SVILUPPI DI NAB-PACLITAXEL IN EARLY DISEASE CON CHECKPOINT INIBITORI

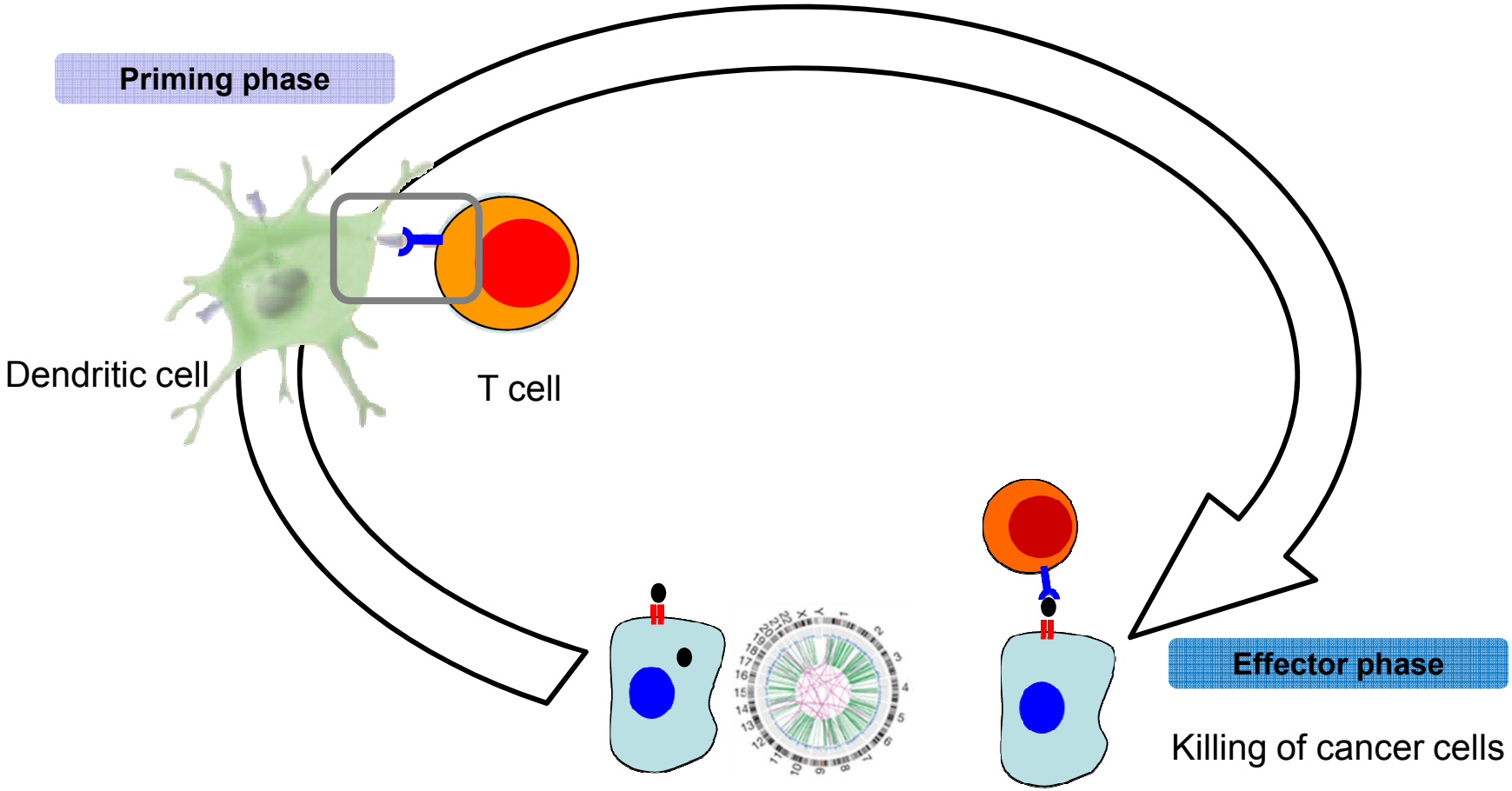
NeoTRIPaPDL1

Neo-Adjuvant study with the PDL1-directed antibody in Triple Negative Locally Advanced Breast Cancer undergoing treatment with nab-paclitaxel and carboplatin

Giampaolo Bianchini

OSPEDALE SAN RAFFAELE

The Cancer-Immunity cycle



Tumor cell

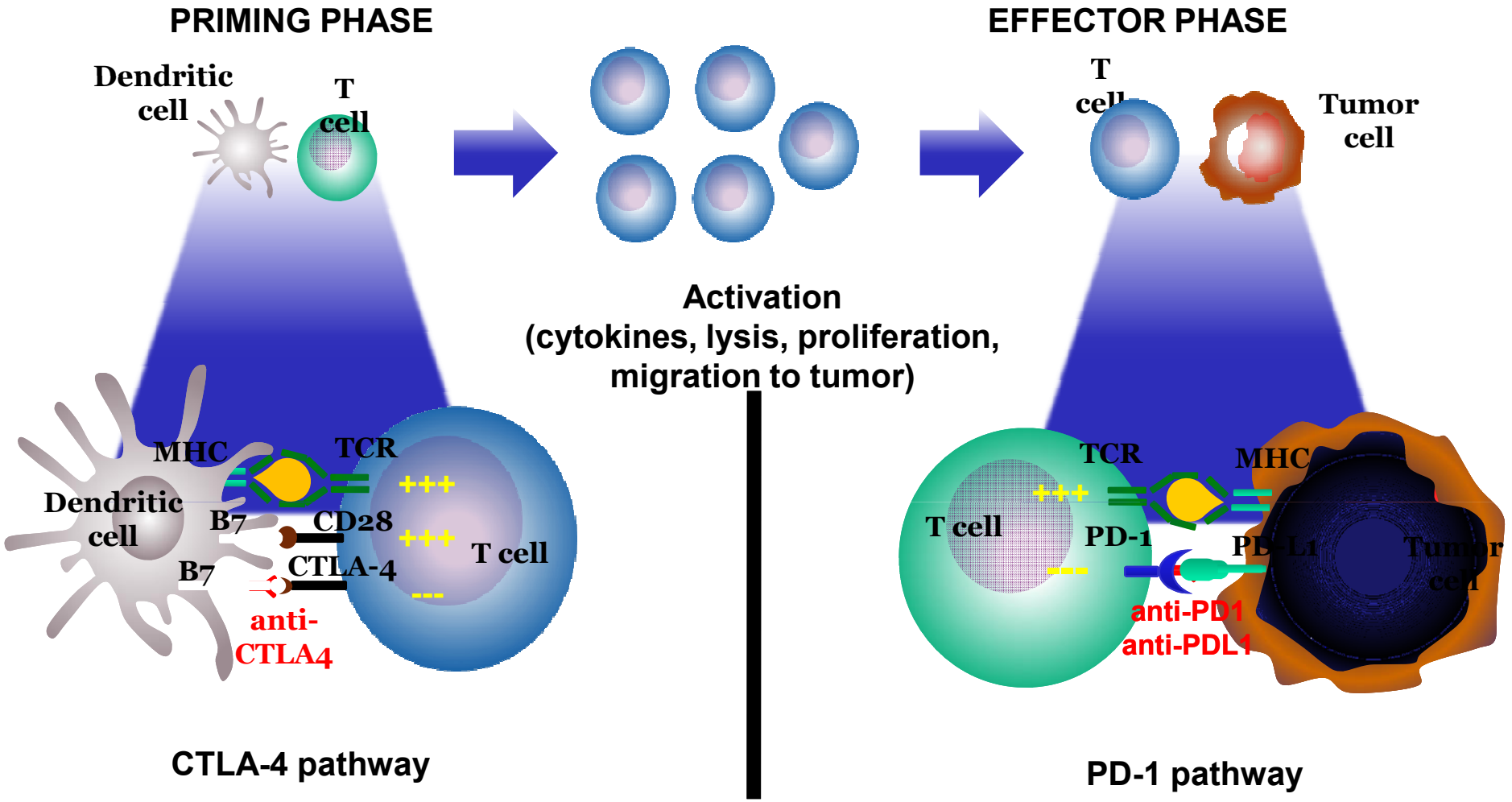
Cytotoxic T-cell

MHC I

TCR

Neoantigens

Targeting CTLA-4 and PD-1 pathways (immune checkpoint inhibitors)



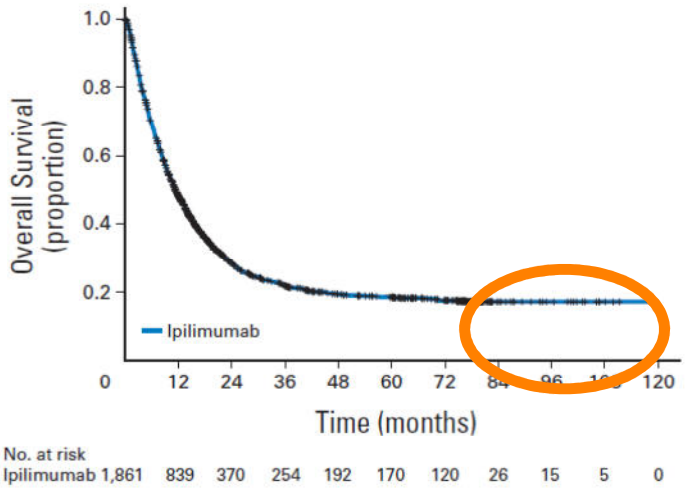
CTLA-4 = cytotoxic T-lymphocyte-associated antigen 4 ; MHC = major histocompatibility complex; PD-1 = programmed death-1; PD-L1 = programmed death ligand 1; TCR = T-cell receptor.

