Memorial
Cancer Institute

Immunotherapy for Breast Cancer

Aurelio B. Castrellon

Medical Oncology

Memorial Healthcare System

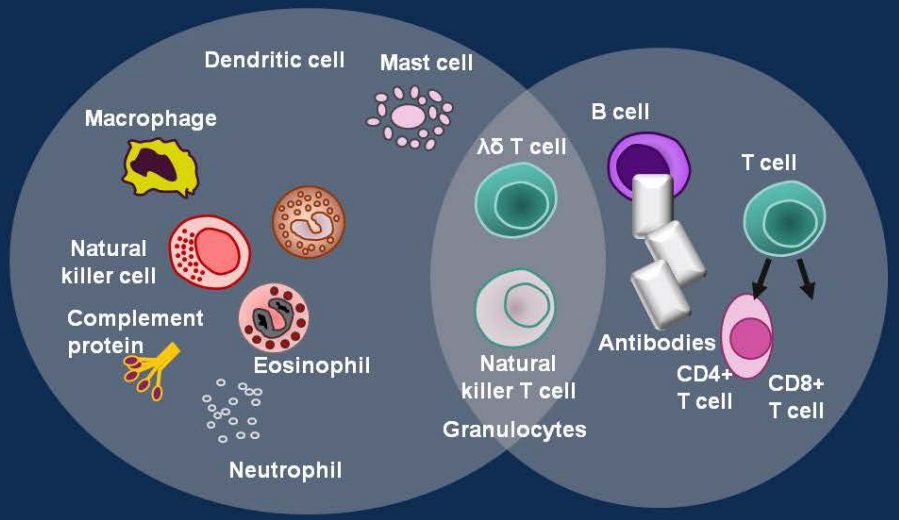
Conflicts

- Research support : Cascadian therapeutics , Puma biotechnology, Odonate therapeutics, Pfizer, Novartis.

Background: The Immune System

Innate Immunity

- Nonspecific, activated quickly in response to a pathogen
- Activates the adaptive response



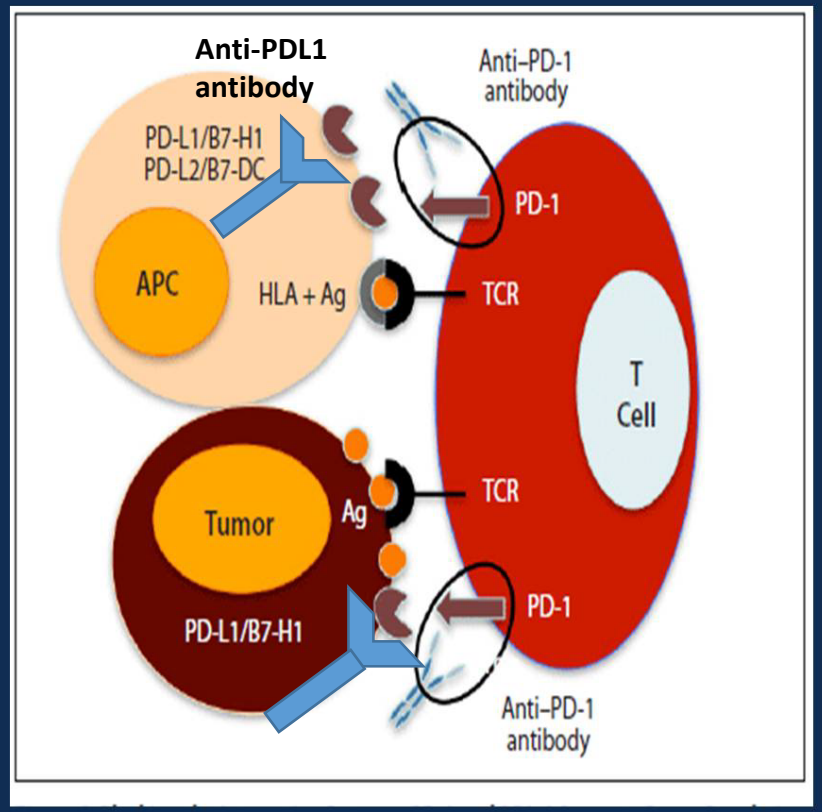
Adaptive Immunity

- Specific, activated in response to recognition of a specific pathogen
- Includes T-cell stimulation, B-cell antibody production
- Has a memory component

What should happen: tumor-associated antigens recognized by the immune system and destroyed by both innate and adaptive immune mechanisms (including activation of T cells)

What often happens: Tumors evade detection and destruction by the immune system through immune tolerance and acquiring resistance to killing by activated immune cells.

Evading the immune system: Programmed Cell Death (PD-1) Pathway



Amin A and White RL. Oncology. 2013.

- Numerous mechanisms to evade the immune system (immunosuppressive cytokines including TGF-β, IL-4, IL-6, IL-10, etc)
- The PD-1:PD-L1 signaling axis is a mechanism of tumor anti-immunity
- PD-1 receptor on T cells binds PD-L1 and PD-L2 on normal host tissues to down-regulate the immune response to protect host tissues; PD-1:PD-L1 binding leads to T cell suppression
- Cancer cells may usurp this pathway to evade immune killing by expressing PD-L1
- Blocking the PD-1:PDL-1 interaction releases the stop on T cells, leading to T cell mediated immune responses against tumor cells

- Anti PD-1 and PDL-1 agents
- Rationale for use in Triple Negative Breast Cancer
- Potential Biomarkers to predict response to therapy
- Clinical evidence
- Monotherapy
- Strategies to increase response:
- Chemotherapy
- Radiation

Rise of Immunotherapy

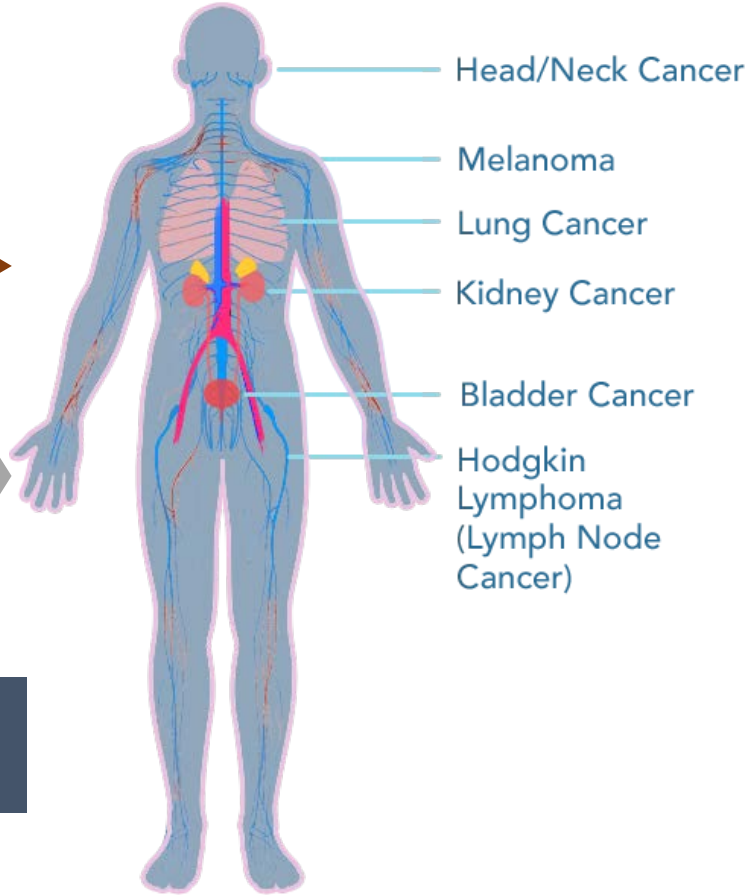
- Long-term disease control against recalcitrant cancers
- Game-changing discoveries – more coming

2011 — Ipilimumab introduced for melanoma

2014 — Pembrolizumab, nivolumab approved for melanoma

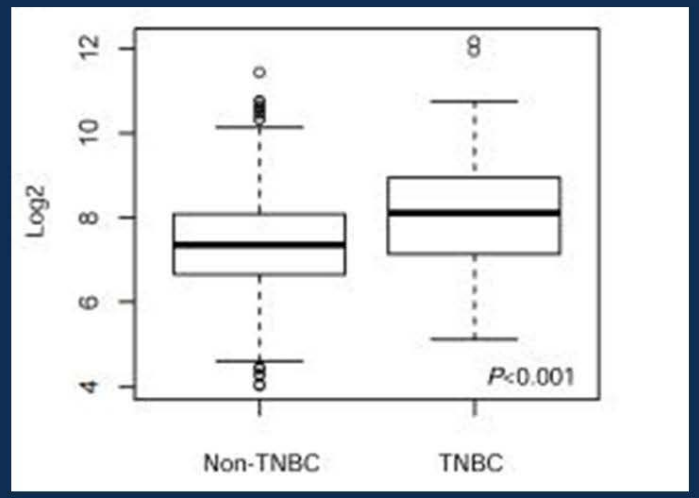
2015-2016 — PD-1/L-1 drugs benefit even more of cancers

2016 ASCO Advance of the Year

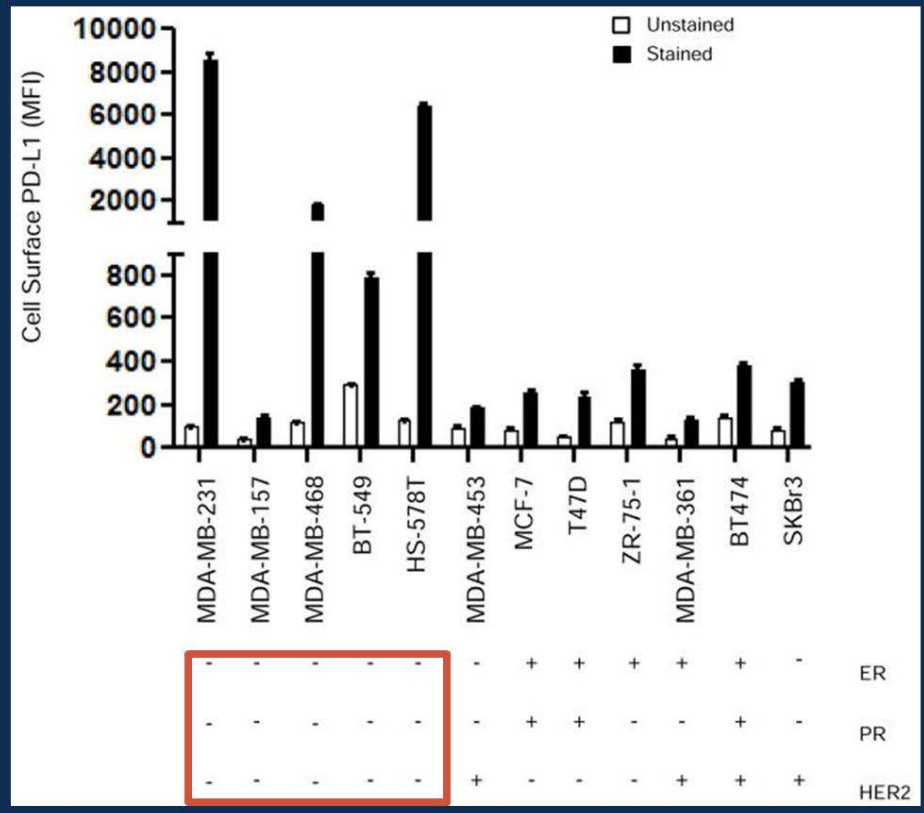


CancerProgress.Net

Why immunotherapy in Triple-Negative Breast Cancer (TNBC)?



- Analysis of TCGA data show higher expression of PD-L1 mRNA in TNBC (n=120) vs non-TNBC (n=716), P<0.001



PD-L1 expression greater in 4 of 5 TNBC cell lines

PD-L1 expression in TNBC

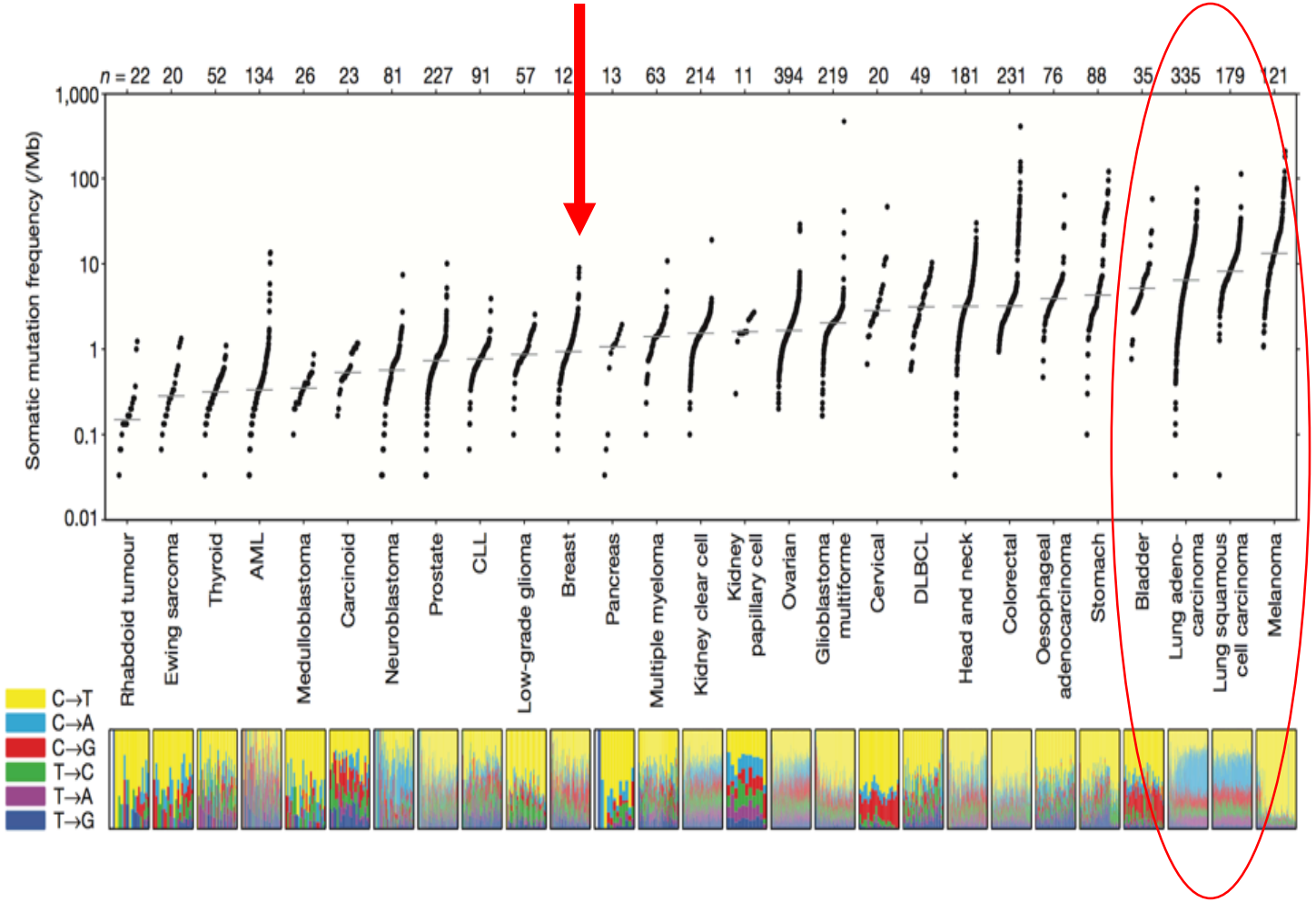
- PDL-L1 expression 26.4% by IHC in a mixed cohort of TNBC patients (n=193)

