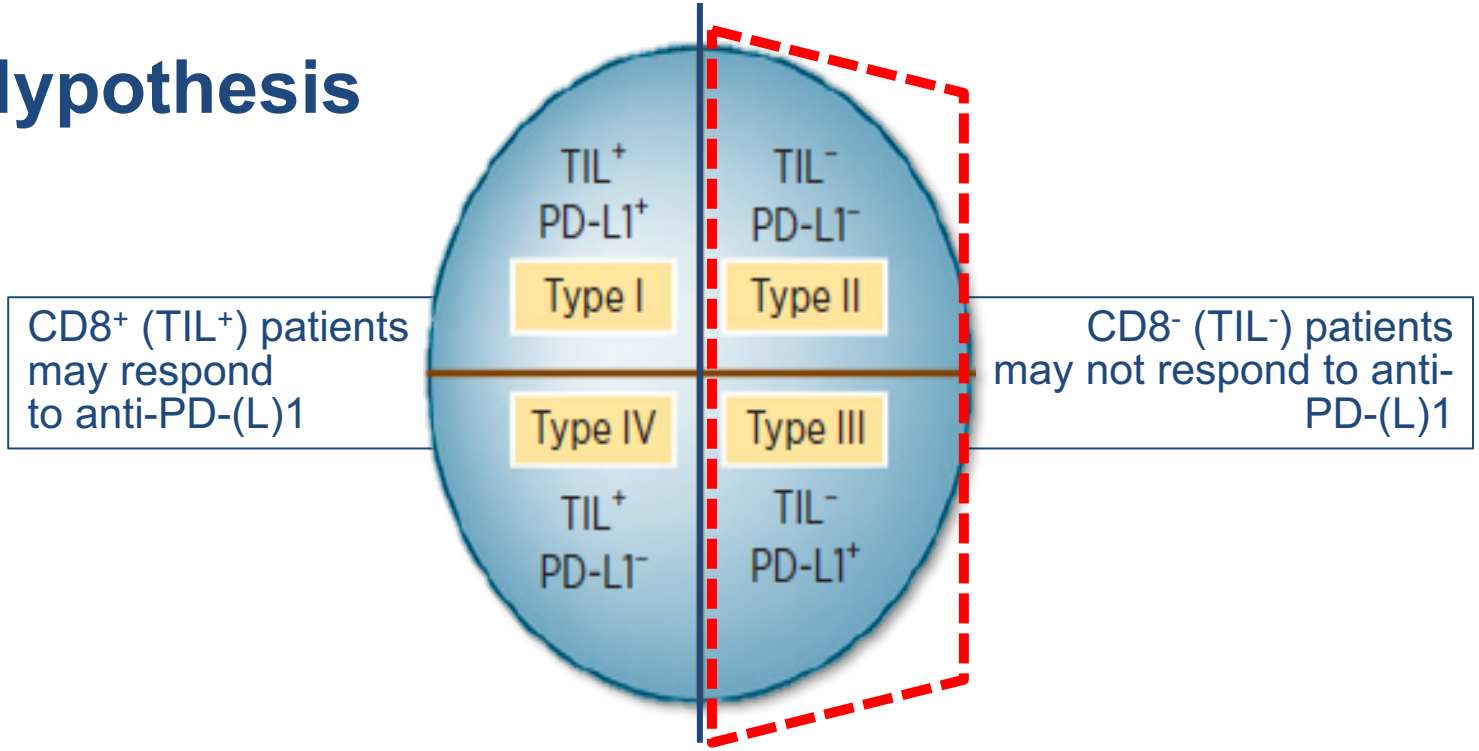


Chen DS, Mellman I. *Immunity*. 2013;39:1-10.

Combining Therapeutic Vaccines with Checkpoint Inhibitors

What might a therapeutic vaccine like HS-110 do?
Generate CD8+ cells (TILs) that penetrate tumors and make them "hot"

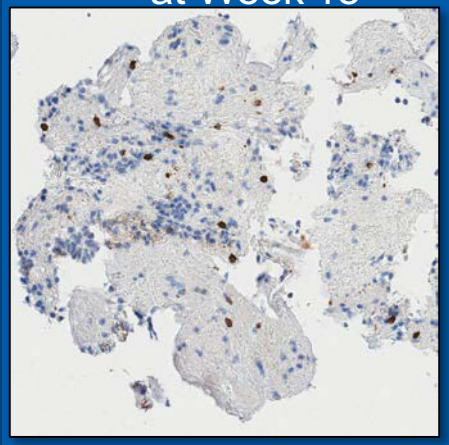
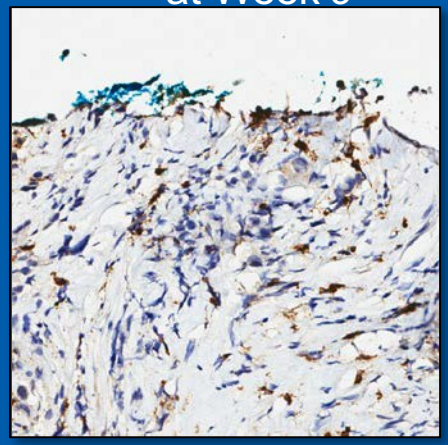
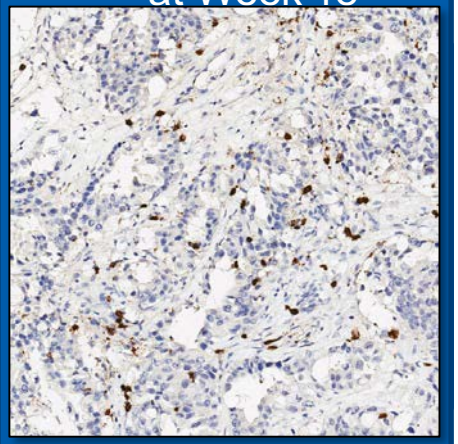
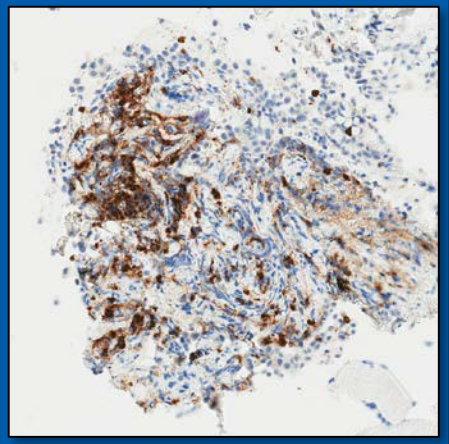
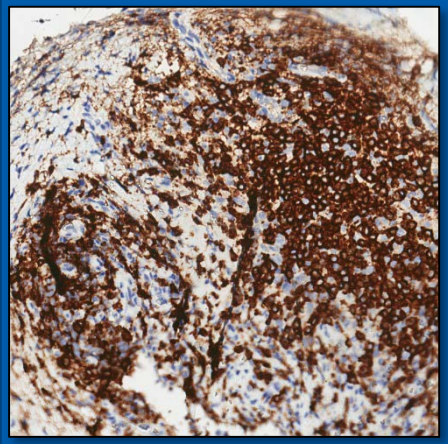
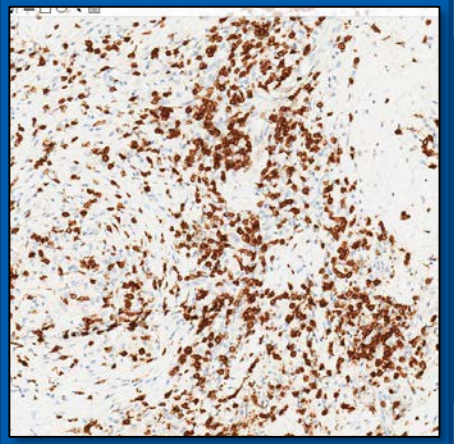
Hypothesis



Teng et al., 2015 Can Res
Gettinger et al., 2015 JCO

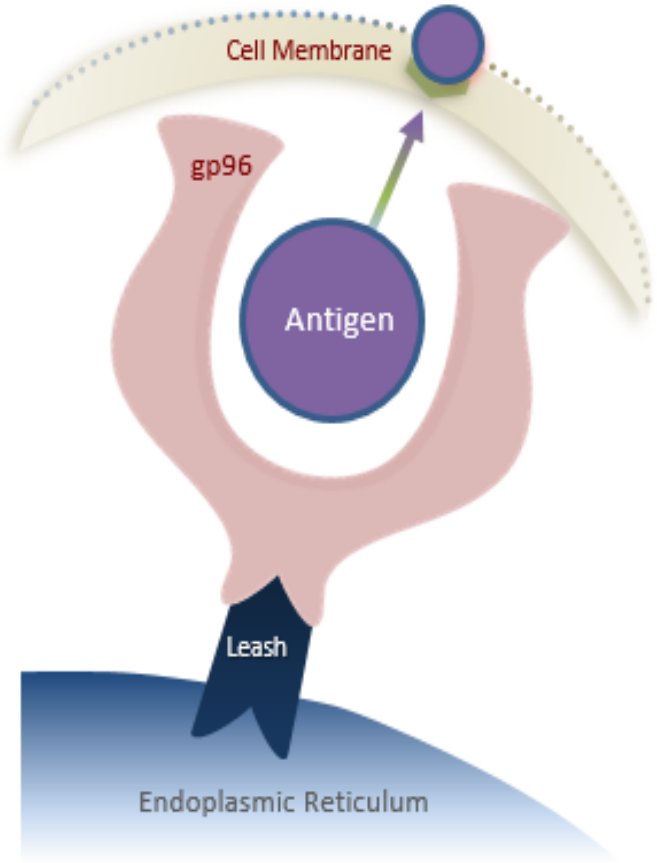
Convert TIL- tumors to TIL+

Biopsies from the DURGA Trial: TIL Infiltration Associated with Clinical Response

	Patient 1: Partial Response at Week 18	Patient 2: Partial Response at Week 9	Patient 3: Partial Response at Week 18
Baseline			 Low CD8+ TIL (≤10%)
Week 10	 High CD8+ TIL (>10%)	 High CD8+ TIL (>10%)*	 High CD8+ TIL (>10%)

Previous lung cancer vaccines were not designed to elicit a robust CD8+ T-cell response

