MEDICINA E ASSISTENZA DI PRECISIONE
*Firenze – 22 Novembre 2017*

# Immuno-Oncologia: verso una immunoterapia di precisione?


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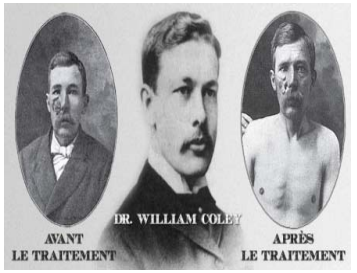
# Cancer immunotherapy, a very long standing concept

The concept that a vaccine could be useful in the treatment of cancer is a long-held hope coming from the observation that patients with cancer who developed bacterial infections experienced remission of their malignancies.

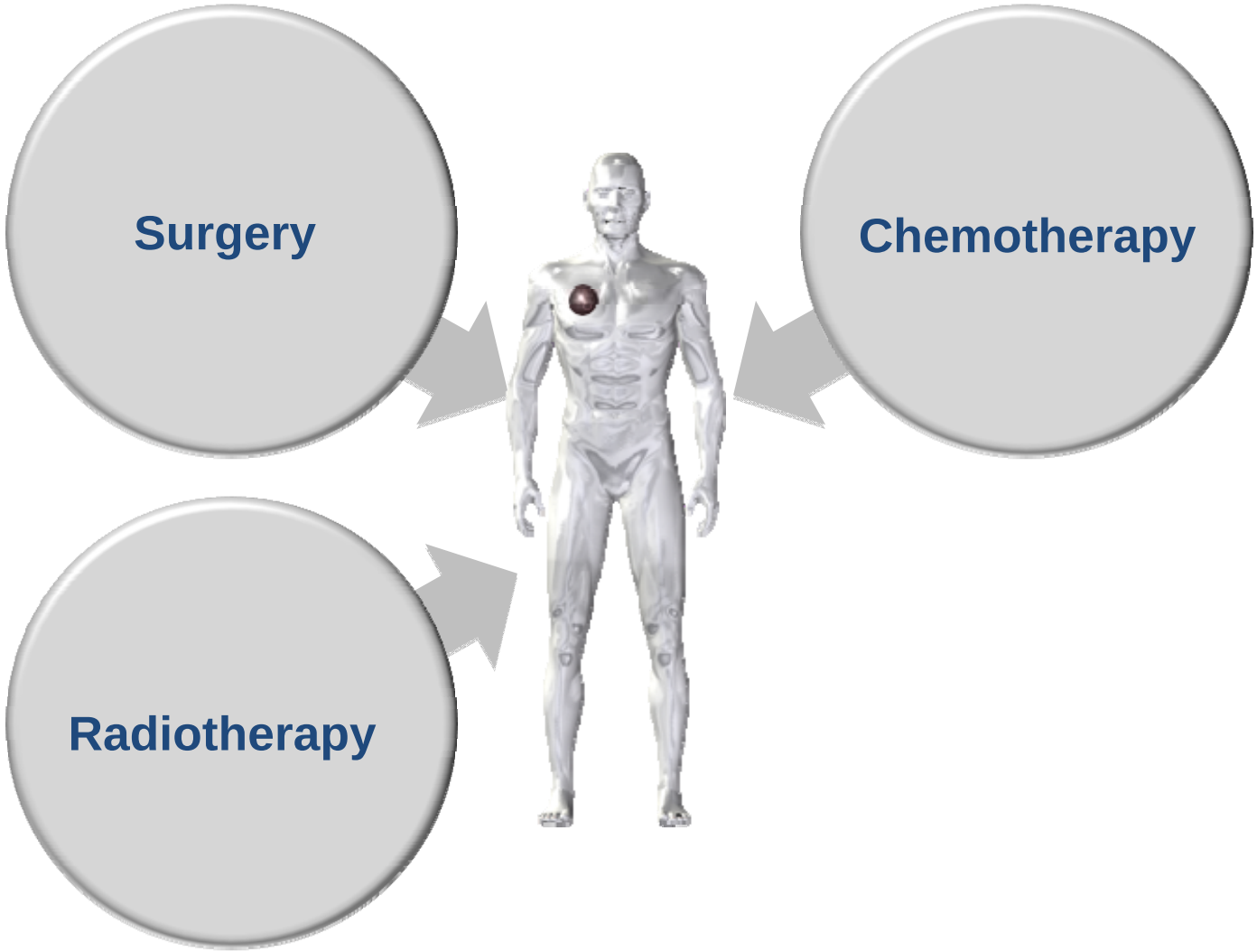
The earliest mention of cancer-fighting infections dates to a citation from Ebers papyrus (1550 B.C.) attributed to the Egyptian physician Imhotep (2600 B.C.), who recommended to treat tumors (swellings) with a poultice followed by an incision which would result in infection of the tumor and therefore its regression.

In 1896, the surgeon William Coley locally injected streptococcal broth cultures to induce erysipelas in an Italian patient (Mr. Zola) with an inoperable neck sarcoma, obtaining a tumour regression. Although therapy was toxic, the patient's tumour ultimately regressed, and he lived disease-free for 8 years before succumbing to his cancer.

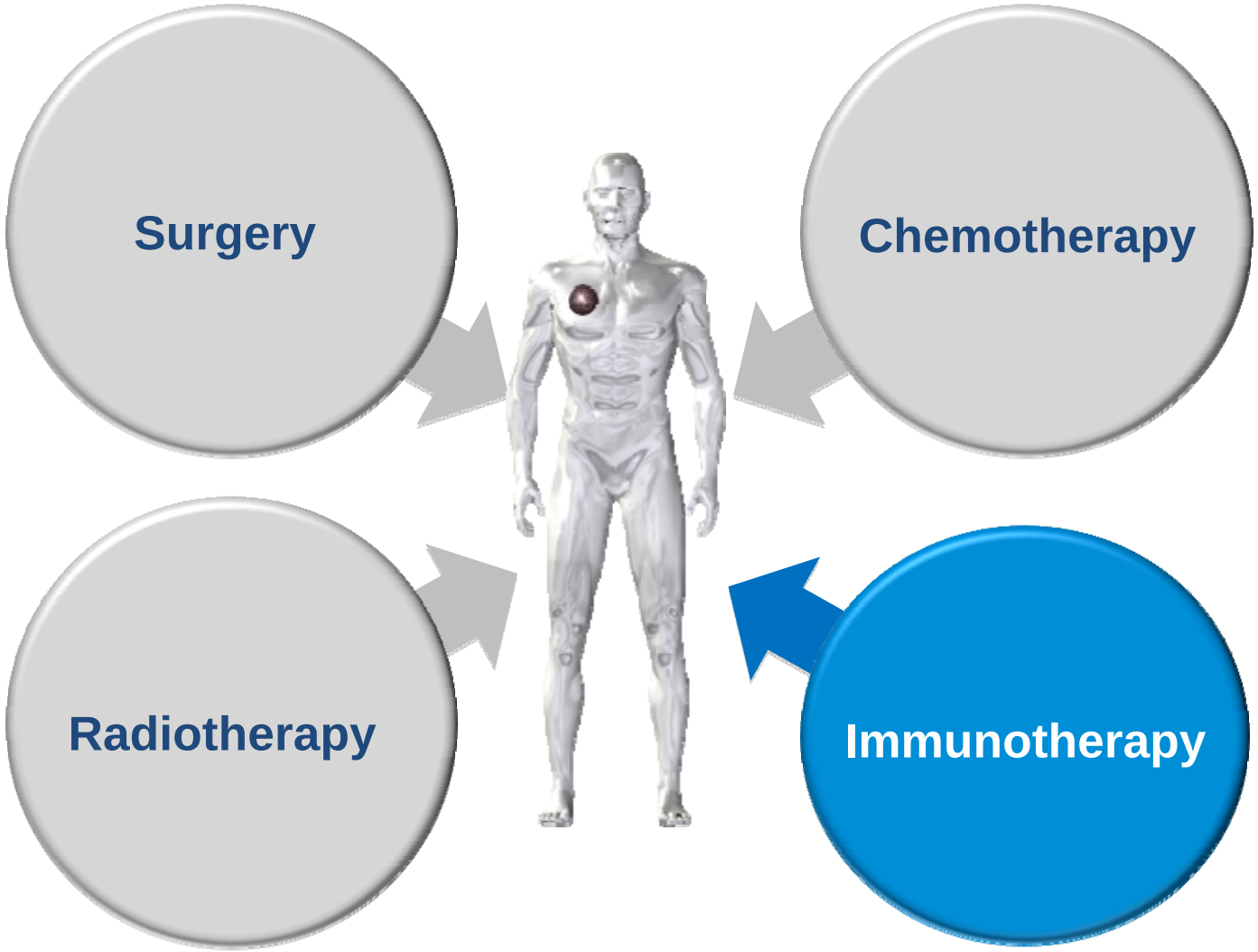



Venuti A. J Exp Clin Cancer Res. 2009.

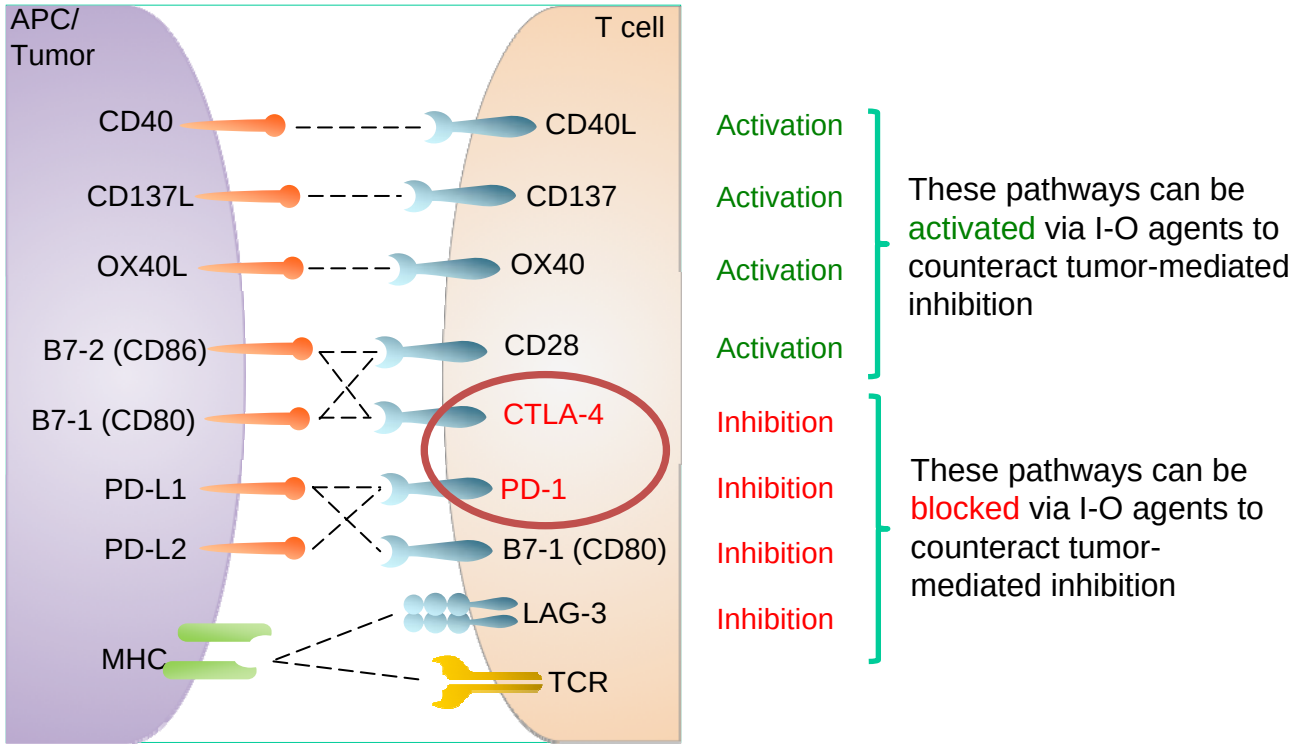
# Evolving Therapeutic Options for Cancer Treatment



# Evolving Therapeutic Options for Cancer Treatment



# T-cell Checkpoint and Co-stimulatory Pathways




Adapted from Pardoll DM 2012.

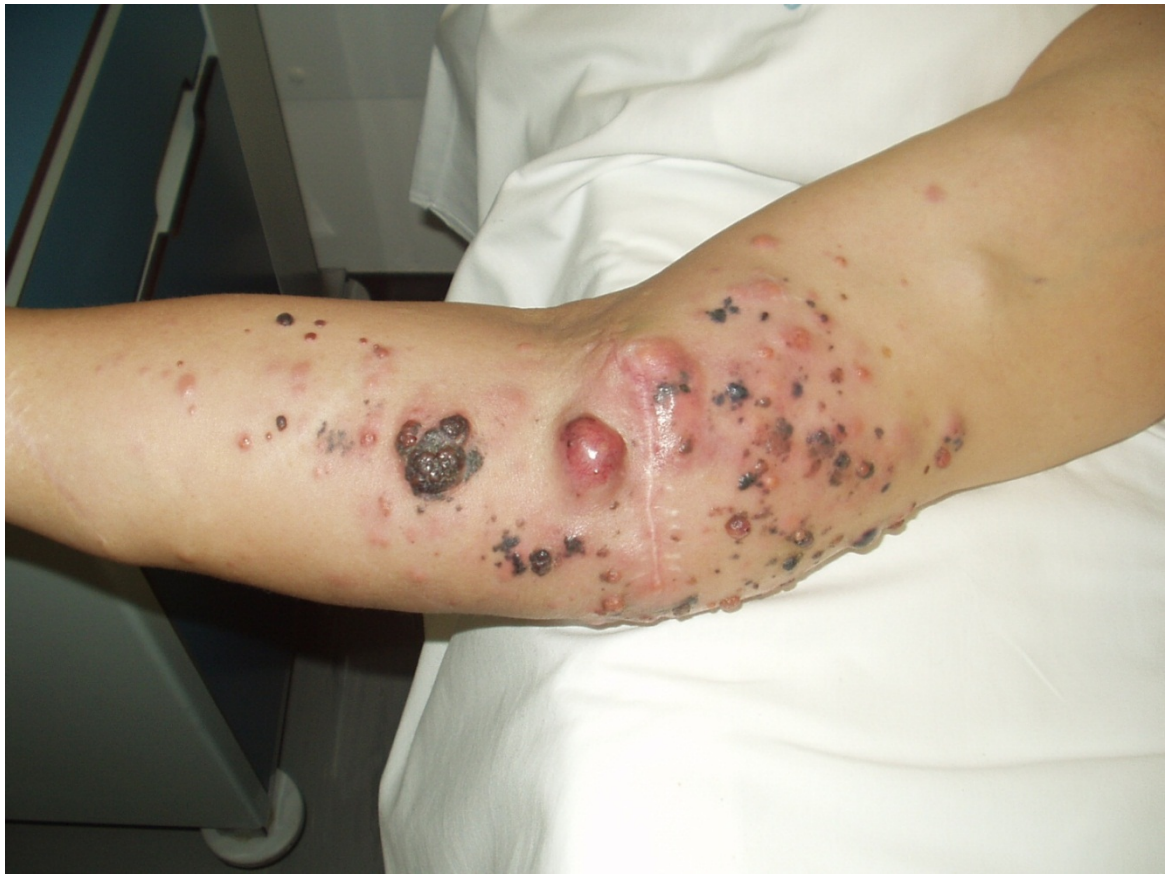
APC=antigen-presenting cell; CTLA-4=cytotoxic T-lymphocyte antigen-4; LAG-3=lymphocyte activation gene-3; MHC=major histocompatibility complex;
PD-1=programmed death-1; PD-L1=PD ligand-1; PD-L2=PD ligand-2; TCR=T-cell receptor.