Table 2. Tissue microarray immunohistochemistry results

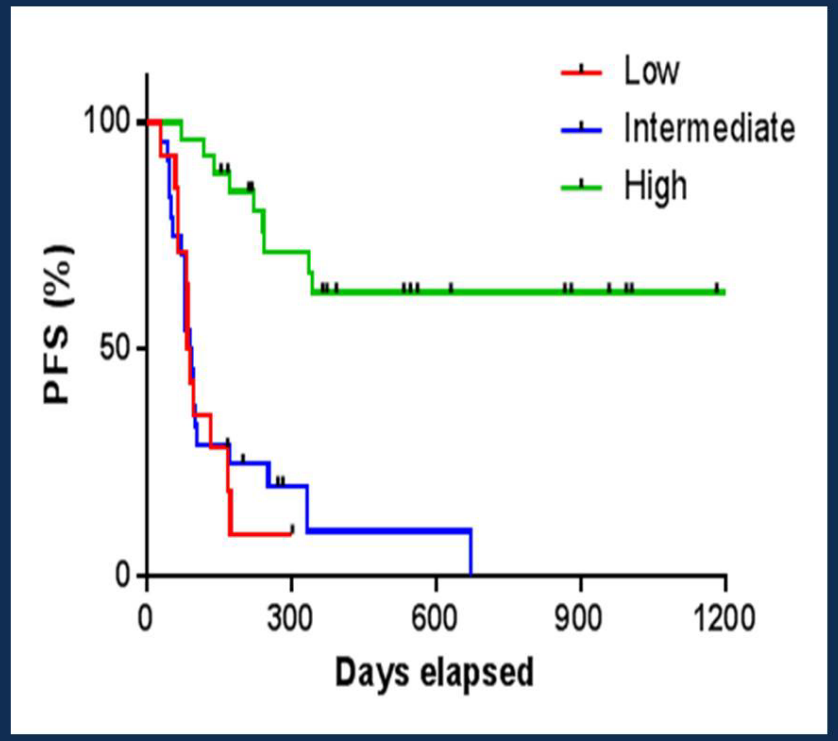
	BRCA1 Carrier (n = *78*)	*Noncarrier* (n = *119*)	*P-value*
EGFR—*n* (%)			0.10
Negative	14 (18.9)	35 (29.7)	
Positive	60 (81.1)	83 (70.3)	
Unknown[a]	4	1	
Cytokeratin 5/6—*n* (%)			0.002
Negative	19 (24.4)	55 (46.2)	
Positive	59 (75.6)	64 (53.8)	
Unknown[a]	0	0	
Cytokeratin 14—*n* (%)			0.42
Negative	37 (48.7)	65 (54.6)	
Positive	39 (51.3)	54 (45.4)	
Unknown[a]	2	0	
Androgen receptor—*n* (%)			0.02
Negative	69 (90.8)	90 (76.3)	
Weakly positive	4 (5.3)	9 (7.6)	
Positive	3 (3.9)	19 (16.1)	
Unknown[a]	2	1	
Androgen receptor—*n* (%)			0.01
Negative	69 (90.8)	90 (76.3)	
Weakly positive/ positive (⩾1%)	7 (9.2)	28 (23.7)	
Unknown[a]	2	1	
Androgen receptor—*n* (%)			0.01
Negative/weakly positive	73 (96.1)	99 (83.9)	
Positive (>10%)	3 (3.9)	19 (16.1)	
Unknown[a]	2	1	
PD-L1 cancer—*n* (%)			0.35
Negative	58 (77.3)	84 (71.2)	
Positive (⩾1%)	17 (22.7)	34 (28.8)	
Unknown[a]	3	1	
PD-L1 cancer/inflammatory—*n* (%)			0.17
Negative[b]	3 (4.3)	11 (10.3)	
Positive (⩾ 1%)[c]	67 (95.7)	96 (89.7)	
Unknown	8	12	

[a]Insufficient measurable tumor.
[b]Cancer cells and inflammatory cells lack PD-L1 staining.
[c]Either cancer cells or inflammatory cells stain for PD-L1.

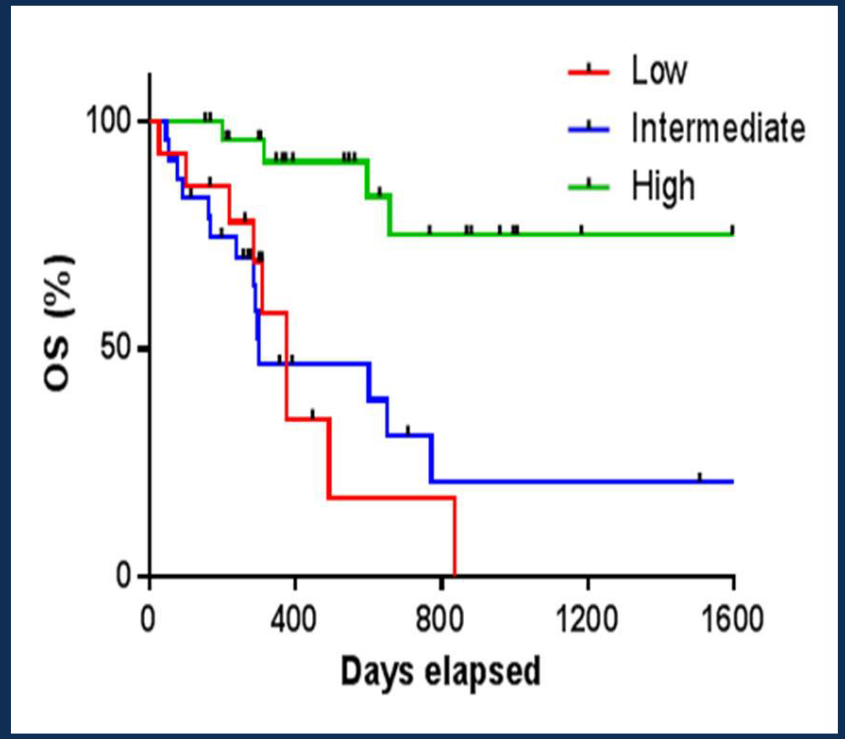
Mutational Load



Mutation load and survival



Median PFS
Not reached vs. 89 days vs. 86 days
P < 0.001



Median OS
Not reached vs. 300 days vs. 375 days
P < 0.001

Johnson D et al, ASCO 2016

Mutational burden

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.

Genomic correlates of response to CTLA-4 blockade in metastatic melanoma

Eliezer M. Van Allen,[1,2,3*] Diana Miao,[1,2*] Bastian Schilling,[4,5*] Sachet A. Shukla,[1,2] Christian Blank,[6] Lisa Zimmer,[4,5] Antje Sucker,[4,5] Uwe Hillen,[4,5]

Genomic and Transcriptomic Features of Response to Anti-PD-1 Therapy in Metastatic Melanoma

Willy Hugo,[1,6,9] Jesse M. Zaretsky,[2,6,9] Lu Sun,[1,6] Chunying Song,[1,6] Blanca Homet Moreno,[3] Siwen Hu-Lieskovan,[3] Beata Berent-Maoz,[3] Jia Pang,[3] Bartosz Chmielowski,[3] Grace Cherry,[3] Elizabeth Seja,[3] Shirley Lomeli,[1,6] Xiangju Kong,[1,6] Mark C. Kelley,[7] Jeffrey A. Sosman,[8] Douglas B. Johnson,[8] Antoni Ribas,[2,3,4,5,6] and Roger S. Lo[1,2,5,6,*]

Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer

Naiyer A. Rizvi,[1,2*†] Matthew D. Hellmann,[1,2*] Alexandra Snyder,[1,2,3*] Pia Kvistborg,[4] Vladimir Makarov,[3] Jonathan J. Havel,[3] William Lee,[5] Jianda Yuan,[6] Phillip Wong,[6] Teresa S. Ho,[6] Martin L. Miller,[7] Natasha Rekhtman,[8] Andre L. Moreira,[8] Fawzia Ibrahim,[1] Cameron Bruggeman,[9] Billel Gasmi,[10] Roberta Zappasodi,[10] Yuka Maeda,[10] Chris Sander,[7] Edward B. Garon,[11] Taha Merghoub,[1,10] Jedd D. Wolchok,[1,2,10] Ton N. Schumacher,[4] Timothy A. Chan[2,3,5,‡]

Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial

Jonathan E Rosenberg, Jean Hoffman-Censits, Tom Powles, Michiel S van der Heijden, Arjun V Balar, Andrea Necchi, Nancy Dawson, Peter H O'Donnell, Ani Balmanoukian, Yohann Loriot, Sandy Srinivas, Margitta M Retz, Petros Grivas, Richard W Joseph, Matthew D Galsky, Mark T Fleming, Daniel P Petrylak, Jose Luis Perez-Gracia, Howard A Burris, Daniel Castellano, Christina Canil, Joaquim Bellmunt, Dean Bajorin, Dorothee Nickles, Richard Bourgon, Garrett M Frampton, Na Cui, Sanjeev Mariathasan, Oyewale Abidoye, Gregg D Fine, Robert Dreicer

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

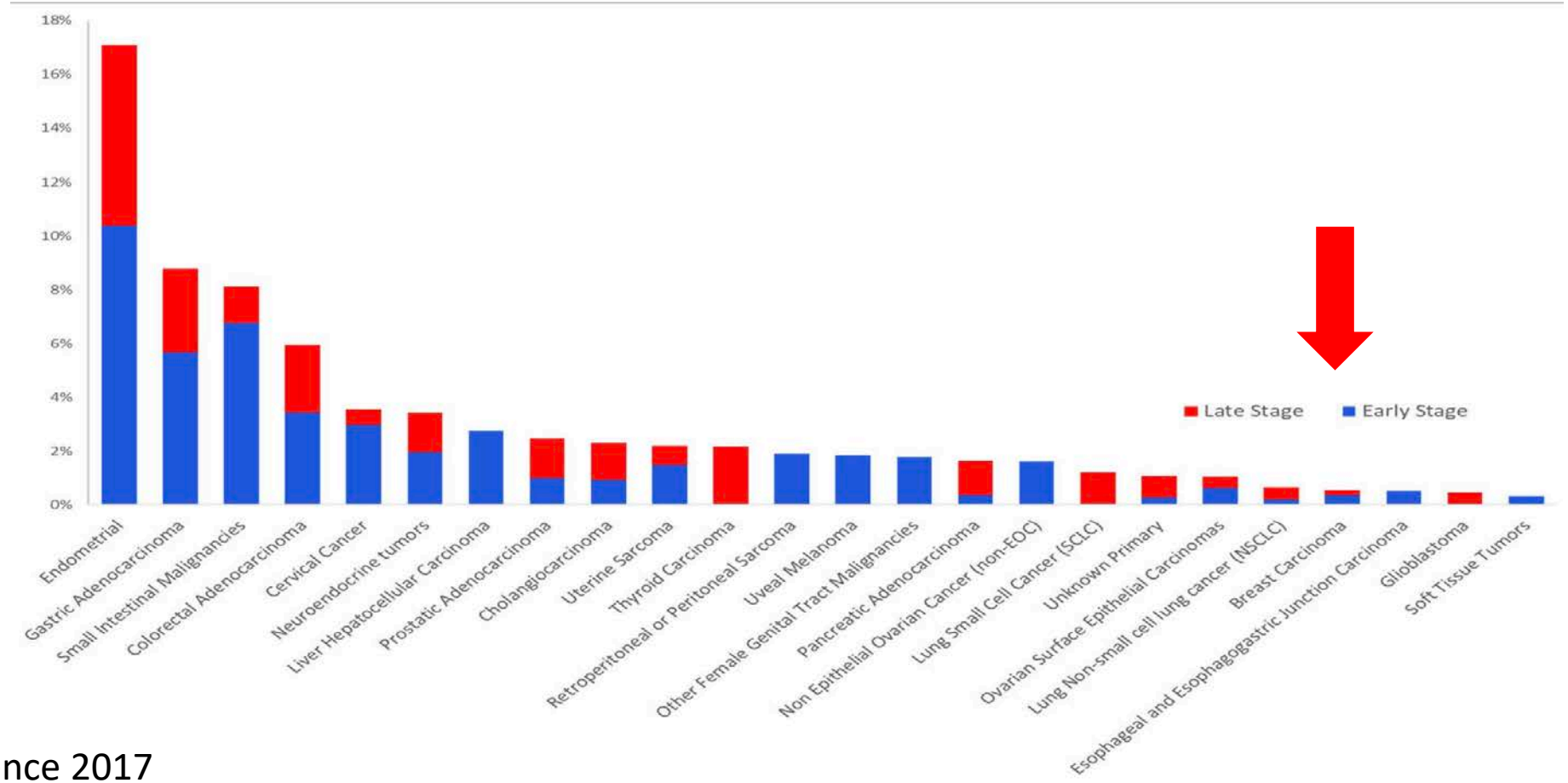
The genetic damage that occurs within tumors can generate tumor-specific antigens that can be recognized by the immune system