Mod da: Wolchock J, et al. JCO 2013 Volume 31, Issue 15_suppl ; abstr 9012^

Immunotherapy is set to revolutionise the treatment of cancer: a promise of cure for some

Immunotherapy: the promise of cure (for some)

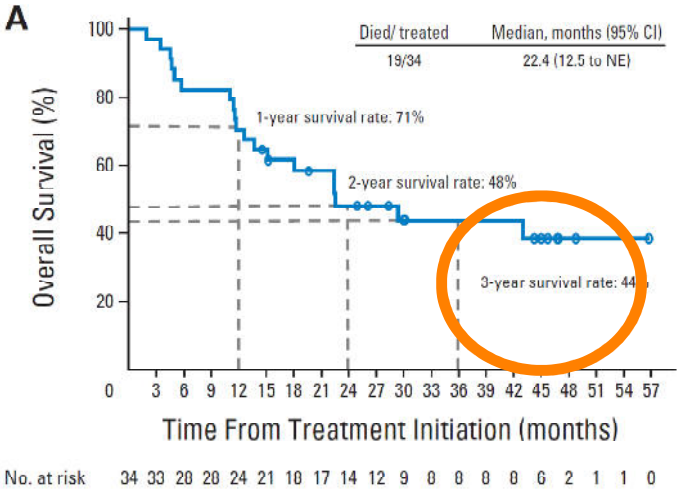
Melanoma



Ipilimumab

Schadendorf D JCO 2015

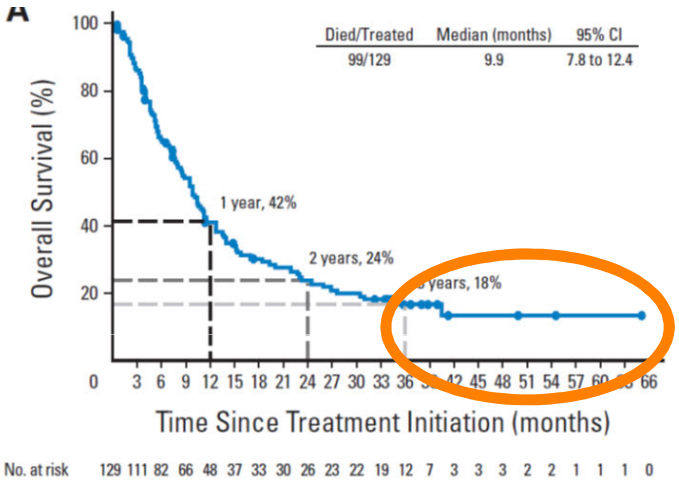
RCC



Nivolumab

McDermott DF JCO 2015

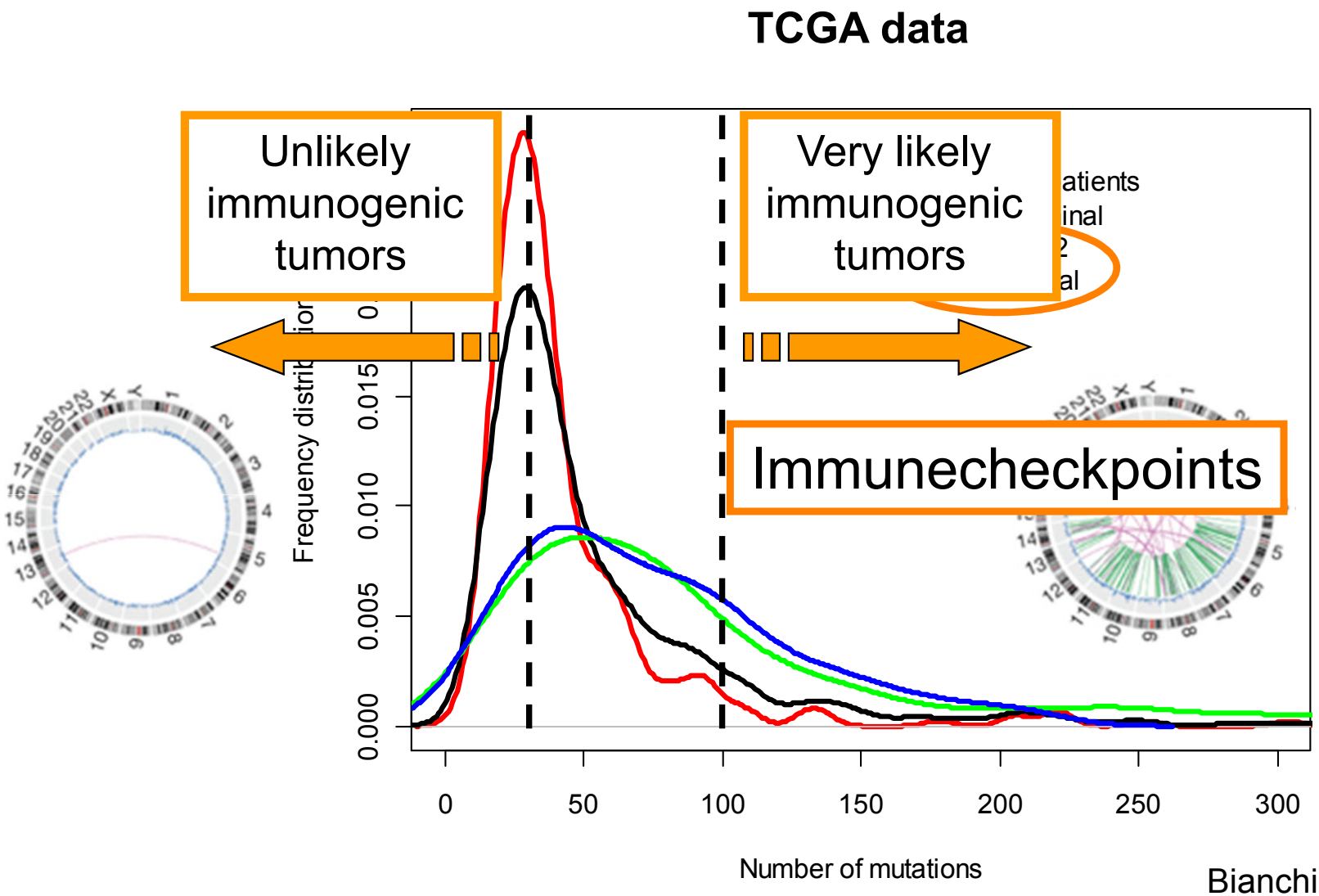
NSCLC



Nivolumab

Gettinger SN JCO 2015

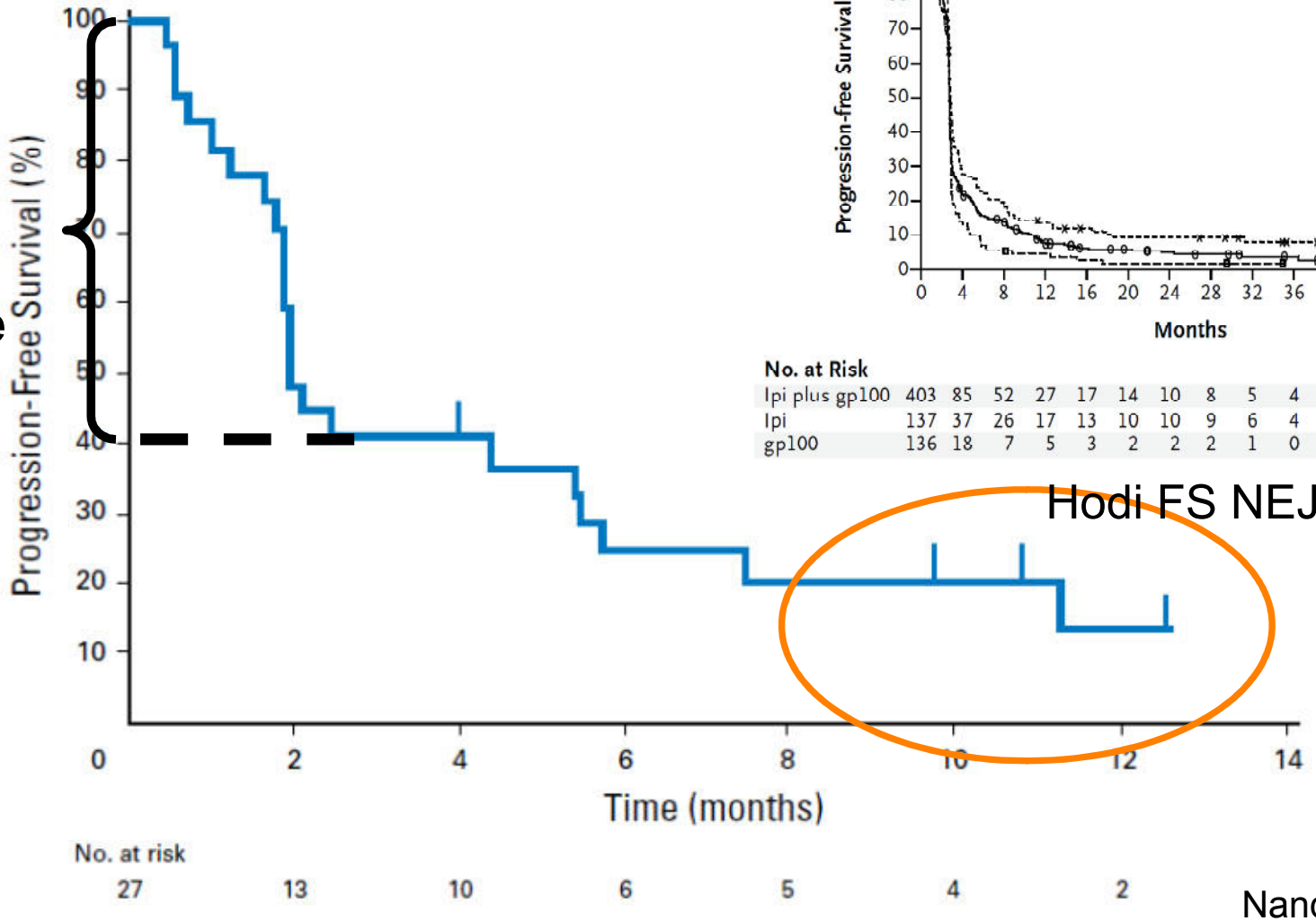
Mutational burden by BC subtypes
Immunotherapy in BC is for some, but *NOT* all



Bianchini G (personal data)