Introducing gp96- *The Immune System's "Swiss Army Knife"**



A Natural "Molecular Warning System"

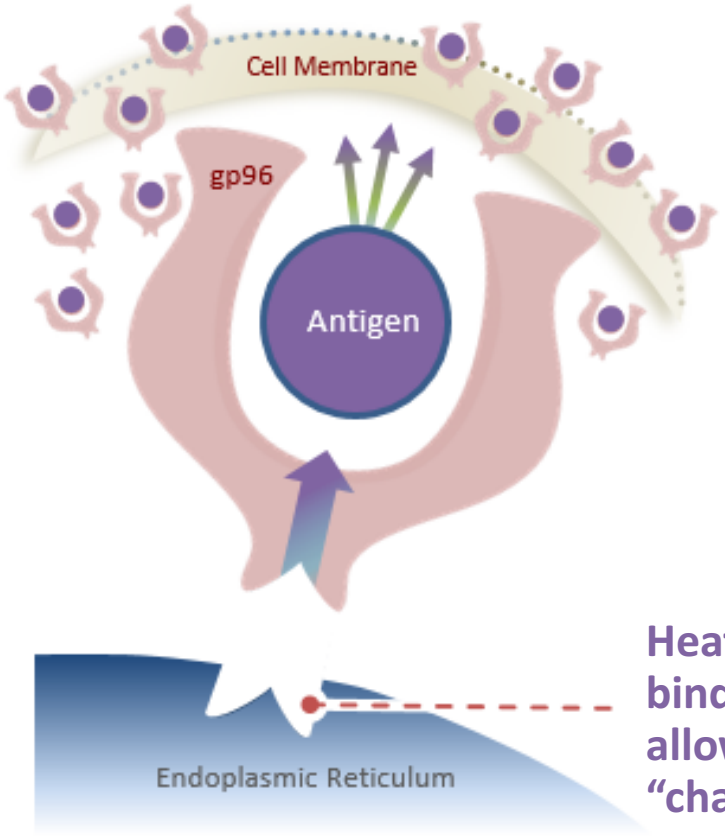
- Gp96 "chaperones" newly-created proteins to the cell membrane where they are released and embedded
- Gp96 + its ferried protein are naturally released only via necrosis
  - Exposure of gp96 outside the cell activates an immune response to the antigen it is carrying
  - Enables MHC I antigen cross-presentation specifically to CD8+ T-cells
  - Activates a cytotoxic T-cell response to the cargo antigen
- Gp96 among the most powerful immune adjuvants
- Gp96 is the only adjuvant that generates exclusively CD8+ ("killer") T-cells

*Schild, H. & Rammensee, H. ***Gp-96 – The Immune System's Swiss Army Knife***. Nature Immunology 2, 100-101 (2000)

Heat's gp96 *ImPACT* Therapy

Heat Biologics *ImPACT*® technology reprograms cancer cells to continuously secrete their own antigens bound to heat shock protein gp96

Severing the Leash



- Genetically modify tumor cells by "severing the leash" that binds the gp96 to the endoplasmic reticulum of the cell and replacing it with a sequence that pumps gp96 out of the cell
- Enables living cancer cells to "pump-out" their own surface antigens along with the gp96 chaperone
  - This process mimics necrotic cell death
- Activates a powerful pan-antigen cytotoxic T-cell immune response

Heat Biologics *ImPACT* technology removes the leash that binds gp96 to the cell, replacing with a sequence that allows cells to continually secrete gp96 along with their "chaperoned" antigens

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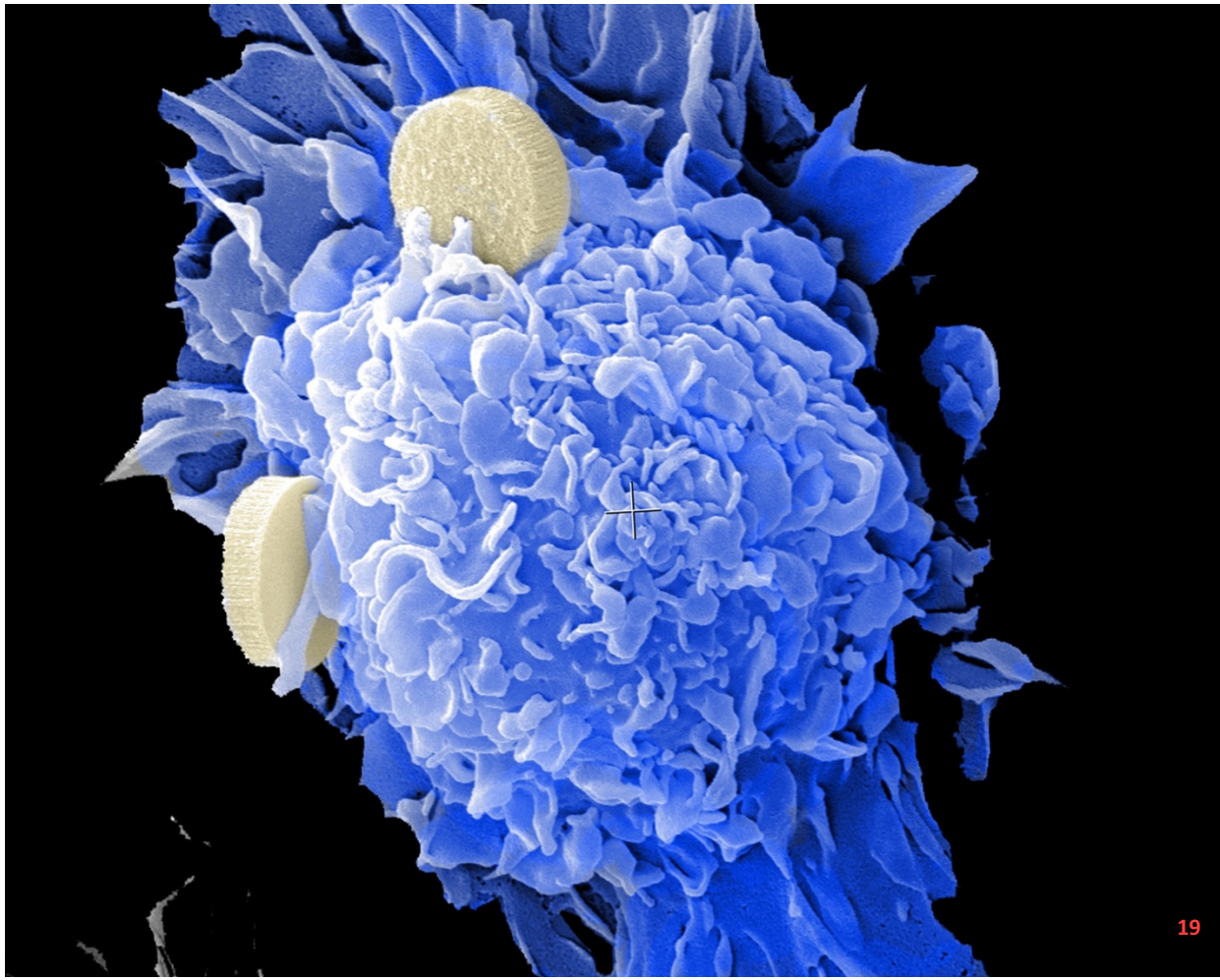
ImPACT Mechanism of Action
Jeff Hutchins PhD
Chief Scientific Officer
February 28, 2018

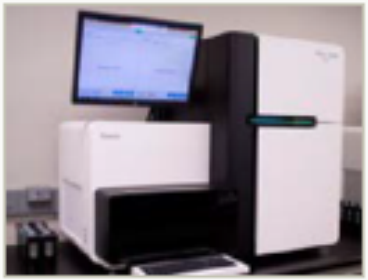


ImPACT/ComPACT Manufacturing

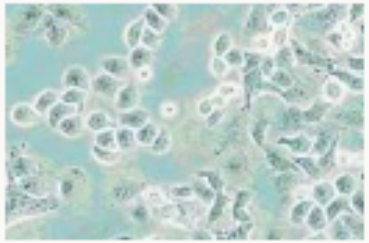
Cell-Based, Multi-Antigen T Cell Activation

Screen → **Select** → **Scale-Up**

Compare CTA Expression on Tissue/Cell Lines

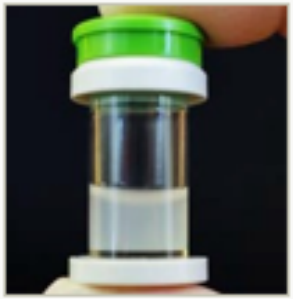


ID Cell Line with Most Antigen Overlap



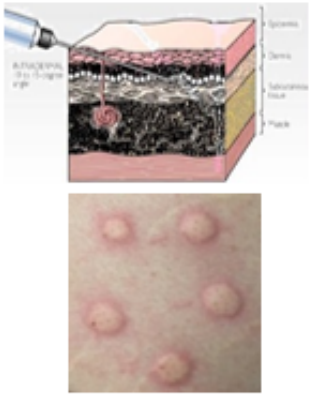
Transfect with Activation Technology

Scale-Up for Manufacturing by CMO

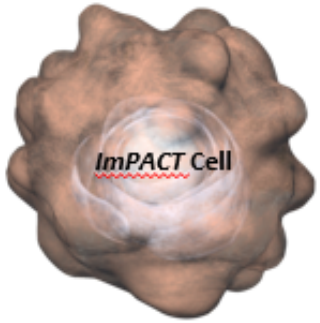


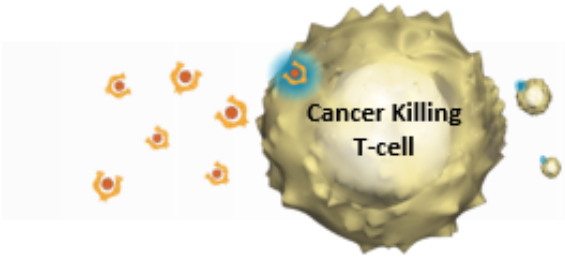
Low COG, off-the-shelf alternative to autologous therapies