Science

REPORTS

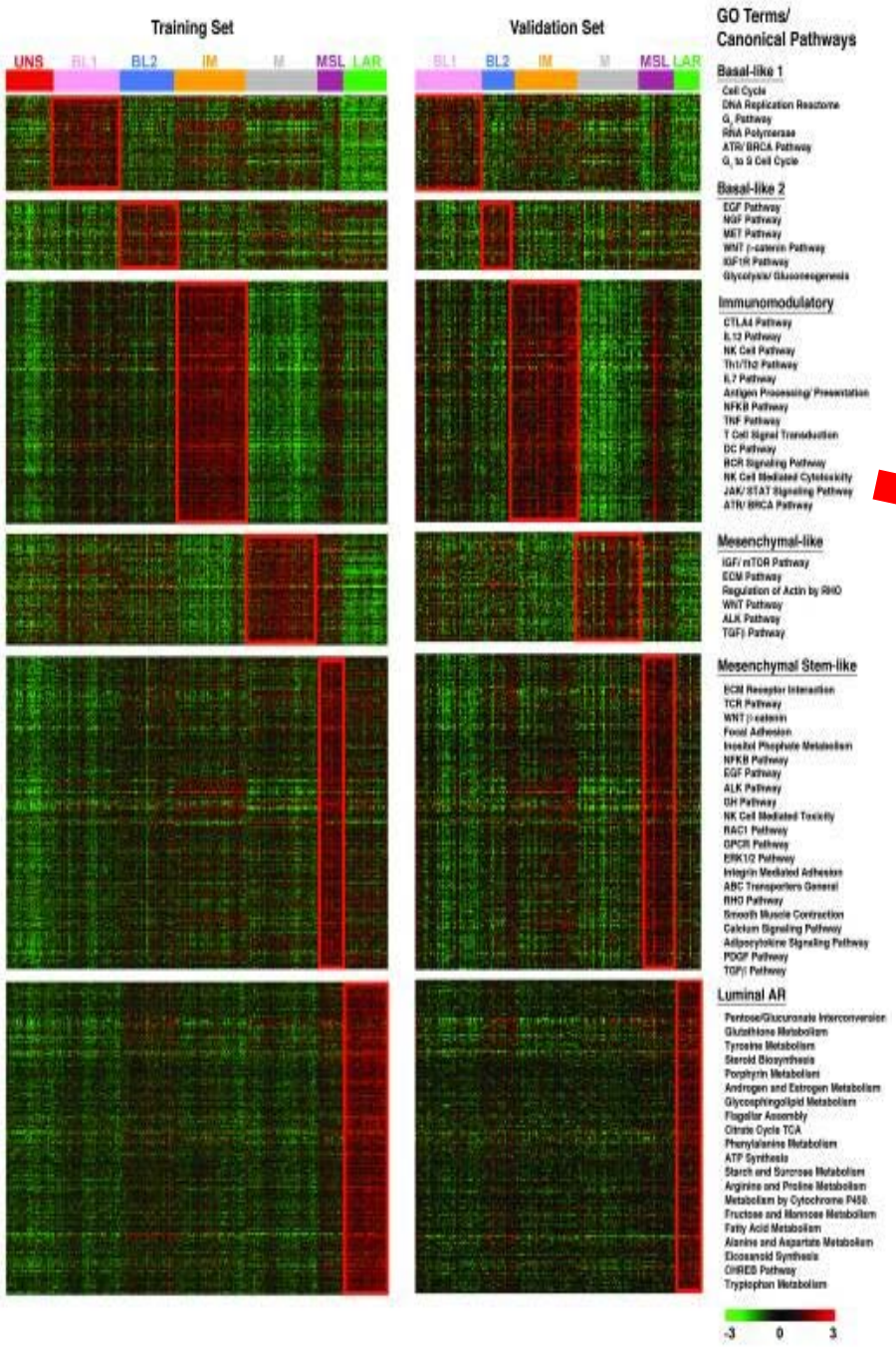
Cite as: D. T. Le *et al.*, *Science*
10.1126/science.aan6733 (2017).

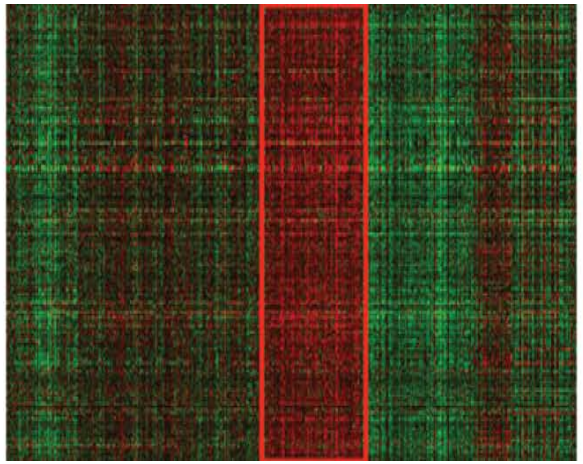
Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade

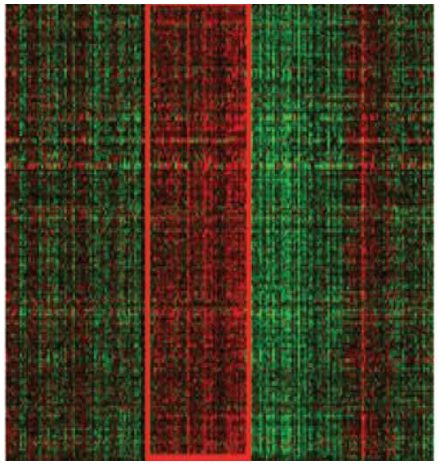


Le et al., Science 2017

Subtype of TNBC that could possibly benefit from immunotherapy







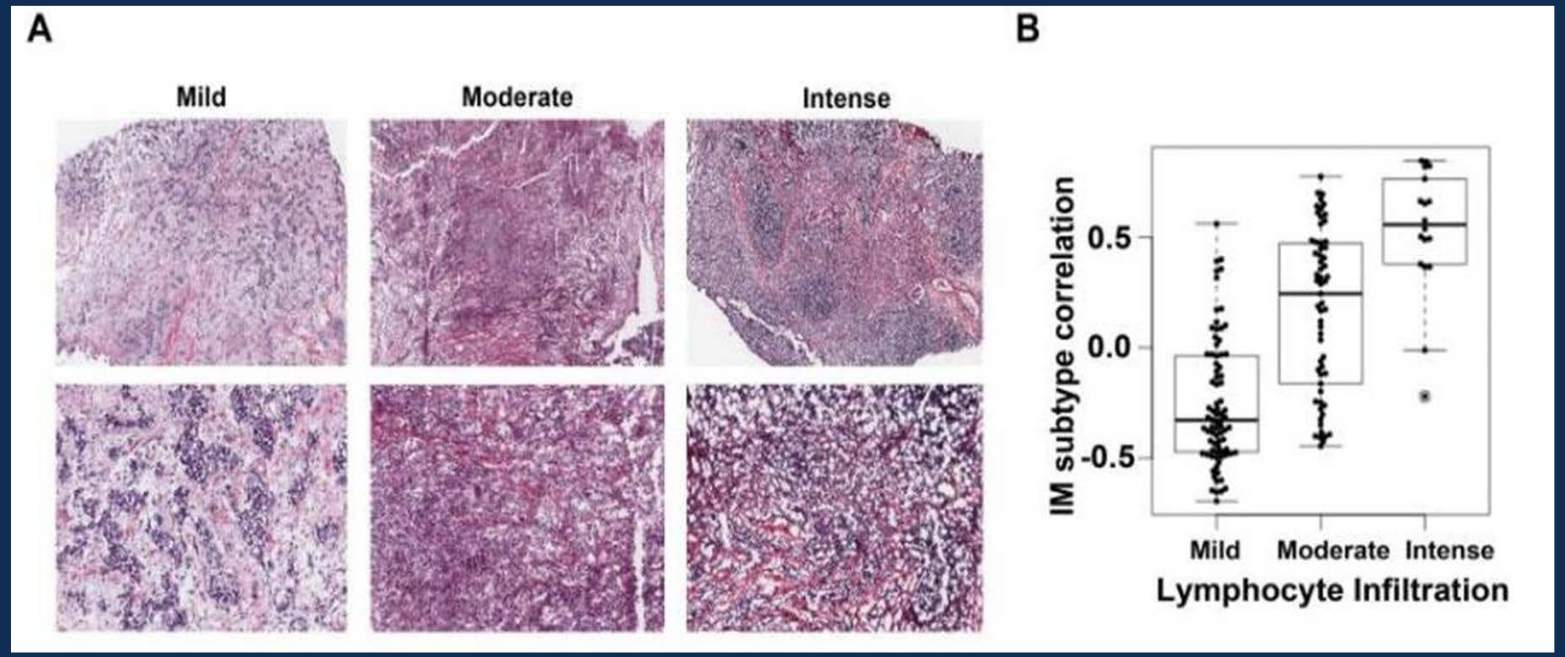
Immunomodulatory
- CTLA4 Pathway
- IL12 Pathway
- NK Cell Pathway
- Th1/Th2 Pathway
- IL7 Pathway
- Antigen Processing/ Presentation
- NFKB Pathway
- TNF Pathway
- T Cell Signal Transduction
- DC Pathway
- BCR Signaling Pathway
- NK Cell Mediated Cytotoxicity
- JAK/ STAT Signaling Pathway
- ATR/ BRCA Pathway

- BL1
- BL2
- IM
- M
- MSL
- LAR

Immunomodulatory subtype: Associated with an immune modulatory gene signature characterized by elevated expression of genes involved in T-cell function, immune transcription, interferon (IFN) response and antigen processing.

Lehman et al, JCI 2011

Immunomodulatory subtype is associated with increased lymphocytes



Correlation between TILs in cancer tissue and better prognosis.

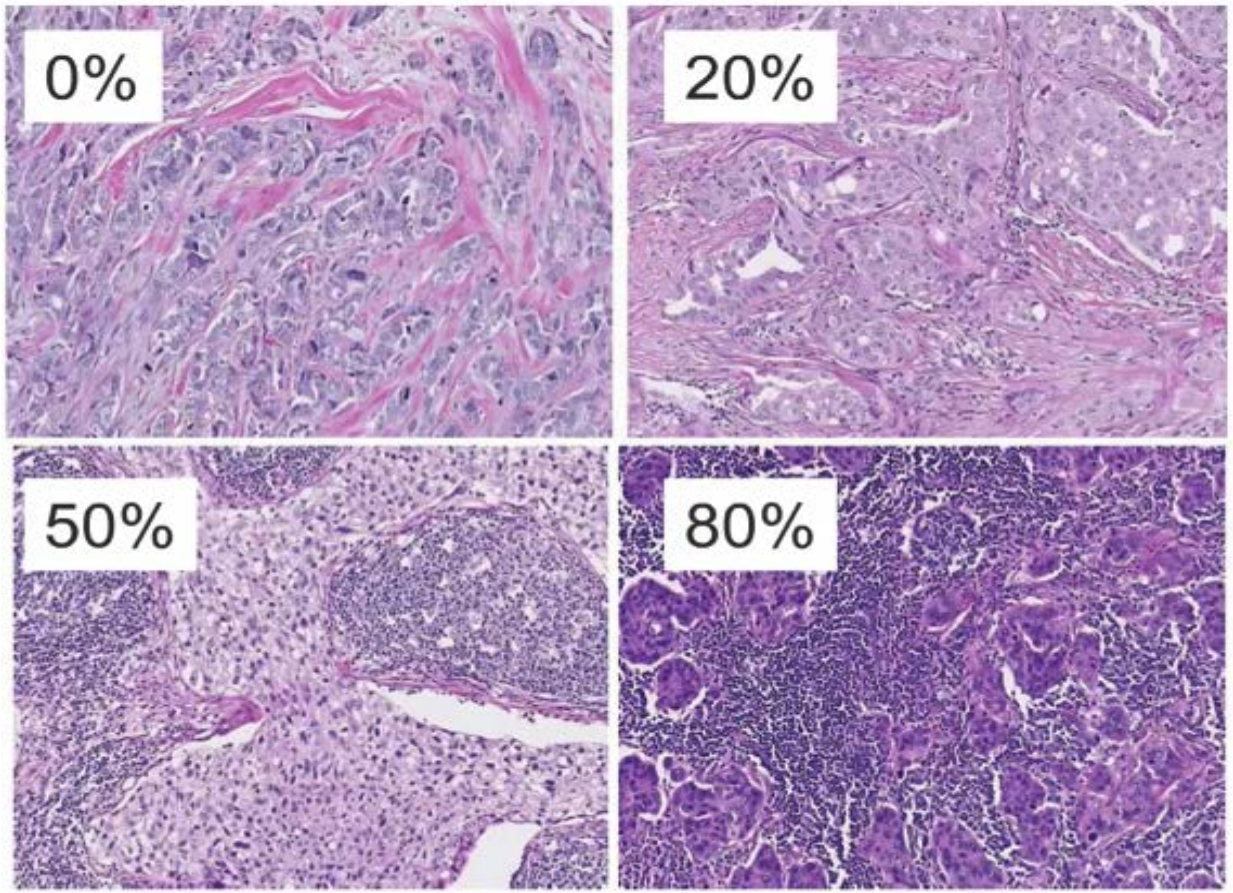
The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control

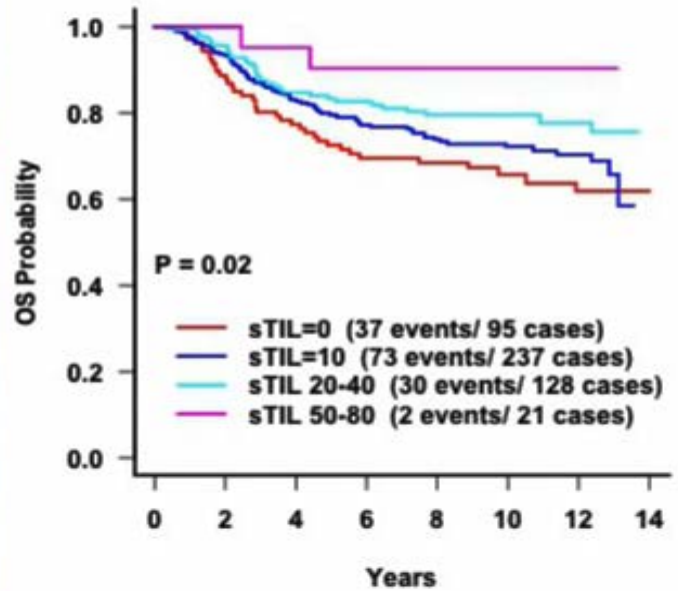
PD-L1 expressed in TNBC and half of all breast cancers

PD-1/PD-L1 interaction plays a critical role in immune evasion by tumors → attractive target for therapeutic interventions