Anti-PD1 therapy in advaced TNBC

Immune intrinsic resistance



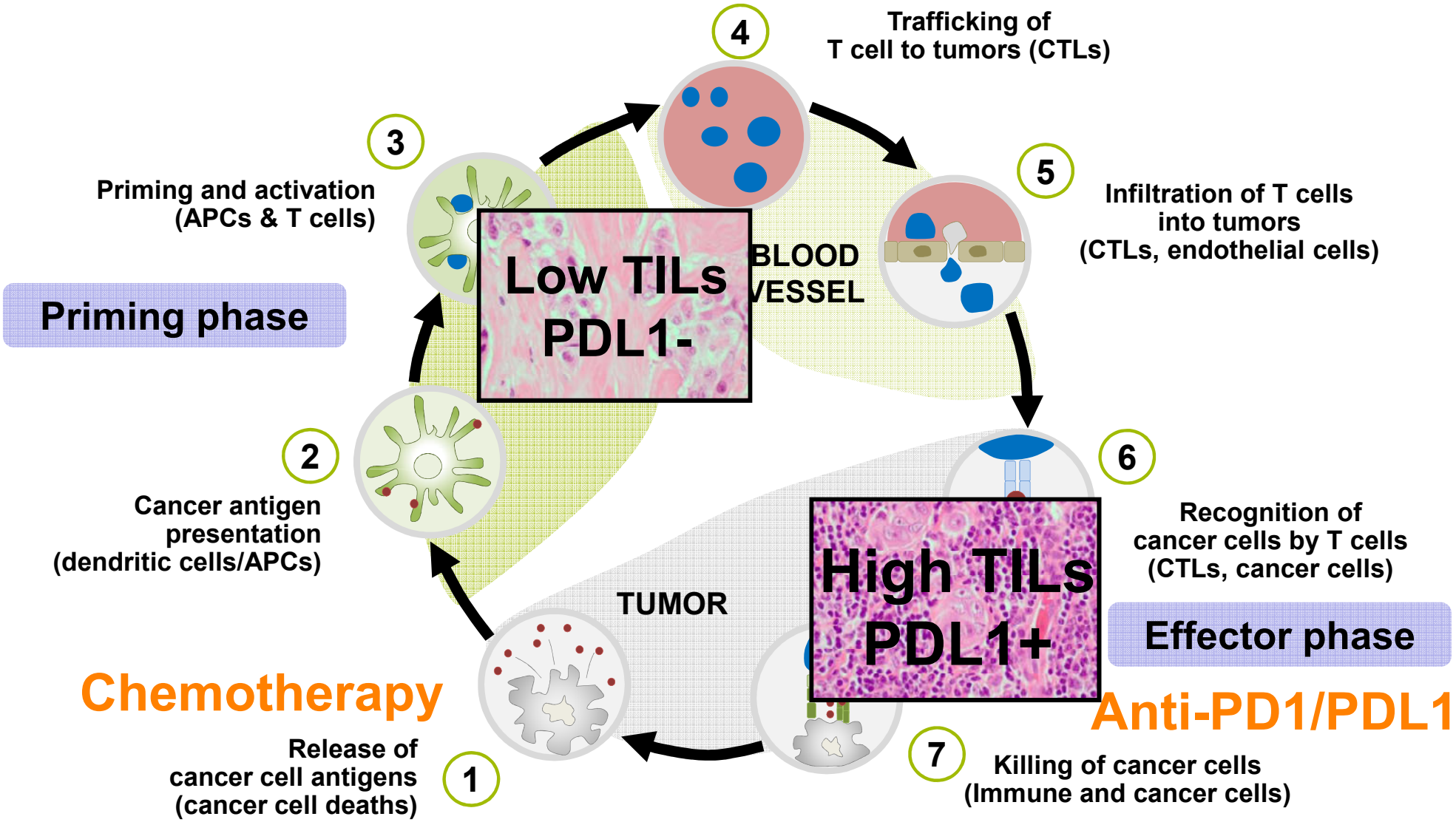
Hodi FS NEJM 2010

Nanda R JCO 2016

Immune checkpoint inhibitors monotherapy in advanced breast cancer

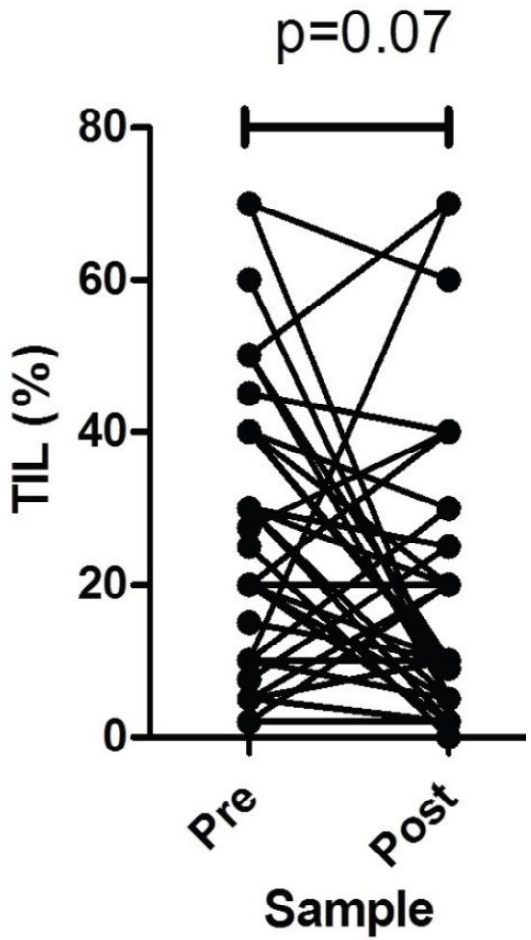
Molecular subtype	Drug	Response rate	Selection
TN	Pembrolizumab	18.5%	PDL1+
	Atezolizumab	19.0%	
	Avelumab	8.6%	ORR PD-L1+ 44.4% ORR PD-L1- 2.6% (*PD-L1 expression defined as >10% Ics*)
ER+/HER2-	Pembrolizumab	12.0%	
	Avelumab	2.8%	
HER2+	Avelumab	3.8%	All

The tumor-immunity cycle

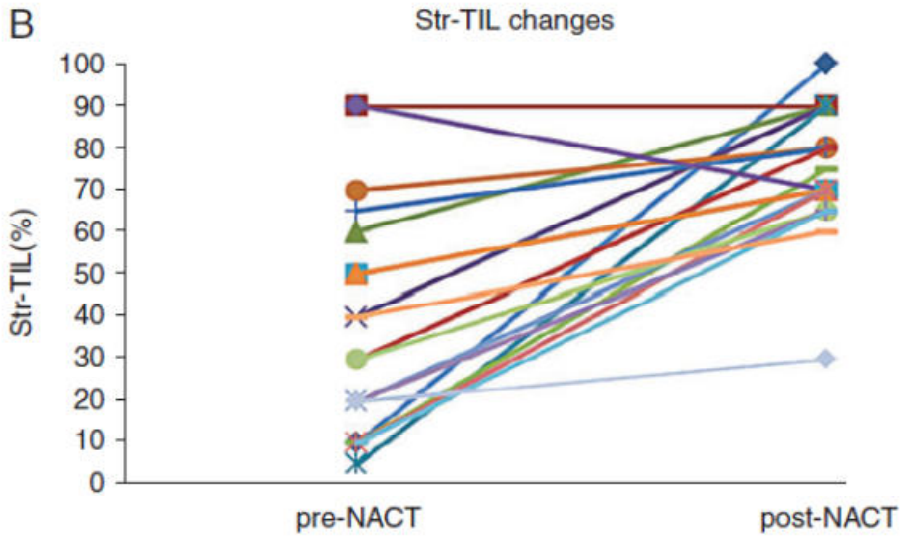


Modified from Chen DS & Mellman I *Immunity* 2013

Evidence for modulation of immune infiltration by neoadjuvant CT in TNBCs



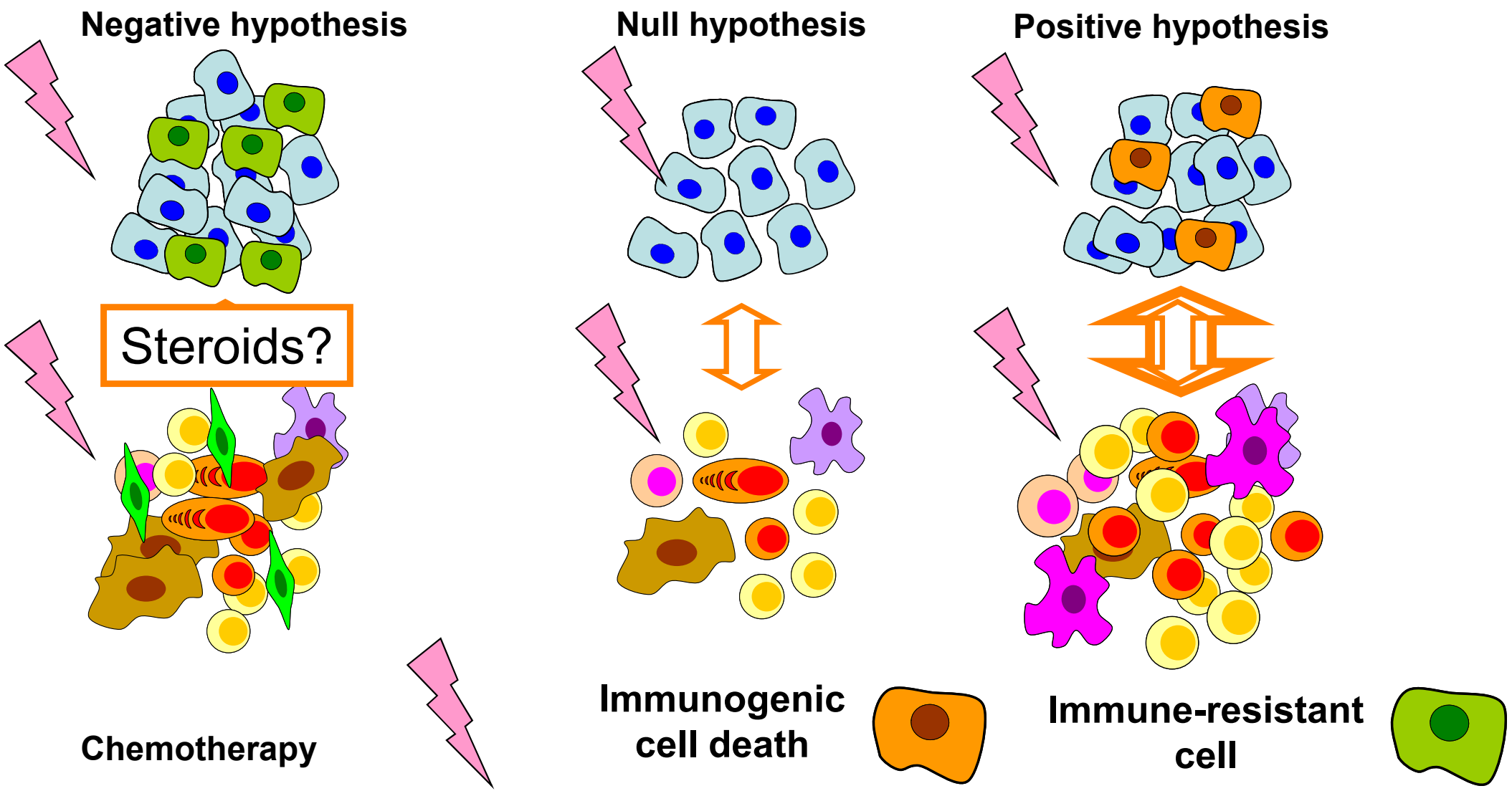
Loi S Clin Cancer Res 2015



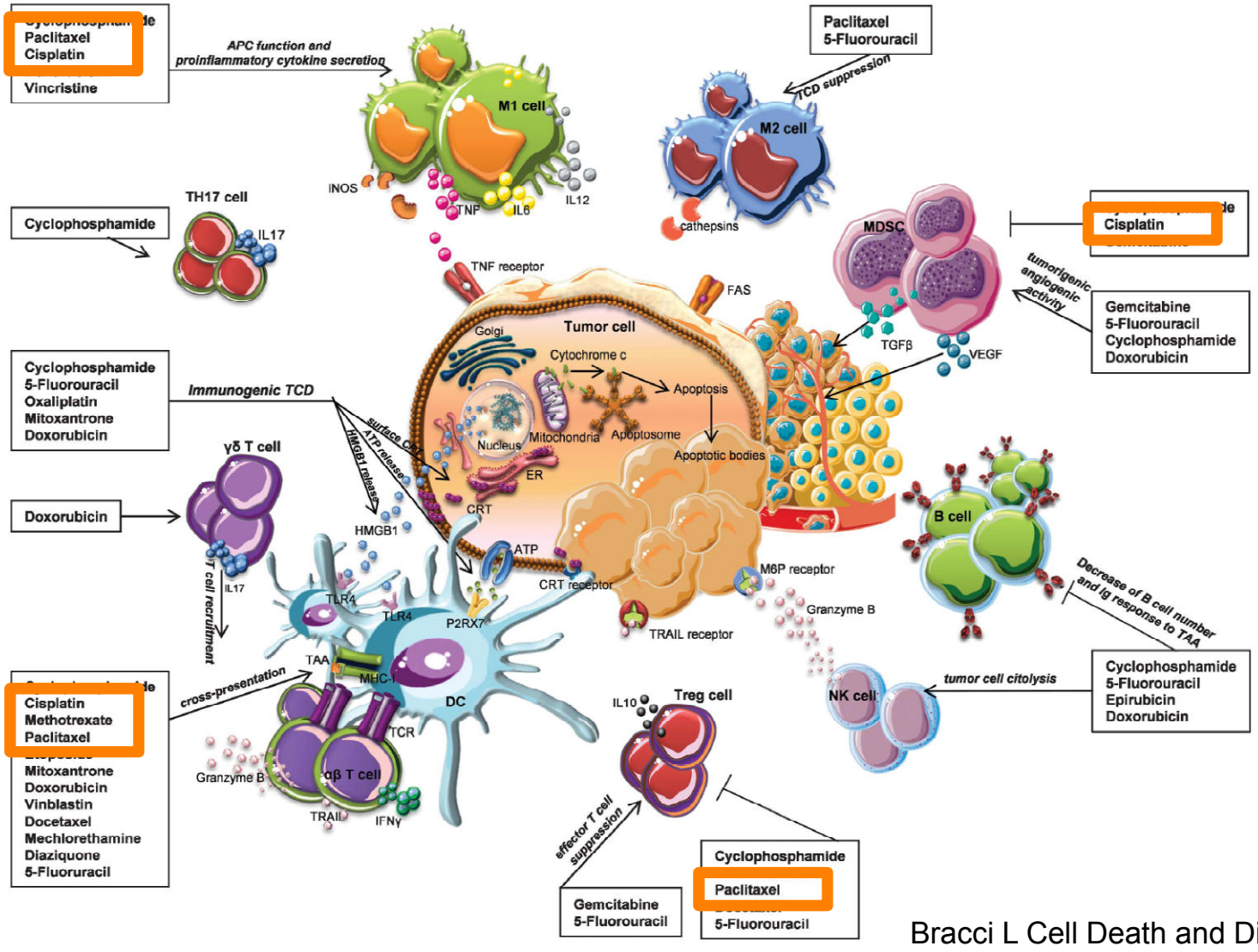
Note: Only patients with high TIL after neoadjuvant CT are presented in the figure