ImPACT: Immune Pan-antigen Cytotoxic Therapy



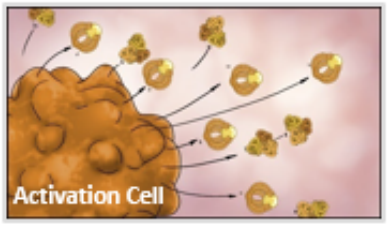
Cluster of five 0.1 mL intradermal injections



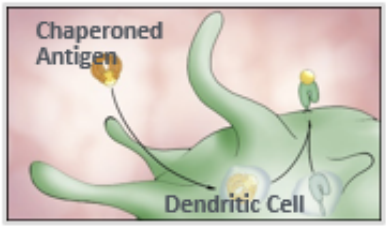


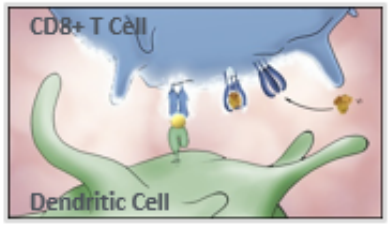
ImPACT cells secrete antigens designed to specifically activate patient's killer T-cells

T-cells circulate to destroy patient's tumor

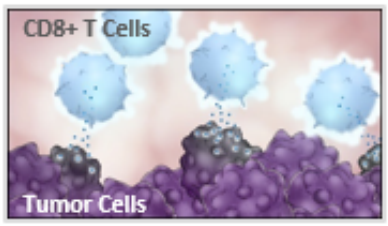


Activated cells **EXPRESS** chaperoned antigens



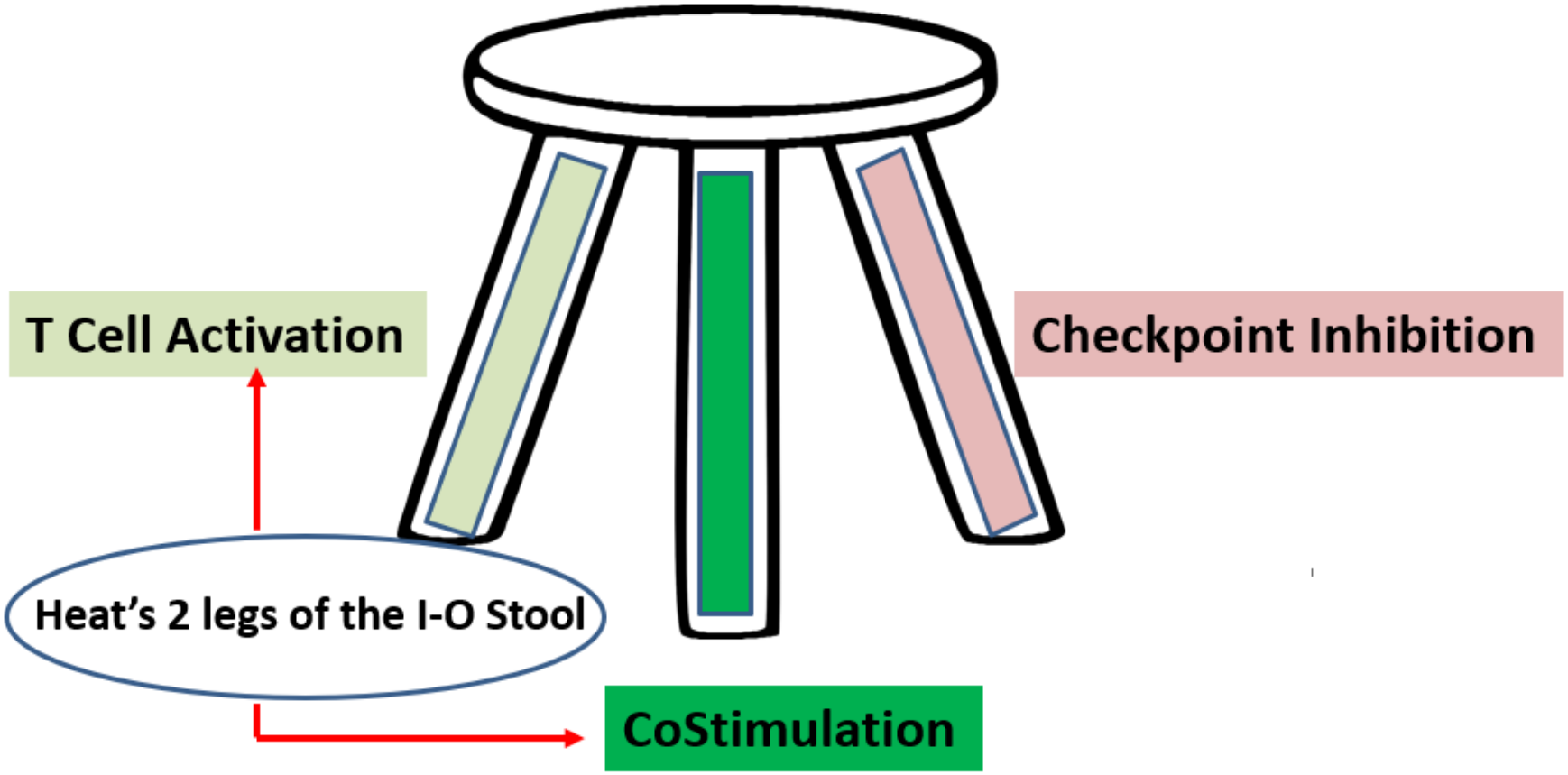


Chaperoned antigens activate dendritic cells, which then **ACTIVATE** & **PROLIFERATE** CD8+ T-cells



CD8+ T-cells locate and **ELIMINATE** cancer cells

Successful Immuno-oncology: A 3 Legged Stool



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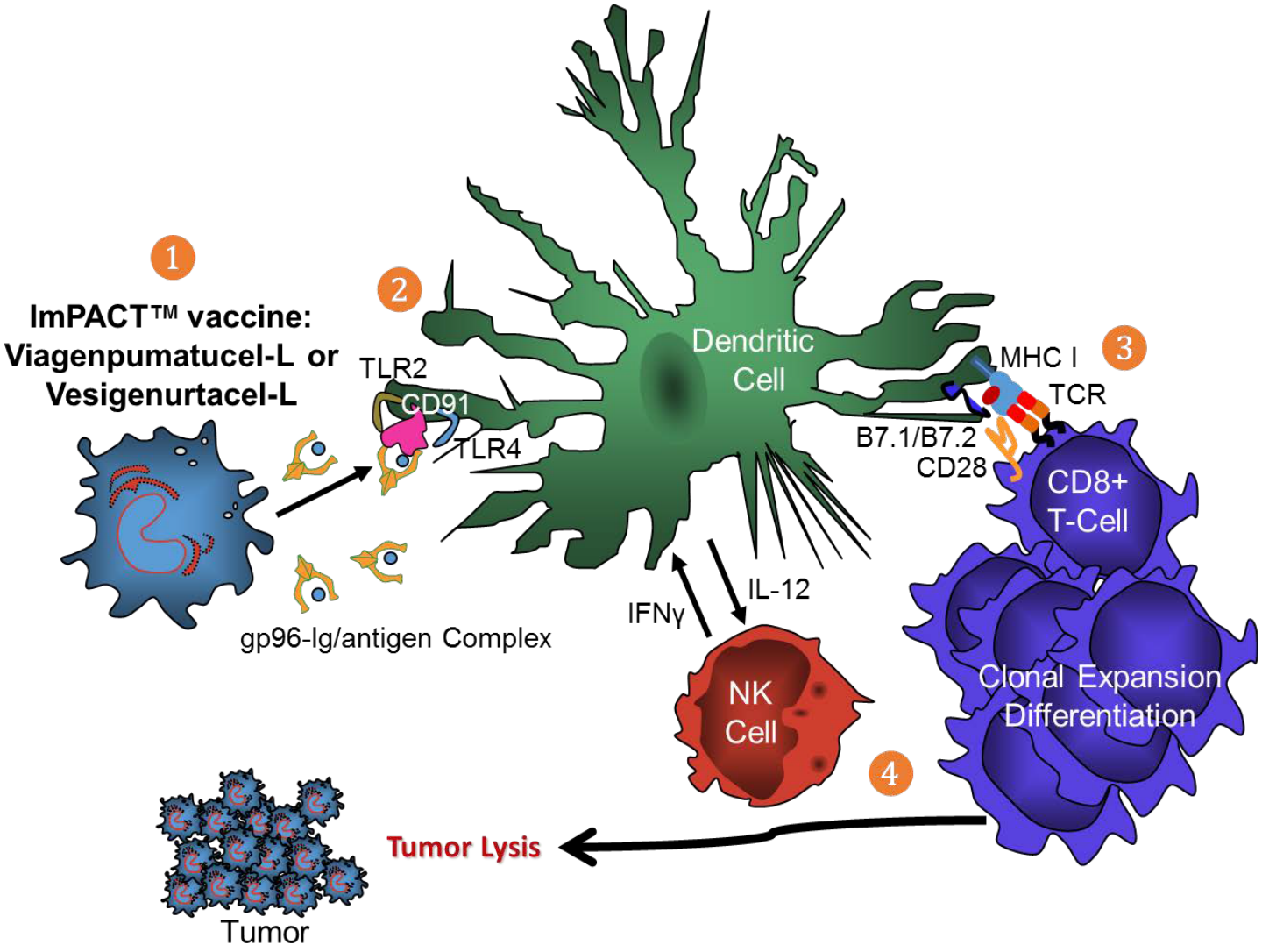
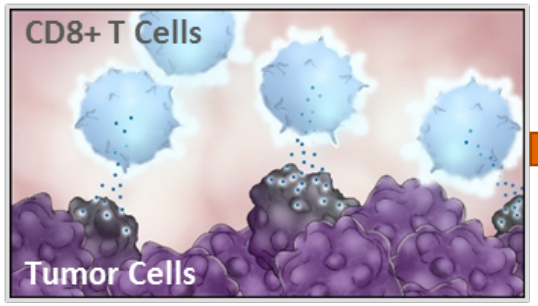
ImPact Generates an Adaptive Immune Response

1. **Secretion of gp96-Ig** carrying tumor specific proteins represented on the patients tumor.
2. **Activation of APCs** (TLR2/4) and cross-presentation of antigens (CD91).
3. **Specific T-cell receptor** engagement.
4. **Clonal Expansion** of Tumor Antigen Specific T cells.