Breast Cancer: The Immune System is Present at the Tumor Site But Incapable of Rejecting Cancer

Immunologic phenotypes of tumor/host in 481 TNBC patients from ECOG trials E2197/E1199





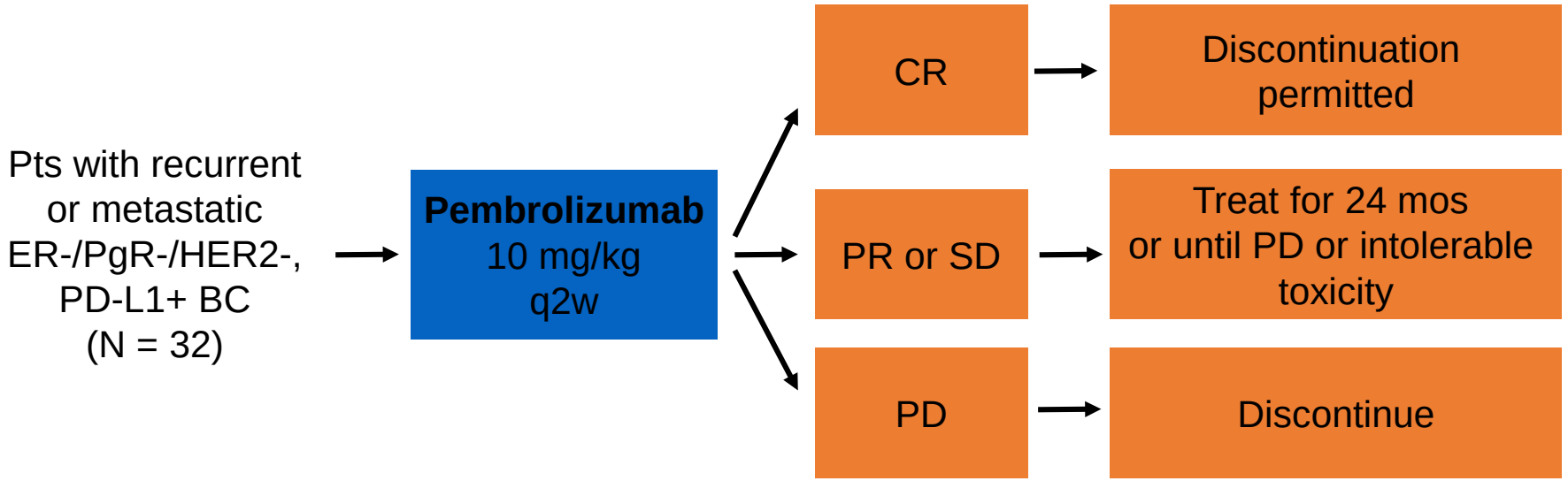
For every 10% increase in TILs, a 14% reduction of risk of recurrence or death

Adams et al JCO 2014 Sep 20;32(27):2959-66.

Clinical Evidence

Monotherapy studies

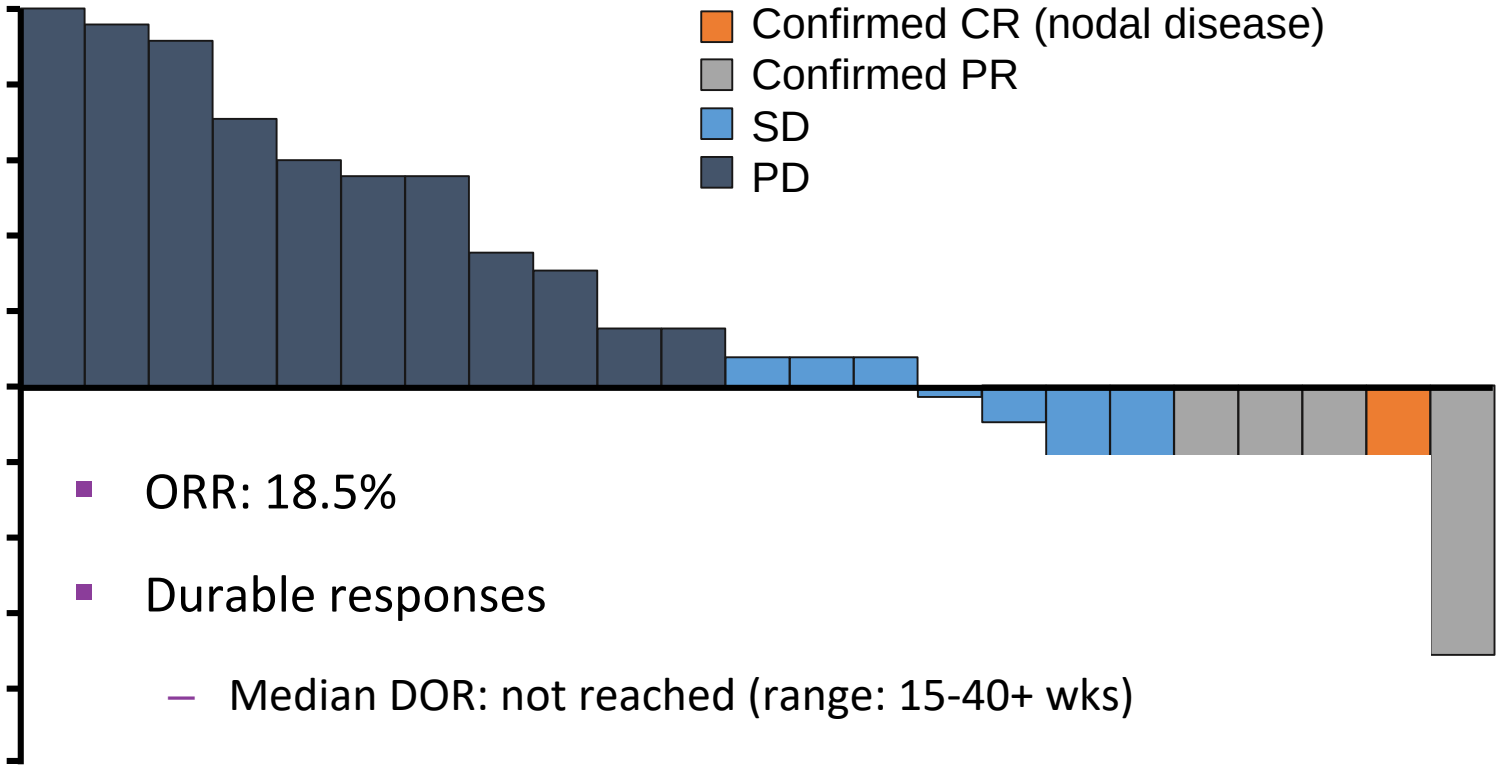
KEYNOTE-012: Pembrolizumab in Advanced TNBC: Study Design



- Pembrolizumab: anti–PD-1 antibody with high affinity for receptor
  - Provides dual ligand blockage of PD-L1 and PD-L2
  - No cytotoxic activity (ADCC/CDC)
  - Clinical activity in multiple tumor types

Nanda R, et al. SABCS 2014. Abstract S1-09.

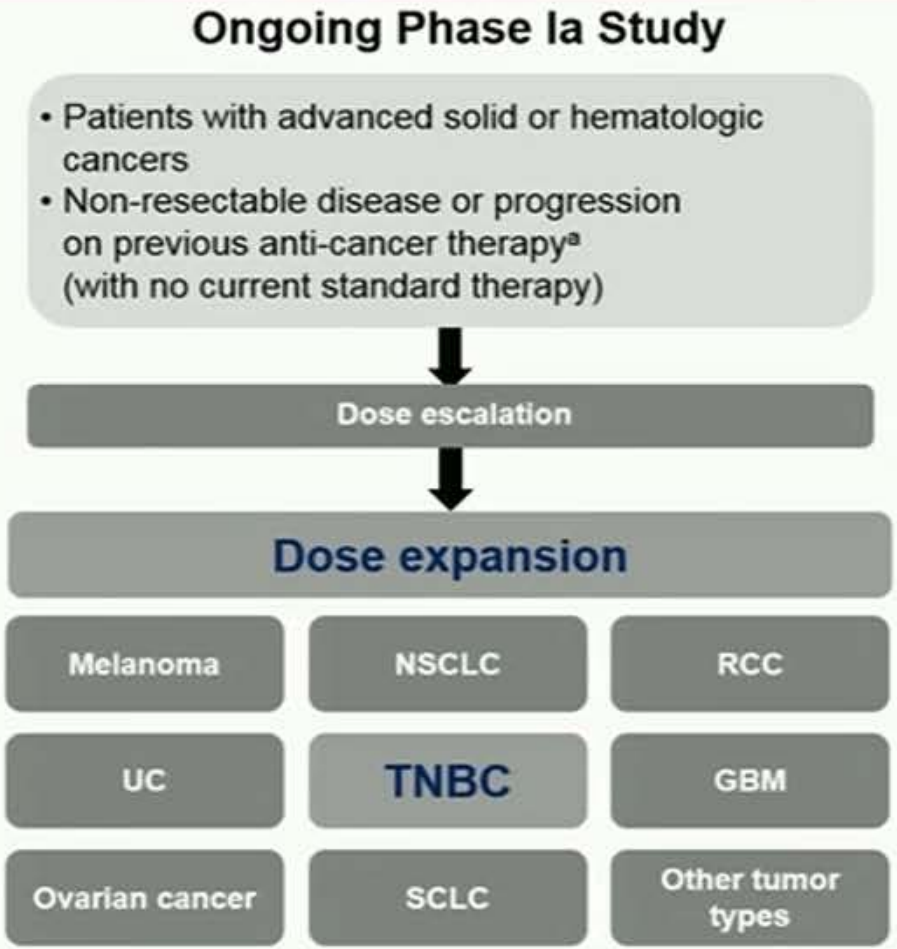
KEYNOTE-012: Pembrolizumab in Advanced TNBC: Tumor Regression



- ORR: 18.5%
- Durable responses
  - Median DOR: not reached (range: 15-40+ wks)
  - 3 responding pts for ≥ 11 mos

Nanda R, et al. SABCS 2014. Abstract S1-09.

Atezolizumab (α-PD-L1)



- Target Population
  - Metastatic TNBC
- Treatment
  - Atezolizumab IV q3w at 15 or 20 mg/kg or 1200 mg flat dose
- Objectives:
  - Primary endpoint: safety
  - Key secondary endpoints: ORR, DOR and PFS (per RECIST v1.1 and irRC)
  - Key exploratory endpoints: OS and biomarkers of clinical activity

Schmid P, et al. *AACR* 2017

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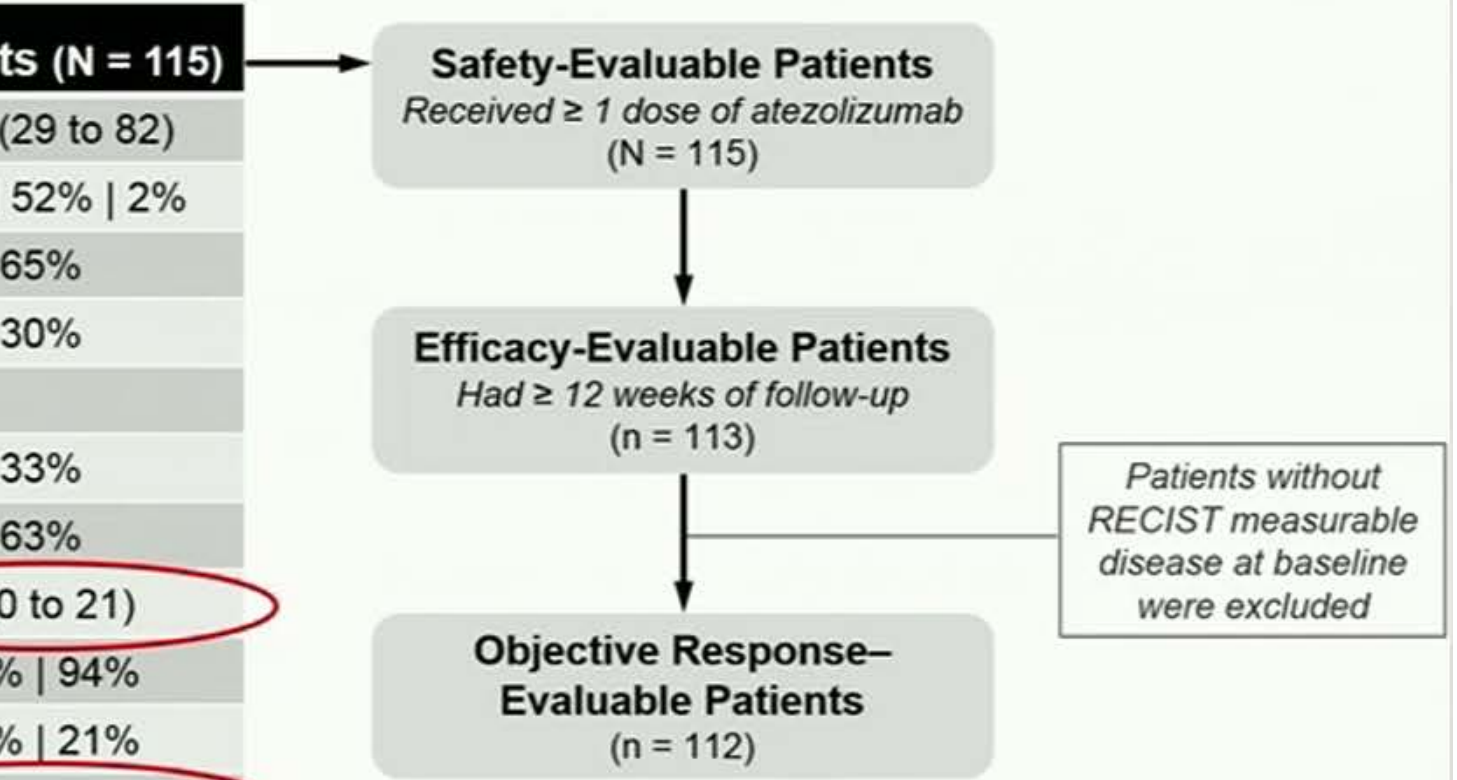
Atezolizumab (α-PD-L1)