Dieci V Ann Oncol 2014

Possible scenarios of treatment action on the cancer–immune system relationship

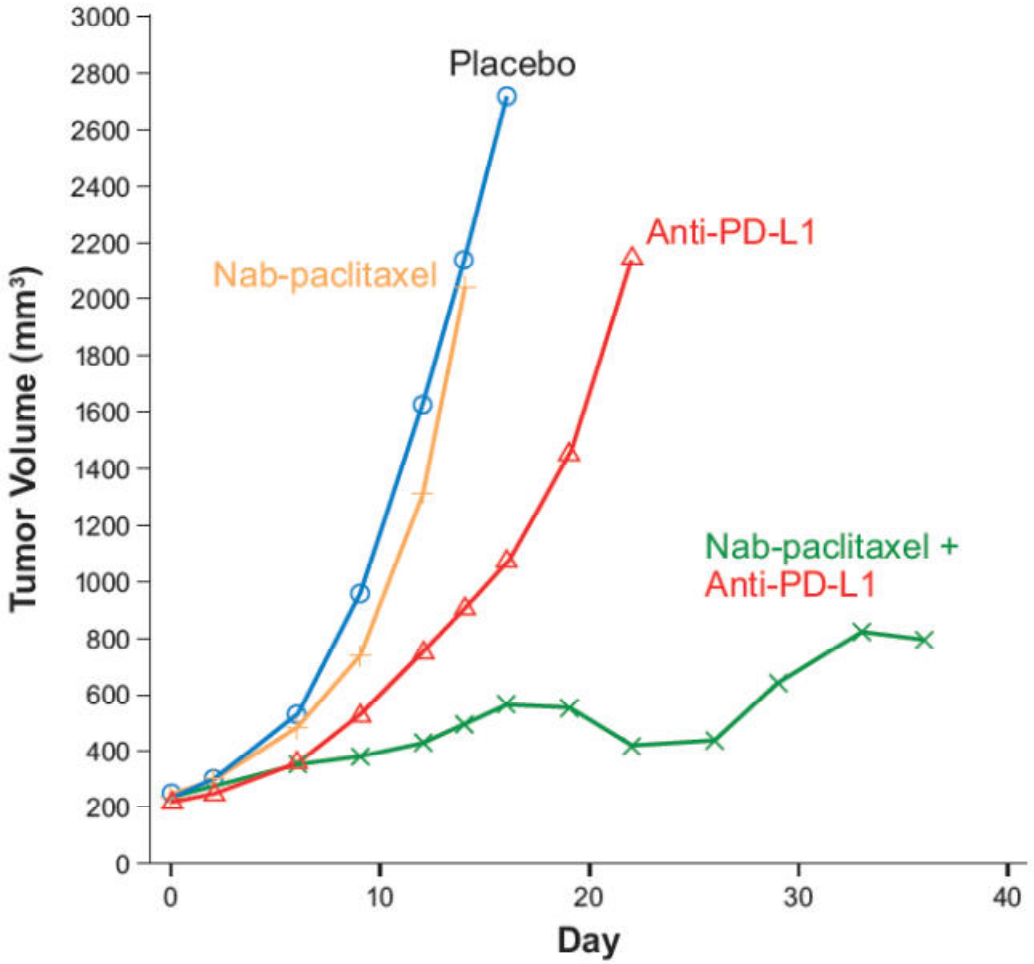


Immunomodulation by conventional cytotoxic drugs



Bracci L Cell Death and Differentiation 2014

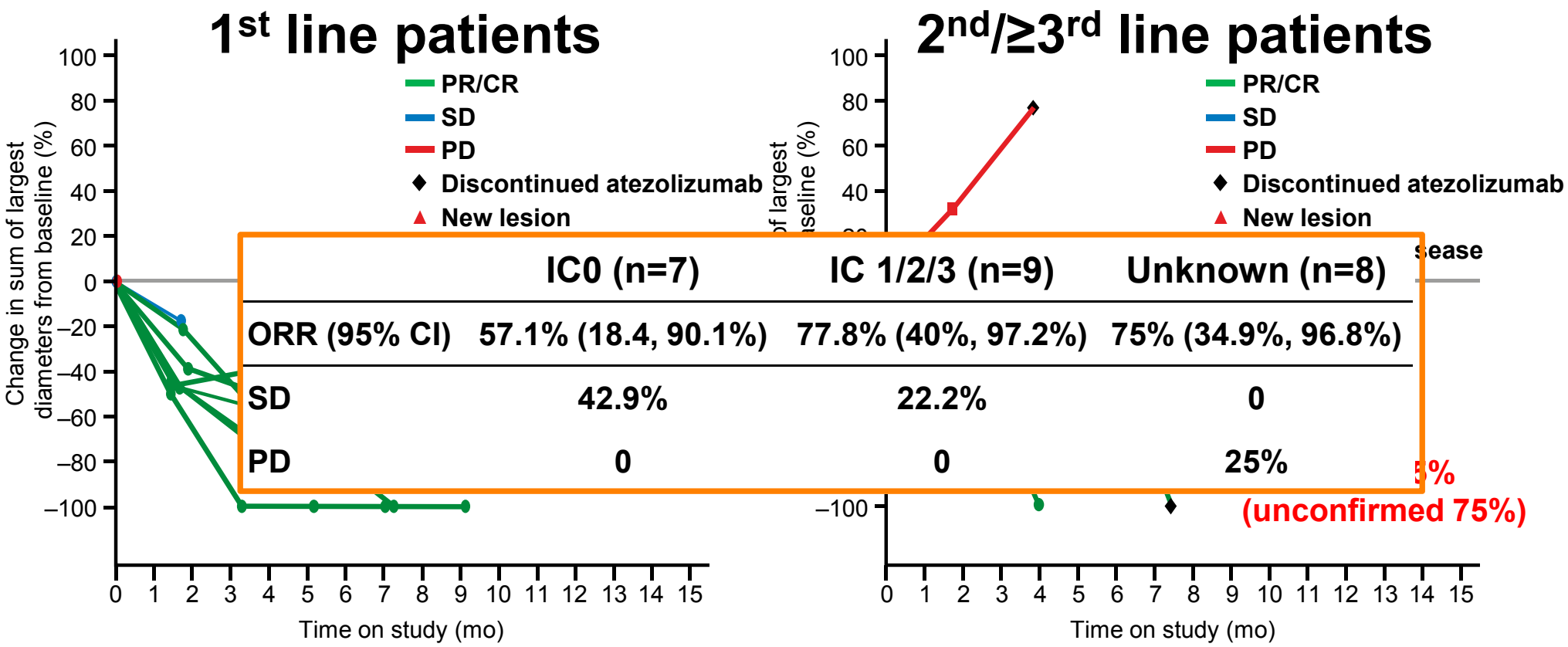
Nab-paclitaxel and anti-PDL1 combination (pre-clinical data)



Jeong Kim, Genentech, unpublished data

Adams S SABCS 2015

Nab-paclitaxel + anti-PDL1 (atezolizumab)



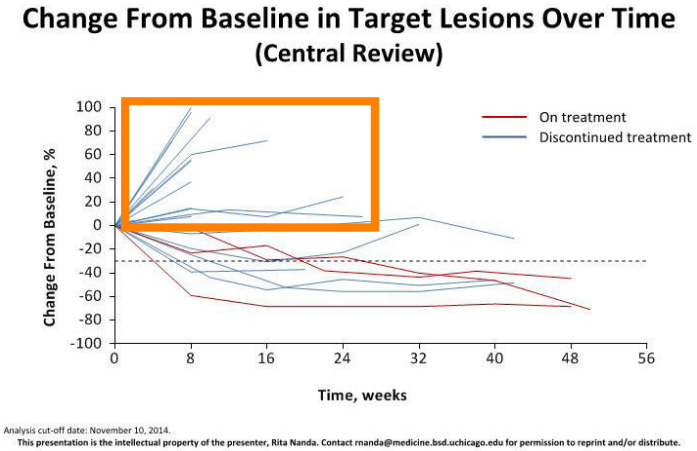
	IC0 (n=7)	IC 1/2/3 (n=9)	Unknown (n=8)
ORR (95% CI)	57.1% (18.4, 90.1%)	77.8% (40%, 97.2%)	75% (34.9%, 96.8%)
SD	42.9%	22.2%	0
PD	0	0	25%

Adapted from Adams, et al. SABCS 2015

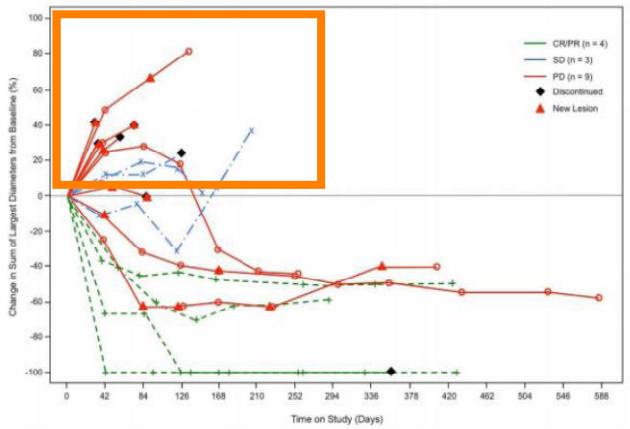
Combination seems to avoid the frequent quick progression observed with monotherapy in TNBC