*Pardoll DM. Nat Rev Cancer. 2012;12:252-264.*

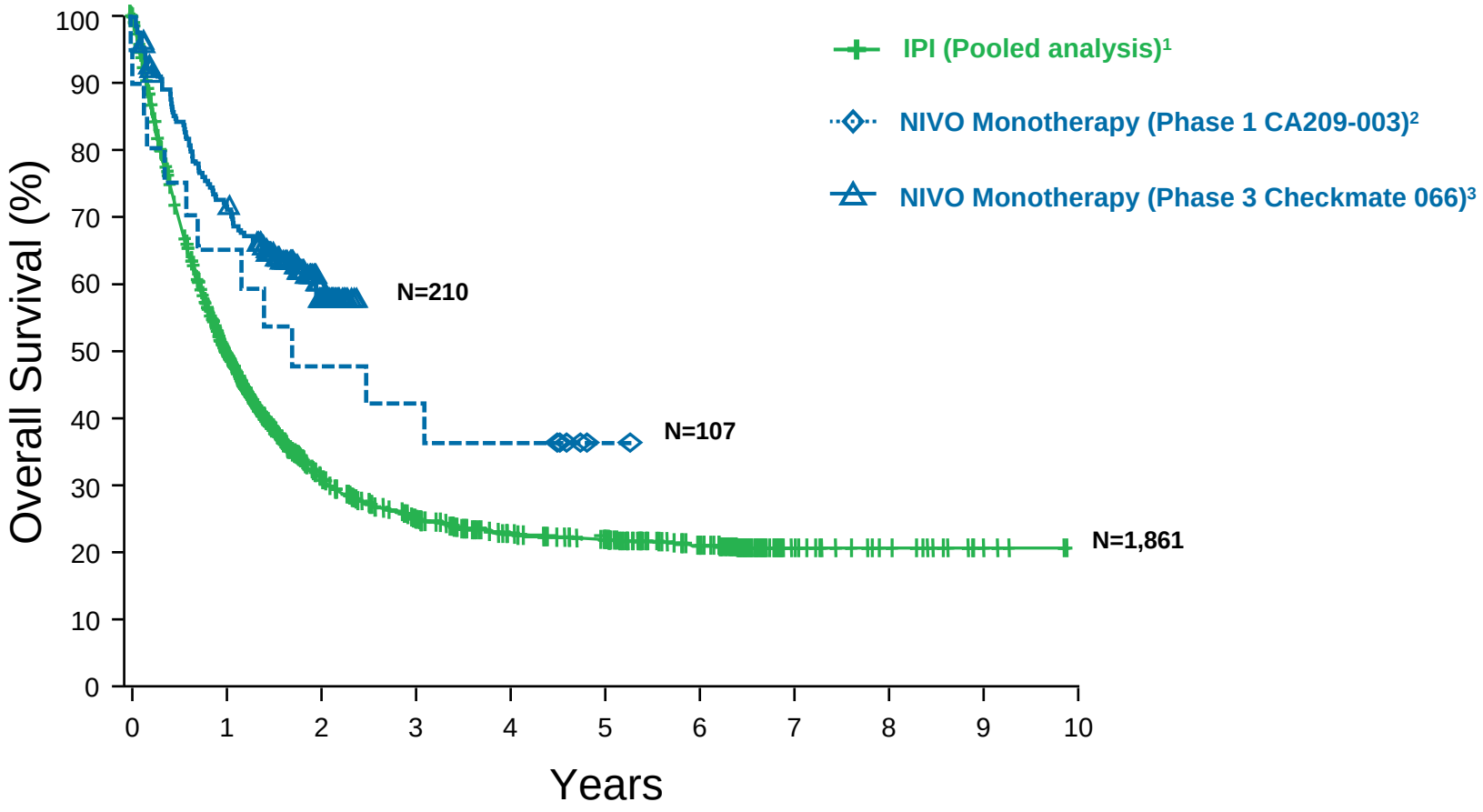
# Breakthrough of the Year 2013

# Melanoma as a tool for cancer research

- ✓ **Tissue samples readily accessible**
- ✓ **Adaptable to tissue culture**
- ✓ **Amenable to testing of novel therapies**

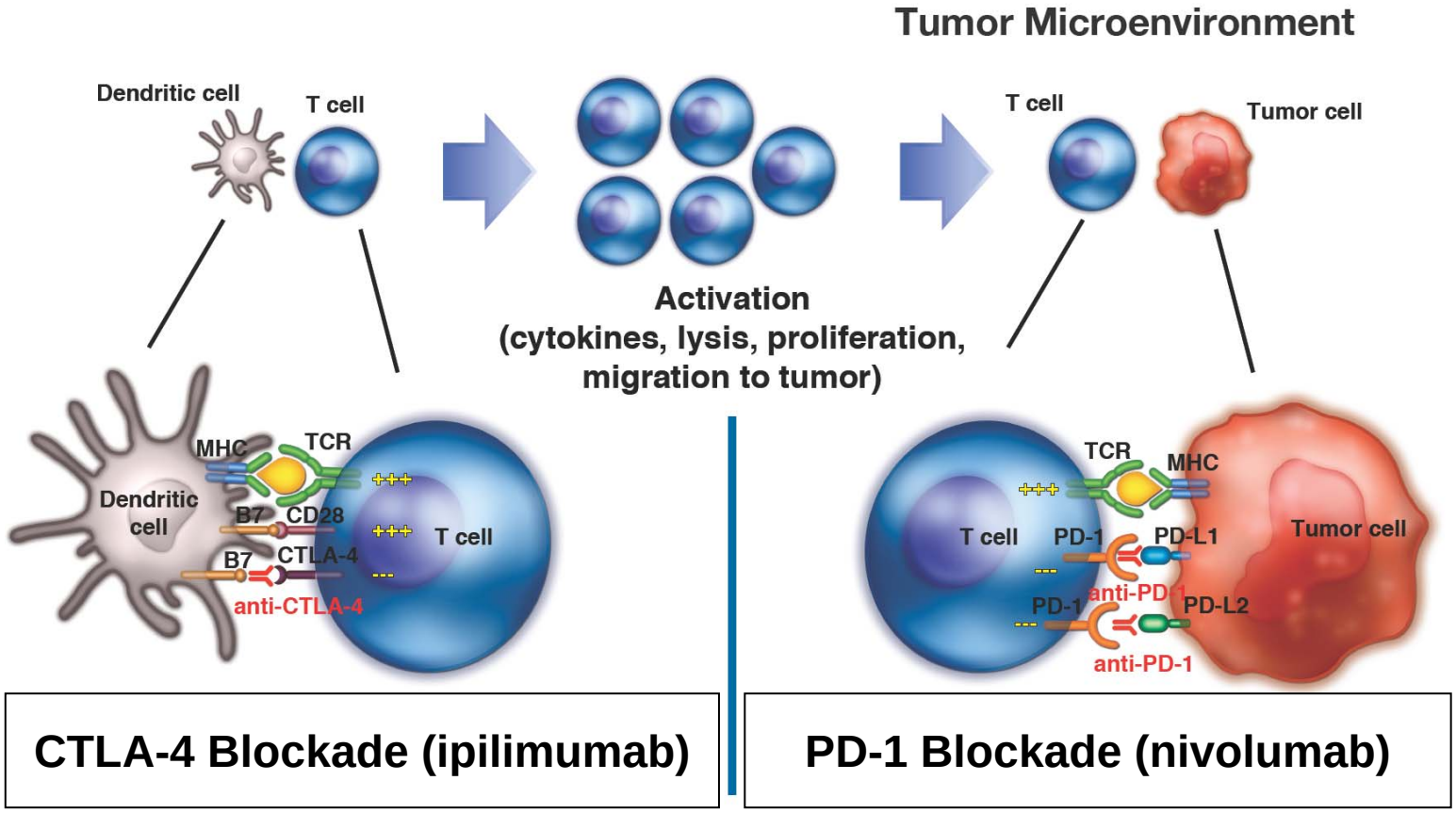


# Immune Checkpoint Inhibitors Provide Durable Long-term Survival for Patients with Advanced Melanoma



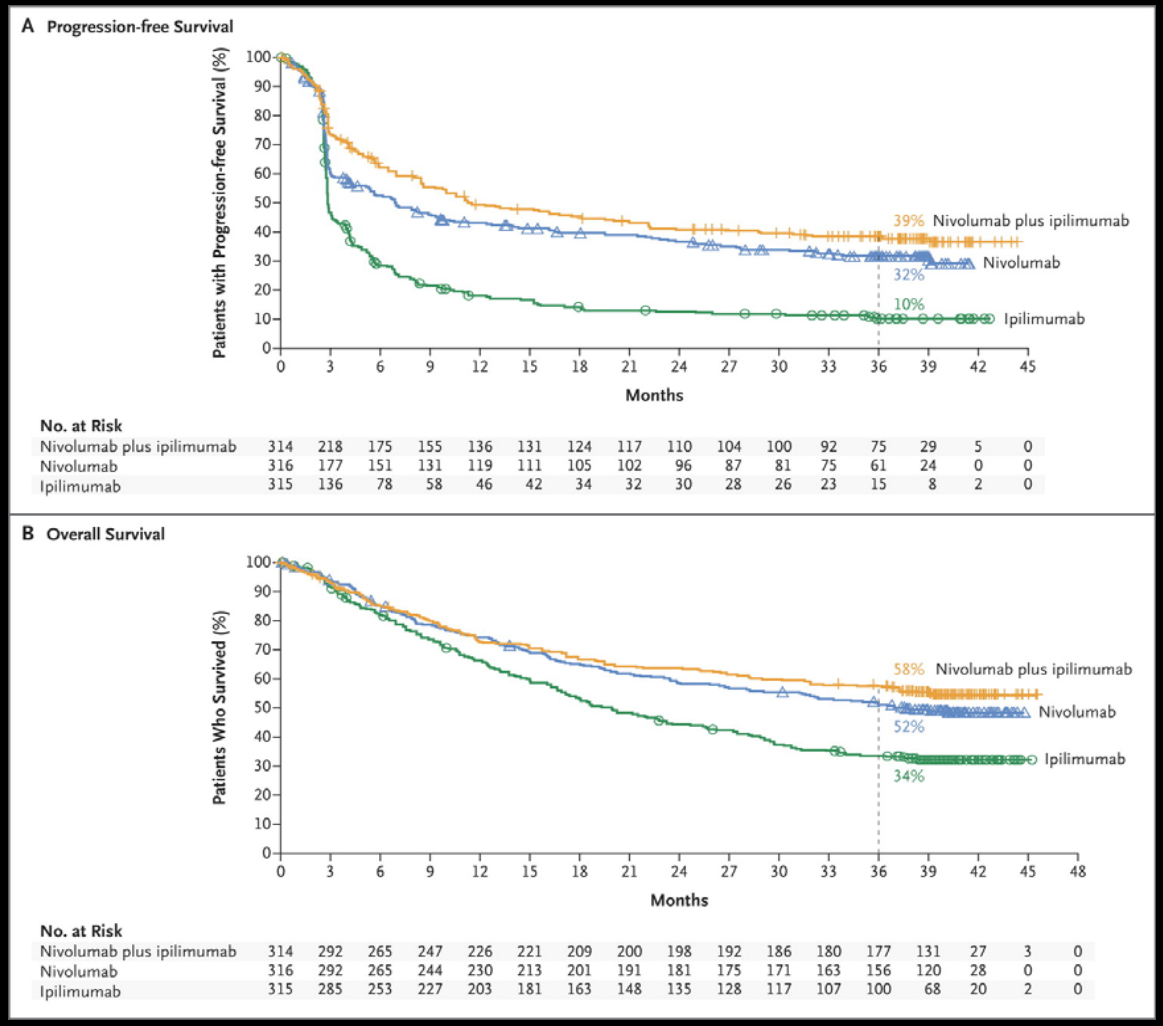

1. Schadendorf et al. *J Clin Oncol* 2015;33:1889-1894; 2. Current analysis; 3. Poster presentation by Dr. Victoria Atkinson at SMR 2015 International Congress.

# Immune Checkpoint Pathways




CTLA-4 = cytotoxic T-lymphocyte-associated antigen 4 ; MHC = major histocompatibility complex; PD-1 = programmed death-1; PD-L1 = programmed death ligand 1; TCR = T-cell receptor.

# Kaplan–Meier Estimates of Survival.




Wolchok JD et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1709684

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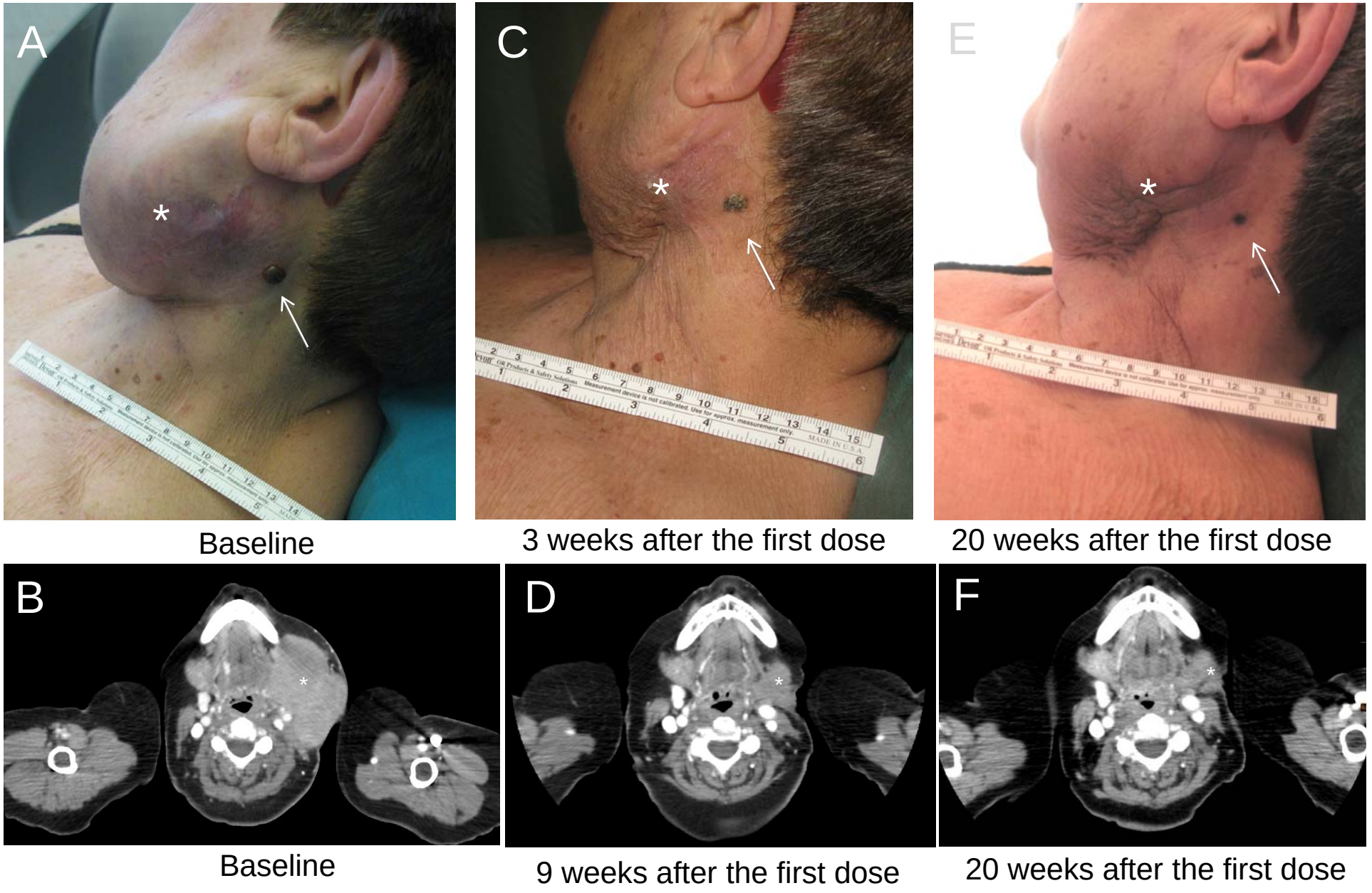
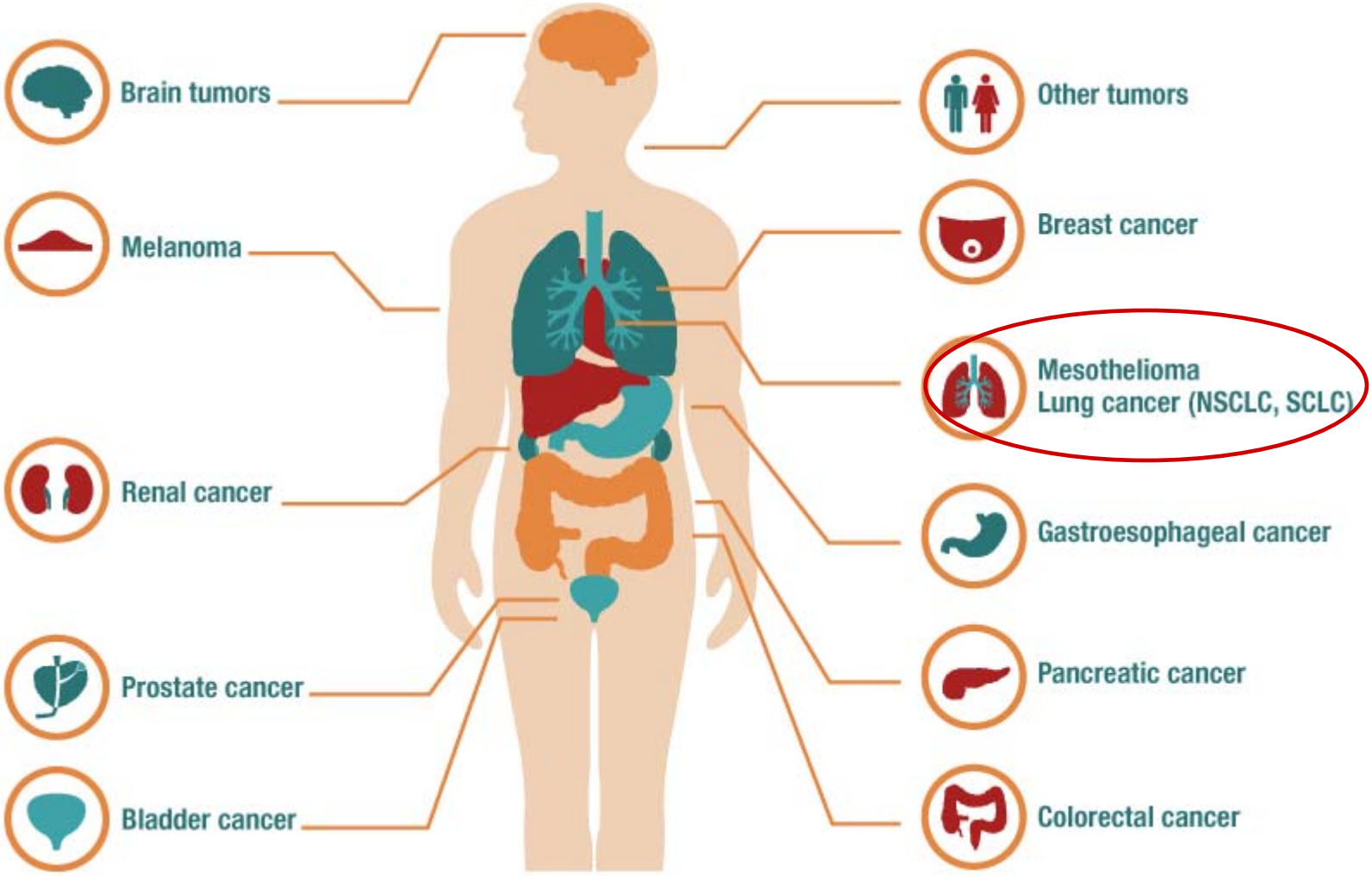