Baseline Characteristics	Patients (N = 115)
Median age (range)	53 y (29 to 82)
ECOG PS, 0 | 1 | 2	46% | 52% | 2%
Visceral metastatic sites	65%
Bone metastatic sites	30%
PD-L1 status on IC	
IC0/1 (< 5%)	33%
IC2/3 (≥ 5%)	63%
Median prior systemic therapies (range)	7 (0 to 21)
Anthracycline | taxane	85% | 94%
Platinum | bevacizumab	58% | 21%
Current line of therapy, 1L | 2L | 3L+	17% | 24% | 58%



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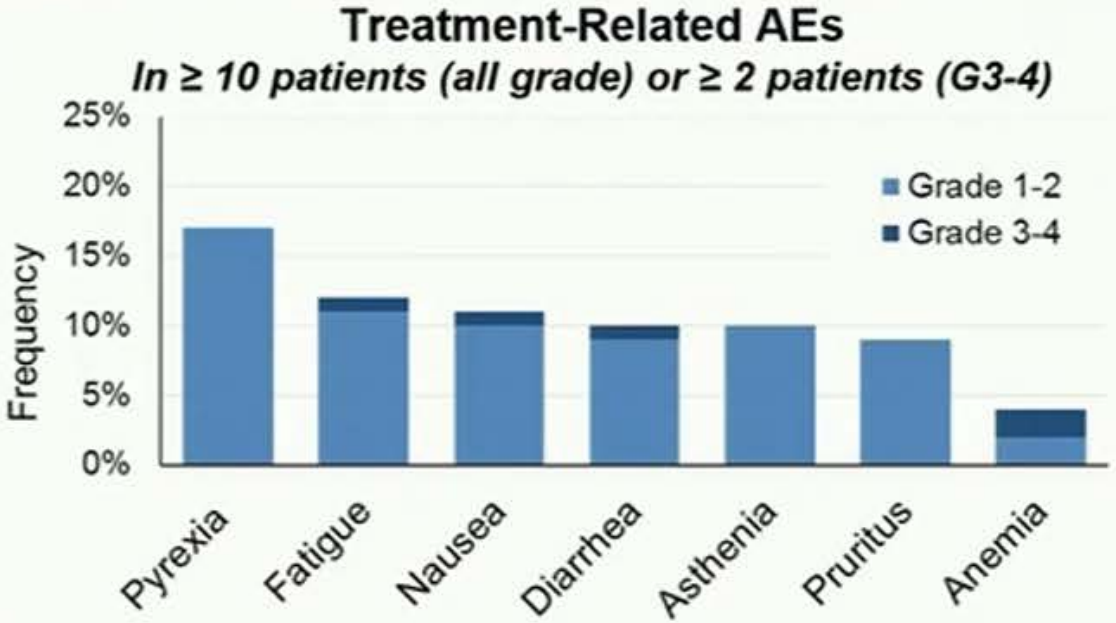
Atezolizumab (α-PD-L1)

Treatment-Related AE (N = 115)	Frequency
Any AE	63%
Grade 3-4	11%
Grade 5	2%
AE leading to treatment withdrawal	3%
AE leading to dose interruption	10%



- The majority of treatment-related AEs were Grade 1-2
  - All individual Grade 3-4 AEs occurred at 1%, except anemia at 2%
  - Two related Grade 4 AEs occurred: hyperglycemia and pneumonitis
  - Two related Grade 5 AEs occurred: pulmonary hypertension and death NOS in a hospitalized patient
- Grade 3-4 AEs of special interest included Grade 3 pruritic rash, lichen planus, increased blood bilirubin and adrenal insufficiency and Grade 4 pneumonitis

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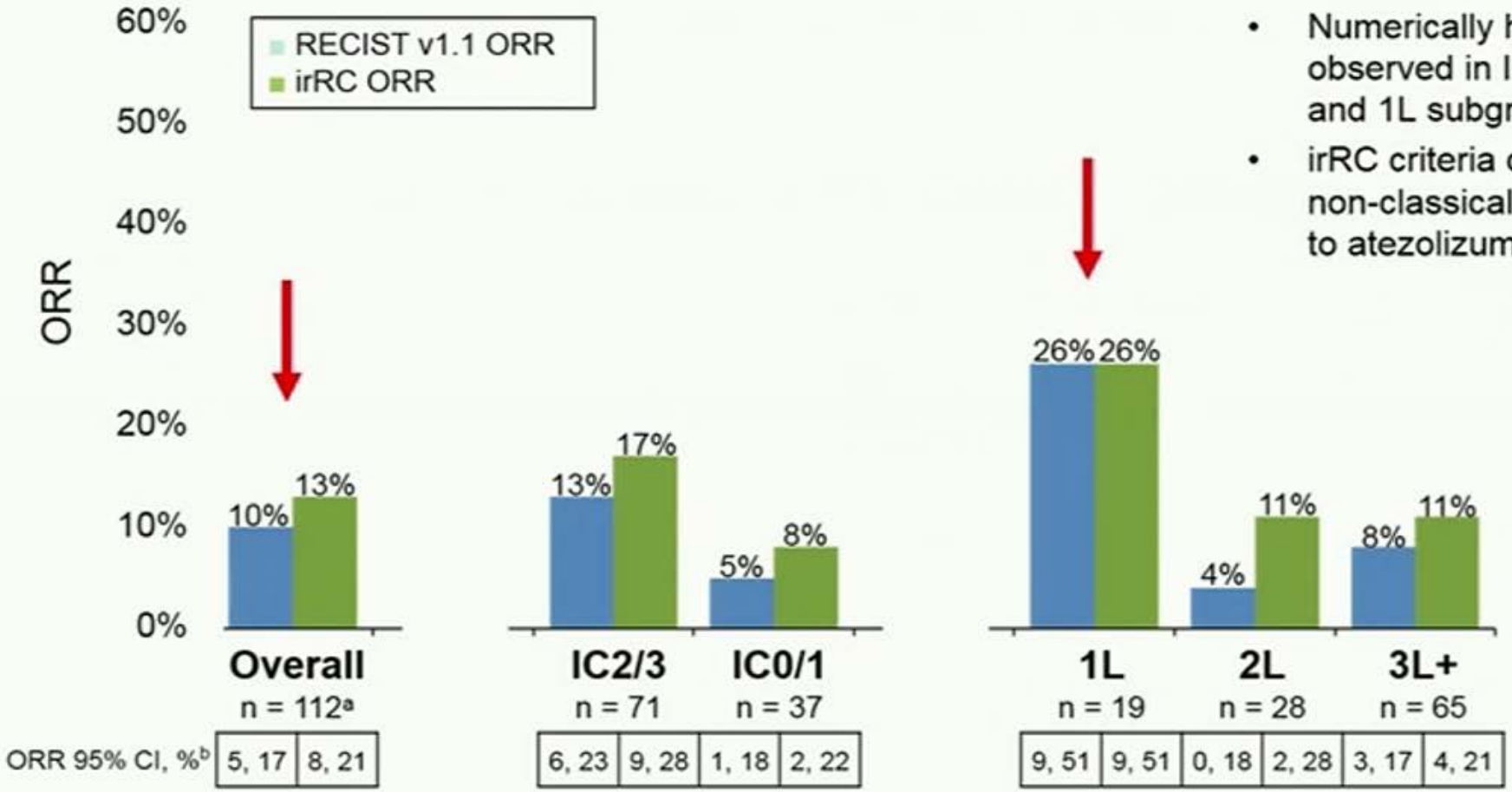
Atezolizumab (α-PD-L1)



- Numerically higher ORRs were observed in IC2/3 and 1L subgroups
- irRC criteria captured non-classical responses to atezolizumab

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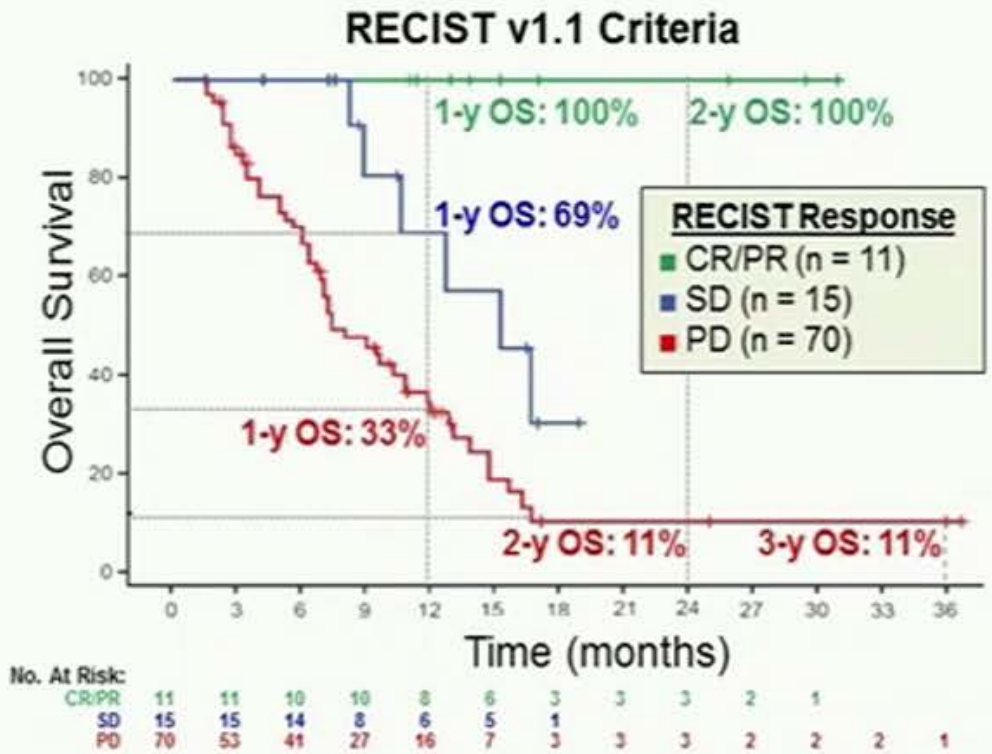
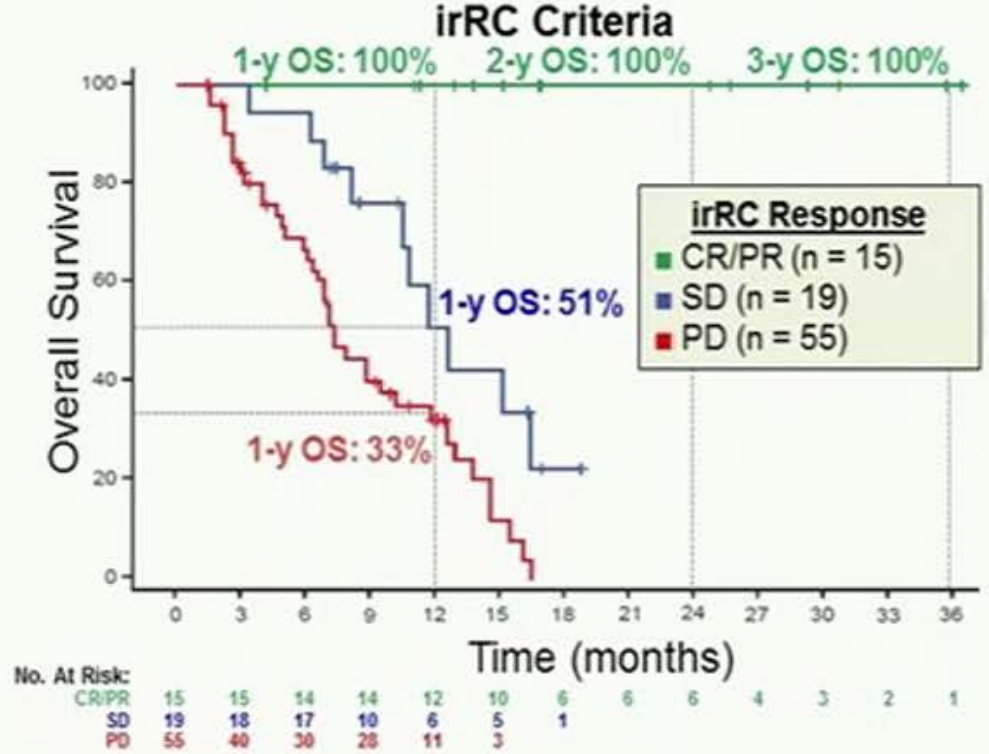
Atezolizumab (α-PD-L1)

- Median OS was 9.3 mo (95% CI: 7.0, 12.6) in all patients (median follow-up, 15.2 mo)
  - Landmark OS rates (95% CI) were: 41% (31, 51) at 1 year, and 22% (12, 32) at both 2 and 3 years





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Checkpoint Inhibitor Monotherapy in MBC

Trial	Agent	Population	Number Evaluable	ORR
KEYNOTE-012	Pembrolizumab (α-PD-1)	Metastatic TNBC	27	18.5%
KEYNOTE-086	Pembrolizumab (α-PD-1)	Metastatic TNBC	170 (cohort A) 84 (cohort B)	4.7% 22.6%
KEYNOTE-028	Pembrolizumab (α-PD-1)	Metastatic HR+/HER2-	25	12%
JAVELIN	Avelumab (α-PD-L1)	Metastatic – any subtype	HR+/HER2- 72 HR-/HER2+ 26 HR-/HER2- 58	2.8% 3.8% 8.6%
Phase Ia trial of Atezolizumab	Atezolizumab (α-PD-L1)	Metastatic TNBC	112	10%

Nanda R, et al. *J Clin Onc* 2016;34:2460-2467
Adams S, et al. *ASCO* 2017
Adams S, et al. *SABCS* 2017
Rugo H, et al. *SABCS* 2015
Dirix L, et al. *SABCS* 2015
Schmid P, et al. *AACR* 2017

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Checkpoint Inhibitor Monotherapy

- Agents generally well tolerated
  - ≈ 60% had any AE, most common grade 1/2
  - ≈ 10% have grade 3/4
- Responses best when administered in first line
- For those who do respond, the responses are durable
- Biomarkers remain somewhat elusive
  - Atezo
    - PD-L1 expression on immune cells in the TME
  - Pembro
    - stromal TIL assoc with response, particularly in 1st line setting
    - PD-L1 expression on tumor, lymphocytes and macrophages not associated with response