Pembrolizumab

December 9-13, 2014
SAN ANTONIO BREAST CANCER SYMPOSIUM



Atezolizumab



ORR (unconfirmed): 19%

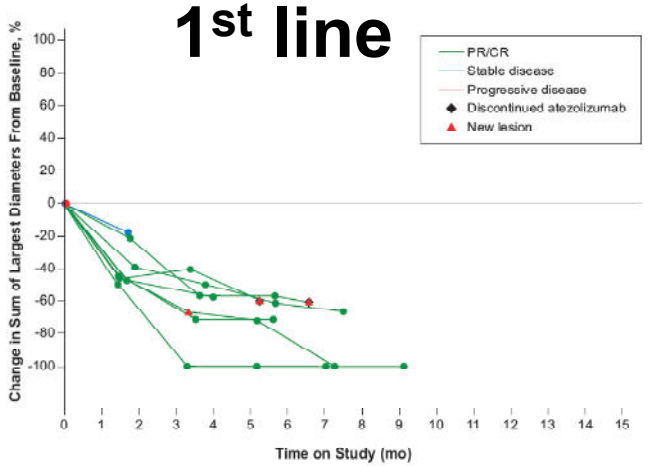
- 2 CRs, 2 RR
- Pseudoprogression noted

24-week PFS: 27%

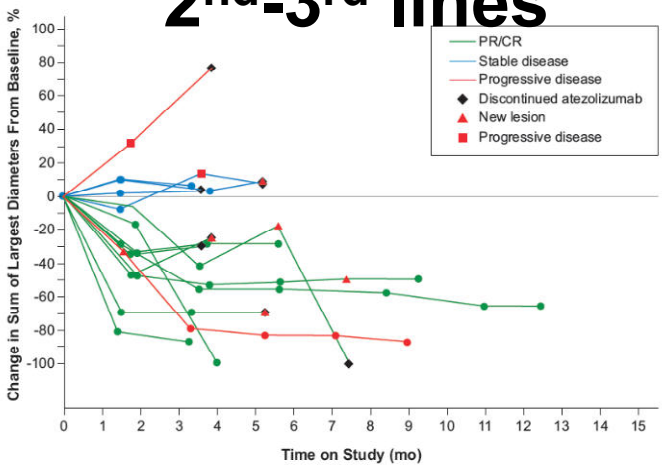
Emens L, et al., AACR 2015
Abstract 2859

Atezolizumab/nab-paclitaxel

1st line

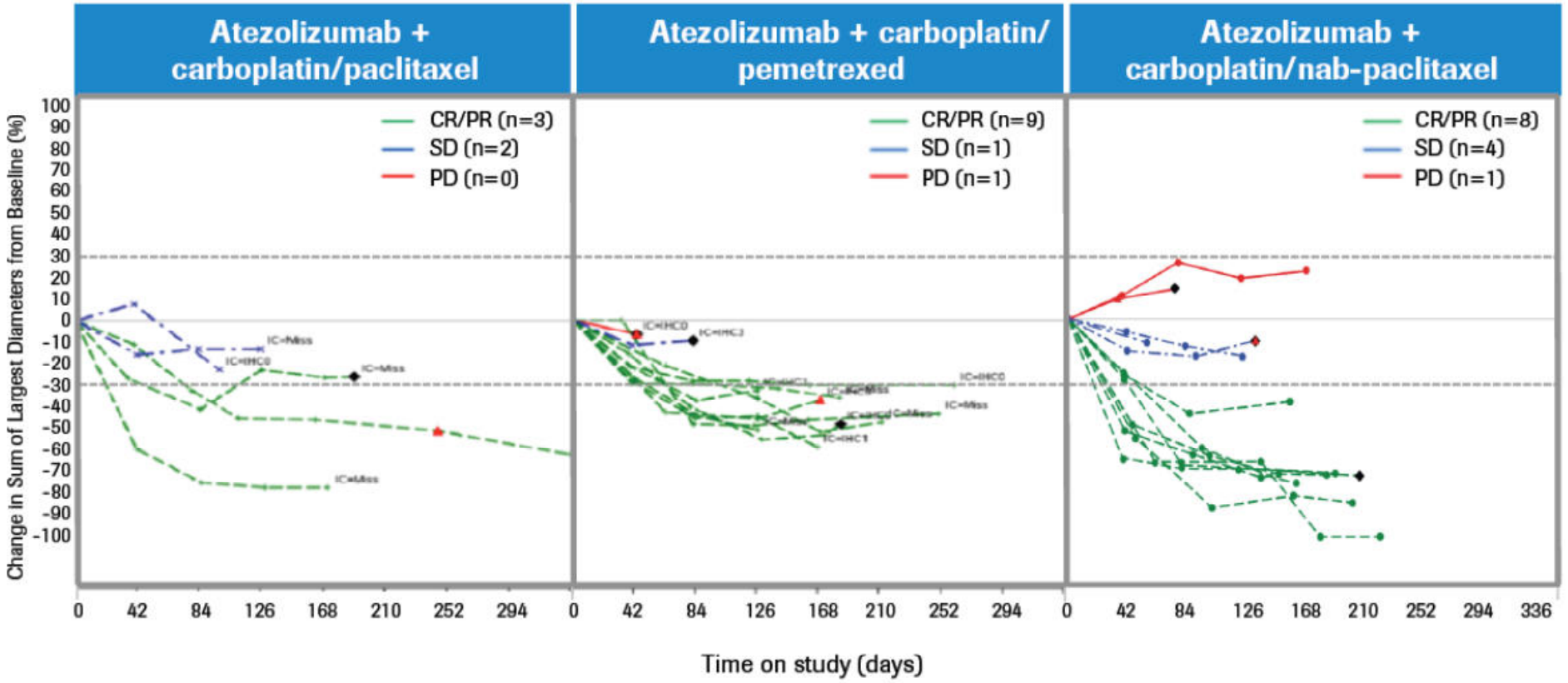


2nd-3rd lines



Adams S SABCS 2015

Atezolizumab and chemotherapy is remarkable effective also in NSCLC

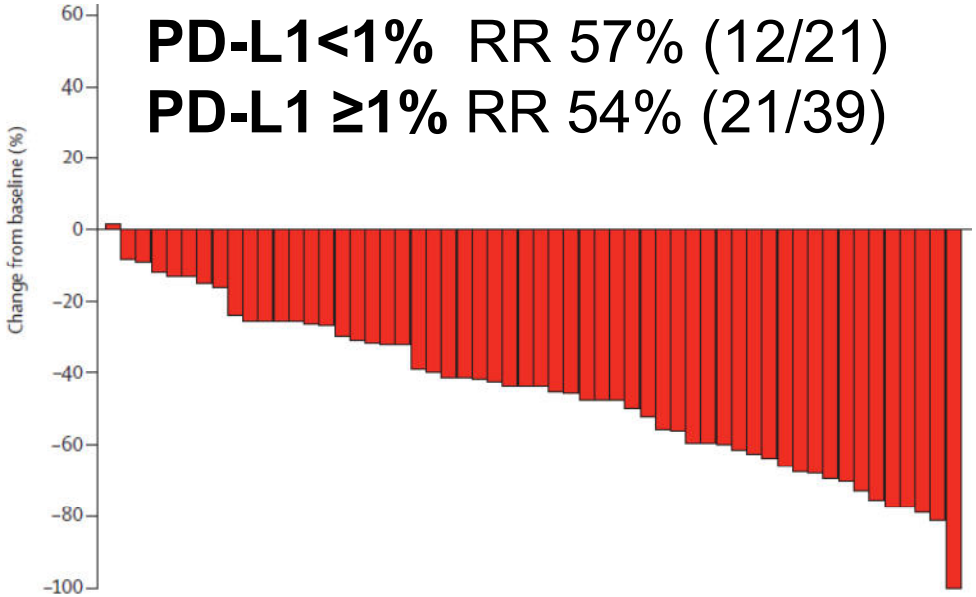


Liu et al ASCO 2015

Carboplatin and pemetrexed with or without pembrolizumab
NSCLC

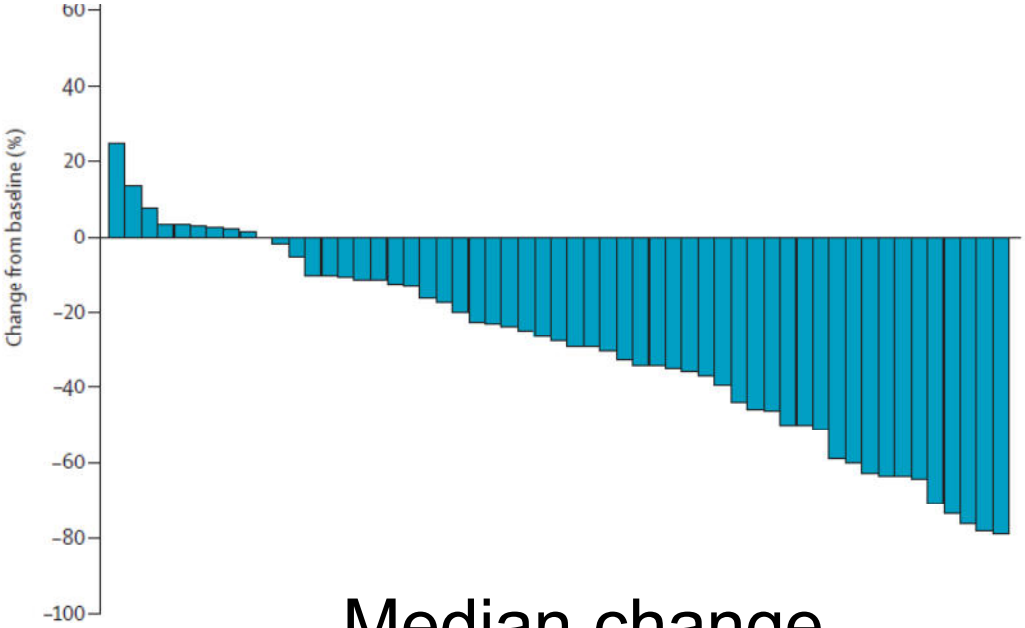
Chemotherapy + Pembrolizumab

PD-L1<1% RR 57% (12/21)
PD-L1 ≥1% RR 54% (21/39)



Median change
–44%

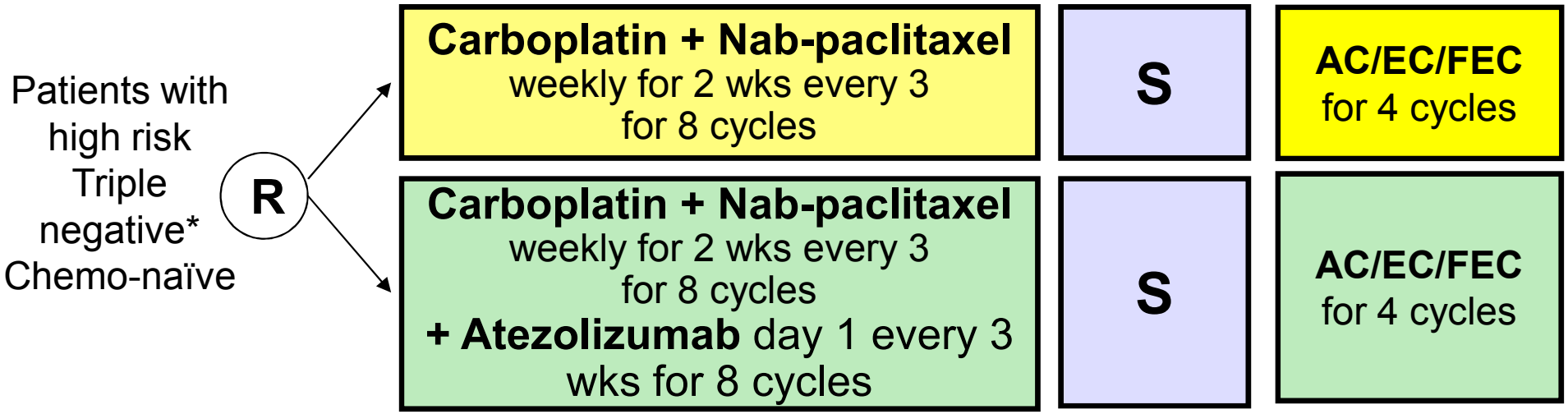
Chemotherapy



Median change
–28%

Langer C Lancet Oncol 2016

NeoTRIP-aPDL1 - Study Scheme



Neoadjuvant phase (8 cycles)