Baseline | 3 weeks after the first dose | 20 weeks after the first dose

Baseline | 9 weeks after the first dose | 20 weeks after the first dose

***Danielli R et al, unpublished***

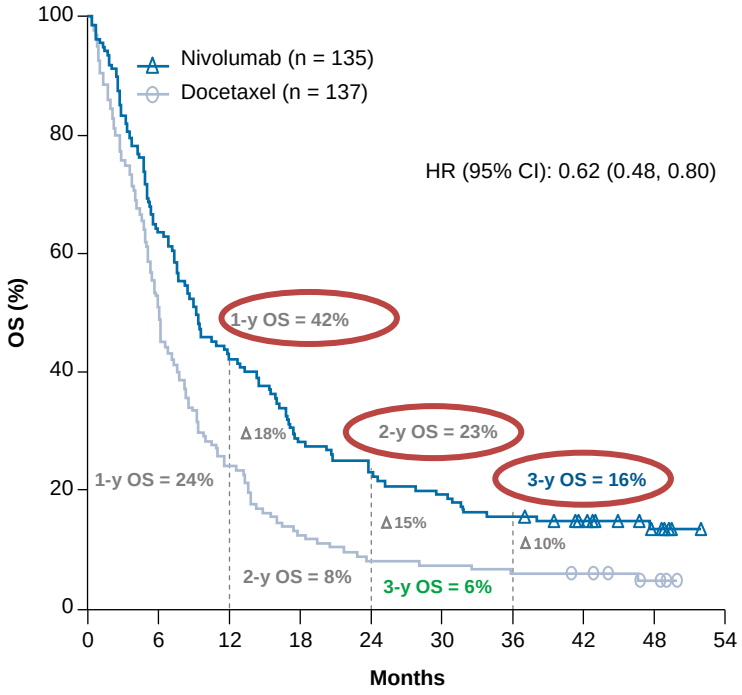
# Immunotherapy in solid tumors with immunomodulating antibodies




www.ImmunOncologia.org

# NSCLC Kaplan–Meier Estimates of OS (3 Years Minimum Follow-up)

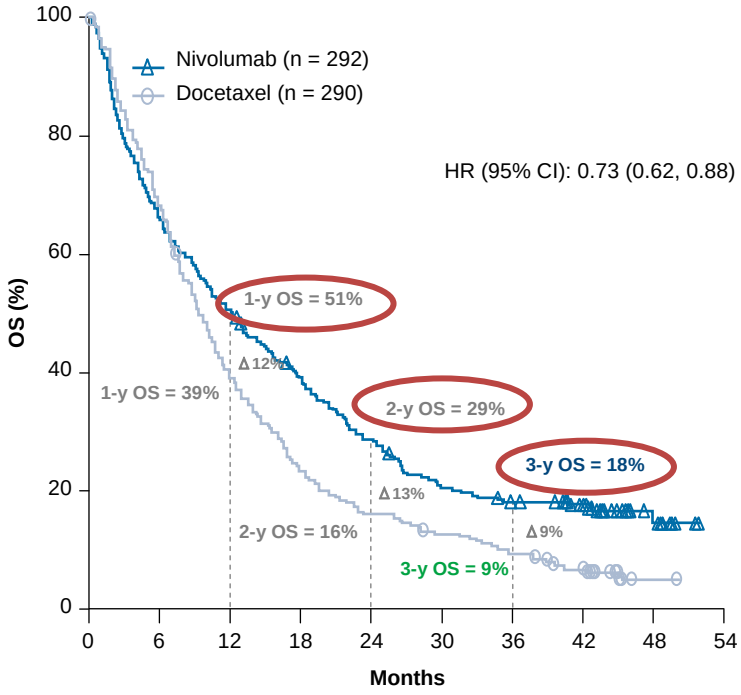
### CheckMate 017 (SQ NSCLC)




**No. of patients at risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab | 135 | 86 | 57 | 38 | 31 | 26 | 21 | 16 | 8 | 0 |
| Docetaxel | 137 | 69 | 33 | 17 | 11 | 10 | 8 | 7 | 3 | 0 |

### CheckMate 057 (non-SQ NSCLC)



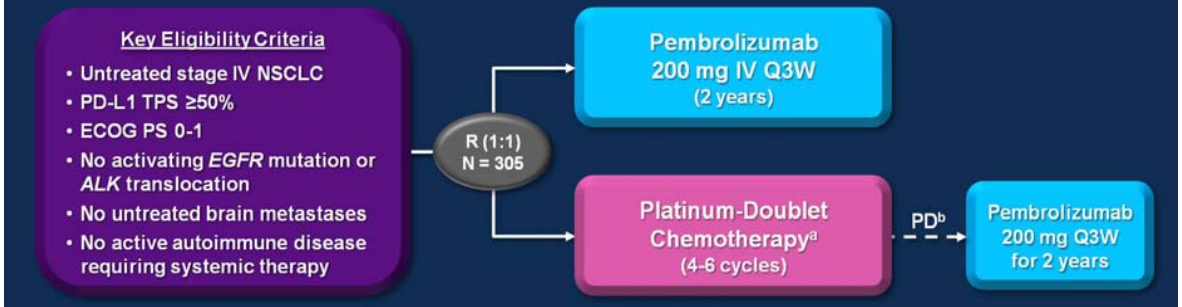

**No. of patients at risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab | 292 | 192 | 142 | 112 | 82 | 58 | 49 | 39 | 7 | 0 |
| Docetaxel | 290 | 148 | 67 | 46 | 35 | 26 | 16 | 1 | 0 | |

CI = confidence interval; HR = hazard ratio

*Felip E, ESMO 2017*

# KEYNOTE-024 Study Design (NCT02142738)




**Key End Points**

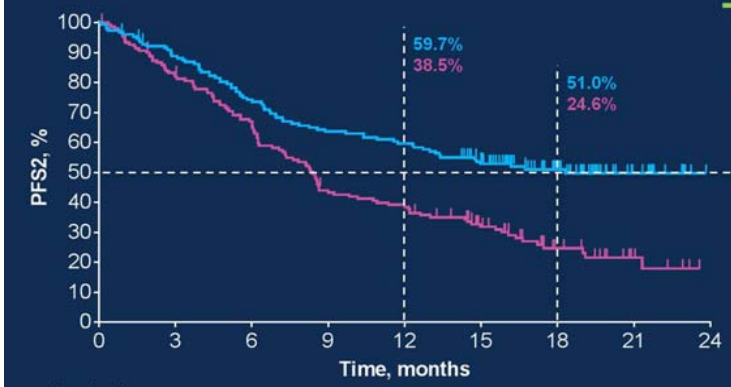
Primary: PFS (RECIST v1.1, blinded independent central review)

Secondary: OS, ORR, safety

Exploratory: DOR, PFS2

[a]Optional pemetrexed maintenance therapy for nonsquamous disease.
[b]To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.

# Kaplan-Meier Estimate of PFS2




| | Events, n | HR (95% CI) |
|---|---|---|
| Pembrolizumab | 74 | 0.54 (0.40-0.72) |
| Chemotherapy | 110 | $P < 0.001$[a] |

Median (95% CI)
18.3 mo (12.7-NE)
8.4 mo (6.8-9.8)

No. at risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 154 | 134 | 112 | 96 | 90 | 71 | 40 | 16 | 3 |
| 151 | 121 | 99 | 64 | 56 | 36 | 18 | 6 | 1 |

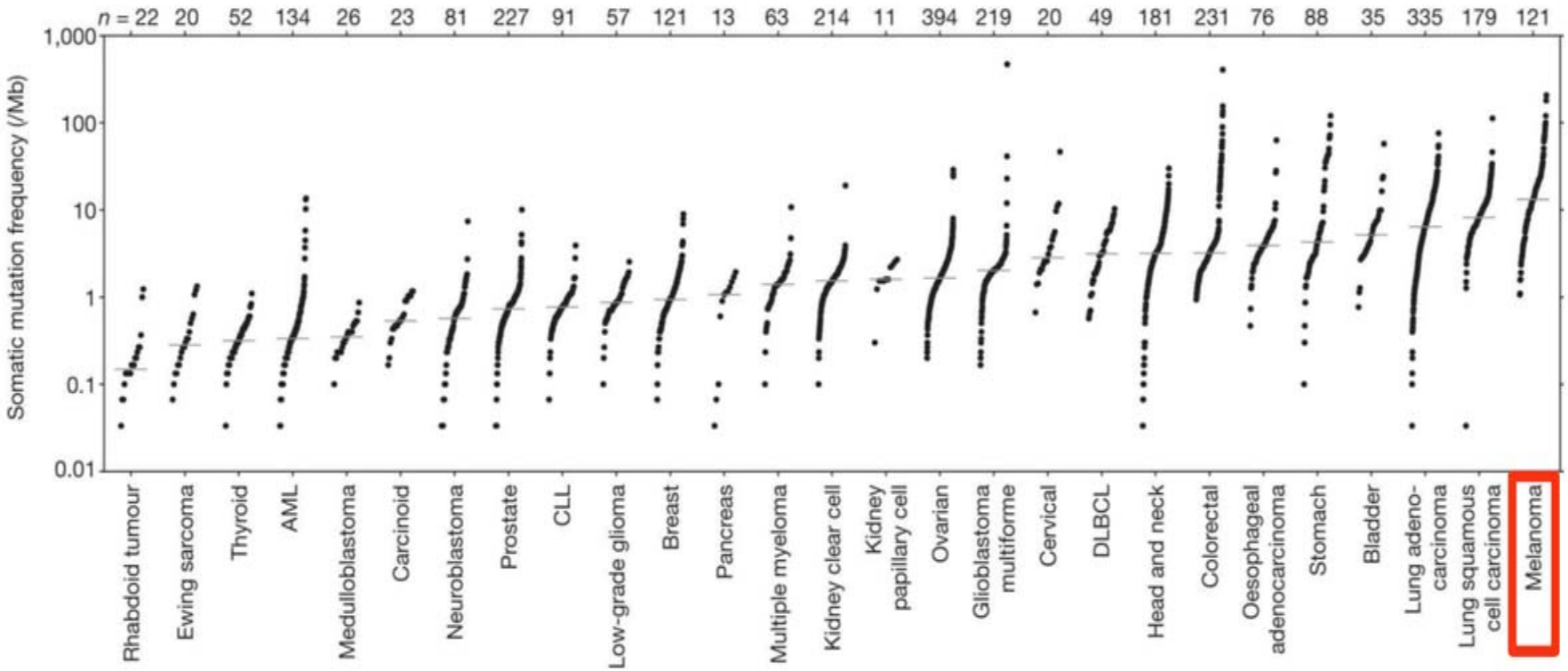
PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17



[a]Nominal *P* value.
Assessed per RECIST v1.1 by investigator review.
Data cutoff: Jan 5, 2017.

Presented By Julie Brahmer at 2017 ASCO Annual Meeting

# Somatic mutation frequencies observed in exomes from 3,083 tumour–normal pairs




*Lawrence et al, Nature 2013*

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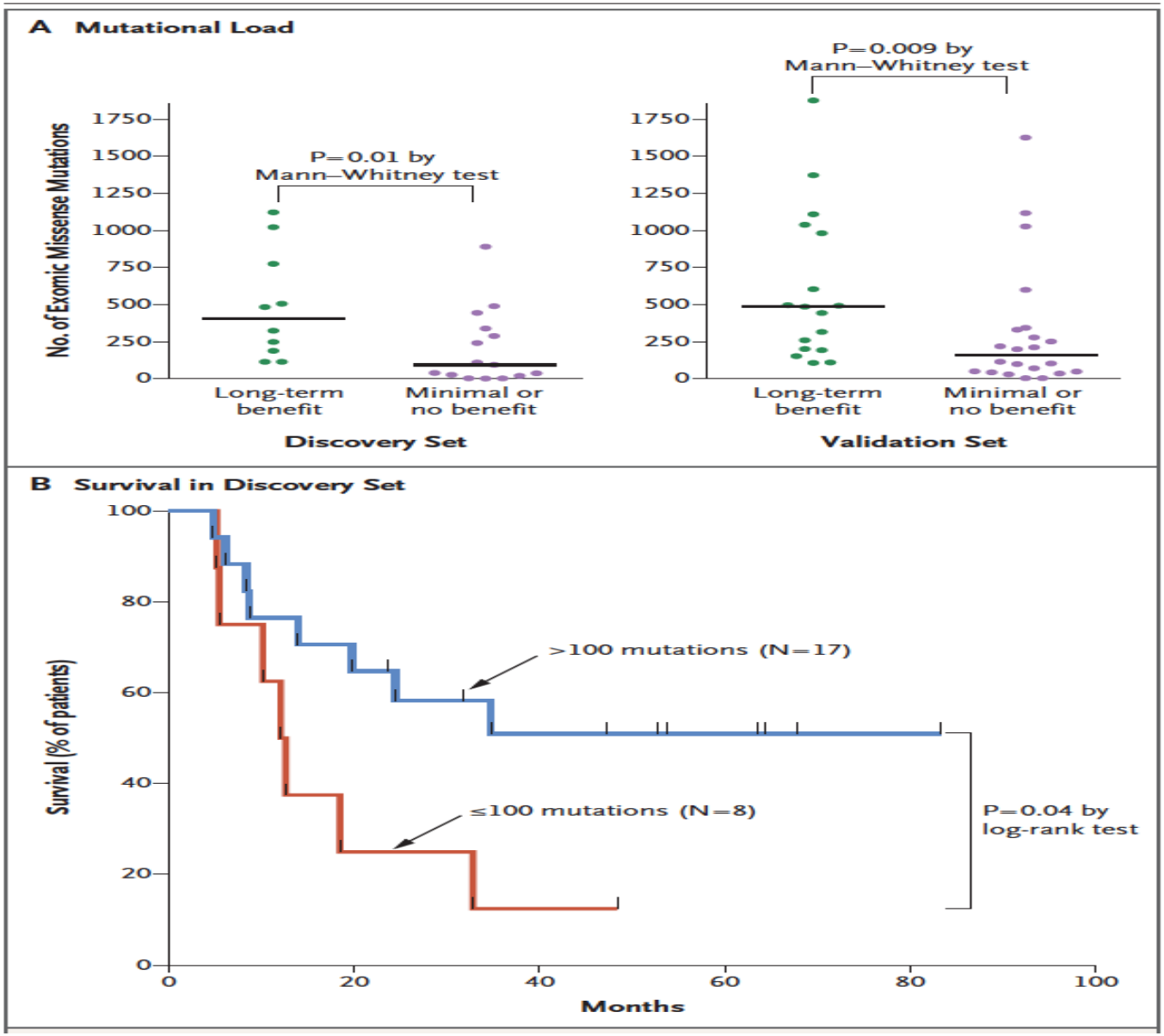
ORIGINAL ARTICLE

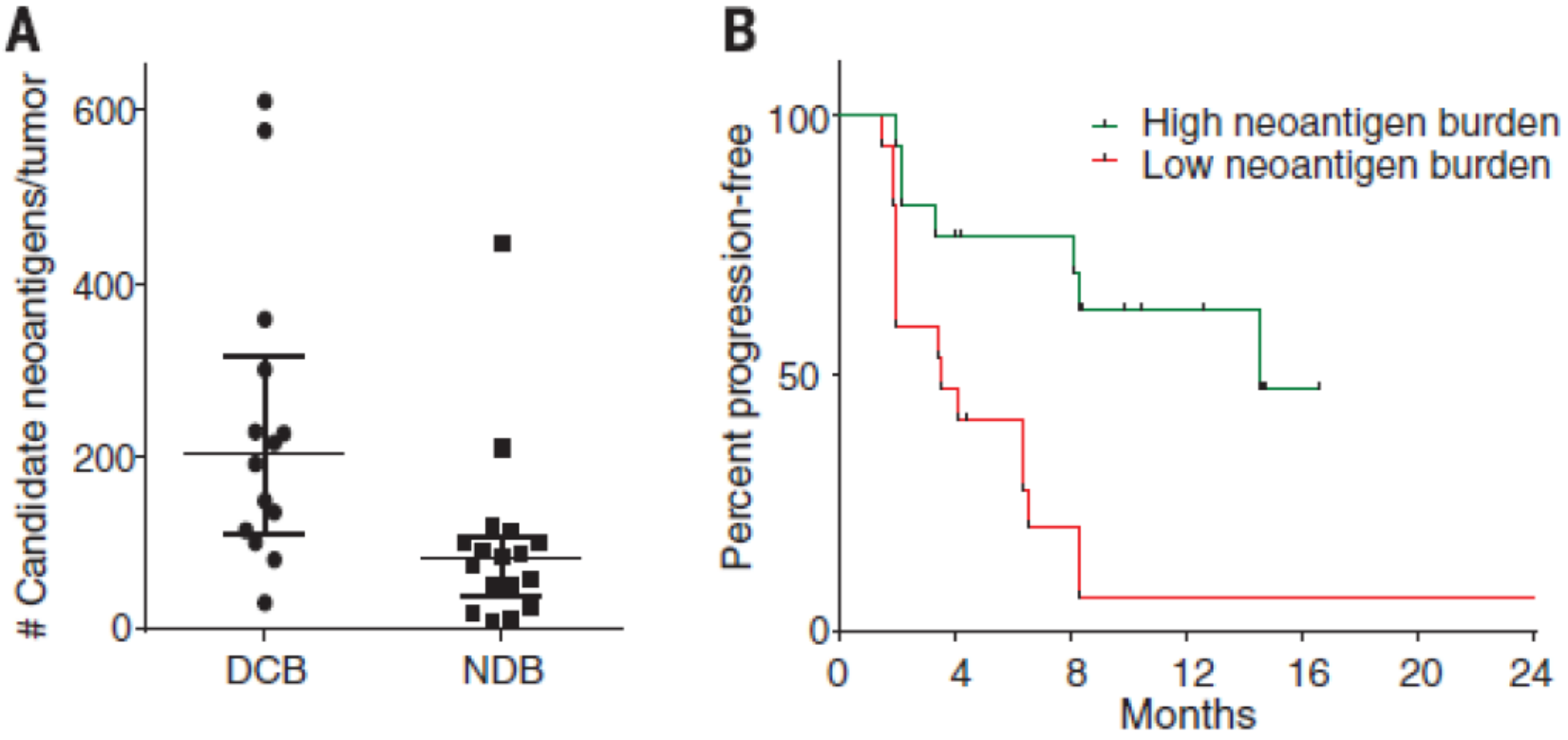
# Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma

Alexandra Snyder, M.D., Vladimir Makarov, M.D., Taha Merghoub, Ph.D., Jianda Yuan, M.D., Ph.D., Jesse M. Zaretsky, B.S., Alexis Desrichard, Ph.D., Logan A. Walsh, Ph.D., Michael A. Postow, M.D., Phillip Wong, Ph.D., Teresa S. Ho, B.S., Travis J. Hollmann, M.D., Ph.D., Cameron Bruggeman, M.A., Kasthuri Kannan, Ph.D., Yanyun Li, M.D., Ph.D., Ceyhan Elipenahli, B.S., Cailian Liu, M.D., Christopher T. Harbison, Ph.D., Lisu Wang, M.D., Antoni Ribas, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., and Timothy A. Chan, M.D., Ph.D.