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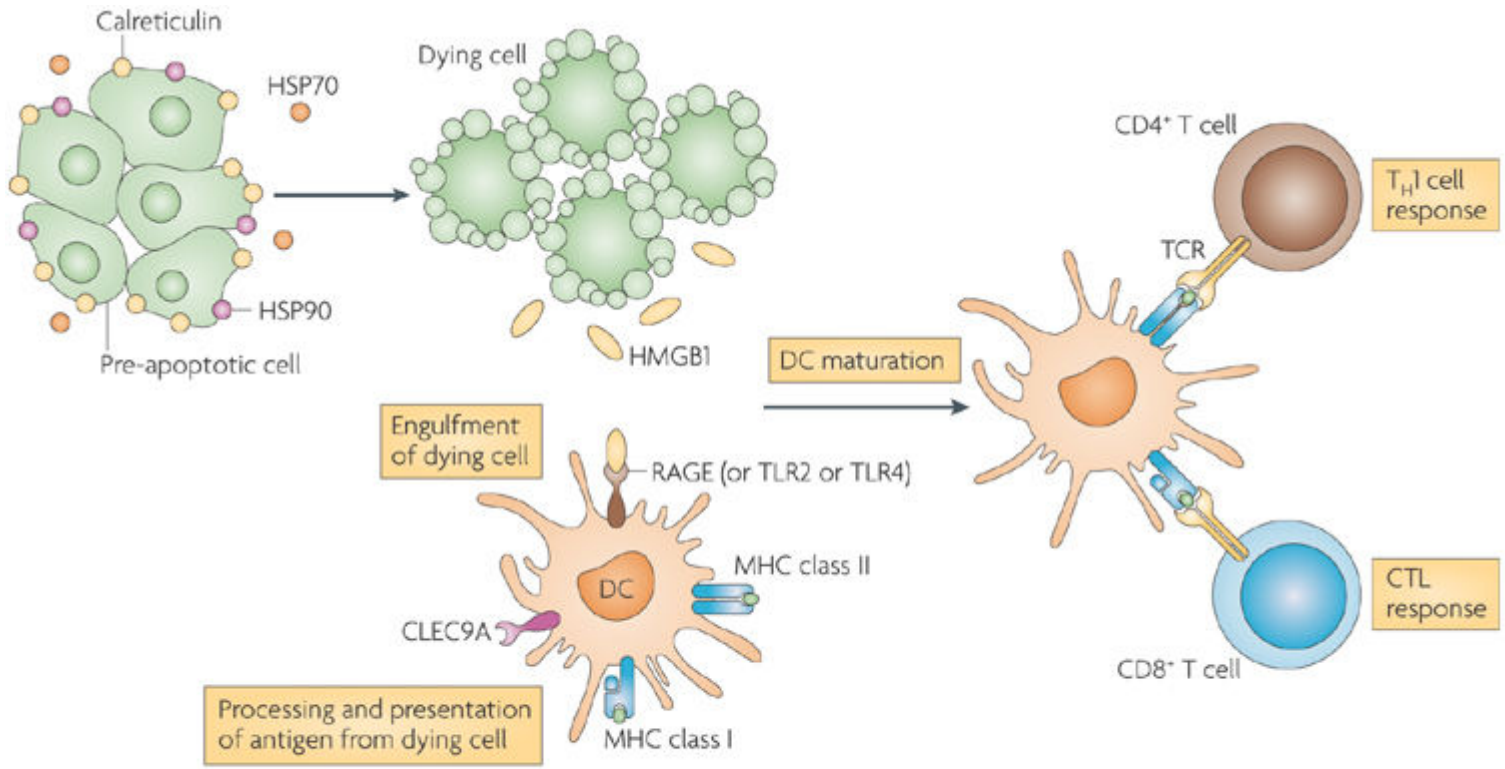
Chemotherapy + immunotherapy studies



Nature Reviews | Immunology

Atezolizumab + Albumin-Bound Paclitaxel in mTNBC Cohort: Study Design

- Phase Ib multicohort study

Pts with locally advanced or metastatic TNBC; 1-2 previous cytotoxic chemotherapy regimens; ECOG PS 0-1 (N = 32)

→ **Atezolizumab** 800 mg Q2W + **Albumin-bound paclitaxel** 125 mg/m^2 IV QW (3 wk on/1 wk off)*

- Primary endpoint: Safety/tolerability
- Other endpoints: ORR, DoR, PFS

Atezolizumab + Nab-Paclitaxel in mTNBC: Safety and Tolerability (Primary Endpoint)

- Median safety follow-up: 6.1 mos (range: 1.7-17.1 mos)
- Median duration of exposure: 5.4 mos (range: 0-17 mos) for atezolizumab; 4.2 mos (range: 0-12 mos) for nab-paclitaxel
- No reported deaths were related to study treatment

Treatment-Related AE (Grade 3/4 AEs Occurring in ≥ 1% of Pts), %	Pts (N = 32)	
	All Grades	Grade ≥ 3
All	100	69
Neutropenia/decreased neutrophil count	66	46
Thrombocytopenia and decreased platelet count	16	9
Diarrhea	41	6
Anemia	22	6
Decreased white blood cell count	9	6

Adams S, et al. ASCO 2016. Abstract 1009.

Atezolizumab + Albumin-Bound Paclitaxel in mTNBC Cohort: Antitumor Activity

Best Overall Response, %	All pts (N = 24)	1st-line pts (n = 9)	2nd-line pts (n = 8)	3rd-line + pts (n = 7)
ORR	70.8	88.9	75.0	42.9
CR	4.2	11.1	0	0
PR	65.7	77.8	75.0	42.9
SD	20.8	11.1	25.0	28.6

- 11 of 17 (65%) responses ongoing at time of reporting
- Responses reported in both PD-L1+ (77.8%; IC1/2/3) and PD-L1- (57.1%; IC 0) patients

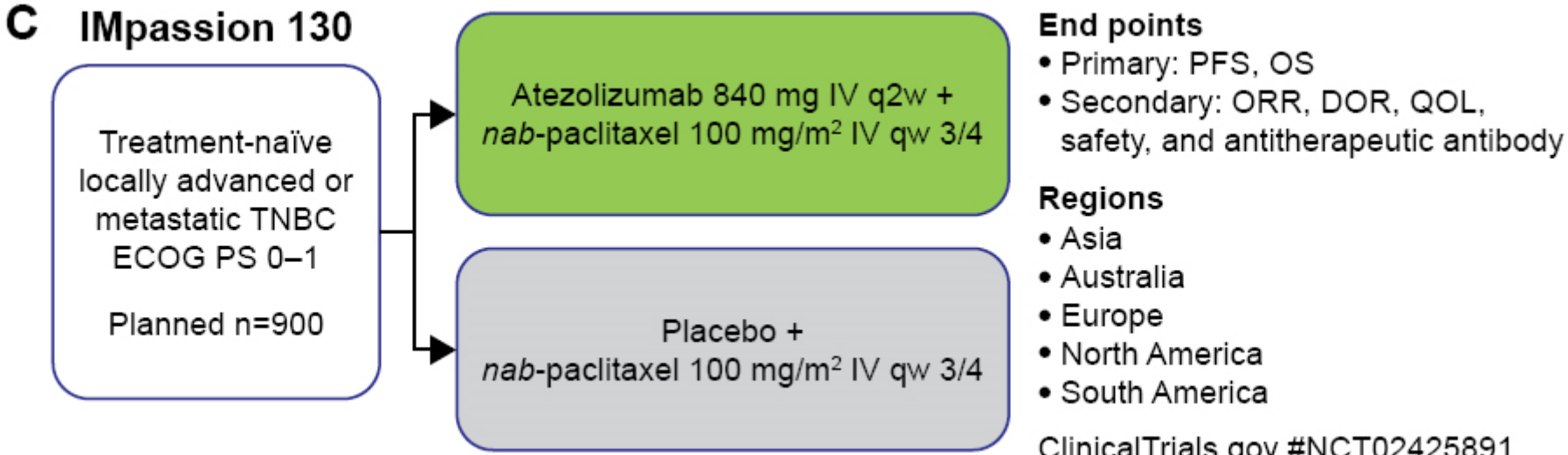
Adams S, et al. SABCS 2015. Abstract P2-11-06.

Slide credit: clinicaloptions.com

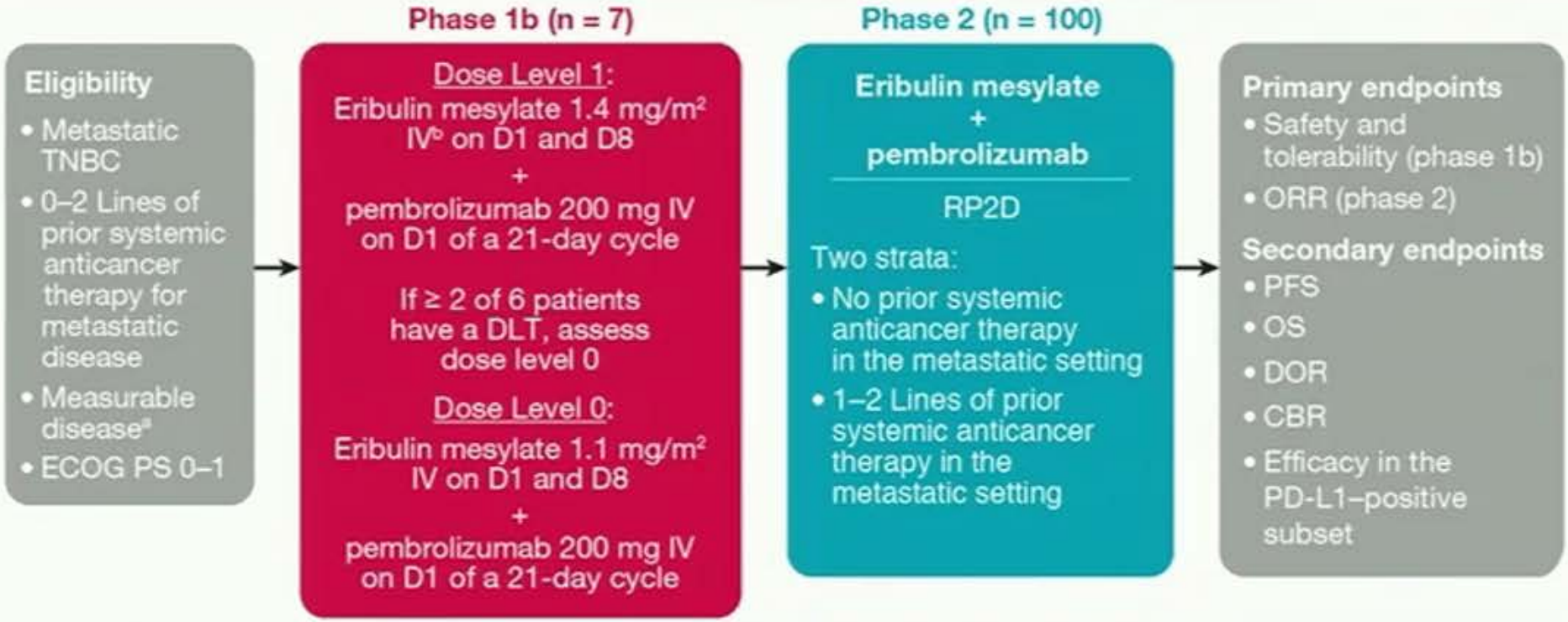
Atezolizumab + Nab-Paclitaxel in mTNBC: Conclusions

- Atezolizumab + nab-paclitaxel well tolerated and active in mTNBC
  - Safety profile similar to that of single agent
  - Durable responses achieved across all lines of therapy
  - Clinical response seen regardless of PD-L1 expression
- Ongoing phase III randomized trial evaluating this combination in previously untreated mTNBC

1. Adams S, et al. ASCO 2016. Abstract 1009.
2. ClinicalTrials.gov. NCT02425891.


C
IMpassion 130
Treatment-naïve locally advanced or metastatic TNBC ECOG PS 0–1
Planned n=900
Atezolizumab 840 mg IV q2w + nab-paclitaxel 100 mg/m² IV qw 3/4
Placebo + nab-paclitaxel 100 mg/m² IV qw 3/4
End points
• Primary: PFS, OS
• Secondary: ORR, DOR, QOL, safety, and antitherapeutic antibody
Regions
• Asia
• Australia
• Europe
• North America
• South America
ClinicalTrials.gov #NCT02425891

ENHANCE 1: Phase Ib/2 study to evaluate eribulin mesylate in combination with pembrolizumab in patients with mTNBC



Patients remained on 1 or both study drugs in the presence of clinical benefit until intercurrent illness, unacceptable toxicity, or disease progression, or until withdrawal of patient consent.

[a]≥ 1 Lesion of ≥ 10 mm in long-axis diameter (nonlymph node) or ≥ 15 mm in short-axis diameter (lymph node) serially measurable by RECIST v1.1. Lesions that have had radiotherapy must show subsequent radiographic evidence of increased size to be deemed a target lesion.

[b]Equivalent to 1.23 mg/m² eribulin (expressed as free base).

CBR, clinical benefit rate; D, day; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; RP2D, recommended phase 2 dose; TNBC, triple-negative breast cancer.

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Demographic, Baseline and Disease Characteristics

Parameter	Total (N = 107) n (%)
Age (years)	
Mean (SD)	54.6 (11.2)
Median	55.0
Minimum, maximum	32, 88
ECOG performance status	
0	70 (65.4)
1	37 (34.6)
Enrollment Strata	
1: no prior systemic therapy in the metastatic setting	66 (61.7)
2: 1-2 lines of prior systemic therapy in the metastatic setting	41 (38.3)
Tumor PD-L1 status[a]	
Negative	49 (45.8)
Positive	49 (45.8)
Not available	9 (8.4)

[a]PD-L1 positivity is defined as staining in the stroma or ≥ 1% tumor cells. The threshold was 1% combined positive score

Tolaney S, et al. *SABCS* 2017

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Efficacy

	Evaluable Analysis Set		
	Stratum 1 (n = 65)	**Stratum 2 (n = 41)**	**Total (n = 106)**
Objective Response Rate (CR + PR), n (%) (95% CI)	19 (29.2) (18.6–41.8)	9 (22.0) (10.6–37.6)	28 (26.4) (18.3–35.9)
CR, n (%)	1 (1.5)	2 (4.9)	3 (2.8)
PR, n (%)	18 (27.7)	7 (17.1)	25 (23.6)
CBR (CR + PR + durable SD [duration ≥ 24 weeks]), n (%)	26 (40.0)	13 (31.7)	39 (36.8)
Patients With Objective Response Rate	**Stratum 1 (n = 19)**	**Stratum 2 (n = 9)**	**Total (n = 28)**
DOR (months), median (95% CI)	8.3 (4.4–12.9)	NE (4.3–NE)	8.3 (6.5–12.9)
DOR > 6 months, n (%)	10 (52.6)	5 (55.6)	15 (53.6)
DOR > 12 months, n (%)	2 (10.5)	2 (22.2)	4 (14.3)
	Full Analysis Set		
	Stratum 1 (n = 66)	**Stratum 2 (n = 41)**	**Total (N = 107)**
PFS (months), median (95%CI)	4.9 (4.1–6.1)	4.1 (2.1–6.2)	4.2 (4.1–5.6)
PD/death, n (%)	47 (71.2)	30 (73.2)	77 (72.0)
OS (months), median (95% CI)	4.1 (2.1–6.2)	16.3 (12.4–19.2)	17.7 (13.7–NE)
Death, n (%)	30 (73.2)	19 (46.3)	42 (39.3)

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Study Design

This is a randomized, placebo-controlled, double-blind, global Phase III study of pembrolizumab + chemotherapy vs placebo + chemotherapy for subjects with locally recurrent inoperable or metastatic triple negative breast cancer (TNBC), which has not been previously treated with chemotherapy.