CARBOPLATIN, AUC 2 i.v. on day 1 and 8 q 3 weeks

Nab-paclitaxel, 125 mg/m^2 i.v. on day 1 and 8 q 3 weeks

Atezolizumab, 1200 mg i.v. infusion on day 1 q 3 weeks

All drugs will be delivered i.v., toxicity permitting, for total 8 cycles

Adjuvant phase

AC or EC or FEC (per investigator's selection) day 1 q 3 weeks

All drugs will be delivered i.v., toxicity permitting, for total 4 cycles

* HER2 negative, ER and PR less than 1% cells staining

NeoTRIPaPDL1
Study Design

Open-label, randomized phase III trial

Randomized in a 1:1 ratio

The stratification variables will be:

- Site's Geographycal Area
- Disease stage [early high-risk (T1N1; T2N1; T3N0)
  vs non inflammatory
  (T3N1; T4a,b,c; any T and N2-3)
  vs inflammatory (T4d any N)]
- PD-L1 expression immune cell testing
  [yes (IHC 1,2,3) vs no (IHC 0)]

NeoTRIPaPDL1
Endpoints

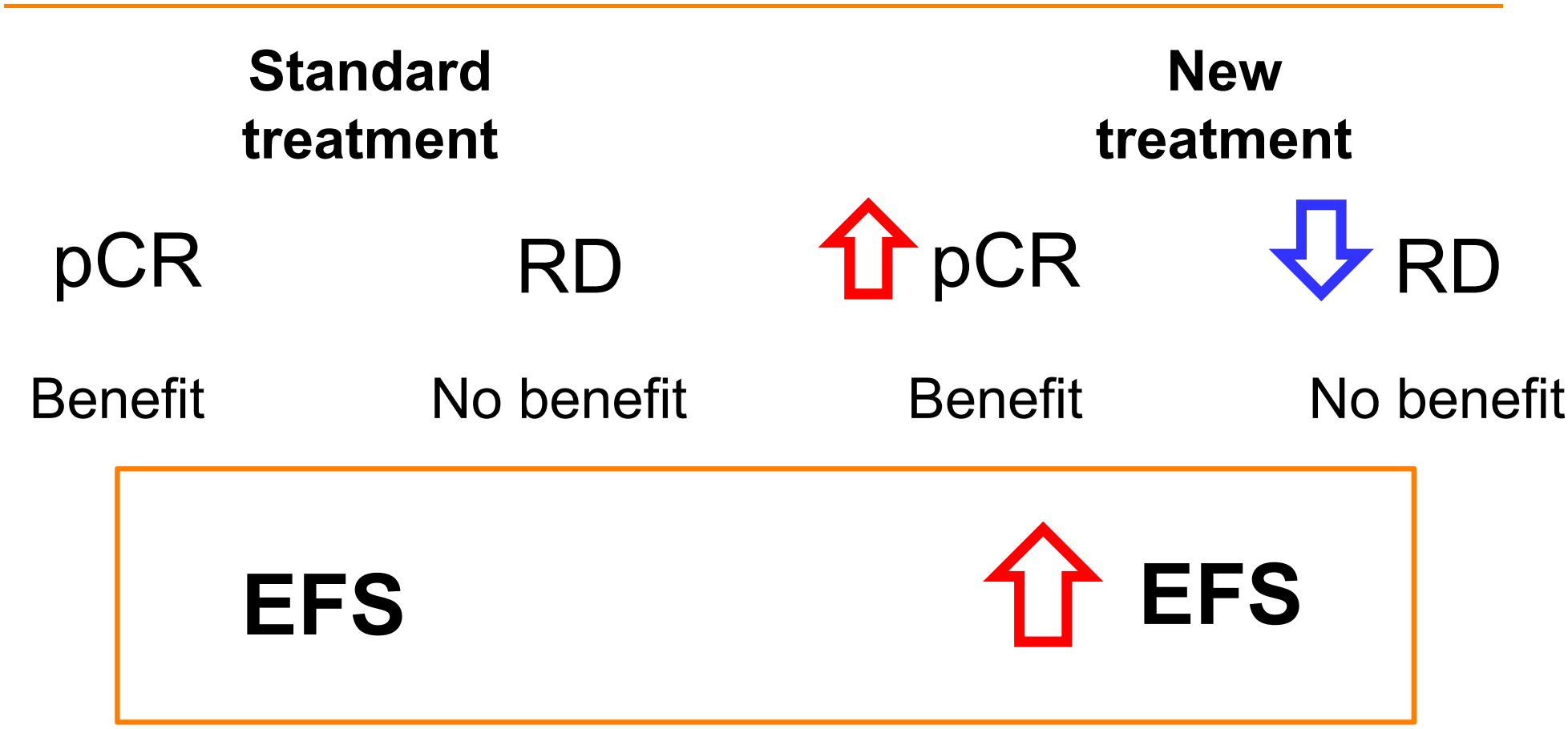
Primary objective:

- Compare **Event Free Survival (EFS)** in the 2 study arms from the time of randomization

Secondary objectives:

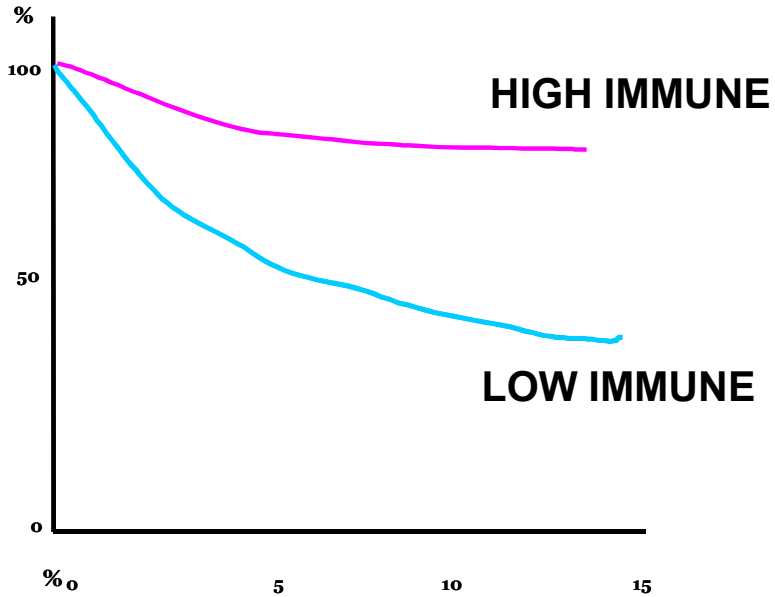
- Compare EFS according to PD-L1 expression
- Compare the rate of pathological complete response (pCR) defined as ypT0-ypTis ypN0 at surgery
- Compare the rate of clinical objective remission (cOR)
- Compare Distant EFS (DEFS) and overall survival (OS) from the time of randomization
- Evaluate tolerability of the treatment regimens

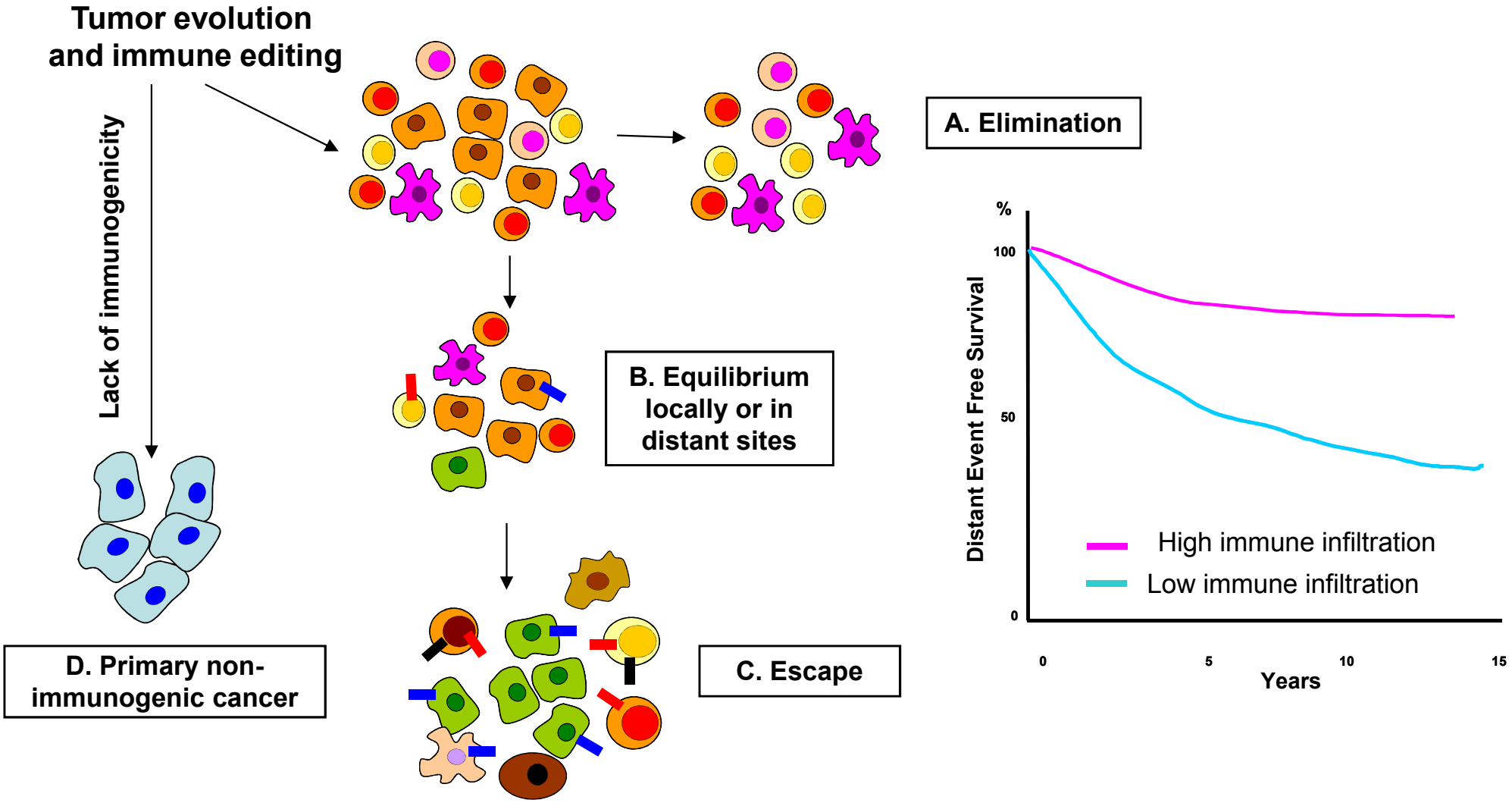
pCR issue


Standard treatment
New treatment
pCR
RD
pCR
RD
Benefit
No benefit
Benefit
No benefit
EFS
EFS