# Mutational landscape of tumor according to Clinical Benefit from ipilimumab therapy (Snyder et al., 2014)

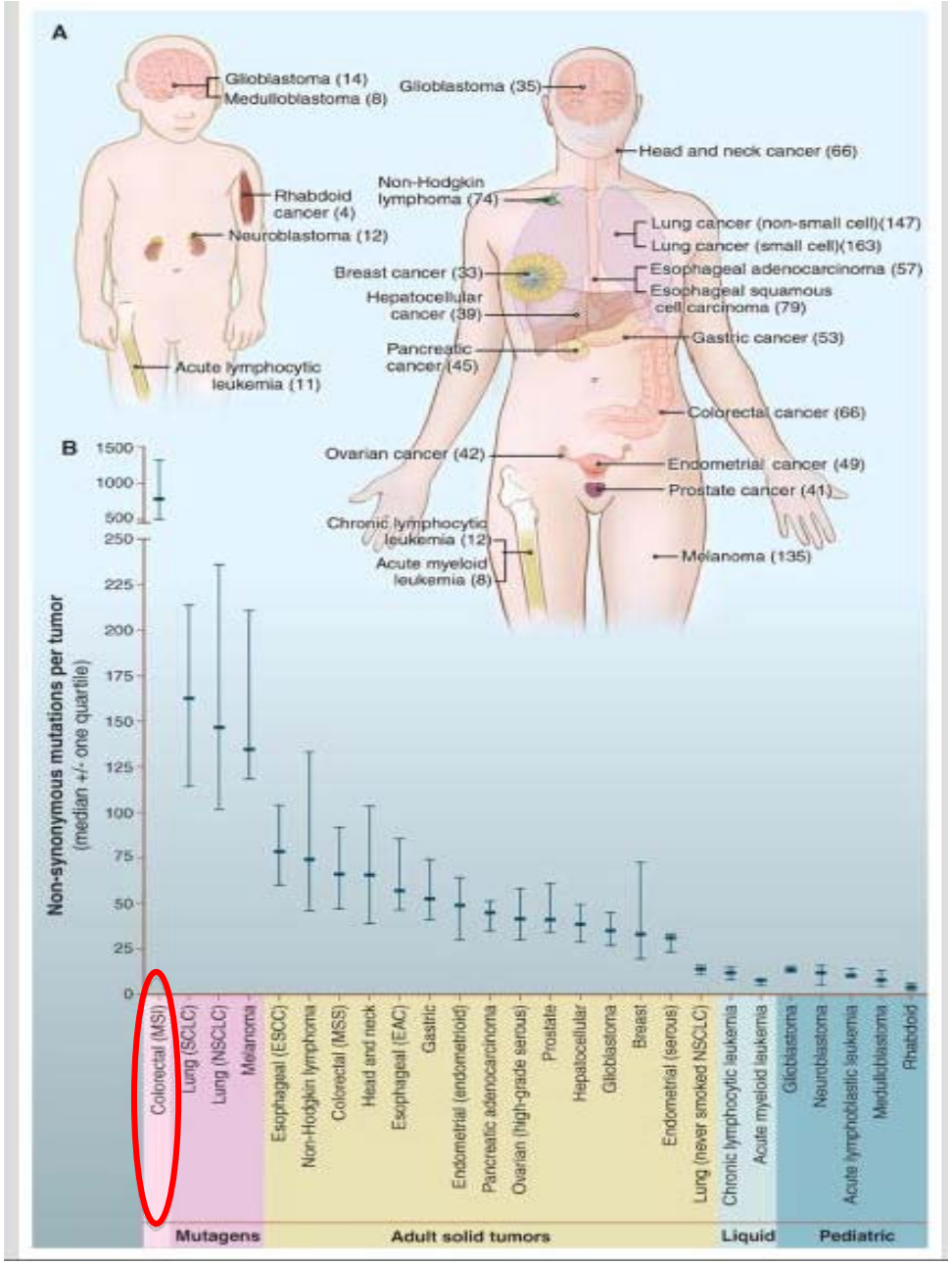


# Higher Neoantigen Burden is Associated with Response to Pembrolizumab in NSCLC

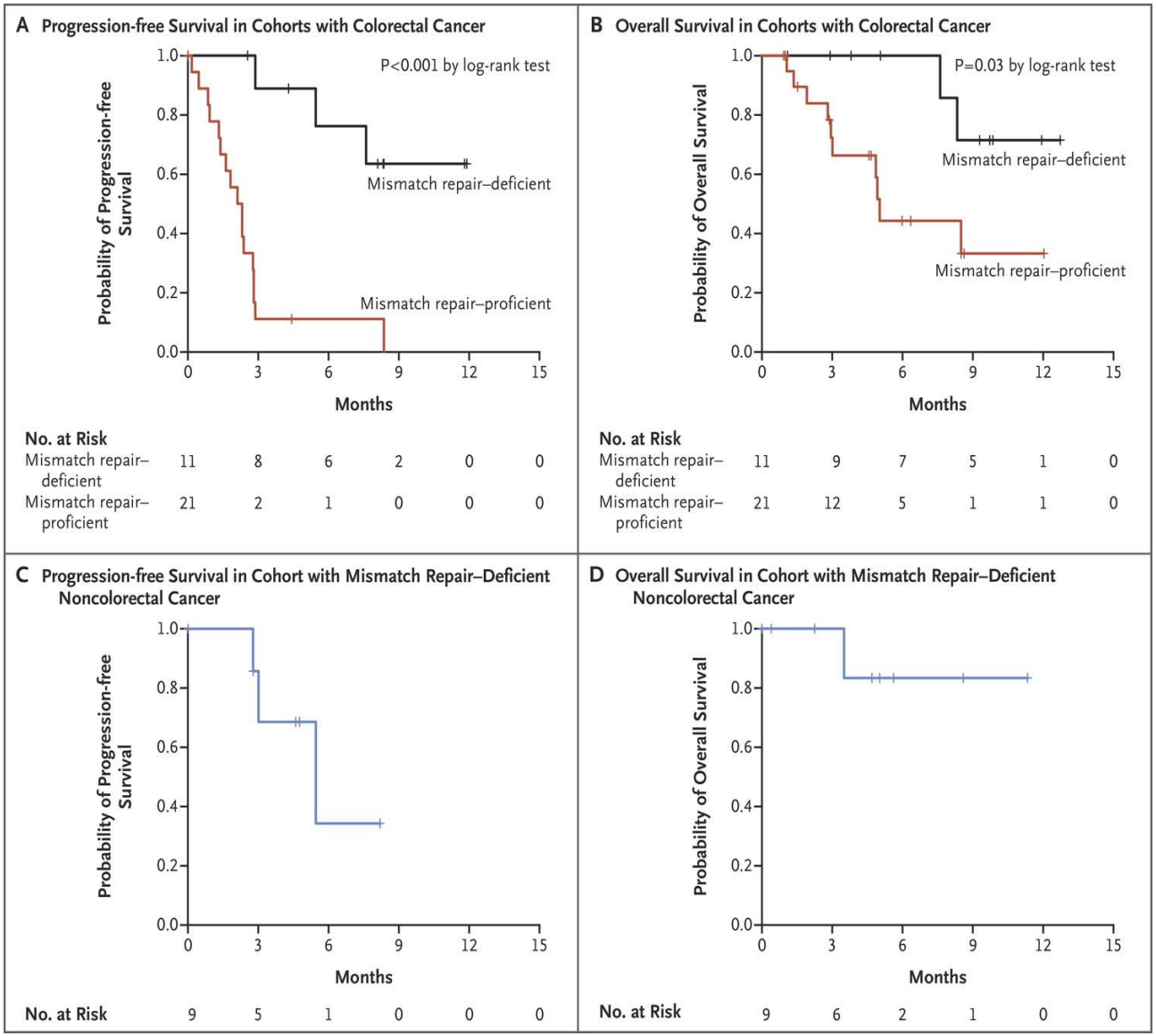



DCB: Durable clinical benefit (PR/SD >6months)
NDB: No durable benefit

Rizvi et al *Science* 2015

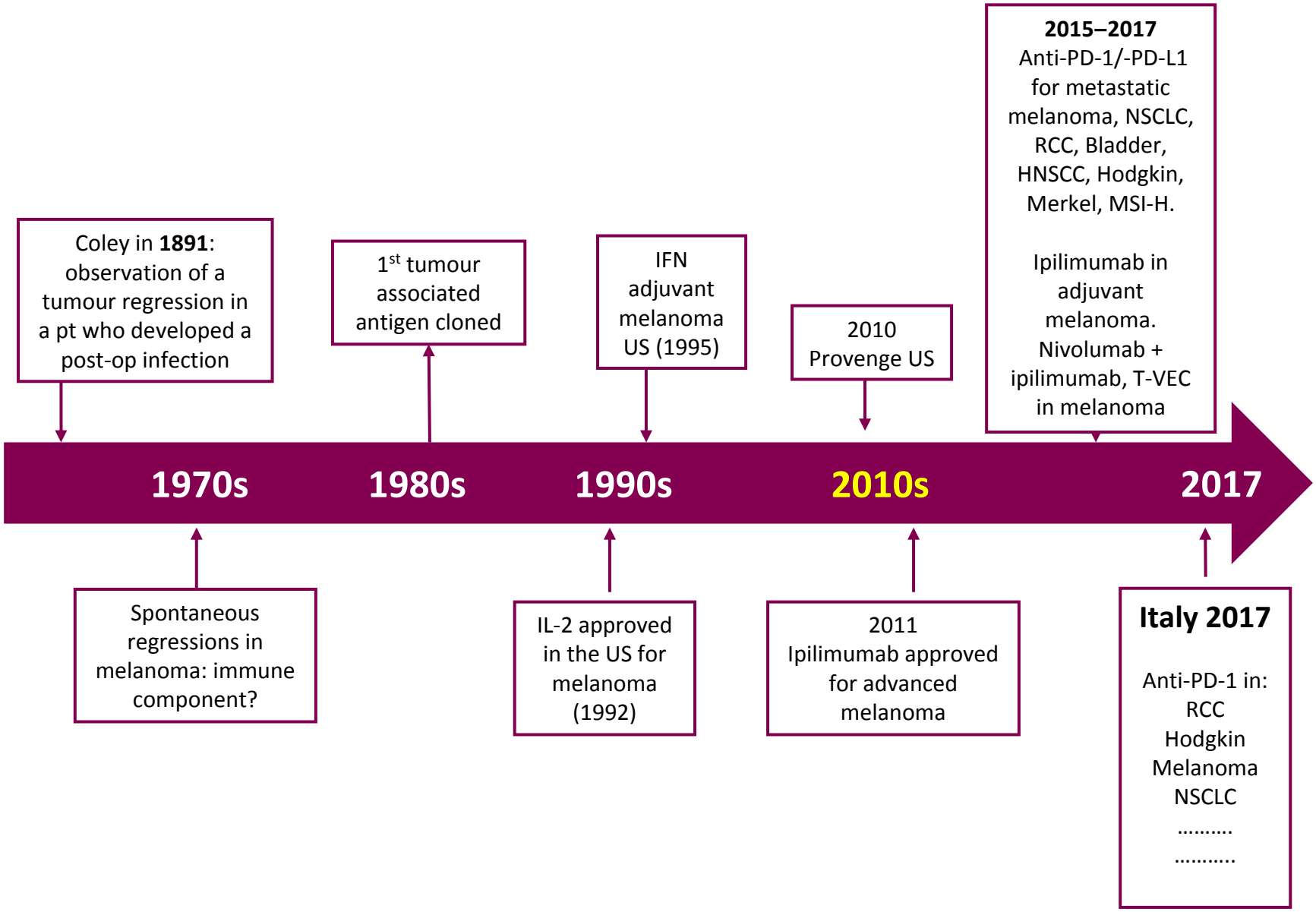

A
Glioblastoma (14)
Medulloblastoma (8)
Rhabdoid cancer (4)
Neuroblastoma (12)
Acute lymphocytic leukemia (11)
Glioblastoma (35)
Head and neck cancer (66)
Non-Hodgkin lymphoma (74)
Lung cancer (non-small cell)(147)
Lung cancer (small cell)(163)
Breast cancer (33)
Esophageal adenocarcinoma (57)
Esophageal squamous cell carcinoma (79)
Hepatocellular cancer (39)
Gastric cancer (53)
Pancreatic cancer (45)
Colorectal cancer (66)
Ovarian cancer (42)
Endometrial cancer (49)
Prostate cancer (41)
Chronic lymphocytic leukemia (12)
Acute myeloid leukemia (8)
Melanoma (135)
B
Non-synonymous mutations per tumor
(median +/- one quartile)
1500
1000
500
250
225
200
175
150
125
100
75
50
25
0
Colorectal (MSI)
Lung (SCLC)
Lung (NSCLC)
Melanoma
Esophageal (ESCC)
Non-Hodgkin lymphoma
Colorectal (MSS)
Head and neck
Esophageal (EAC)
Gastric
Endometrial (endometrioid)
Pancreatic adenocarcinoma
Ovarian (high-grade serous)
Prostate
Hepatocellular
Glioblastoma
Breast
Endometrial (serous)
Lung (never smoked NSCLC)
Chronic lymphocytic leukemia
Acute myeloid leukemia
Glioblastoma
Neuroblastoma
Acute lymphoblastic leukemia
Medulloblastoma
Rhabdoid
Mutagens
Adult solid tumors
Liquid
Pediatric

# Clinical Benefit of Pembrolizumab Treatment According to Mismatch-Repair Status



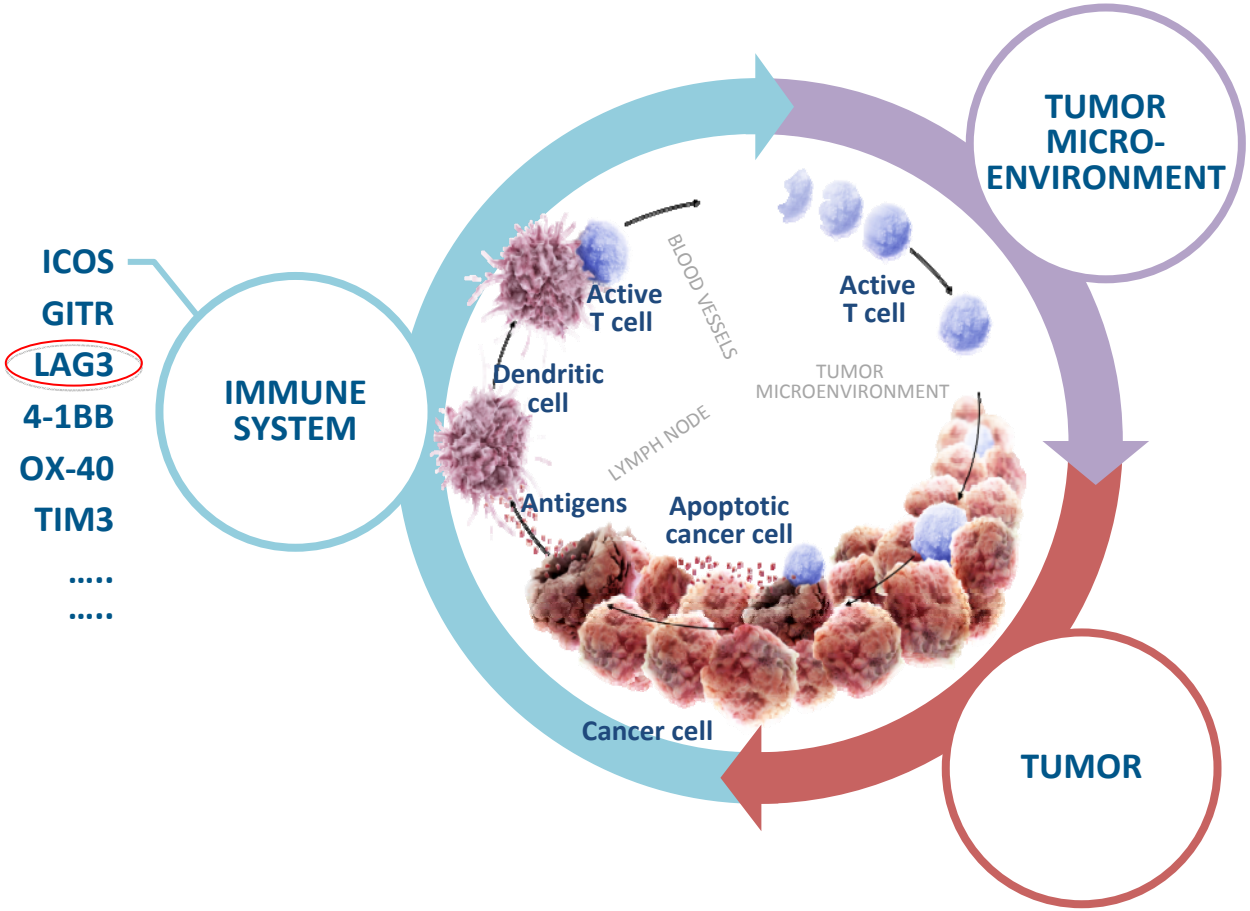

Le DT et al. N Engl J Med 2015; 372:2509-2520.