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Treatment Period	Use
Pembrolizumab	200 mg	Day 1	IV infusion	Every 21 days	Experimental
Nab-paclitaxel	100 mg/m^2	Days 1, 8, and 15	IV infusion	Every 28 days	Chemotherapy background treatment
Paclitaxel	90 mg/m^2	Days 1, 8, and 15	IV infusion	Every 28 days	
Gemcitabine Carboplatin	1000 mg/m^2 AUC 2	Days 1 and 8	IV infusion	Every 21 days	
Placebo (Normal Saline)	NA	Day 1	IV infusion	Every 21 days	Placebo for Pembrolizumab

The study consists of two parts

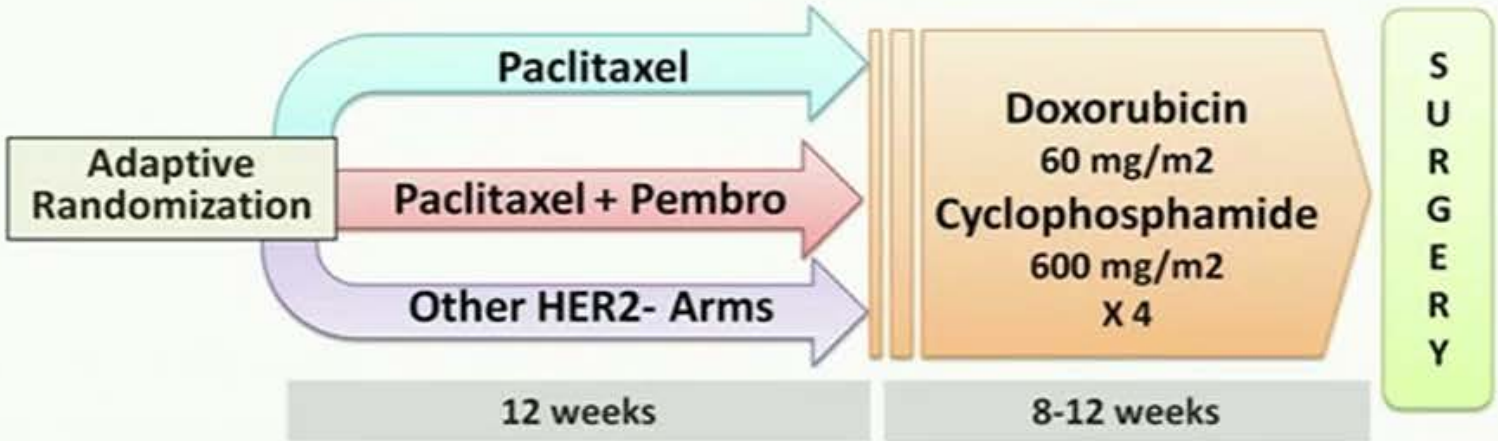
- Part 1
  - open-label
  - 30 subjects
  - 3 arms (10 pts/arm)
    - pembrolizumab + nab-paclitaxel
    - pembrolizumab + paclitaxel
    - pembrolizumab + gemcitabine + carboplatin
- Part 2
  - double-blind
  - 828 pts
  - 2 arms (2:1 randomization)
    - pembrolizumab + chemotherapy
    - placebo + chemotherapy

Enrollment in Part 2 of the study will begin immediately following completion of full enrollment in Part 1.

Pr Proprietary

Neoadjuvant Checkpoint Blockade

I-SPY 2 TRIAL Schema: HER2- Signatures



Control
Paclitaxel 80 mg/m2 every wk x 12

Experimental
Paclitaxel 80 mg/m2 every wk x 12
Pembro 200 mg every 3 wks x 4

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Estimated pCR

Signature	Estimated pCR rate (95% probabilty interval)		Probability pembro is superior to control	Predictive probability of success in phase 3
	Pembro	Control		
All HER2-	**0.46** (0.34 – 0.58)	**0.16** (0.06 – 0.27)	**> 99%**	**99%**
TNBC	**0.60** (0.43 – 0.78)	**0.20** (0.06 – 0.33)	**>99%**	**>99%**
HR+/HER2-	**0.34** (0.19 – 0.48)	**0.13** (0.03 – 0.24)	**>99%**	**88%**

The Bayesian model estimated pCR rates appropriately adjust to characteristics of the I-SPY 2 population.
The raw pCR rates (not shown) are higher than the model estimate of 0.604 in TNBC.

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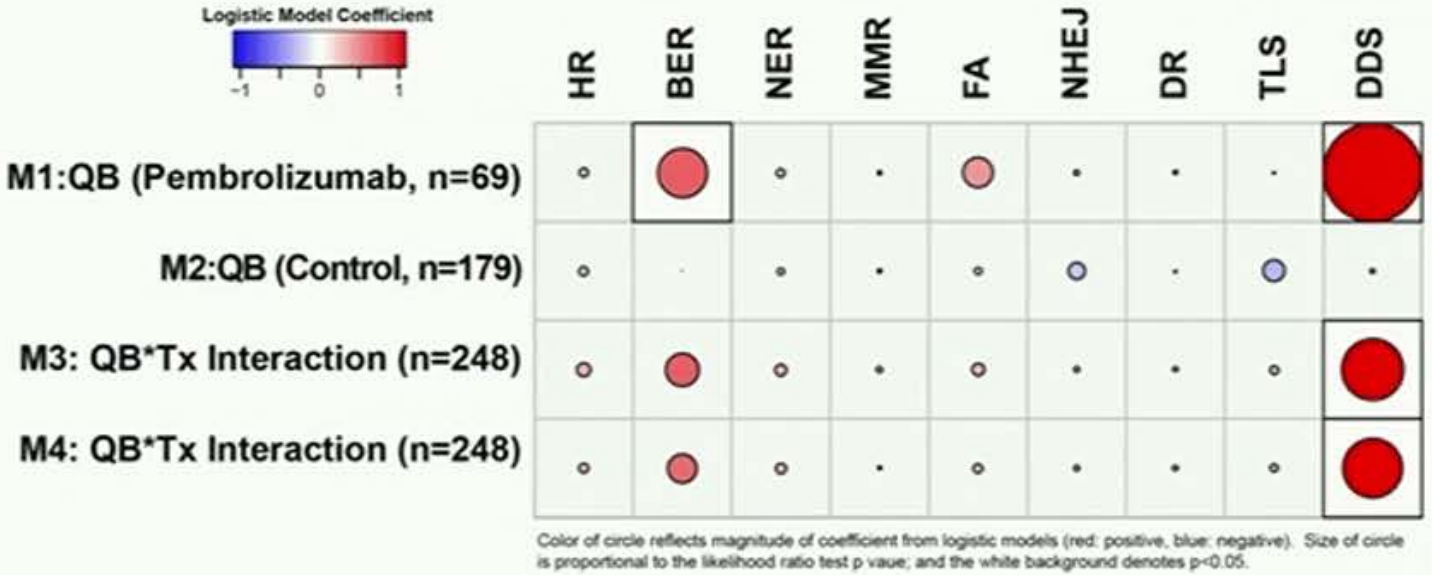
DNA damage and repair

- Evaluated 9 gene expression signatures reflecting different aspects of DNA damage and repair (FA, MMR, BER, HR, TLS, NER, NHEJ, DR, and DNA damage sensing [DDS] pathways)



Both BER and DDS associates with pCR in the pembro arm, but only DDS associates with pCR in pembro arm and not control arm

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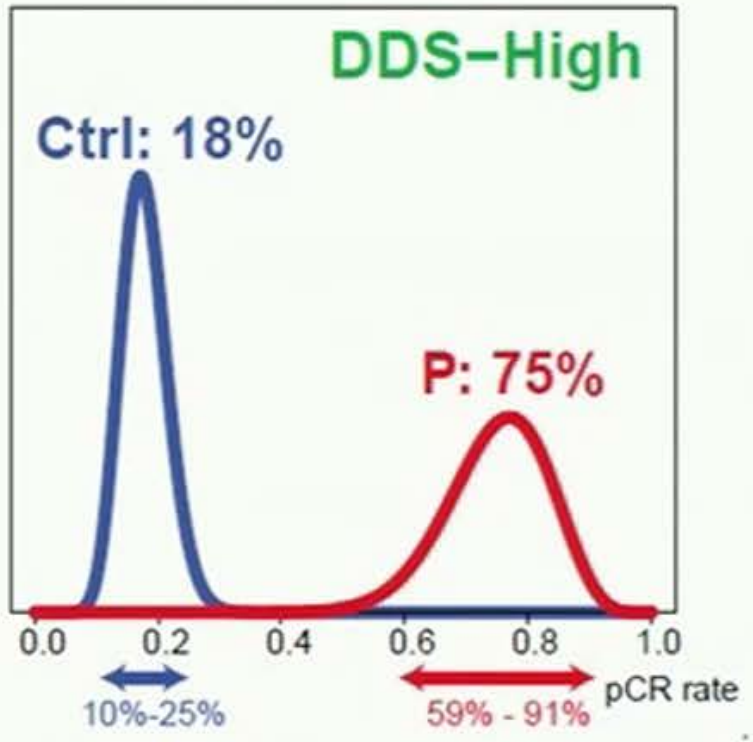
DNA Damage and Repair

- DDS pathway score
  - •Shows significant association with pCR in the pembro arm, but not the control arm
  - •Has significant interaction with treatment
  - •Is a successful biomarker as per pre-specific QBE plan
  - •Using a threshold that maximizes interaction with treatment, patients with DDS score above this threshold have an estimated pCR rate of 75% to pembro compared to 18% with standard chemotherapy



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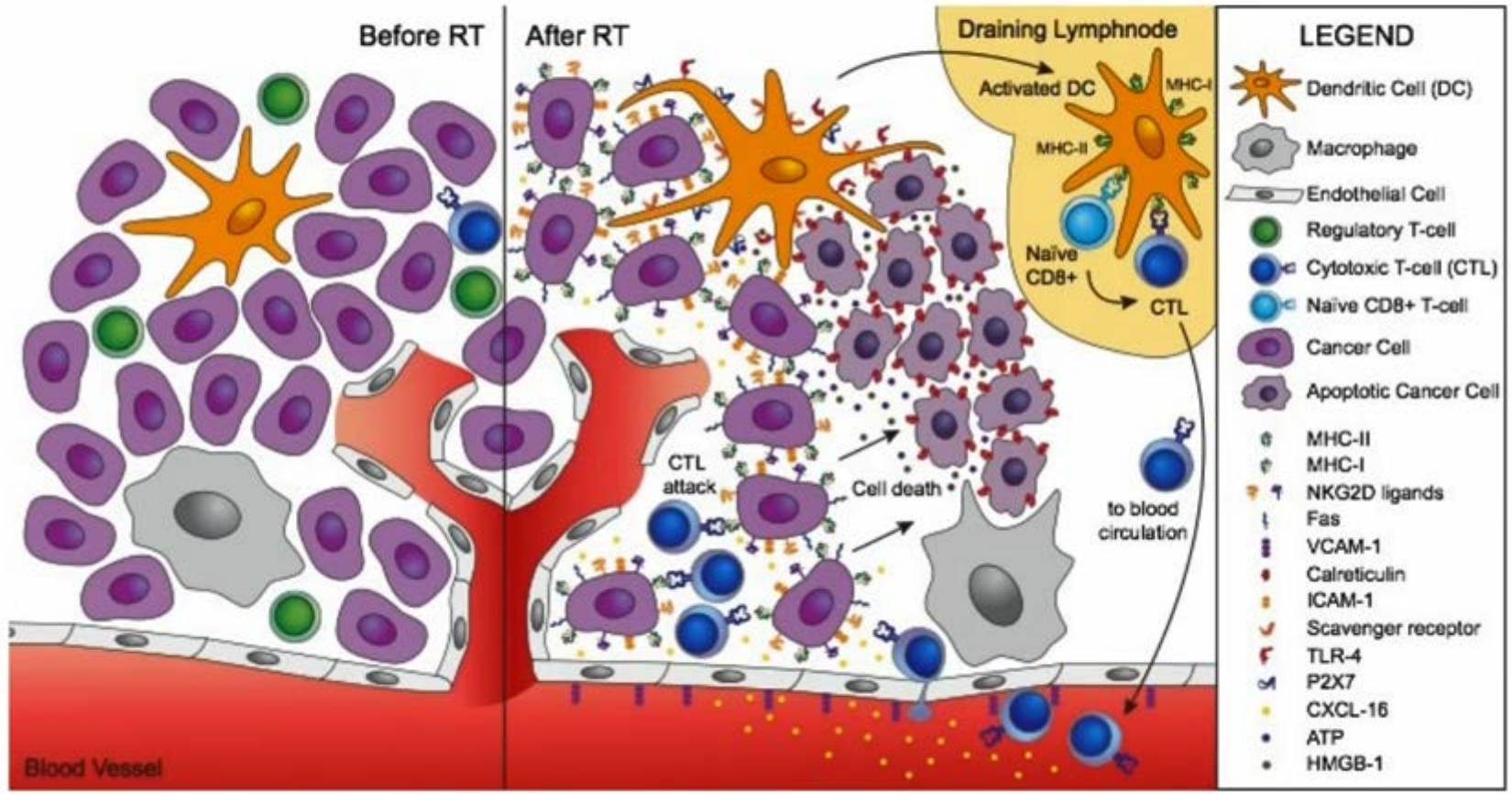
Can RT Reset the Immunologic Phenotypes of a Tumor?