“High immune cell infiltration” is associated with lower risk of recurrence in untreated early breast cancer

ER-/HER2- (TN)	HER2+
Bianchini *JCO* 2010	Alexe *Cancer Res* 2007
Desmedt *Clin Cancer Res* 2008	Bianchini *Cancer Res* 2010
Gu-Trantien *JCI* 2013	Bianchini *JCO* 2010
Nagalla *Genome Biol* 2013	Desmedt Clin Cancer Res 2008
Iwamoto JNCI 2011	Gu-Trantien *JCI* 2013
Rody *Breast Cancer Res* 2009	Nagalla *Genome Biol* 2013
Rody *Breast Cancer Res* 2011	Schmidt *Cancer Res* 2008
Schmidt *Cancer Res* 2008	Staaf *JCO* 2010
Staaf *JCO* 2010	Teschendoff *Genome Biol* 2007
Teschendoff *Genome Biol* 2007	





Immune control

- NK
- CD4
- CD8
- Immunogenic DC

Immune escape

- Tolerogenic DC
- Treg
- MDSC
- TAM2
- PD1
- PDL1
- CTLA4

Tumor cells by immunogenicity

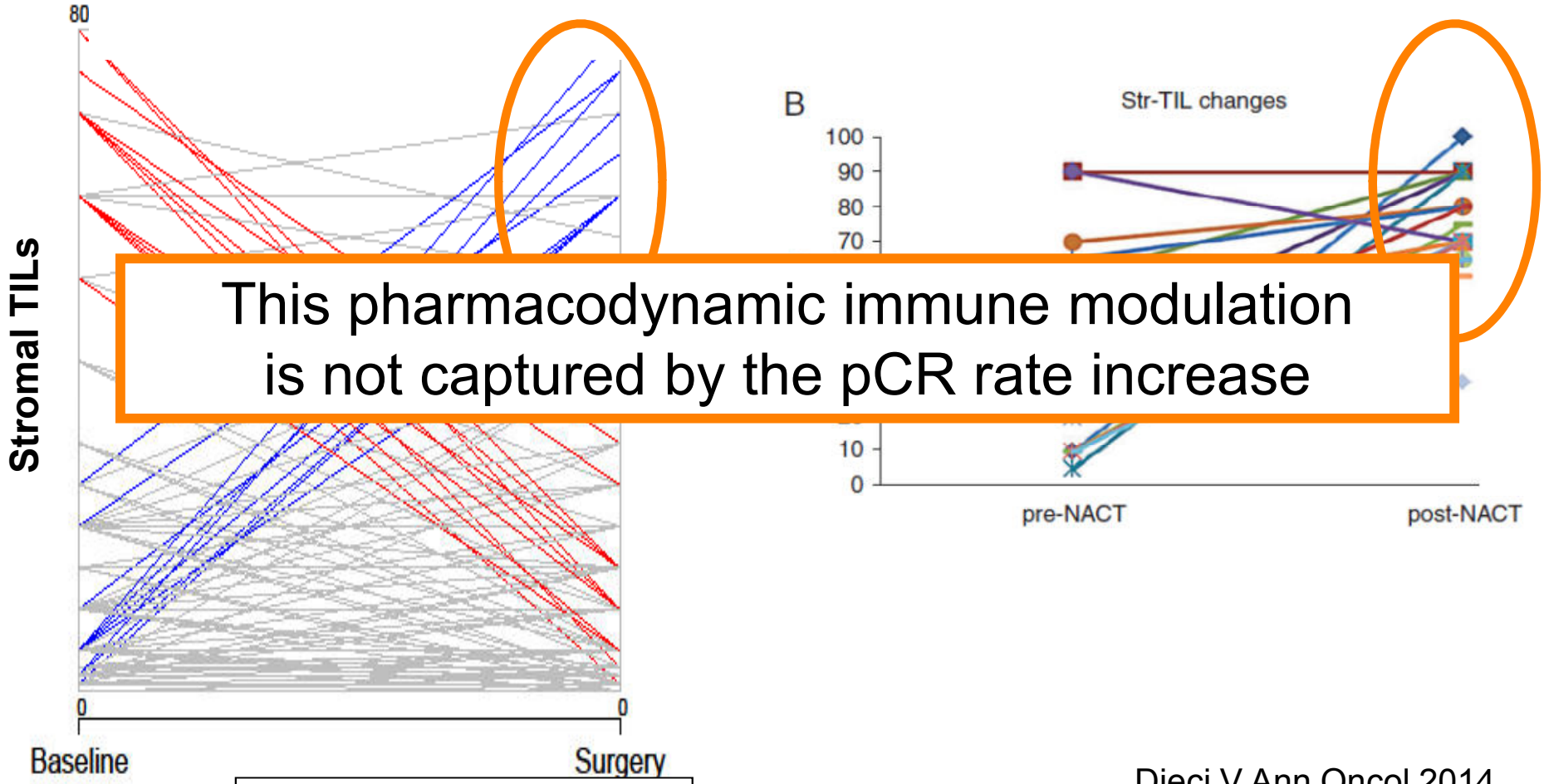
- Immunogenic
- Nonimmunogenic
- Immunoevasive

Pusztai L Clin Cancer Res 2016

Difference between pre- and post- treatment tumor infiltrating lymphocytes (TILs)

HER2+
(HER2 targeted therapies)

TN
(chemoetherapy)



This pharmacodynamic immune modulation is not captured by the pCR rate increase

Bianchini G ASCO 2016

Dieci V Ann Oncol 2014

Ongoing clinical trials in early breast cancer

Phase	Clinical Trial Gov	Disease setting	Breast cancer subtype	Immunotherapies	Combined treatments
I	NCT02826434	Adjuvant	TNBC	Durvalumab PVX-410 (Vaccine)	
I	NCT02605915	Metastatic and neoadjuvant	HER2-pos	Atezolizumab	Trastuzumab/pertuzumab or T-DM1 or Trastuzumab/Pertuzumab/ Carbo/Docetaxel
I	NCT02622074	Neoadjuvant	TNBC	Pembrolizumab	Nab-paclitaxel → AC or Nab-paclitaxel/Carbo → AC
I/II	NCT02489448	Neoadjuvant	TNBC	Durvalumab	Nab-paclitaxel → ddAC
II	NCT01042379	Neoadjuvant	All	Pembrolizumab	Paclitaxel
II	NCT02530489	Neoadjuvant	TNBC	Atezolizumab	Nab-paclitaxel
II	NCT02685059	Neoadjuvant	TNBC	Durvalumab	Nab-paclitaxel ⟶ EC
II	NCT02883062	Neoadjuvant	TNBC	Atezolizumab	Paclitaxel/Carbo
II	NCT02833233	Pre-surgical	All	Ipilimumab and nivolumab	Cryoablation
II	NCT01502592	Pre-surgical	All	Ipilimumab	Cryoablation
III	NCT02926196	Adjuvant	TNBC	Avelumab	
III	NCT02620280	Neoadjuvant	TNBC	Atezolizumab	Nab-paclitaxel/Carbo

AACR American Association for Cancer Research

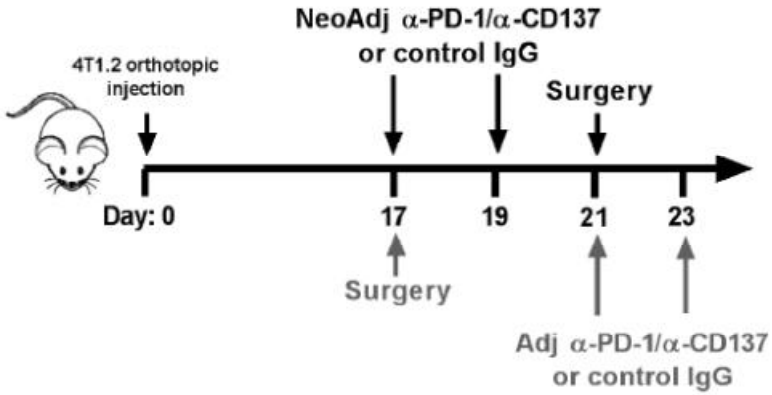
CANCER DISCOVERY

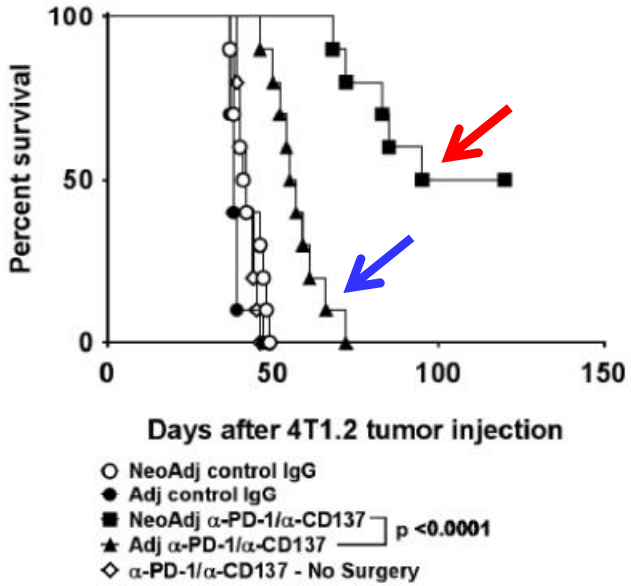
Improved efficacy of neoadjuvant compared to adjuvant immunotherapy to eradicate metastatic disease

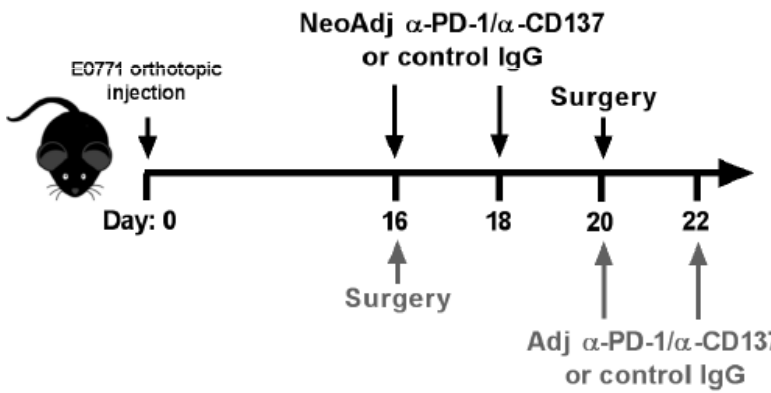
Jing Liu, Stephen J. Blake, Michelle C. R. Yong, et al.

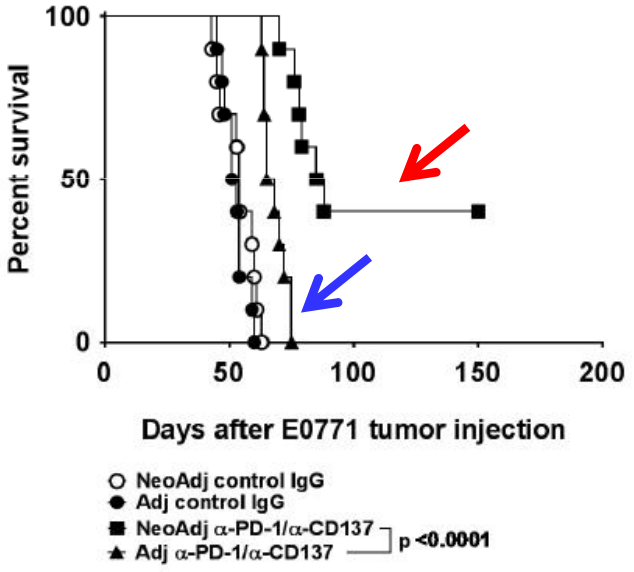
Cancer Discov Published OnlineFirst September 23, 2016.