Clinical Proof of Mechanism in NCSLC

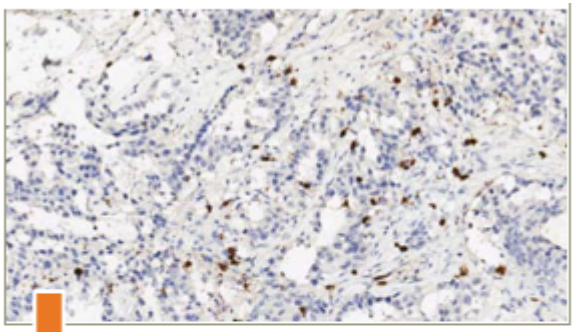
Histopathological evidence that HS-110 is turning COLD tumors HOT



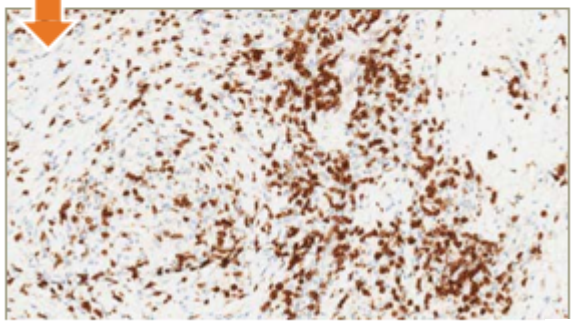
CD8+ T-cells locate and **ELIMINATE** cancer cells

CD8+ Staining

Baseline



Conversion of Low TIL to High TIL After 10 Weeks on HS-110 & Nivolumab Combo

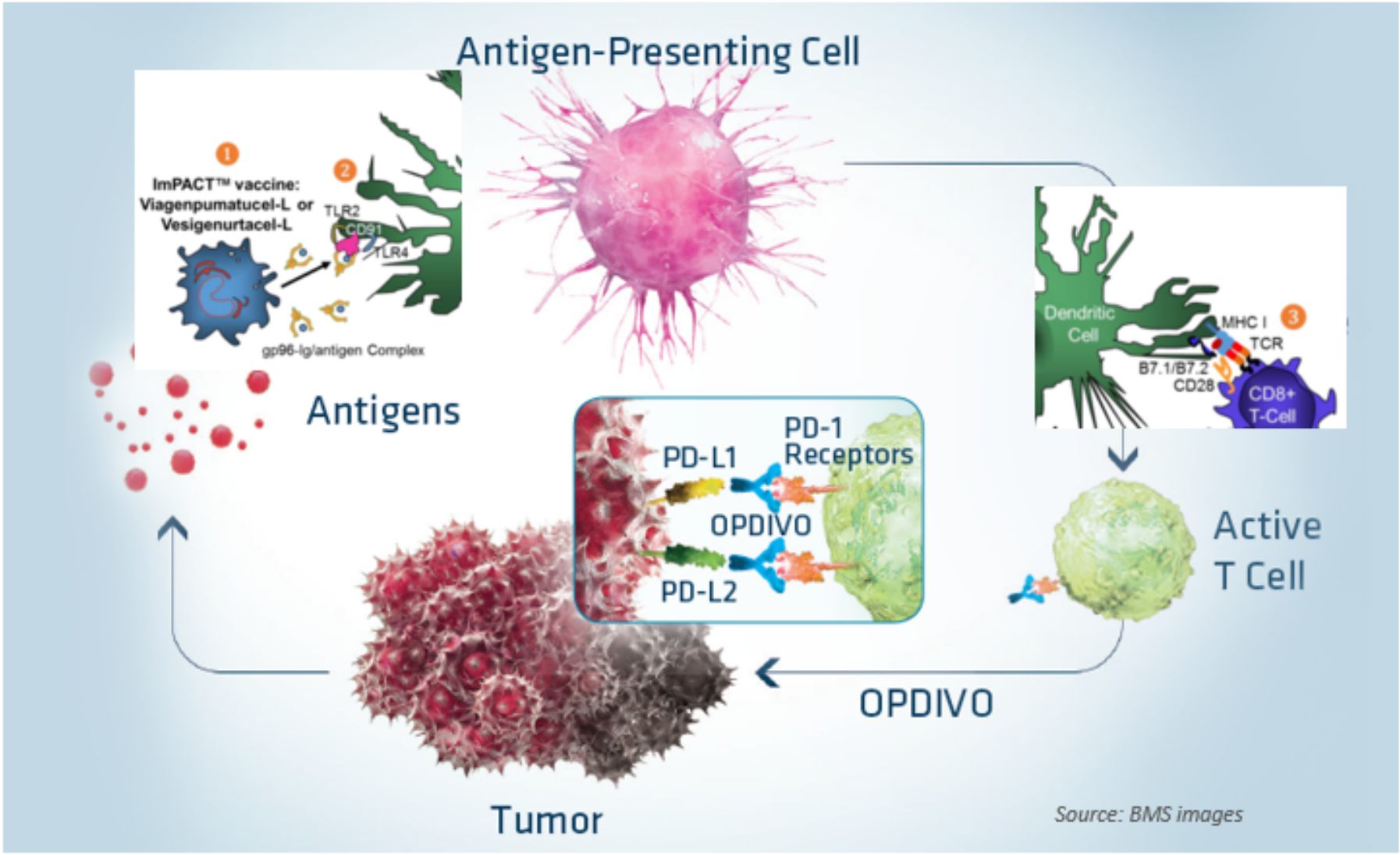


Week 10

- Increased levels of CD8+ T cells deep into the tumor
- Tumors with no previous immune activation made highly active
- Association with radiographic clinical response

ImPACT + Opdivo Combination Therapy

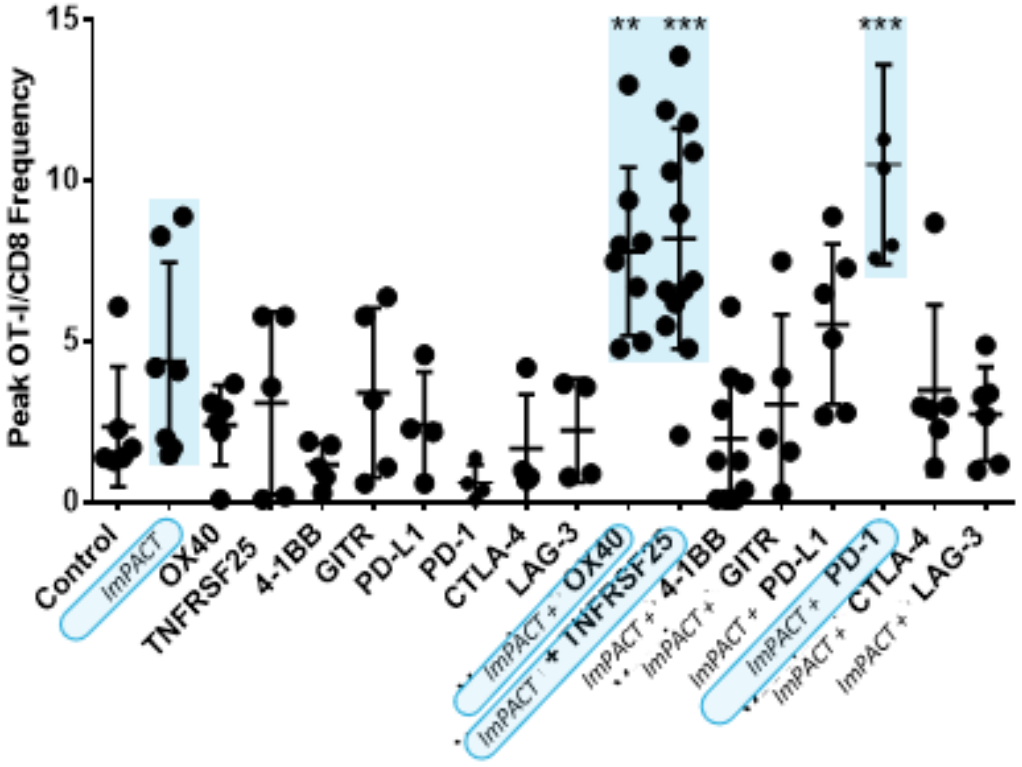
The potential to improve clinical responses and survival, without additional toxicity



Pre-clinical Data of T-cell Expansion

✓ Strong support for our clinical approaches

CD8+ T-cell Expansion



- Higher T-cell responses observed in mice treated with *ImPACT* alone
- *ImPACT* boosted CD8+ T-cells to even higher levels when combined with co-stimulator agonist antibodies: OX40, TNFRSF25, PD-1
- Findings suggest synergies when combining *ImPACT* with Pelican's TNFRSF25 antibody