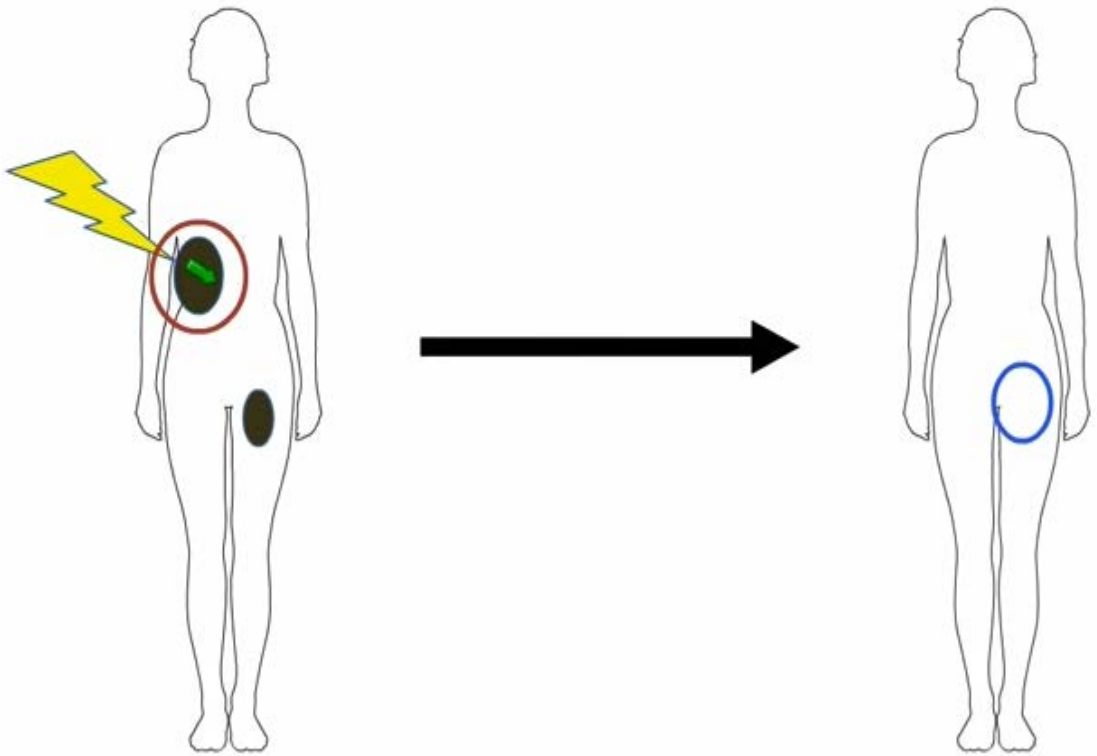


IJROBP 2004, Lancet Oncology 2009, JNCI 2012

Can Radiation Therapy Help the Immune System to Reject Cancer?

Abscopal effects

(ab-scopus = away from the target)



Curr Probl Cancer 40 (2016) 25–37

Contents lists available at ScienceDirect

Curr Probl Cancer

journal homepage: www.elsevier.com/locate/cpcancer

Systematic review of case reports on the abscopal effect

Yazan Abuodeh, MD, Puja Venkat, MD, Sungjune Kim, MD, PhD

1969-2014:

only 46 abscopal cases

Slide courtesy of Dr. Silvia Formenti

THE LANCET Oncology

Volume 16, No. 7, p795–803, July 2015

Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial

Encouse B Golden, MD, Arpit Chhabra, MD, Prof Abraham Chachoua, MD, Sylvia Adams, MD, Martin Donach, MD, Maria Fenton-Kerimian, NP, Kent Friedman, MD, Fabio Ponzo, MD, James S Babb, PhD, Prof Judith Goldberg, ScD, Prof Sandra Demaria, MD, Dr Prof Silvia C Formenti, MD

Patients with stable or progressing metastatic solid tumors, on single agent chemotherapy or hormonal therapy. With at least 3 distinct measurable sites of disease.

→

Concurrent Radiotherapy 35 Gy in 10 fractions over 2 weeks to one metastatic site.
+
GCS-F 125 µg/m2

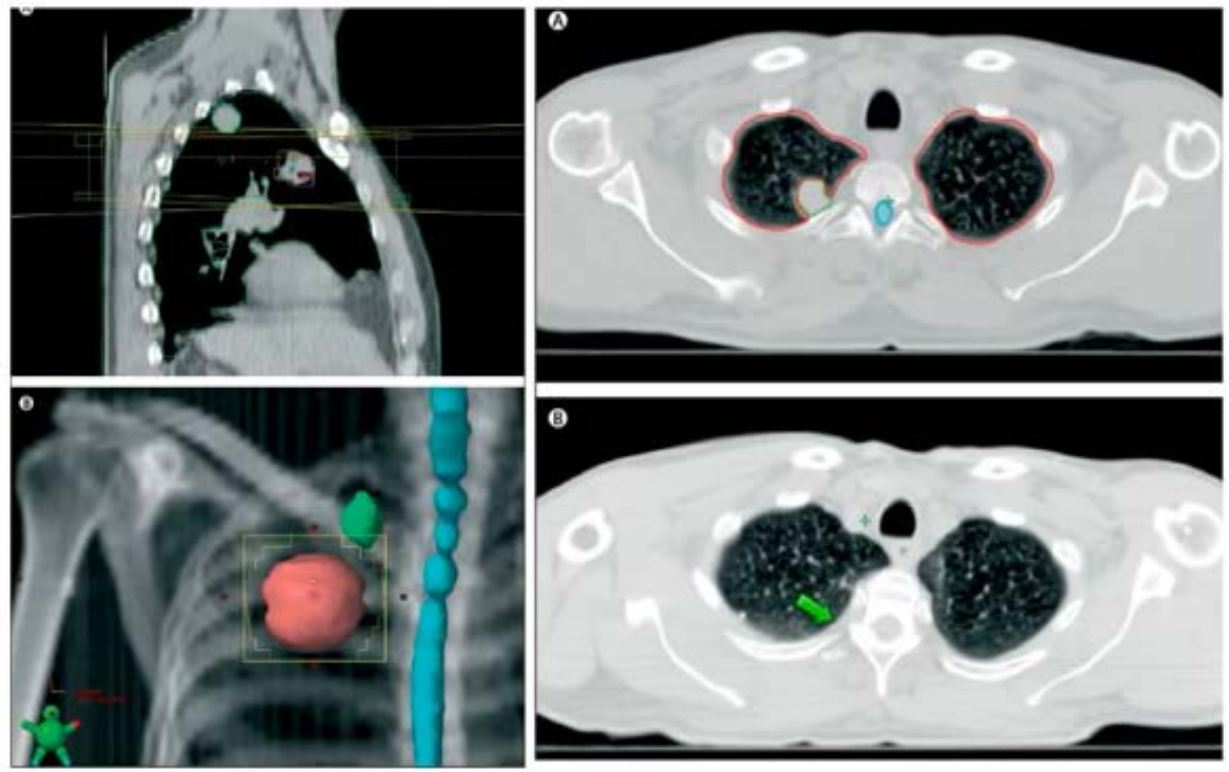
→

Abscopal effect seen in 11/41 patients (26.8%, 95% CI 14.2-42.9)
4 NSCLC, 5 Breast ca, 2 Thymic ca
If effect was seen median overall survival increased from
8.3 months to 21 months

Abscopal Response After Radiation and GM-CSF

RT:
3.5 Gy X 10

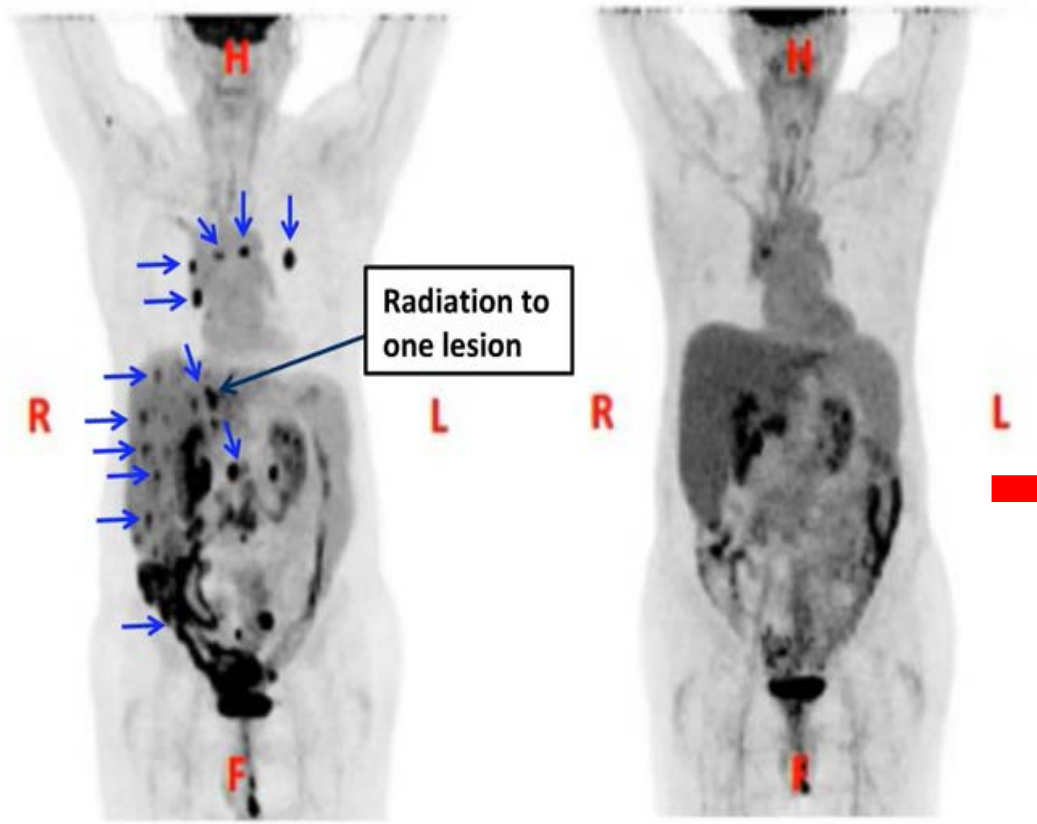
GM-CSF:
125 mg/m^2
Daily X 14 days



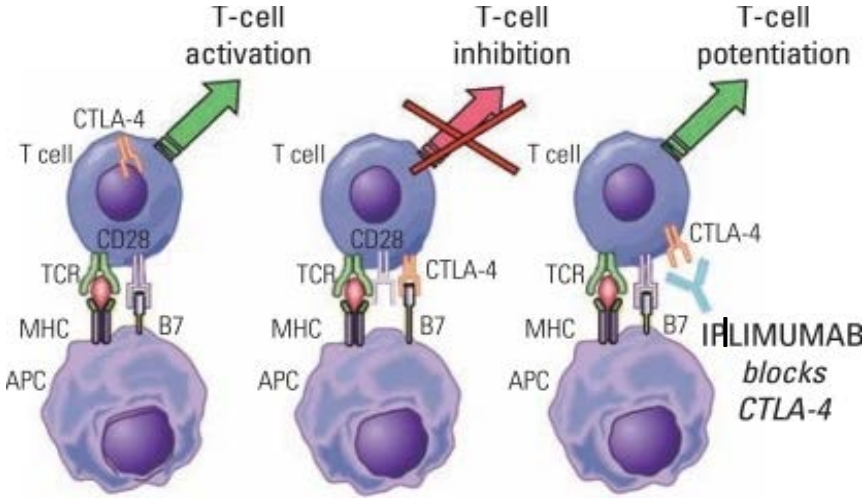
Slide courtesy of Dr. Silvia Formenti

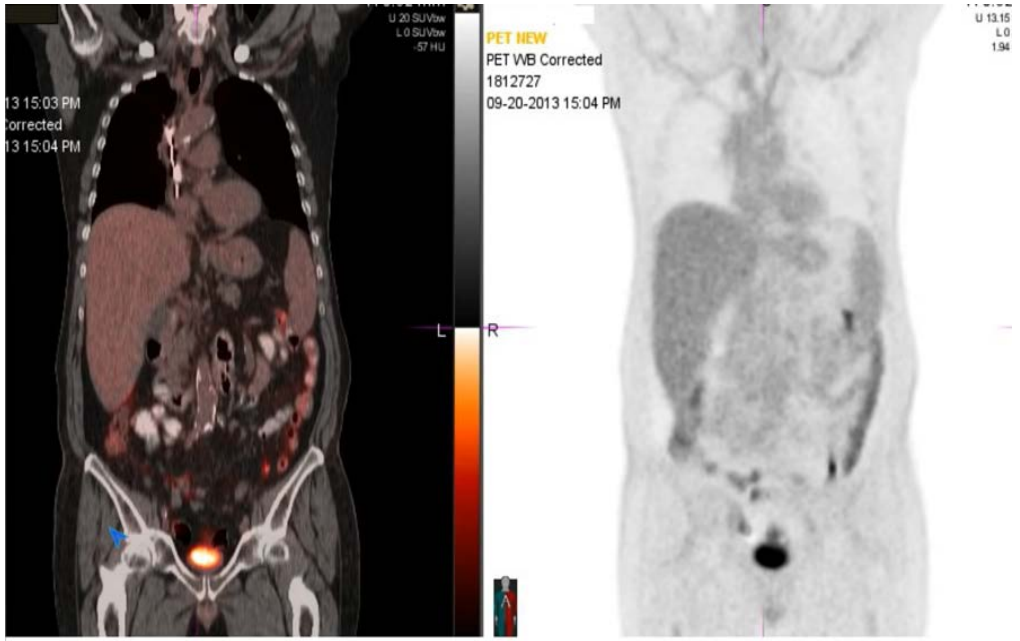
Mr. P: Patient with Lung Cancer Metastasized To Liver, Lung, and Bone Achieves a Complete Response

Treated with **Radiation Plus Checkpoint Blockade**



August 2012 January 2013





Currently at 4 years without any other therapy and with no evidence of disease

Slide courtesy of Dr. Silvia Formenti

Take home points

- Anti PD1/PDL1 agents in monotherapy have shown modest activity in metastatic Breast Cancer
- Toxicity profile is favorable.
- Identification of Biomarkers is key !!!
- Potential Biomarkers include : Intestinal flora, Tumor mutational burden, Microsatellite instability, PD-1 , PDL-1 expression in tumor or microenvironment, gene expression signatures (immune rich type of TNBC, DNA damage and repair DDS), tumor infiltrating lymphocytes.
- Combining these agents with radiation/ chemotherapy / GCS-F could enhance the response to therapy.

Thanks !!!

Please Don’t Forget