Neoadjuvant is more effective than adjuvant therapy with anti-PD-1+anti-CD137



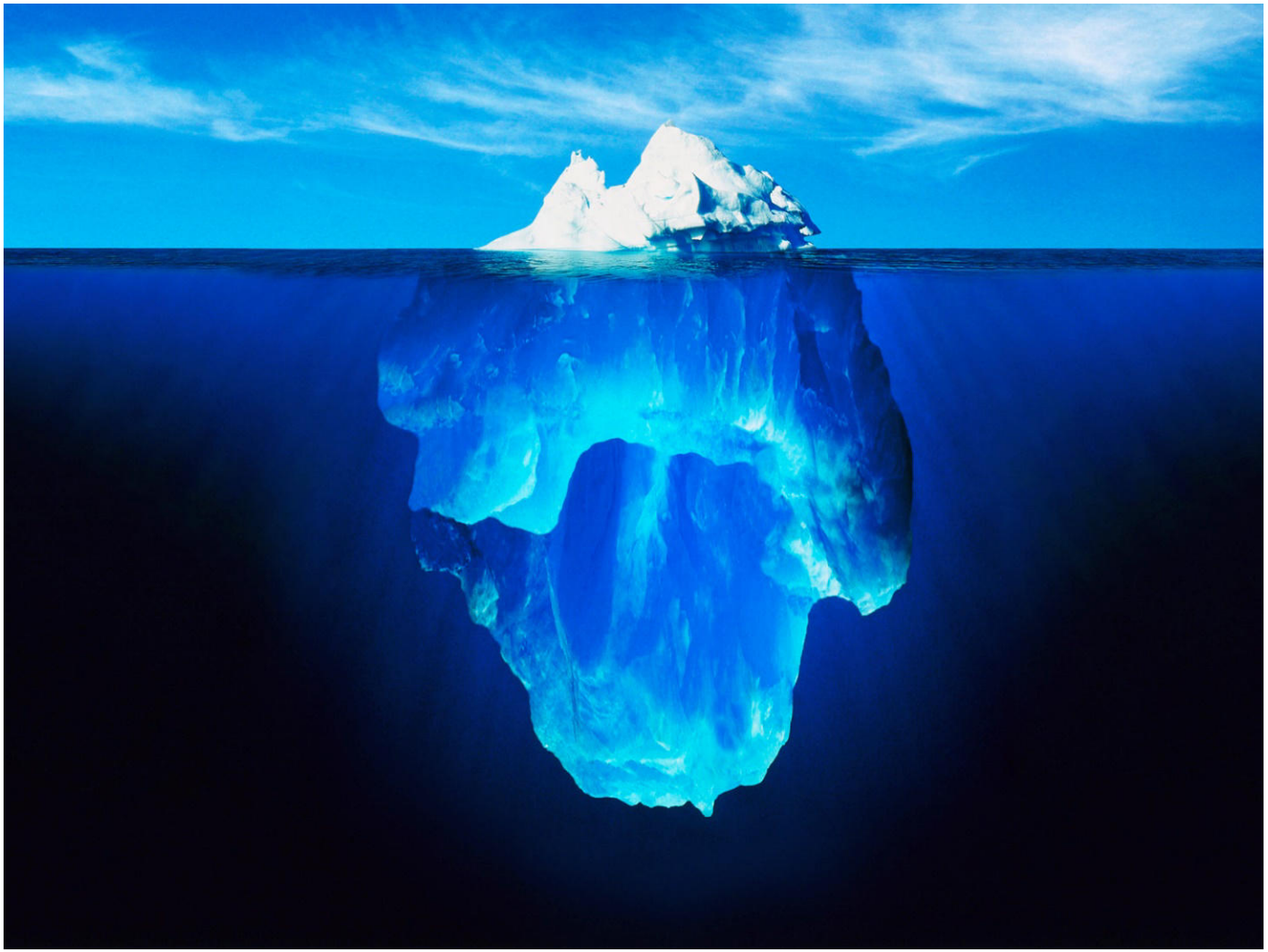




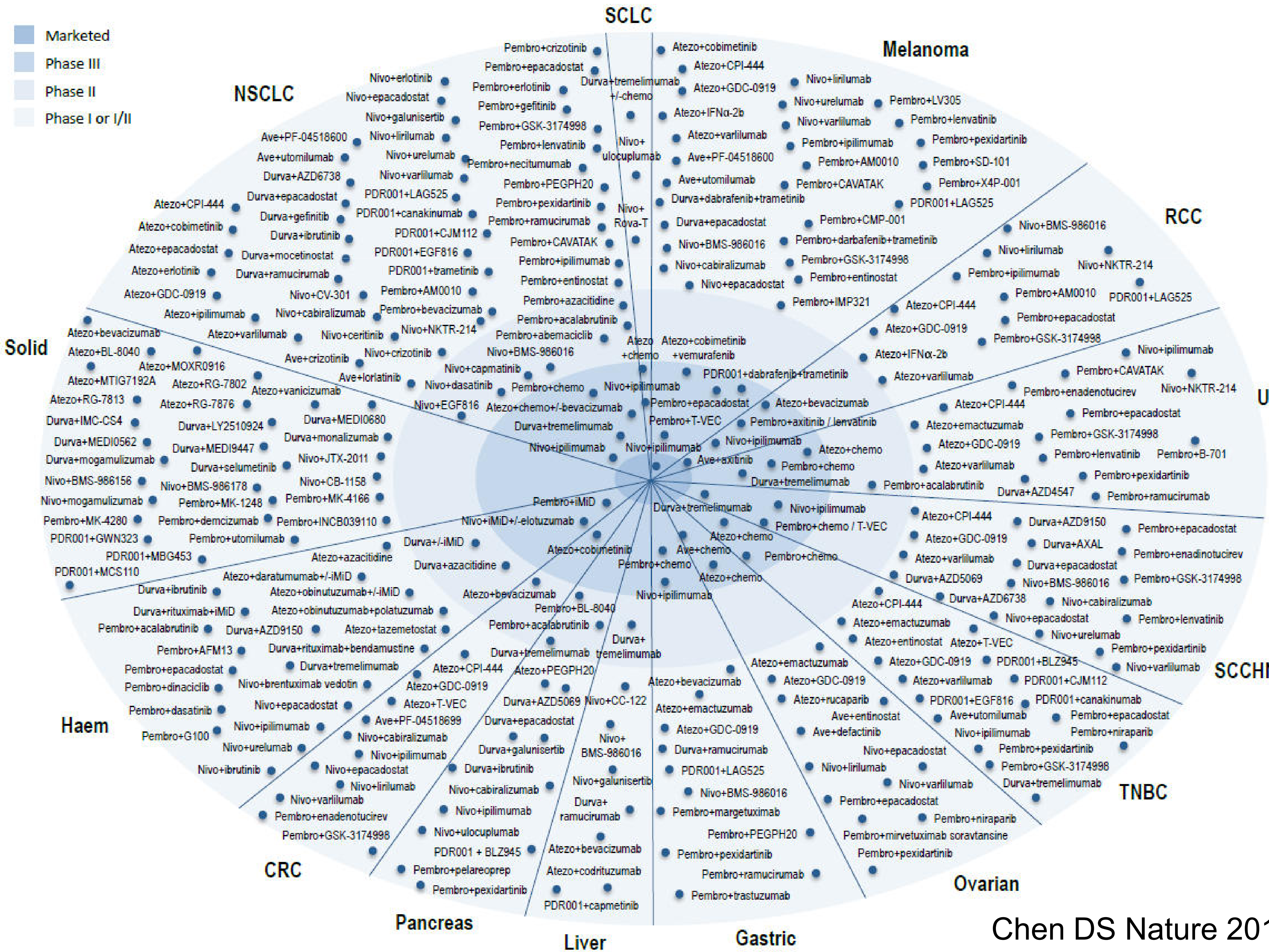


Liu J Cancer Discovery 2016

Immunotherapy revolution: the tip of the iceberg

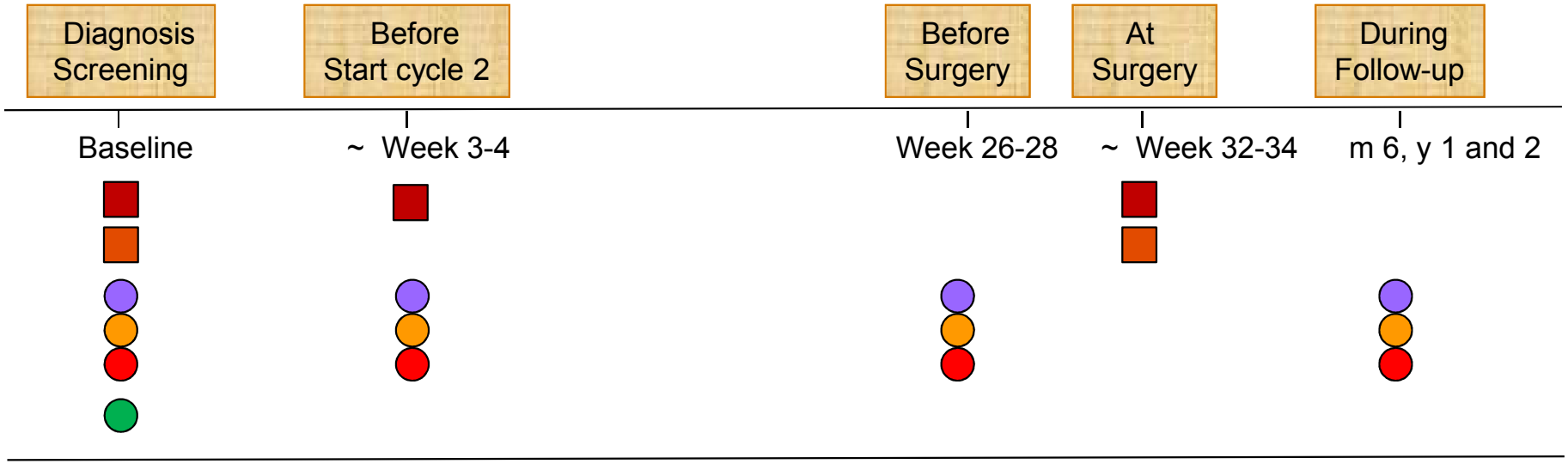


Immunotherapy-based combination studies underway in 2016



Chen DS Nature 2017

Biomarker research samples
Timing for collection



Legend

- **FFPE**
- **Frozen tissue** ***(optional)***
- **Serum**
- **Plasma**
- **Whole blood**
- **Pharmacogenetic** *(optional)* At baseline or any time prior to surgery

Secondary endpoints

Conduct molecular and clinical analyses to assess the presence of predictive markers of benefit or resistance


Immunotherapy in breast cancer:
there is a long journey ahead,
but the future is bright