Source: Fromm et al. Society for Immunotherapy of Cancer Annual Meeting, 2016

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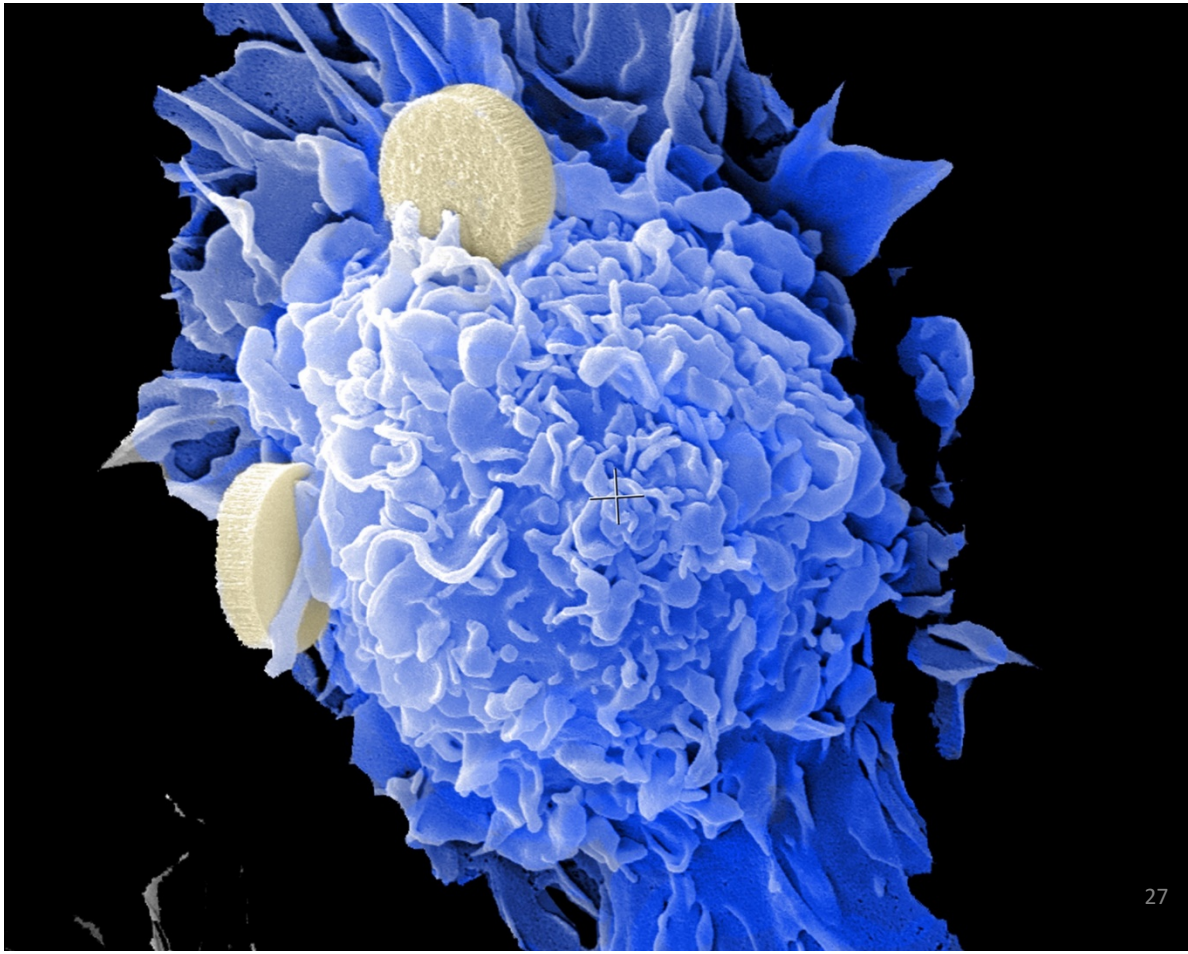
DURGA Interim Data Review
George Peoples MD FACS
Chief Medical Officer
February 28, 2018

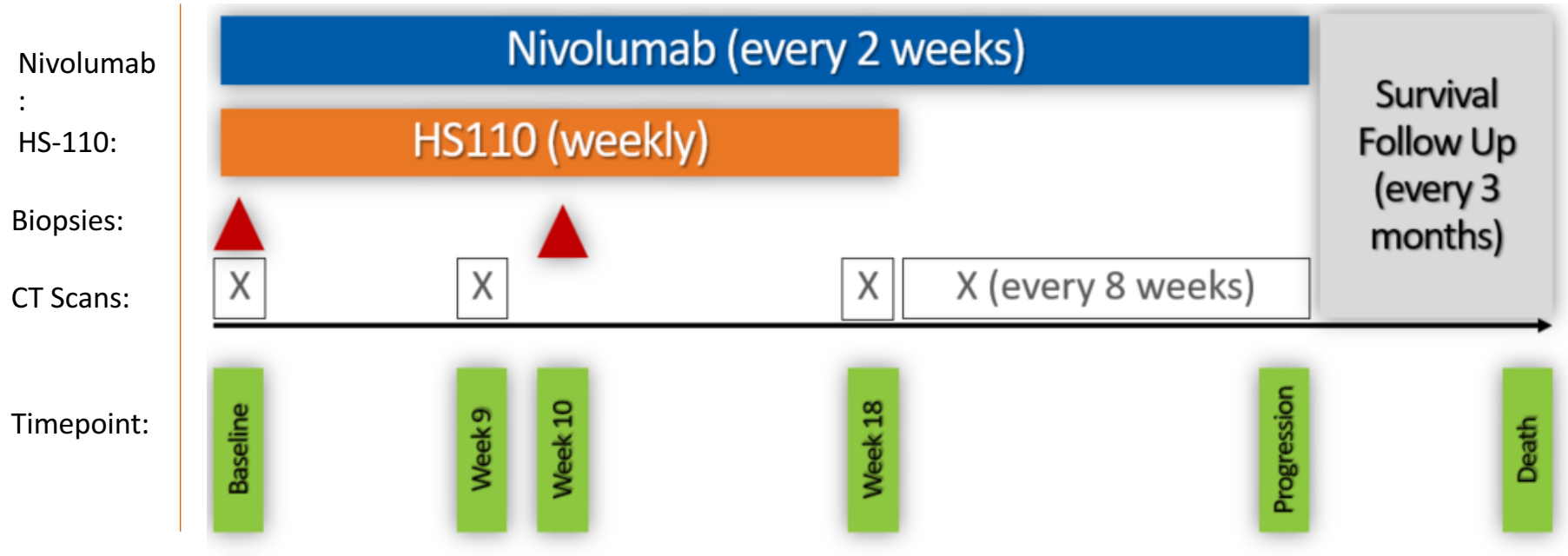


HS-110-102 DURGA Trial

A Phase 1b/2 Study of Viagenpumatucel-L (HS-110) in Combination with Multiple Treatment Regimens in Patients with Non-Small Cell Lung Cancer (The "DURGA" Trial)

Objective	Evaluate objective response rate of HS-110 with a PD-1 checkpoint inhibitor (nivolumab)	
Design	• Single arm multicenter trial of up to 120 patients • Cohort analysis based on histology, prior checkpoint inhibitor therapy, TIL levels and PD-L1 expression	
Endpoints	• Objective Response Rate (RECIST 1.1) • Duration of Response • Progression-free Survival	• Overall Survival • Immune Response • Safety & Tolerability
Population	Previously treated, advanced NSCLC Current Analysis: • Adenocarcinoma • Checkpoint inhibitor naïve New Populations for enrollment: • Squamous cell carcinoma • Checkpoint inhibitor relapsed	

DURGA Schema



KEY:

▲ = Biopsy (or recent archival tissue at baseline)

X = CT Scan

Pre-Specified Patient Populations Analyzed

ITT (n=35)

The Intent-to-Treat Population includes all patients enrolled into the study

- 3 patients died before completing 6 weeks of treatment (2 PD & 1 MI)
- 4 patients had no follow-up scans due to clinical progression
- 2 patients had no follow-up scans due to AEs

PP (n=26)

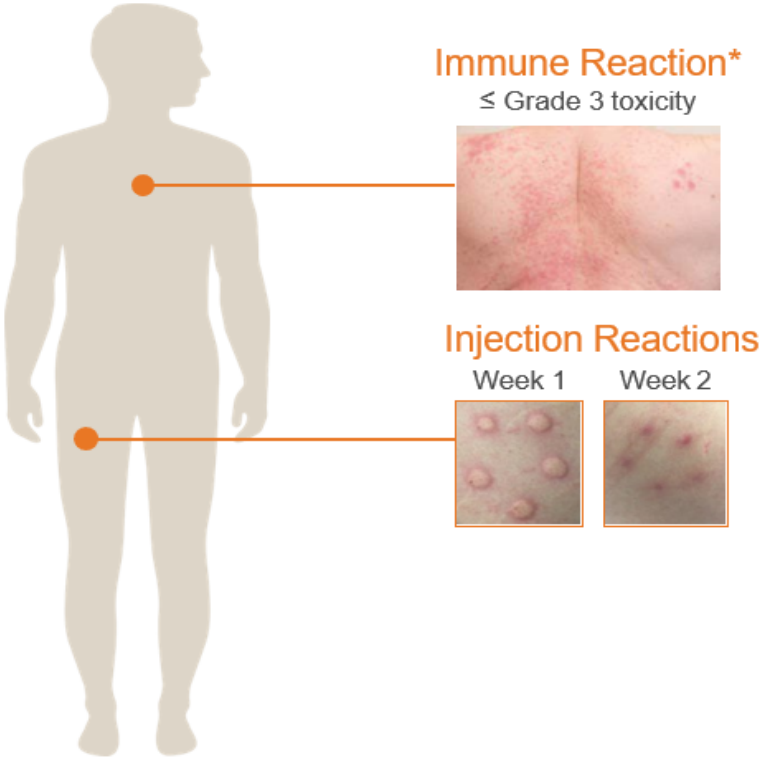
The Per Protocol Population includes patients who have received at least 6 doses of HS-110 and a pre/post treatment tumor assessment

ImPACT (HS-110) Safety Profile to Date

~1,000 Doses – No Serious Adverse Reactions

Favorable Safety Profile To Date

- Almost 1,000 doses administered to ~100 patients
- Only one patient ended treatment due to a non-serious adverse reaction*
- No systemic use of steroids required to treat reactions
- No serious adverse reactions beyond those seen with SOC
- No additive toxicities with SOC



*Represents the only patient of ~100 patients dosed who discontinued treatment for a vaccine-related adverse event