# A historical view of immunotherapy…

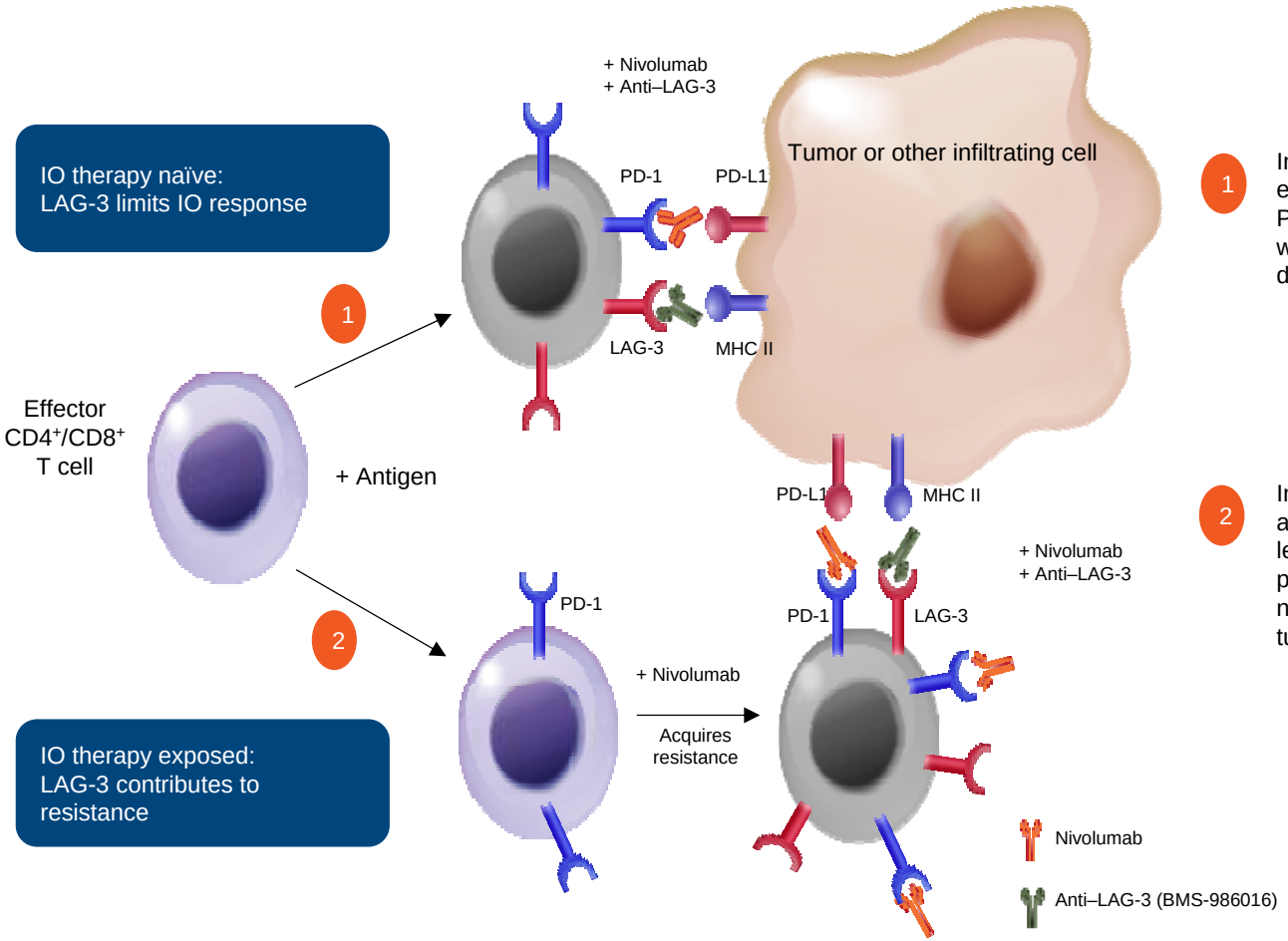


# The future of Cancer Immunotherapy

## Targeting and modulating multiple compartments



# LAG-3 in T-Cell exhaustion and anti–PD-1 resistance




1 In therapy-naïve patients, constitutive LAG-3 expression may limit the antitumor activity of PD-1 pathway blockade. Anti–LAG-3 combined with nivolumab may deepen or increase the durability of responses

2 In patients exposed to PD-1 pathway blockade, adaptive upregulation of LAG-3 expression may lead to treatment resistance and tumor progression. Anti–LAG-3 combined with nivolumab may restore T-cell activation and tumor response

# Anti-Lymphocyte Activation Gene-3 (anti–LAG-3; BMS-986016) in Combination With Nivolumab in Patients With Melanoma Previously Treated With Anti–PD-1/PD-L1

## Study design and endpoints

**BMS-986016 + Nivolumab (N = 212)**

**Dose-Escalation Phase**
(advanced solid tumors)

**Dose-Expansion Phase**
**Melanoma After Prior IO (n = 55)**
(other tumor-specific cohorts)

**Endpoints (dose expansion)**

- Preliminary efficacy[a] (co-primary)
- Safety/tolerability[b] (co-primary)
- Pharmacokinetics and pharmacodynamics
- Immunogenicity and QTc (secondary)
- Biomarkers (LAG-3 and PD-L1; exploratory)[c]

[a]Tumor response evaluated per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1[10] (investigator assessment). [b]Safety evaluated per Common Terminology Criteria for Adverse Events v4.0[11] during treatment and up to 135 days after discontinuation. [c]LAG-3 and PD-L1 expression (percent of positive cells within invasive margin, tumor, and stroma) evaluated using immunohistochemistry (IHC) assays on formalin-fixed, paraffin-embedded tumor sections. Immune cell LAG-3 expression (≥ 1% or < 1%) determined using mouse antibody clone 17B4; tumor cell PD-L1 expression (≥ 1% or < 1%) determined using Dako PD-L1 IHC 28-8 kit.

Ascierto P et al., ASCO 2017

# Results

## Efficacy in the Melanoma Prior–IO Cohort

**Table 4. Preliminary evidence of antitumor activity**

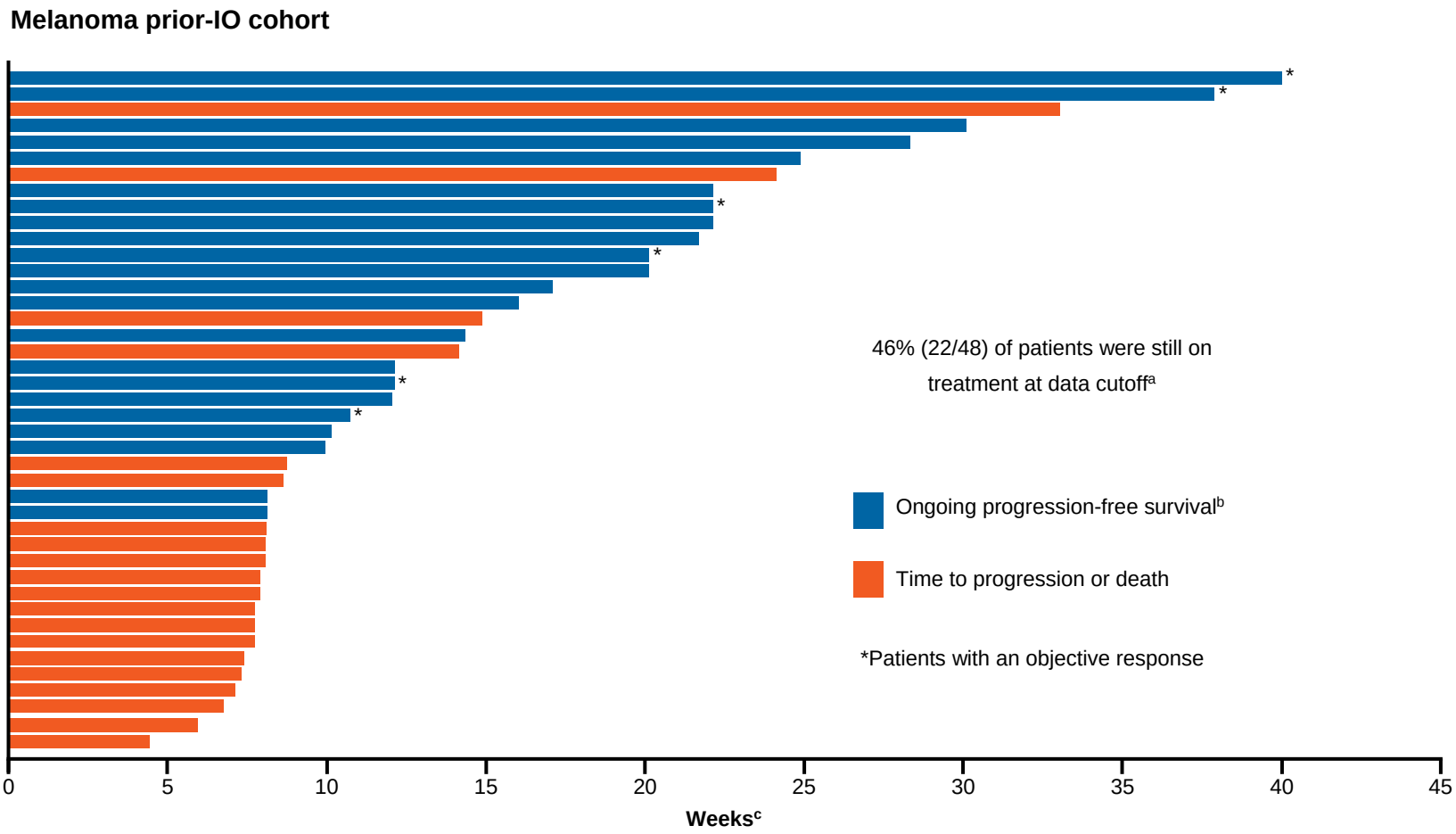
| Patients, n (%) | Mel Prior IO (n = 48[a]) |
|---|---|
| **BOR** | |
| CR | 0 |
| PR[b] | 6 (13) |
| SD | 20 (42) |
| PD | 16 (33) |
| Clinical progressions[c] | 6 (13) |
| **ORR**, 95% CI[b] | 6 (13), 4.7, 25 |
| LAG-3 ≥ 1% (n = 25) | 5 (20), 6.8, 41 |
| LAG-3 < 1% (n = 14) | 1 (7.1), 0.2, 34 |
| **DCR** (CR + PR + SD)[b] | 26 (54) |
| LAG-3 ≥ 1% (n = 25) | 16 (64) |
| LAG-3 < 1% (n = 14) | 5 (36) |

BOR, best overall response; DCR, disease control rate. [a]All response-evaluable patients; all progressed on prior anti–PD-1/PD-L1 therapy. [b]Two responses were unconfirmed. [c]Occurred prior to first radiographic scan.

# Results

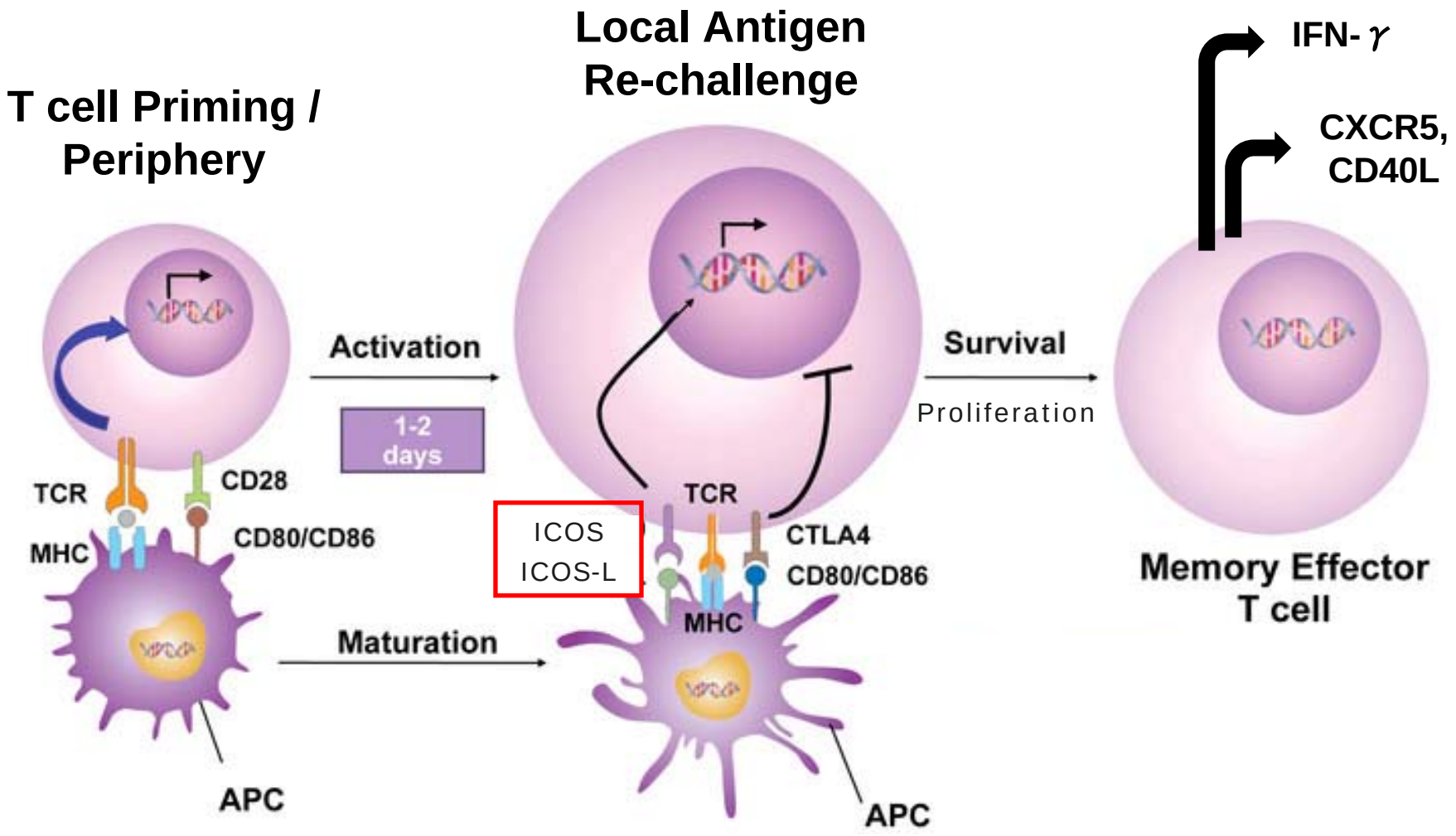
## Efficacy in the Melanoma Prior–IO Cohort

**Figure 5. Ongoing clinical follow-up**



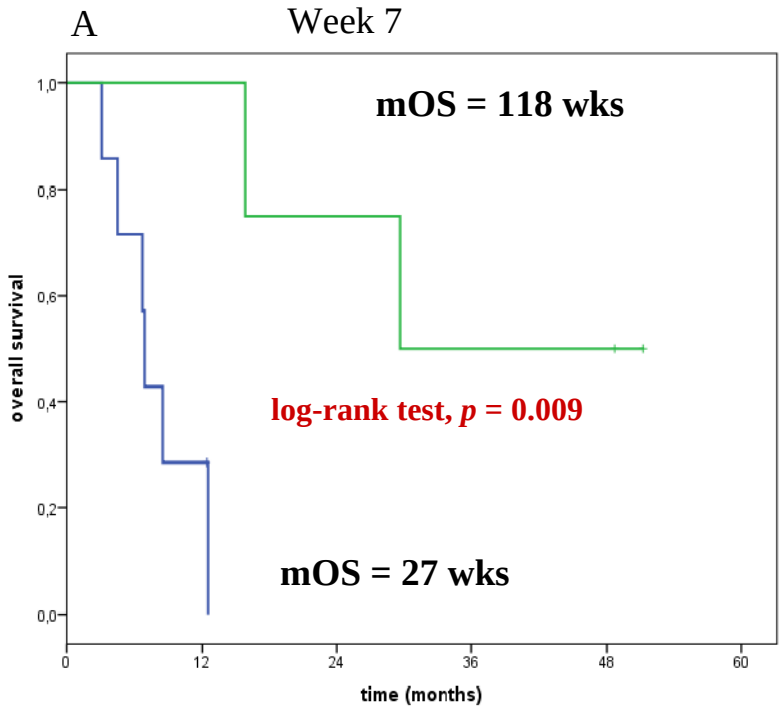

[a]Six patients had clinical progression prior to their first scan and are not included in the plot. [b]Censored on last visit. [c]Evaluations are planned for every 8 weeks.

# ICOS Mechanism of Action



# Activation status of T cells

- Increased levels of CD4+ICOS+ T cells in patients with different tumor types treated with Ipilimumab



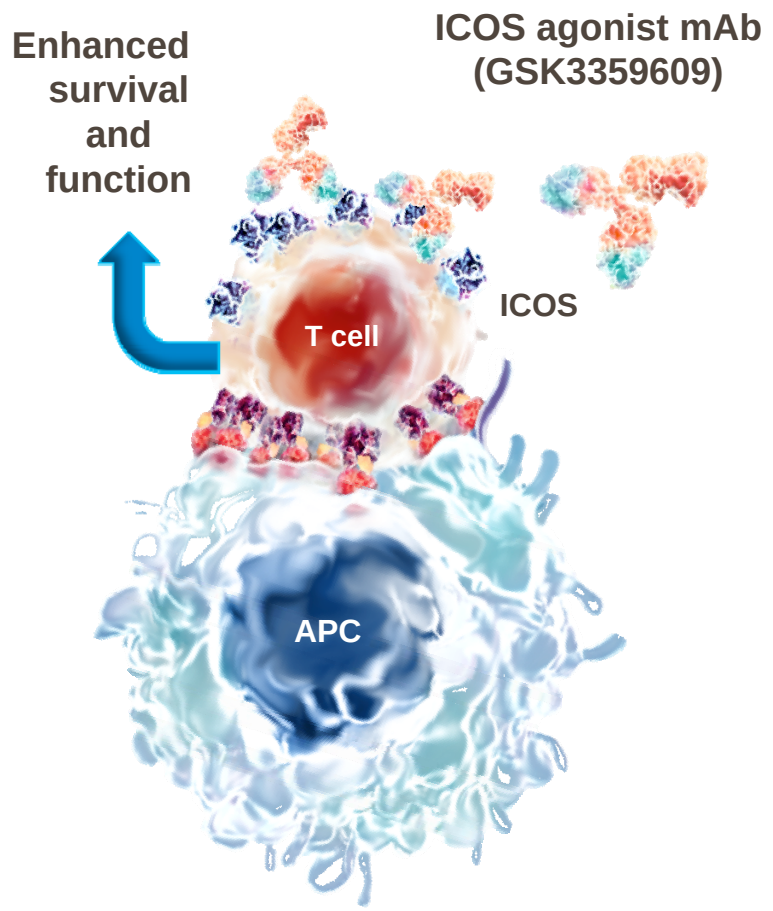

CD4+ICOS+ > 4 fold increase; CD4+ICOS+ ≤ 4 fold increase

Kaplan Meyer curves of overall survival according to the circulating CD4+ICOS+ in A) metastatic melanoma pts treated with ipilimumab at 10mg/Kg within an EAP

Di Giacomo et al CII, 2013

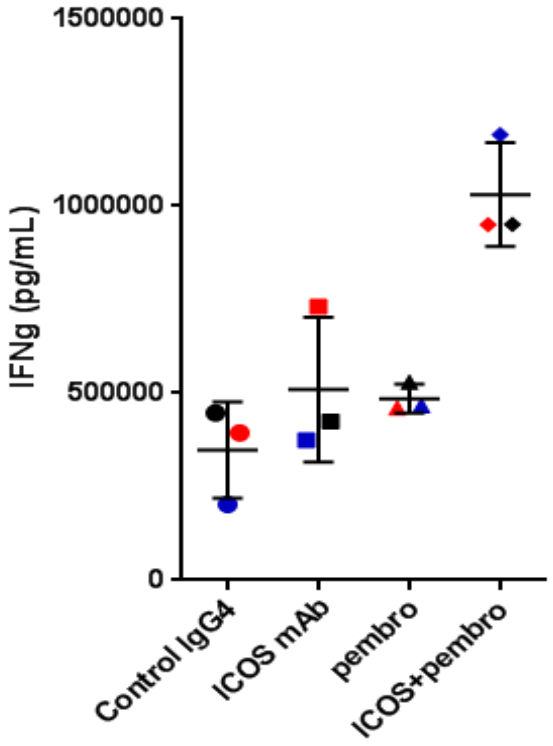
# Summary of GSK anti-ICOS agonist antibody GSK3359609