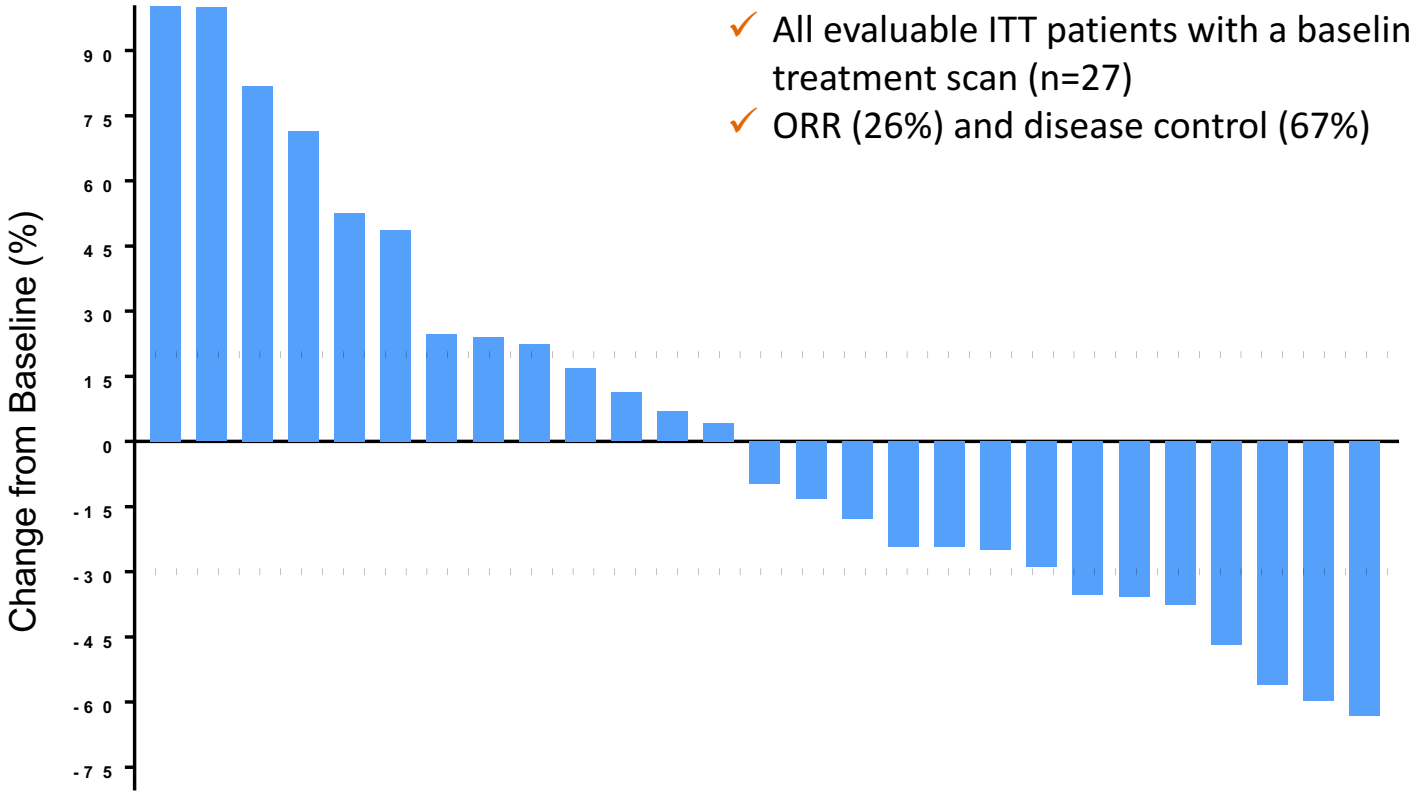
Primary Efficacy Analysis

Population	Objective Response Rate (RECIST 1.1)	Disease Control Rate (RECIST 1.1)
ITT (n=35)	17%	40%
PP (n=26)	23%	50%

ORR: Objective Response Rate is defined as the % of patients who have reached Partial Response (PR) per RECIST 1.1 which requires a 30% reduction in the sum of the longest diameters of all target lesions from baseline.

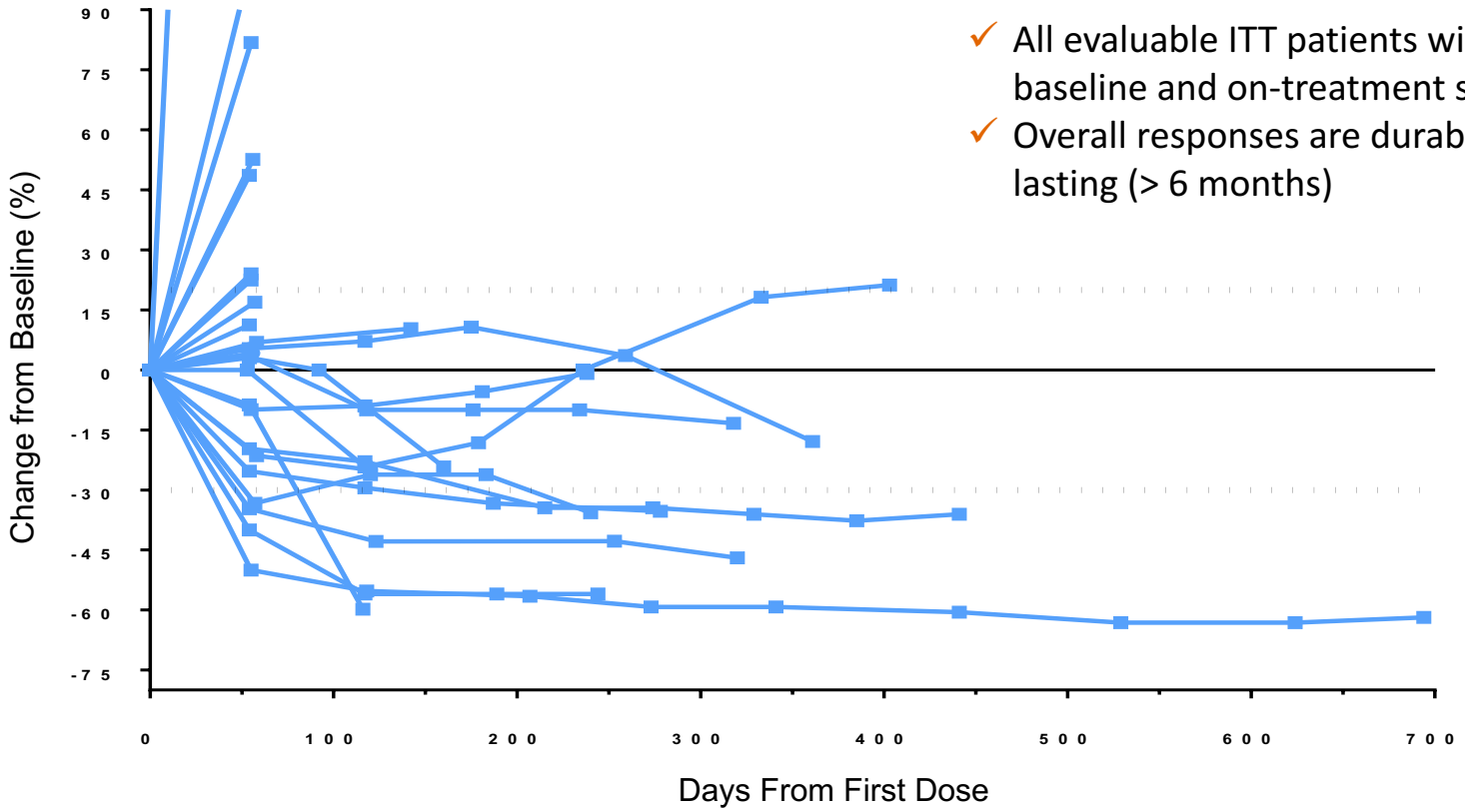
DCR: Disease Control Rate is defined as the % of patients who have reached Partial Response (PR) or Stable Disease (SD) per RECIST 1.1 which requires that the sum of the longest diameters of all target lesions does not increase more than 20% from baseline.

Best Target Lesion Response



- ✓ All evaluable ITT patients with a baseline and on-treatment scan (n=27)
- ✓ ORR (26%) and disease control (67%)

Durable Target Lesion Response

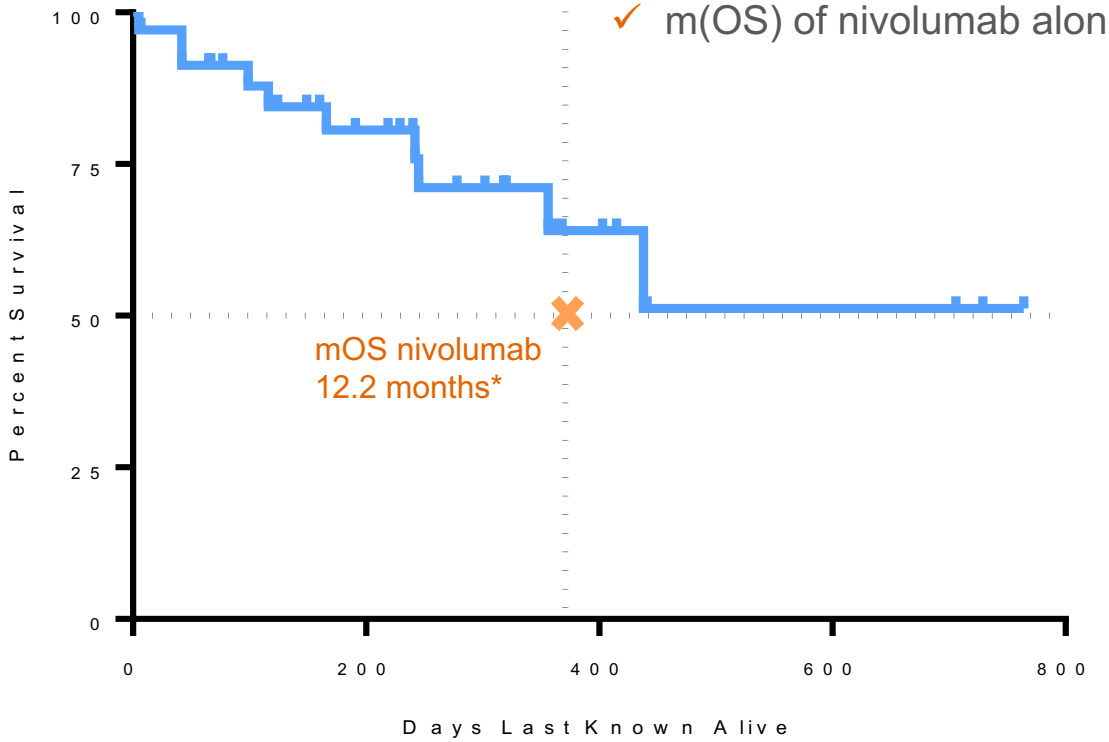


- ✓ All evaluable ITT patients with a baseline and on-treatment scan (n=27)
- ✓ Overall responses are durable and long lasting (> 6 months)

All enrolled patients (ITT) with a baseline and on-treatment scan

ITT Overall Survival: Encouraging and Still Maturing

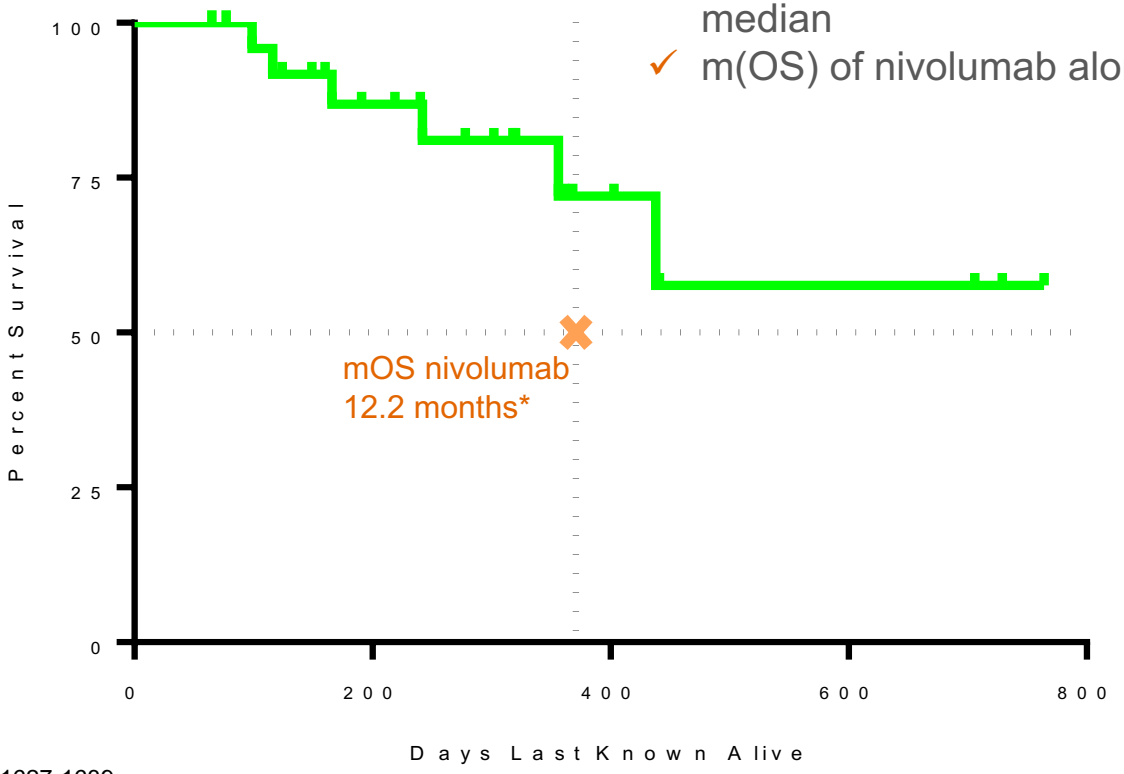
- ✓ ITT survival curve has not yet reached median
- ✓ m(OS) of nivolumab alone = 12.2 months



*N Engl J Med 2015; 373: 1627-1639

PP Overall Survival: Encouraging and Still Maturing

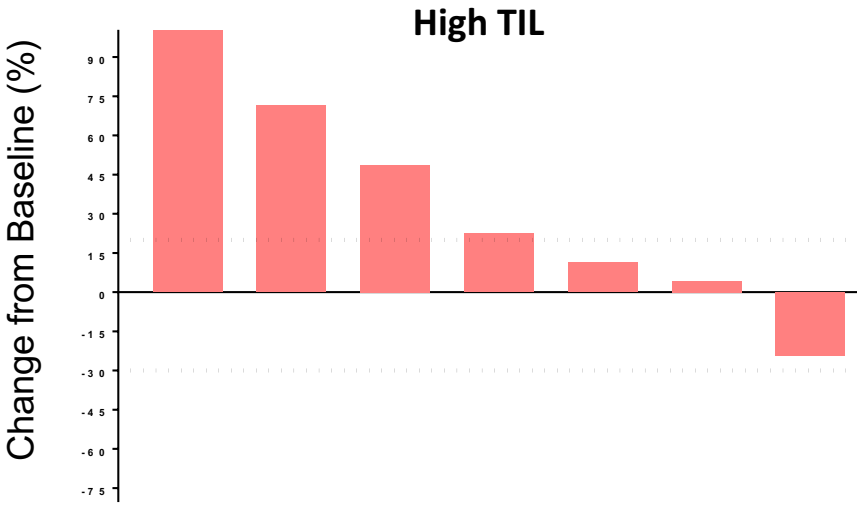
- ✓ PP survival curve has not yet reached median
- ✓ m(OS) of nivolumab alone = 12.2 months



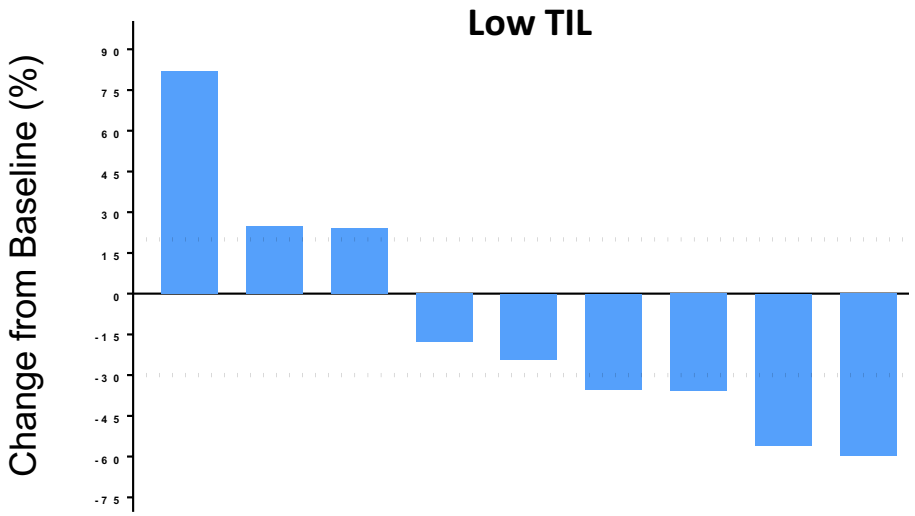
*N Engl J Med 2015; 373: 1627-1639

Target Lesion Response Based on Initial TIL Status

- ✓ HS-110 shows effect in low TIL “cold tumor” patients who typically do not respond well to PD-1 inhibitors
- ✓ 4 of 9 achieved a partial clinical response



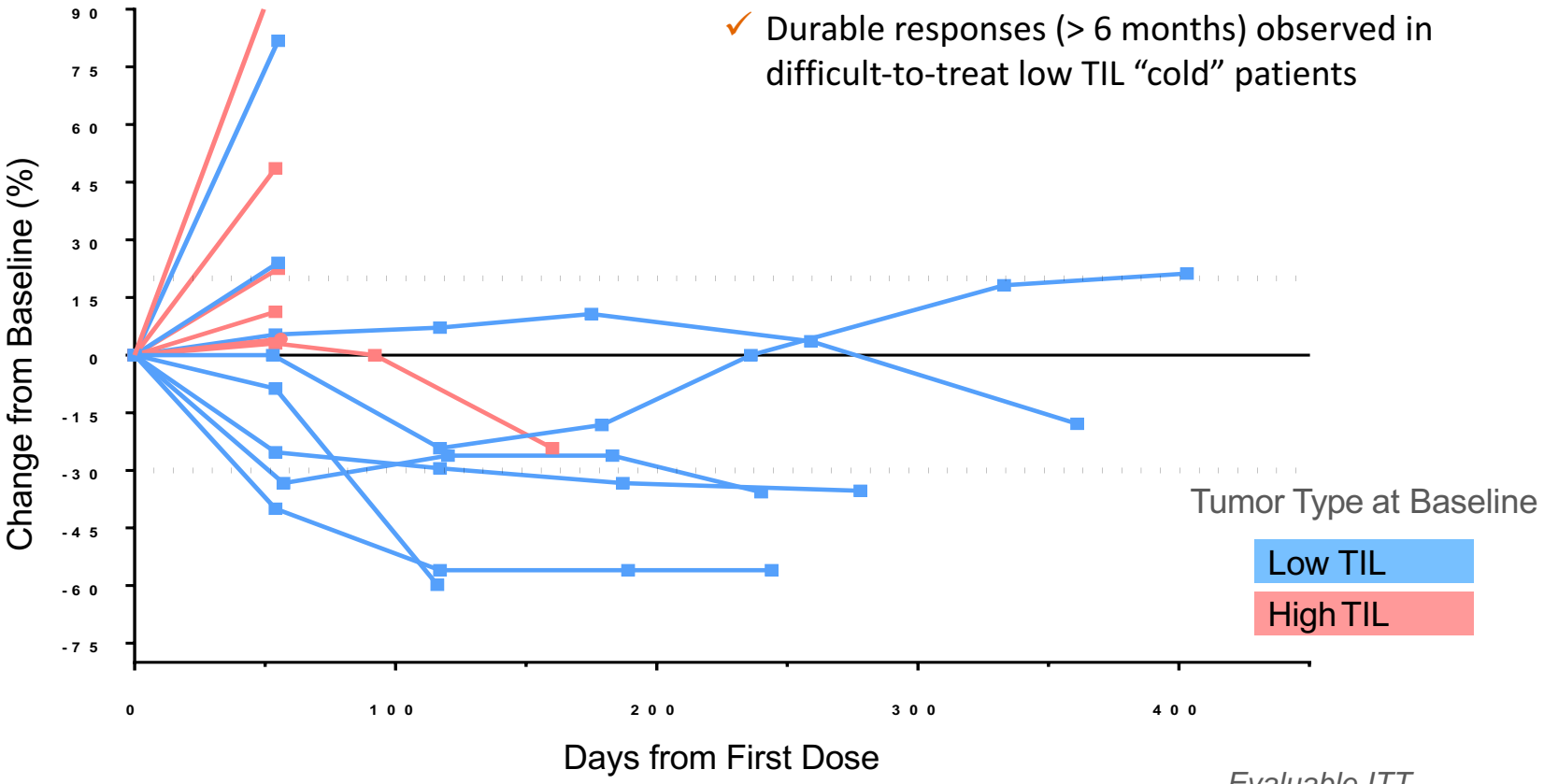
>10% CD8+ TIL at Baseline



≤10% CD8+ TIL at Baseline

Evaluable ITT Population

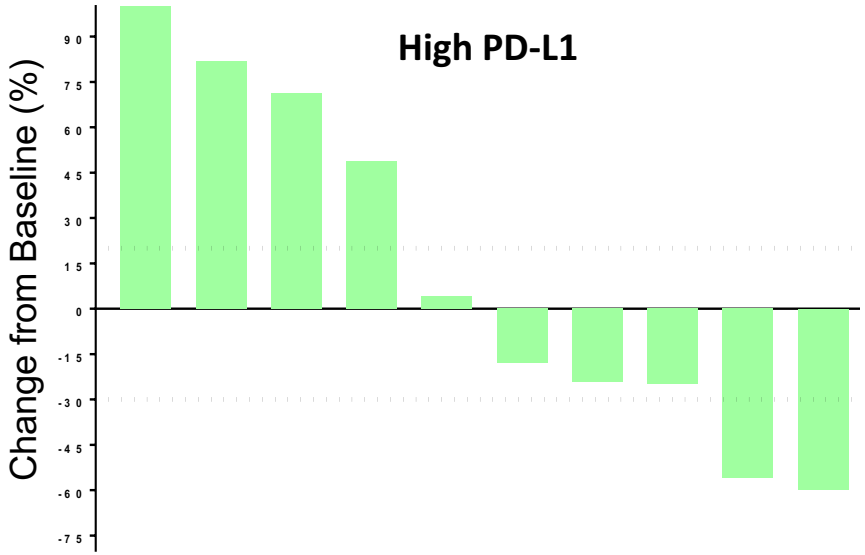
Durable Target Lesion Responses Based on Initial TIL Status