- A humanized, engineered IgG4 anti-ICOS agonist monoclonal antibody (mAb)
- For the treatment of cancer
- First-in-class ICOS agonist antibody in development
- Binds with high affinity to human ICOS
- Enhances the proliferation, survival and function of antigen activated effector T cells
- Well tolerated safety profile in pre-clinical studies
- Strong rationale for combination with other anticancer agents

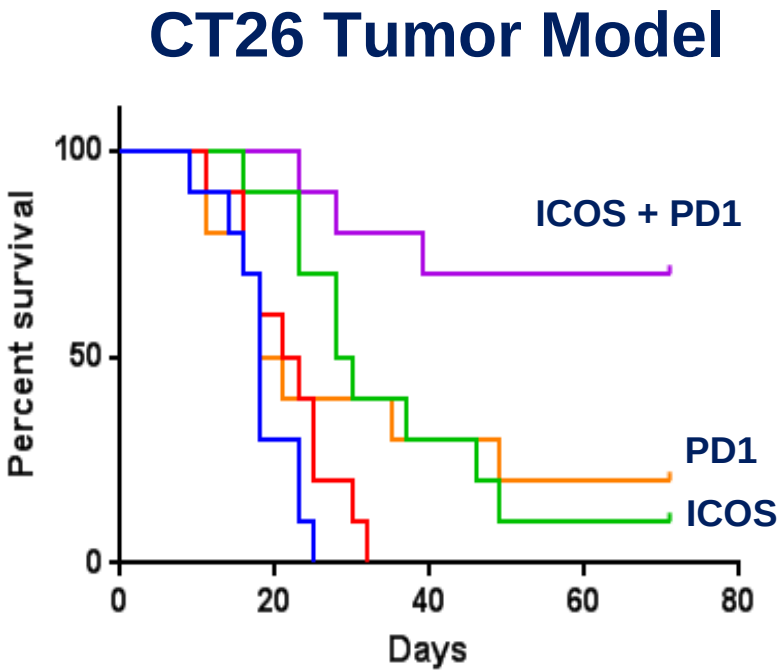


# Preclinical Evidence of ICOS Agonist Combination Potential

**Combination of GSK3359609 with Pembrolizumab in human PBMCs induces synergistic IFN-$\gamma$ production**

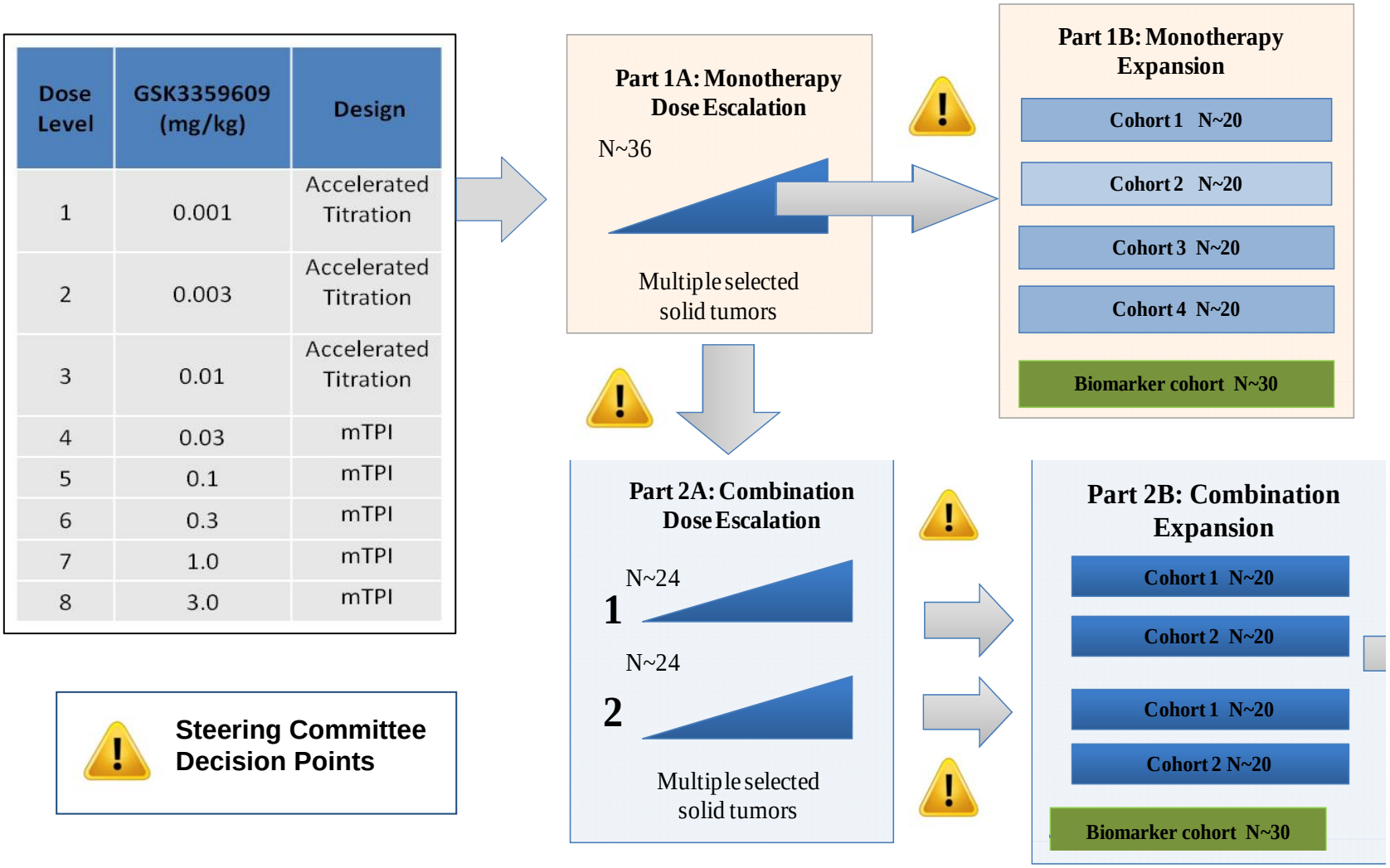



**Synergistic combination of surrogate ICOS agonist antibody with checkpoint mAbs in mouse tumor models**



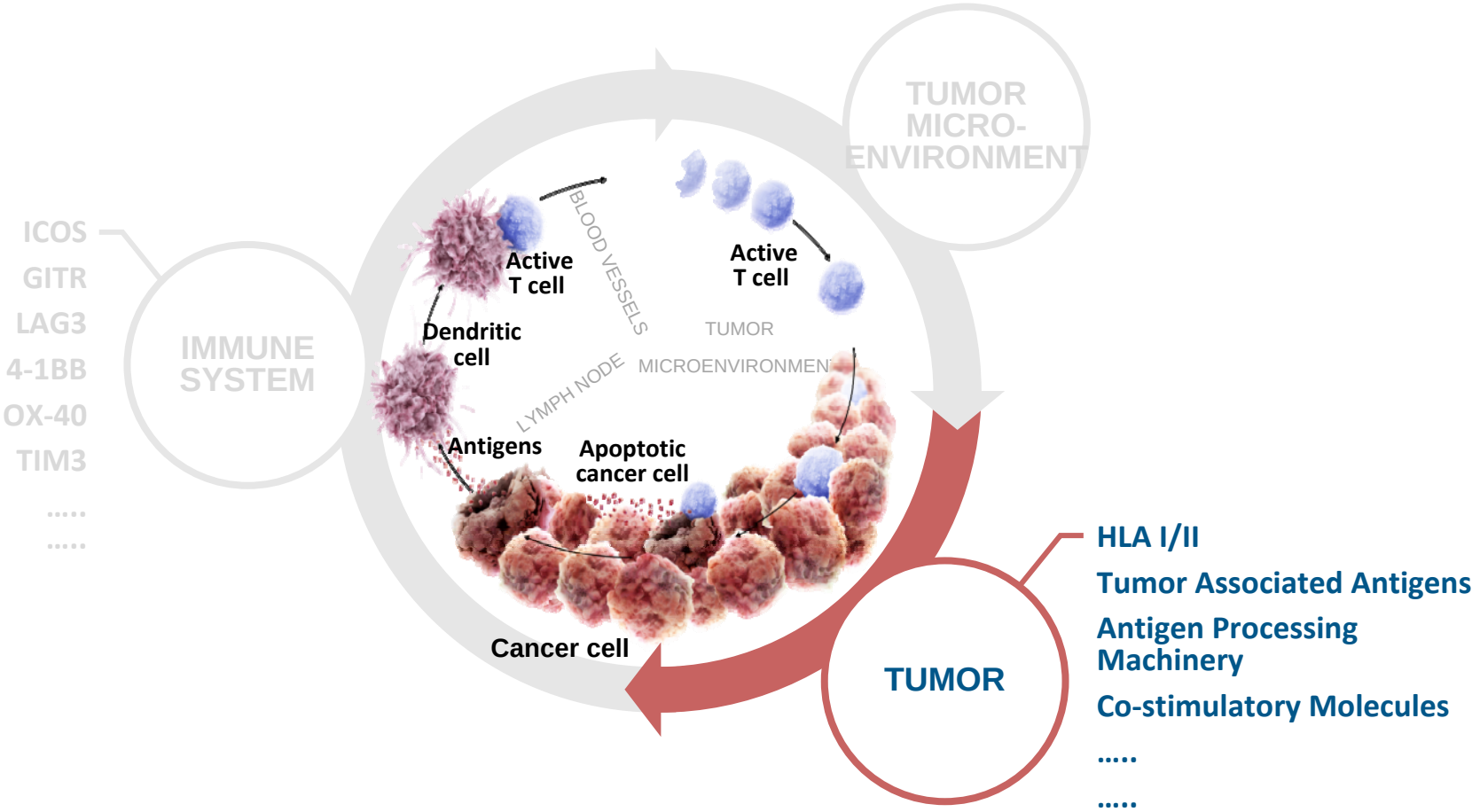
# GSK 204691 (INDUCE-1) Study Design

| Dose Level | GSK3359609 (mg/kg) | Design |
|---|---|---|
| 1 | 0.001 | Accelerated Titration |
| 2 | 0.003 | Accelerated Titration |
| 3 | 0.01 | Accelerated Titration |
| 4 | 0.03 | mTPI |
| 5 | 0.1 | mTPI |
| 6 | 0.3 | mTPI |
| 7 | 1.0 | mTPI |
| 8 | 3.0 | mTPI |

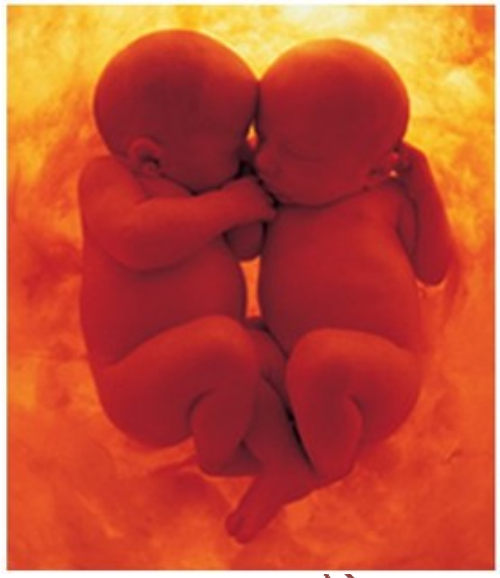


# The future of Cancer Immunotherapy

## Targeting and modulating multiple compartments

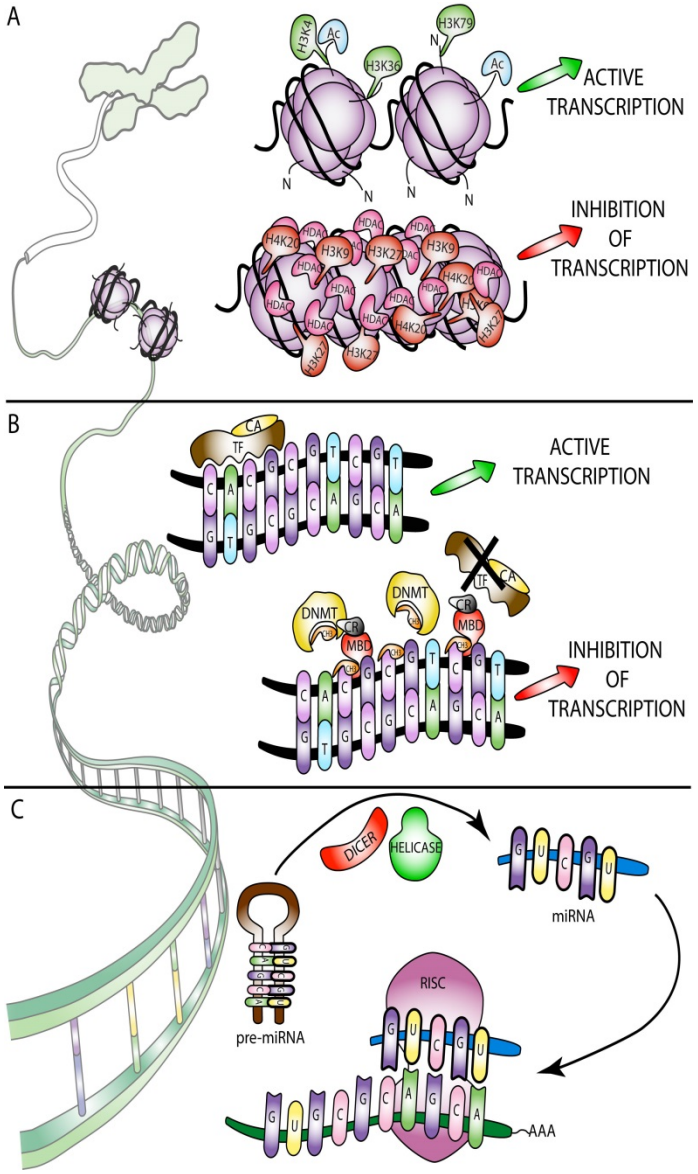


# EPIGENETICS



Heritable changes in gene expression
not based
on modifications of the DNA sequence

# EPIGENETIC MODIFICATIONS




**Histone modifications**

**DNA methylation**

**MicroRNA gene silencing**

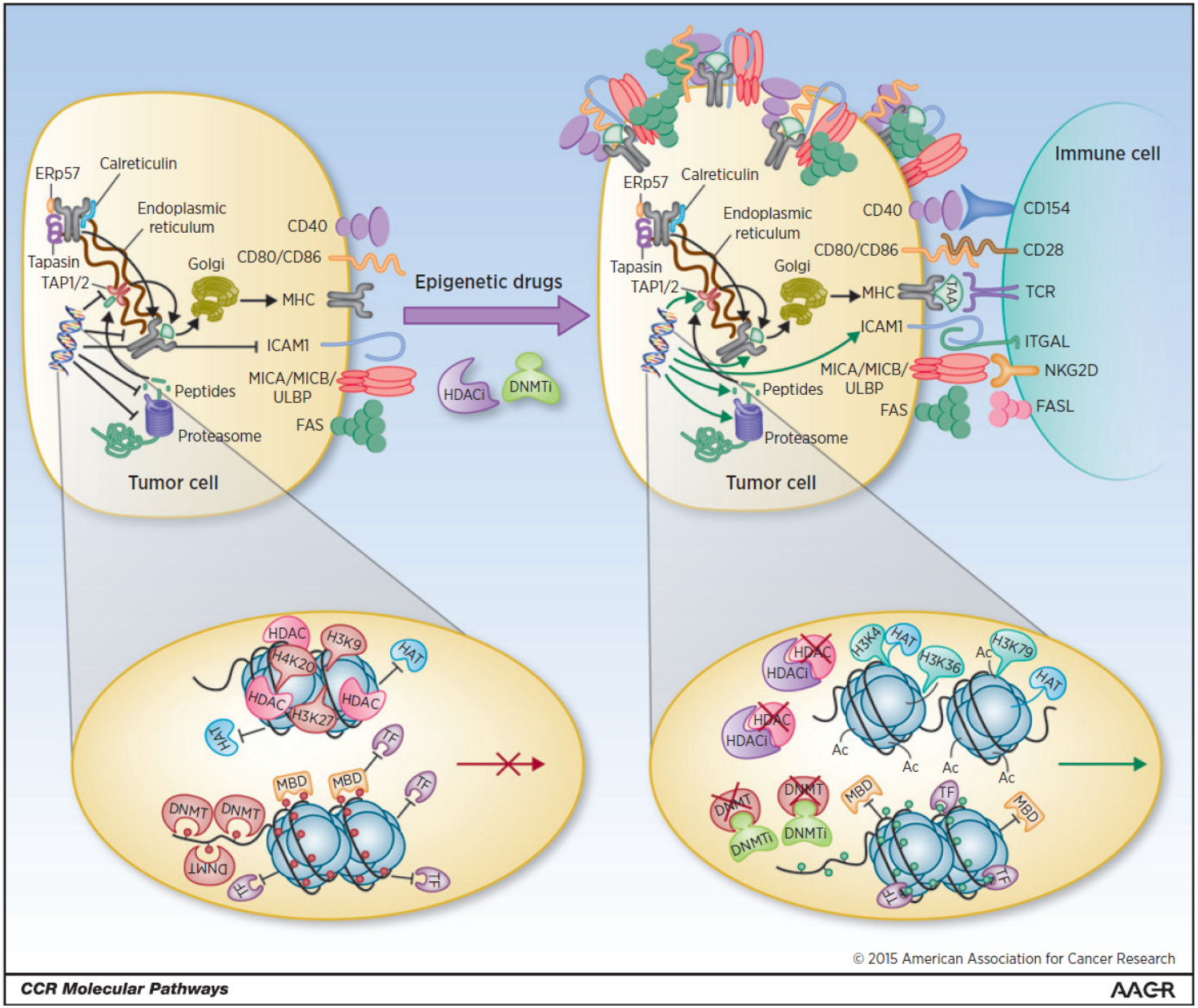
**PHARMACOLOGICALLY REVERSIBLE**

HDAC inhibitors (HDACi)

DNMTs inhibitors (DNMTi)

Maio et al, unpublished

# Epigenetic Immunomodulation of Cancer cell




Maio M. *et al.*, CCR 2015

# Can epigenetic modulation of neoplastic cells be used to design novel immunotherapeutic approaches in cancer?

# Epigenetic immuno-sequencing

Improve host's immune system activity

**HOST**

**Check-point mAb**

**COMBOS**

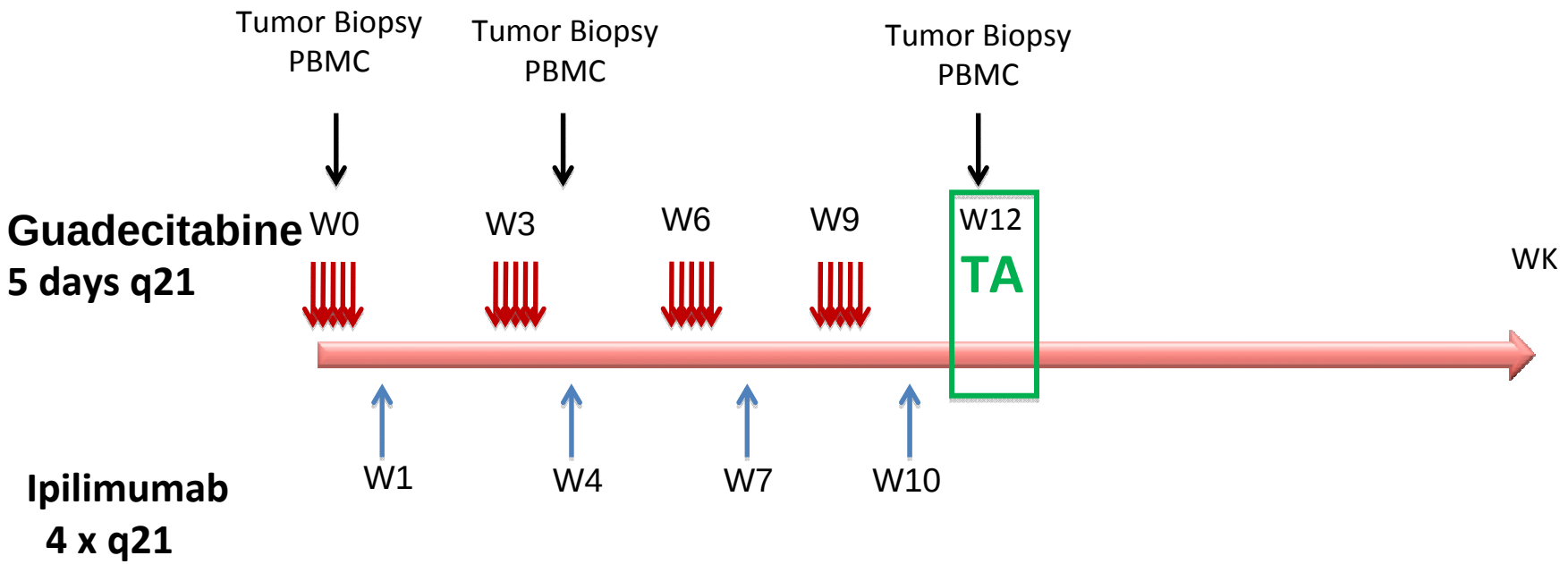
Modulate tumor immunogenicity and immune recognition

**TUMOR**

**Epigenetic drugs**

# Epigenetic immuno-sequencing: the NIBIT-M4 Study

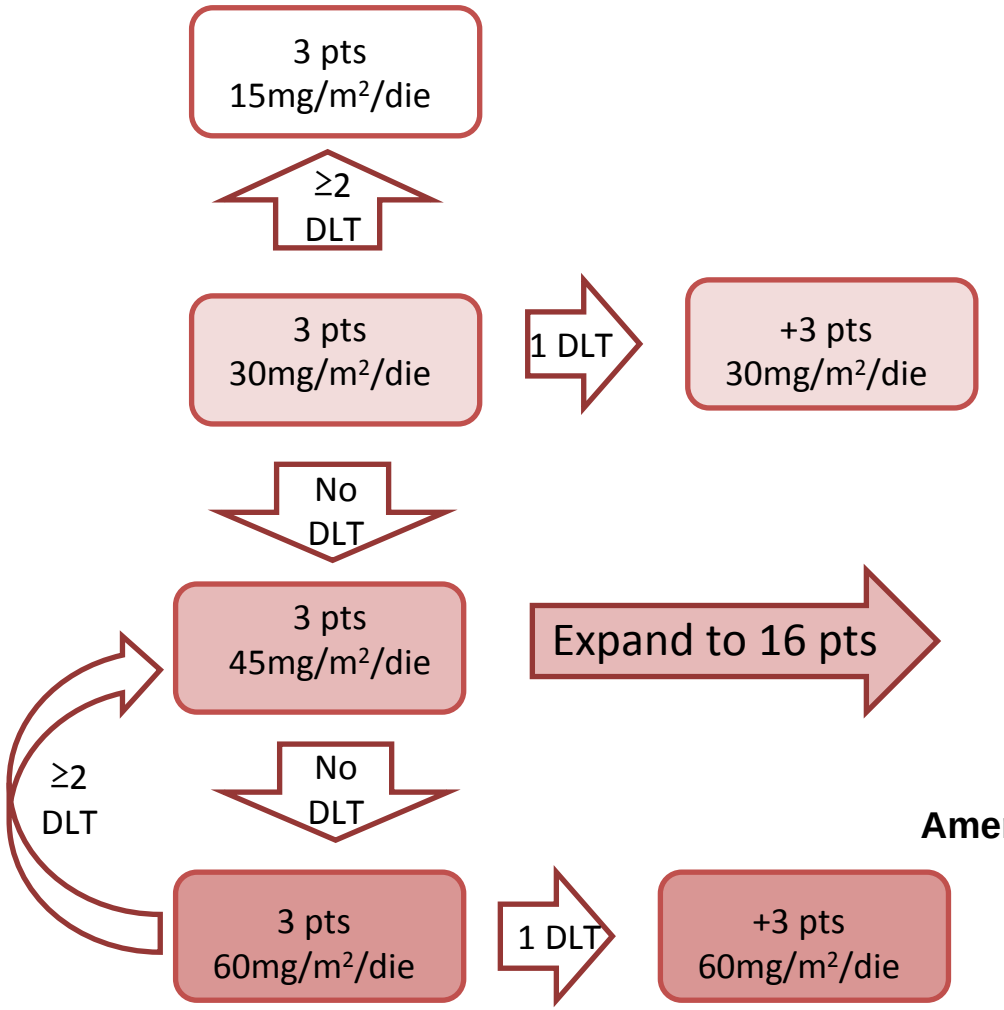
**EUDRACT 2015-001329-17**




**FPFV October 12, 2015**

**A.M. Di Giacomo et al. *Semin Oncol*, 2015**

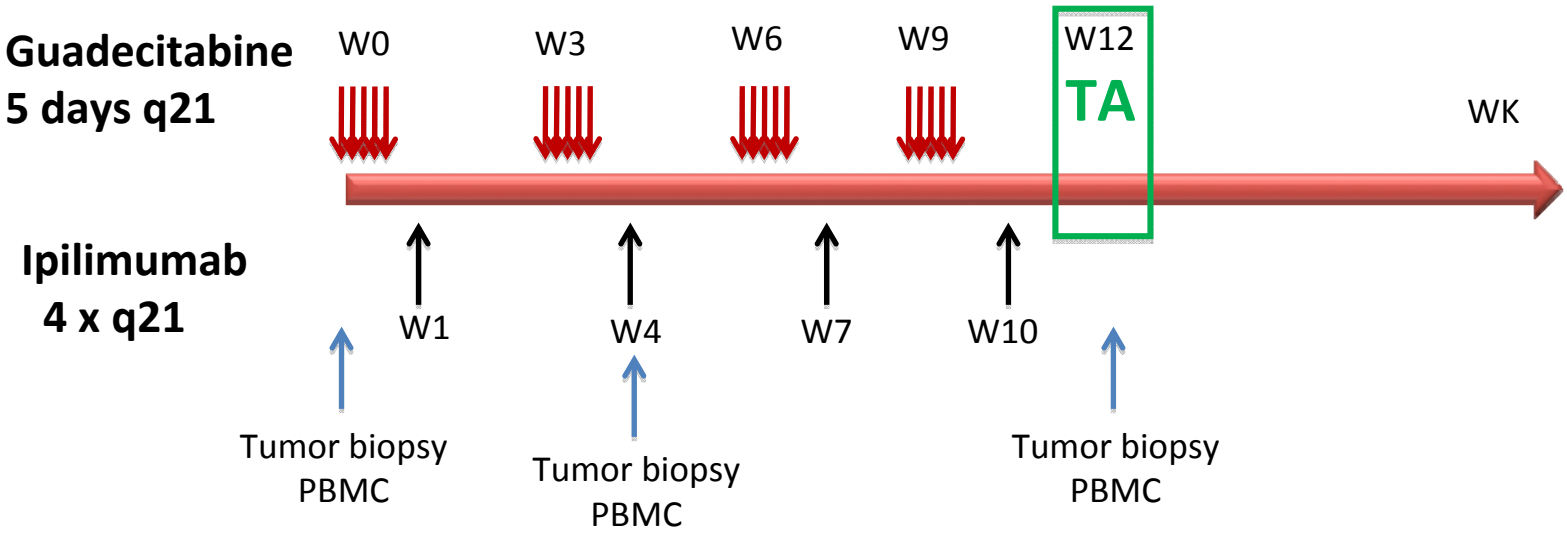
# Epigenetic immuno-sequencing: the NIBIT-M4 Study
# NCT02608437




**To date 11 out of 19 pts enrolled**

**Amendment approved Jan 24rd, 2017**

# Epigenetic immuno-sequencing: the NIBIT-M4 Study
## NCT02608437




## NGS analyses

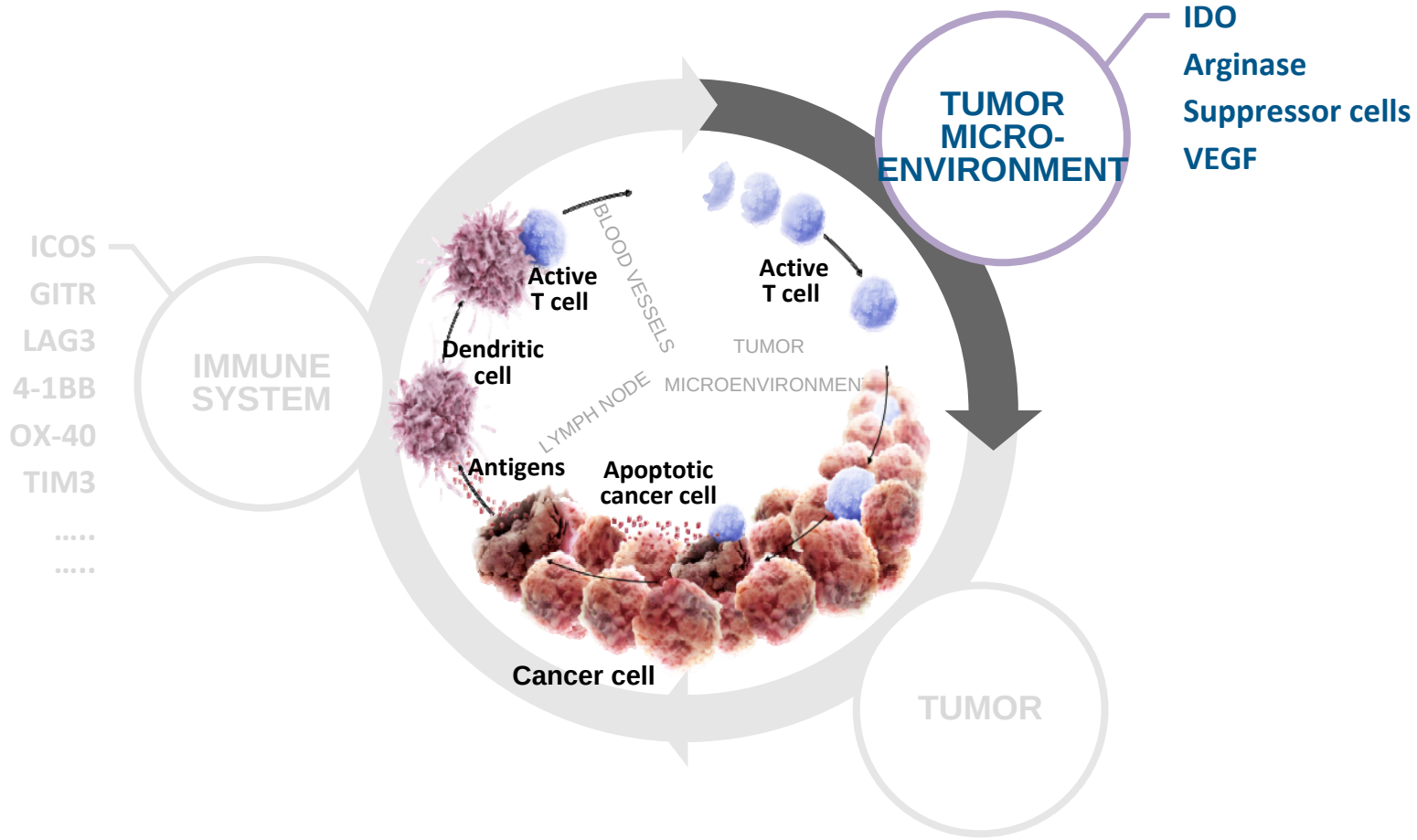
- **Transcriptome** — RNA
- **Methylome** — DNA
- **Exome** — DNA

## Perifery and tumor immunophenotype

- **Phenotipic, functional analyses of PBMC**
- **IMMUNOSCORE** density, location, organization and functional orientation of tumor-infiltrating immune cells — **FFPE**

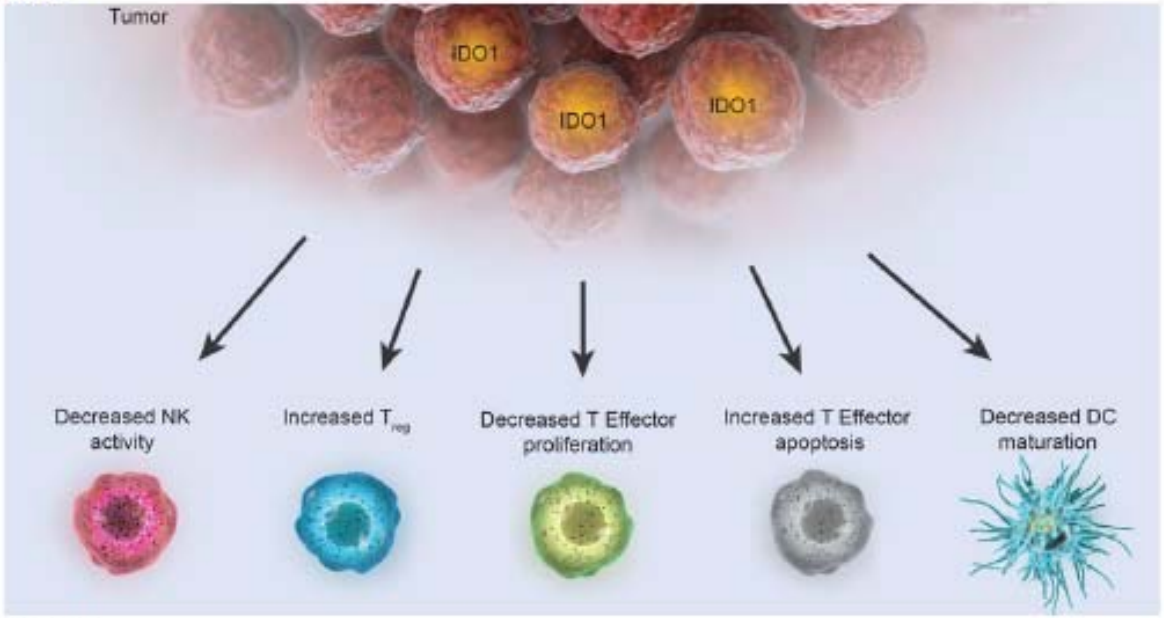
# The future of Cancer Immunotherapy

## Targeting and modulating multiple compartments



# IDO-mediated immunesuppression

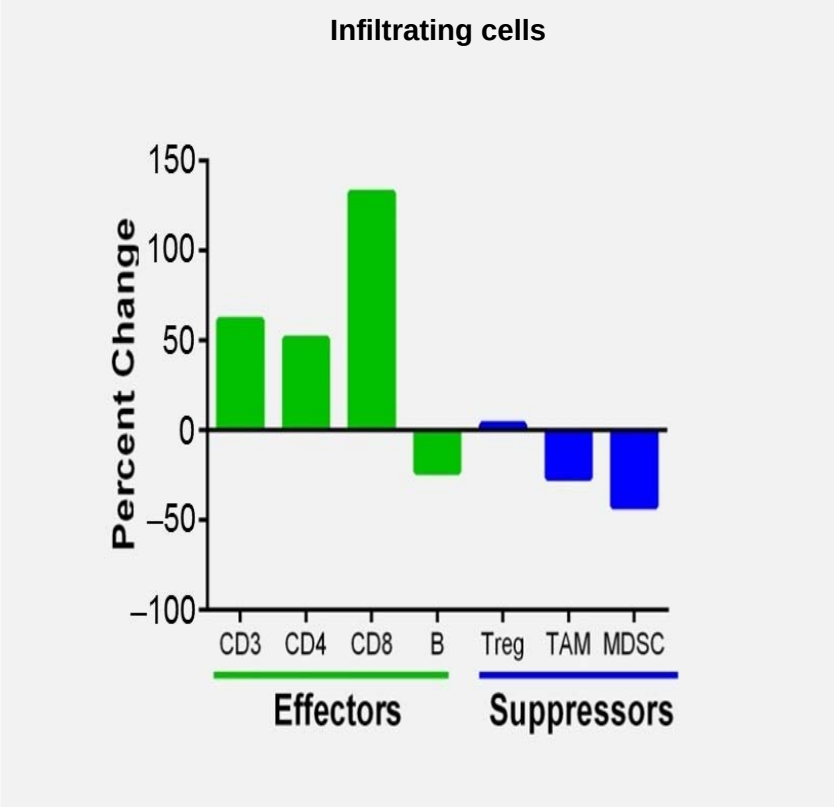
- IDO1 is a tryptophan-catabolizing enzyme that is overexpressed in many cancers[1-3] and induces immune tolerance by suppressing T-cell responses[4]
  - IDO1 is expressed in human tumors and in dendritic cells within tumor draining lymph nodes[5]
  - IDO1 expression is associated with more rapid tumor progression and reduced survival[5]
  - IDO1 inhibition exhibits antitumor activity through the reactivation of effector T cells[3] and is synergistic with PD-1 blockade[6]