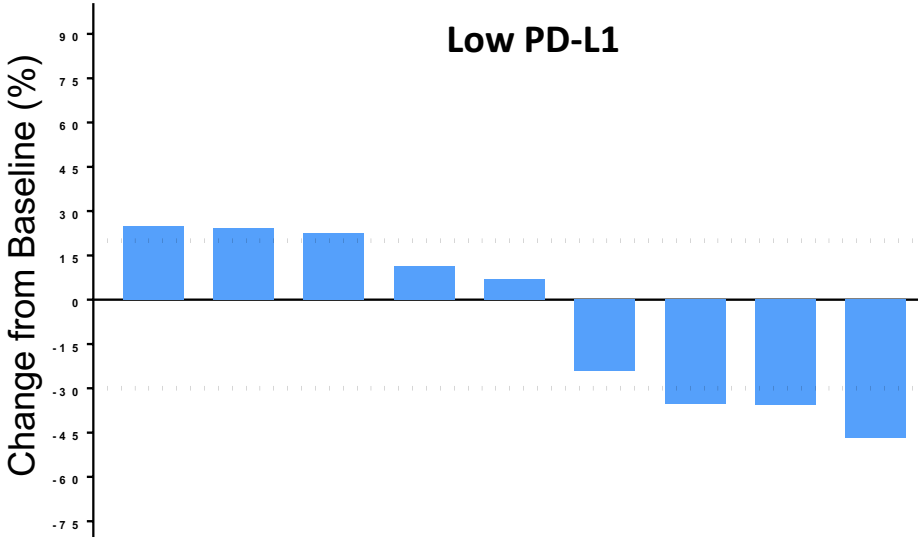
Evaluable ITT Population

Target Lesion Response Based on Initial PD-L1 Status

- ✓ HS-110 shows effect in low PD-L1 patients, who typically do not respond to checkpoint inhibitors



≥1% PD-L1 Tumor Type at Baseline

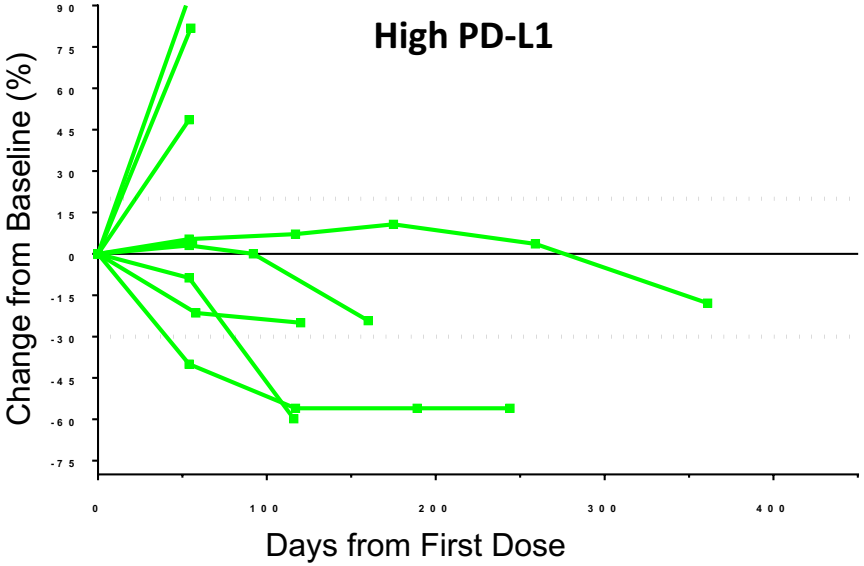


<1% PD-L1 Tumor Type at Baseline

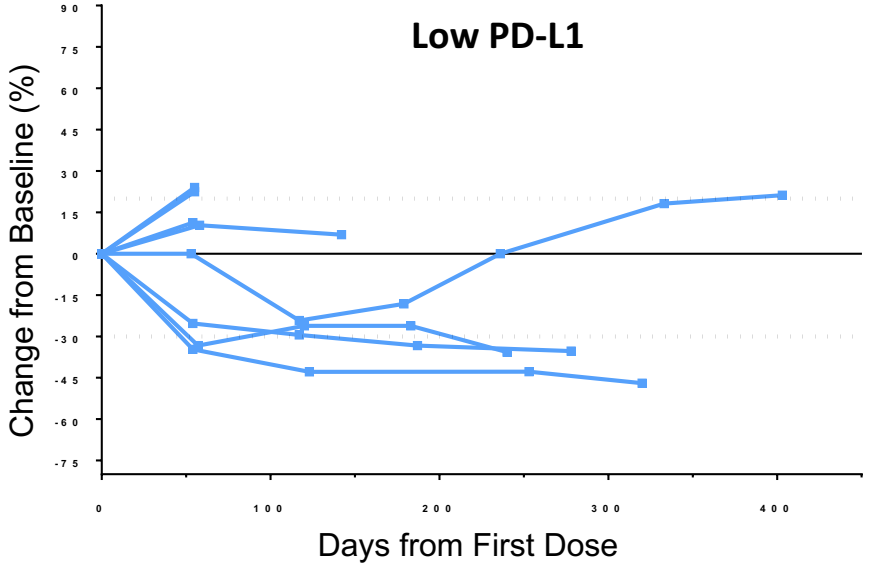
Evaluable ITT Population

Durable Target Lesion Responses Based on Initial PD-L1 Status

- ✓ Durable responses observed in difficult-to-treat low PD-L1 patients



≥1% PD-L1 Tumor Type at Baseline

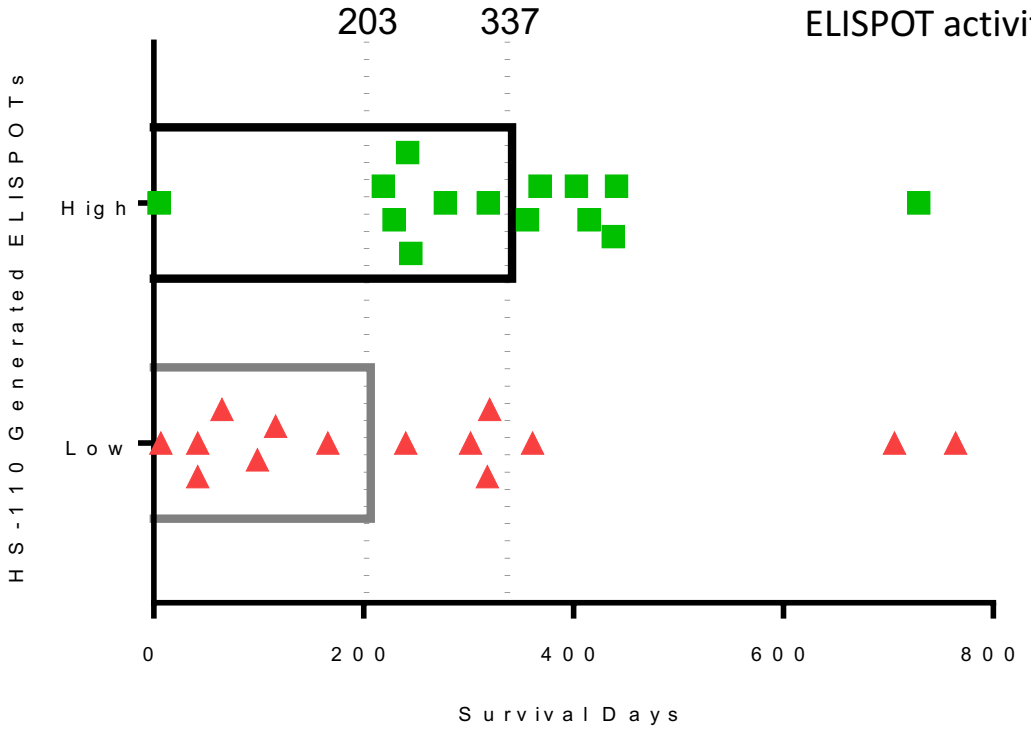


<1% PD-L1 Tumor Type at Baseline

Evaluable ITT Population

ELISPOT Activity and Survival

- ✓ A trend of survival benefit is observed higher ELISPOT activity of immune response



High = ELISPOT activity **above** the median of patients tested
Low = ELISPOT activity **below** the median of patients tested

Summary of Interim Data

- ✓Tumor shrinkage and disease control demonstrated in a majority of evaluable patients
  - ✓Overall responses are durable and long lasting
  - ✓While survival data is still maturing, the median overall survival has not yet been reached
- ✓HS-110 shows durable responses in difficult-to-treat low TIL “cold tumor” patients
- ✓HS110 shows durable responses in low PD-L1 patients, who typically do not respond to checkpoint inhibitors
- ✓A trend of survival benefit is observed with higher ELISPOT activity reflective of tumor antigen-specific immune response

This data is consistent with HS-110 mechanism of action as well as data previously reported in our phase 1 trial