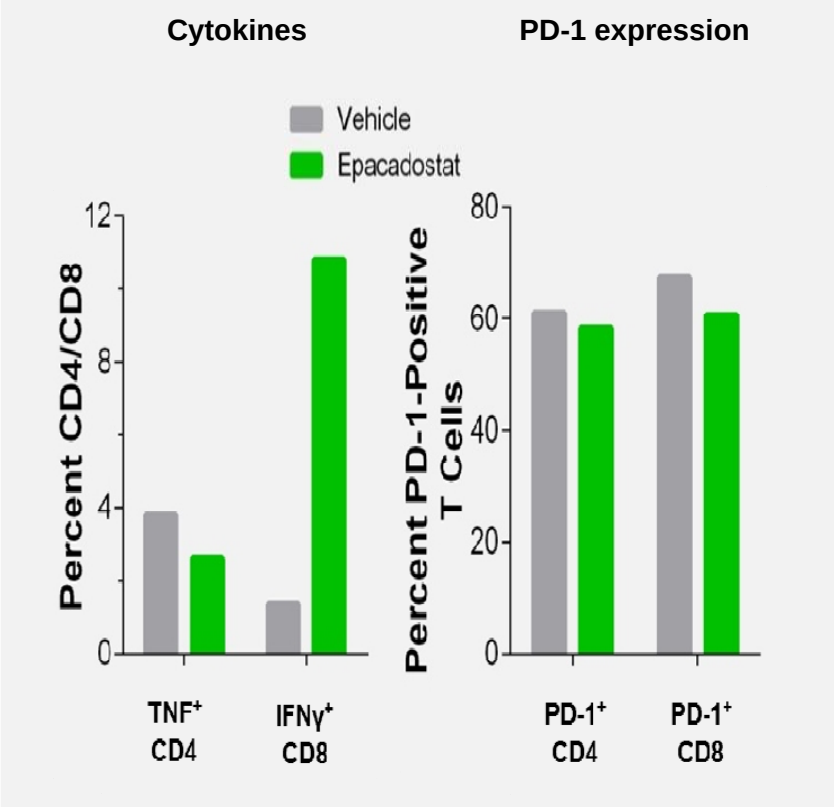



IDO1, indoleamine 2,3 dioxygenase 1.

1. Moretti et al. *J Clin Endocrinol Metab*. 2014:jc20133351; 2. Yu et al. *Clin Dev Immunol*. 2011;2011:469135; 3. Uyttenhove et al. *Nat Med*. 2003; 9(10):1269-1274; 4. Munn et al. *J Clin Invest*. 2007;117(5):1147-1154; 5. Godin-Ethier et al. *Clin Cancer Res*. 2011;17(22):6985-6991; 6. Spranger et al. *J Immunother Cancer*. 2014 Feb 18;2:3.

# IDO1 Inhibition Correlates With Increases in TIL Number and Function



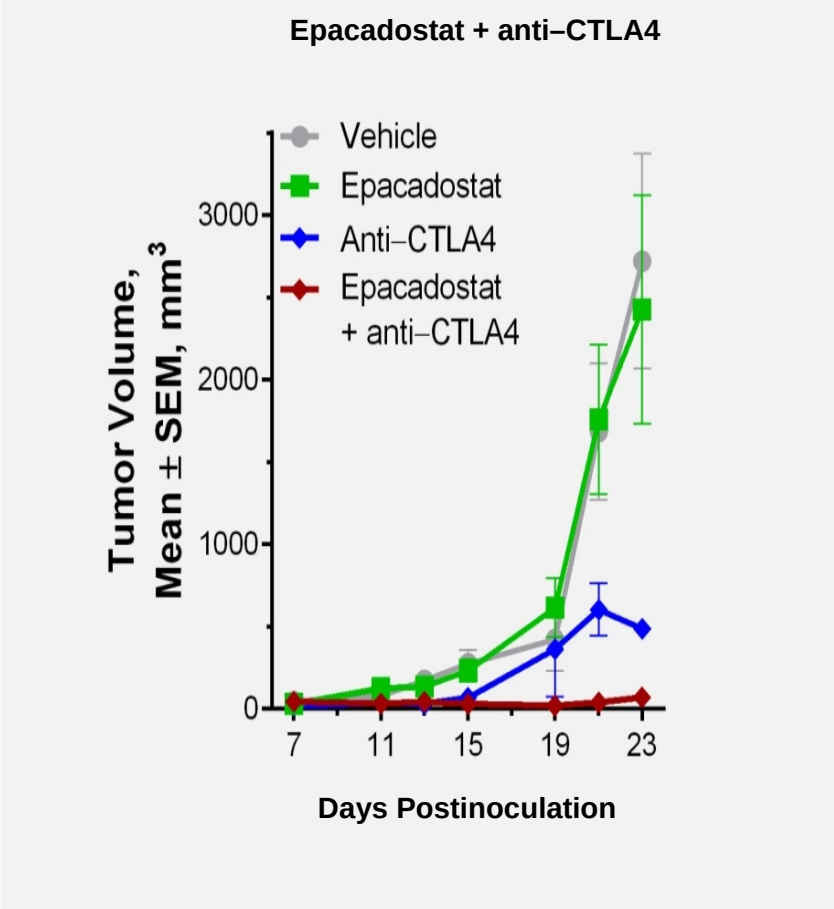

- IDO1 inhibition leads to increased number of TILs and decreased suppressor cells in tumors
- Enhanced IFN-$\gamma$ secretion from TILs was observed following IDO1 inhibitor treatment

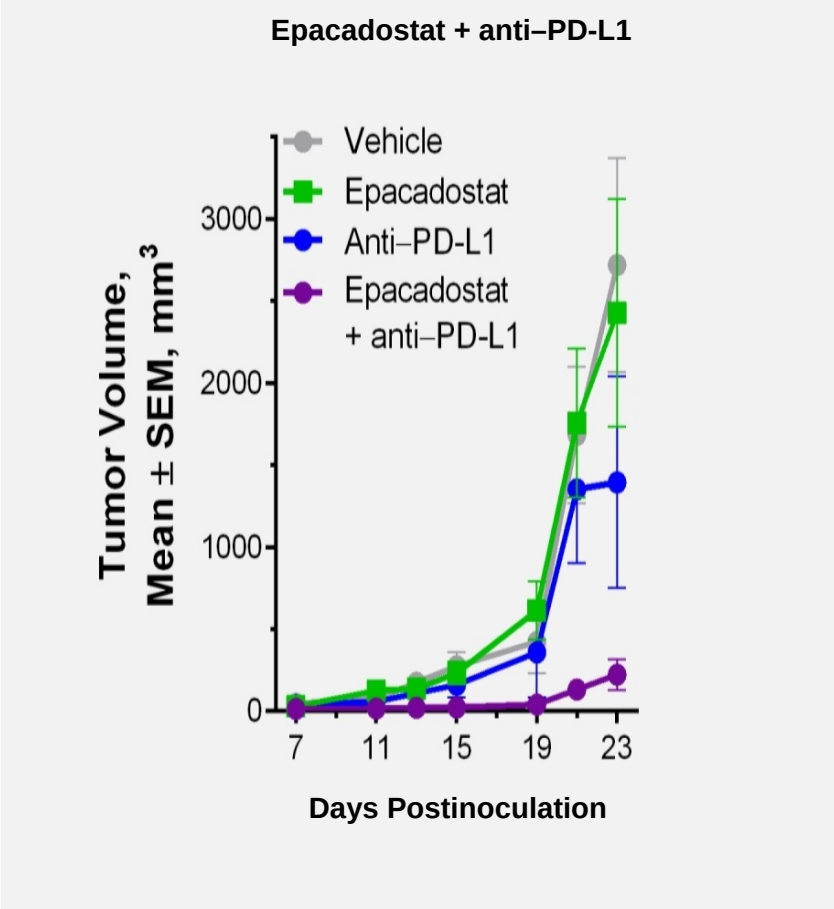


IFN=interferon

Koblish HK, et al. AACR 2015. Poster 1336

# Combinations of Epacadostat and Checkpoint Inhibition Showed Synergistic Inhibition in Preclinical Models




- Combinations of epacadostat and checkpoint inhibition were associated with enhanced T-cell proliferation and cytokine secretion in vivo

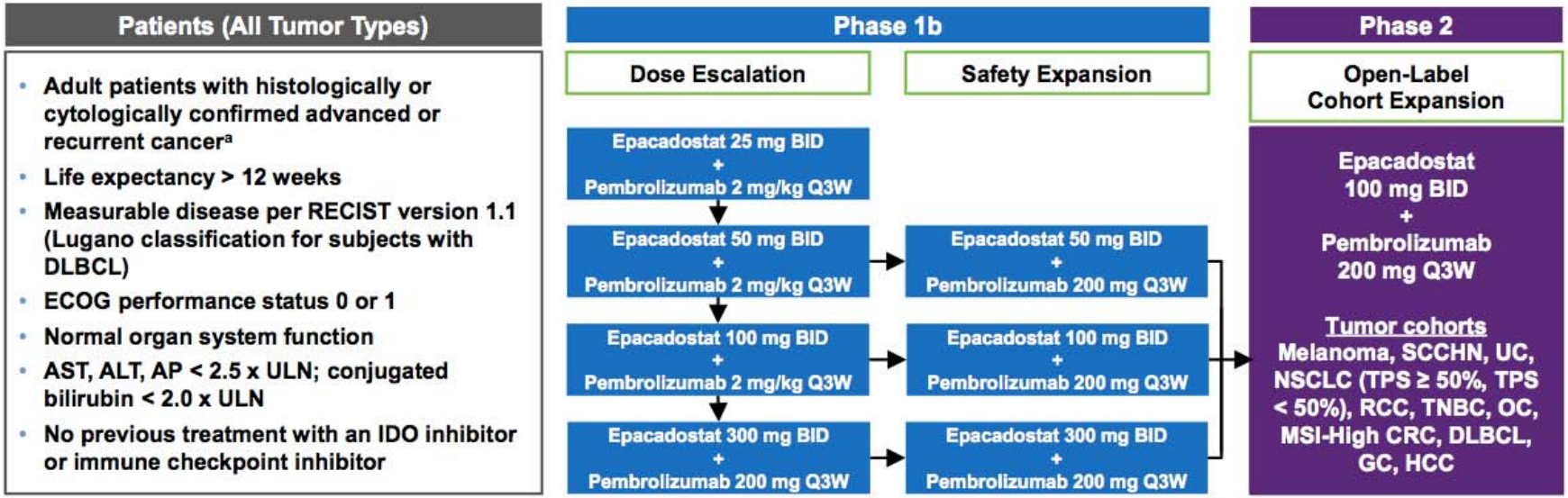


1. Spranger S, et al. *J Immunother Cancer.* 2014;2:3. Data on file, Incyte Corporation

# ECHO-202: Epacadostat + Pembrolizumab

## *Objective, Patient Population and Study Design*

- Non-randomized, open-label, multicenter, phase 1/2 study to assess the safety, tolerability, and efficacy of epacadostat combined with pembrolizumab in patients with selected cancers
- Primary endpoints: DLTs (phase 1) and ORR (phase 2)




BID, twice a day; CRC, colorectal cancer; DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; GC, gastric cancer; HCC, hepatocellular carcinoma; IDO, indoleamine 2,3-dioxygenase; MSI, microsatellite instability; NSCLC, non-small cell lung cancer; OC, ovarian cancer; ORR, objective response rate; Q3W, once every three weeks; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; SCCHN, squamous cell carcinoma of head and neck; TNBC, triple-negative breast cancer; TPS, tumor proportion score (percentage of tumor cells staining positive for PD-L1); UC, urothelial carcinoma; ULN, upper limit of normal.

[a] In phase 1: melanoma, NSCLC, RCC, SCCHN, TNBC, transitional cell carcinoma of the genitourinary tract, adenocarcinoma of the endometrium.

Hamid O et al. Poster presented at: ASCO 2017 [abstract 3012]. ClinicalTrials.gov. http://clinicaltrials.gov. NCT02178722. Accessed August 2, 2017.

# ECHO-202: Phase 1/2 Patients with Melanoma

*Best Objective Response by RECIST 1.1*

| Patients | All patients with melanoma (N = 65) | Treatment-naive for advanced disease, all E doses (n = 54) | Treatment-naive for advanced disease, E 100 mg dose (n = 39) |
|---|---|---|---|
| Per-protocol evaluable[a], n (%) | n = 63 | n = 53 | n = 38 |
| **ORR (CR+PR)** | **35 (56)** | **29 (55)** | **22 (58)** |
| CR | 9 (14) | 7 (13) | 3 (8) |
| PR | 26 (41) | 22 (42) | 19 (50) |
| SD | 10 (16) | 9 (17) | 6 (16) |
| **DCR (CR+PR+SD)** | **45 (71)** | **38 (72)** | **28 (74)** |
| PD or death | 18 (29) | 15 (28) | 10 (26) |
| Not evaluable[b], n (%) | n = 2 | n = 1 | n = 1 |

For all patients, based on irRECIST (n = 63[a]): ORR = 59% (9 CR, 28 PR); DCR = 75% (10 SD)

**Response observed across patient subgroups (n = 63[a])**

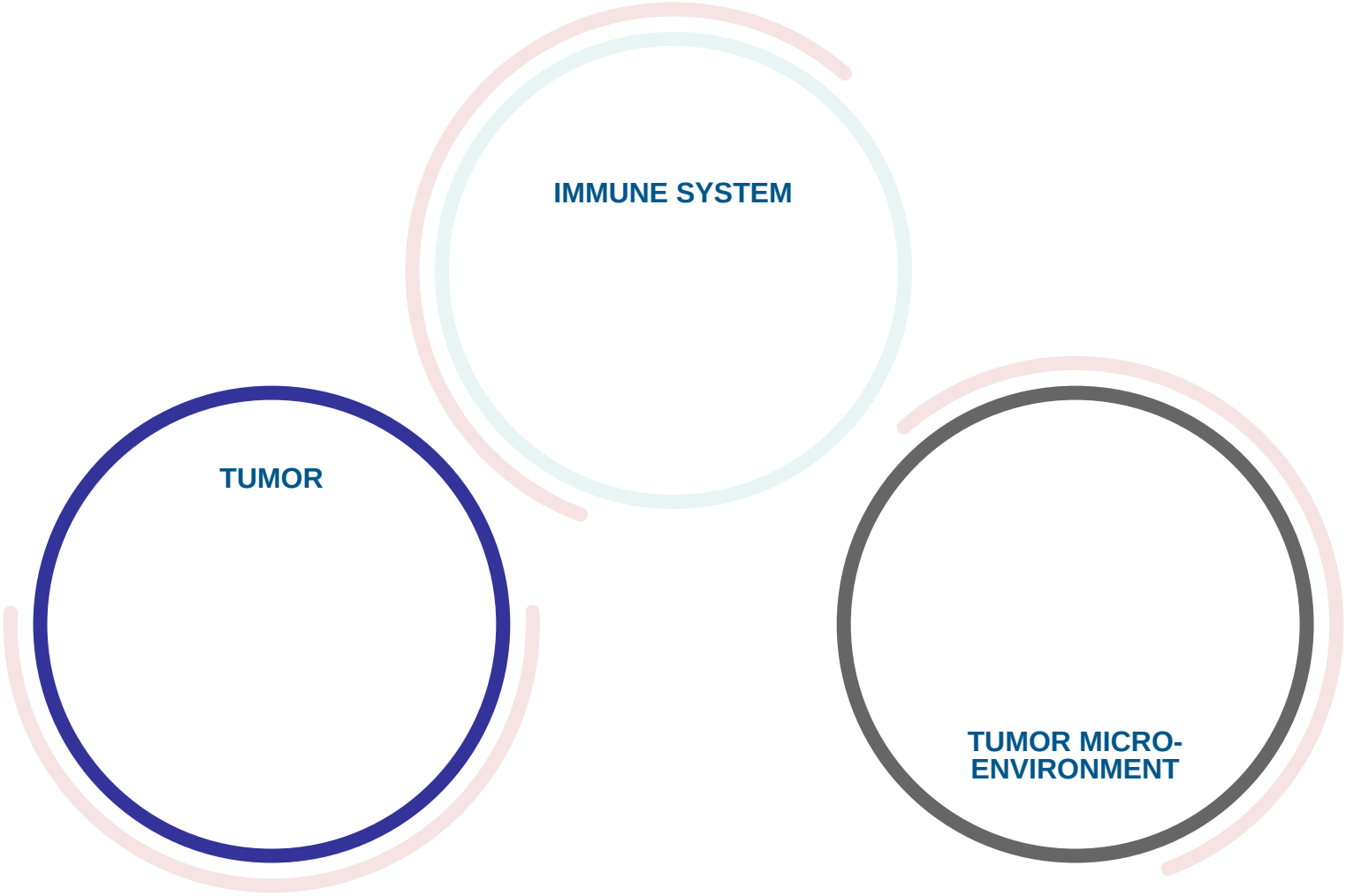
- *BRAF*-mutation–positive (n=18) vs -negative (n=43): 50% vs 56% ORR
- LDH normal (n=39) vs elevated (n=23): 62% vs 48% ORR
- Liver metastases yes (n=24) vs no (n=39): 46% vs 62% ORR
- M1c (n=35) vs non-M1c (n=28): 49% vs 64% ORR

[a] ≥1 postbaseline scan, or discontinuation or death before first postbaseline scan. [b] Scan data not documented in the clinical trial database at time of data cutoff.
E, epacadostat.
Hamid O, et al. Poster presented at: ESMO 2017 [abstract 1214O]; data cutoff: June 9, 2017.

# The future of Cancer Immunotherapy

## Patient-tailored immunotherapeutic approaches

## Targeting and modulating multiple compartments



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