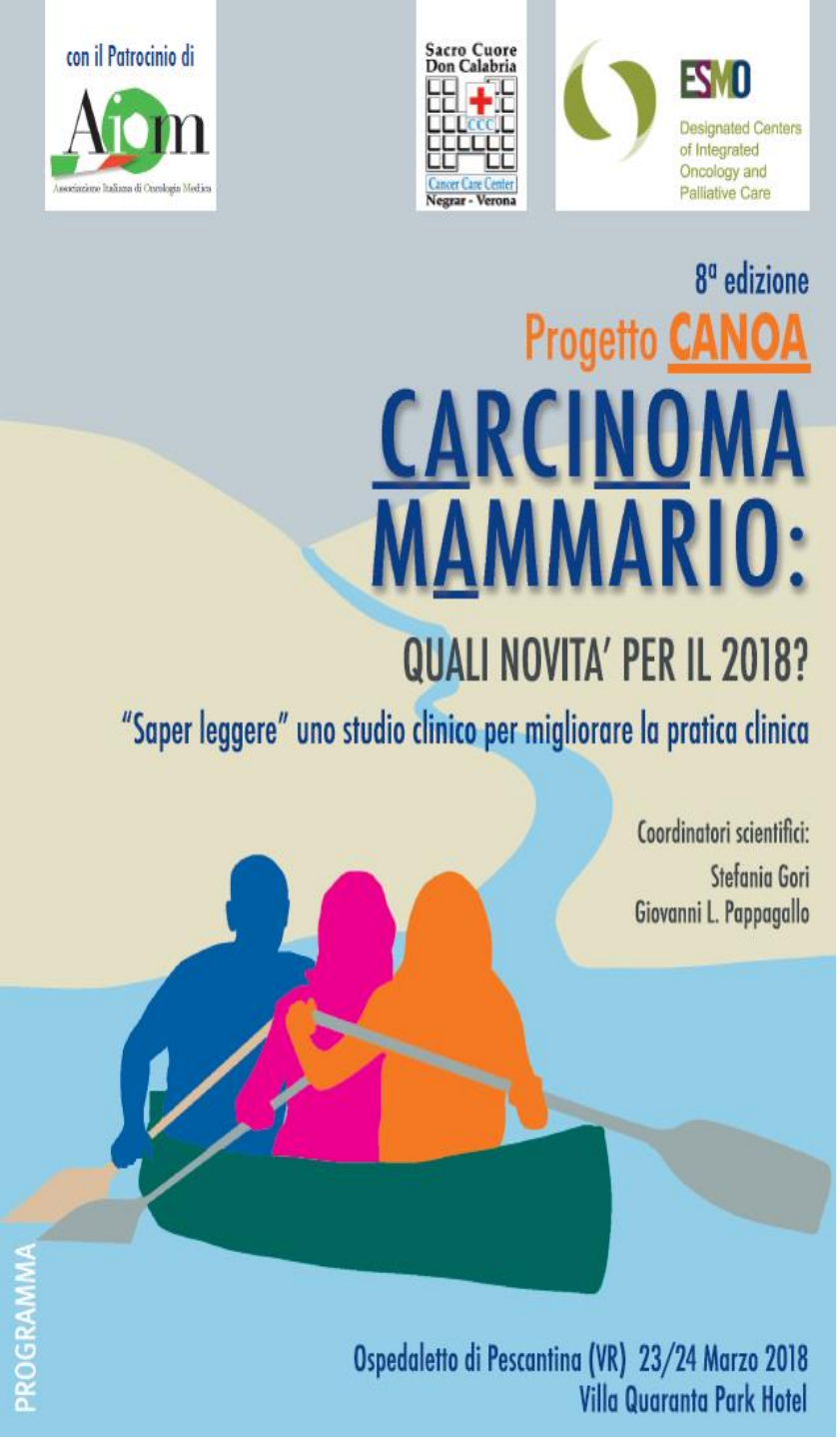


I.O.V. ISTITUTO ONCOLOGICO VENETO I.R.C.C.S.

UNIVERSITAS STUDII PADUANI MCCX XII

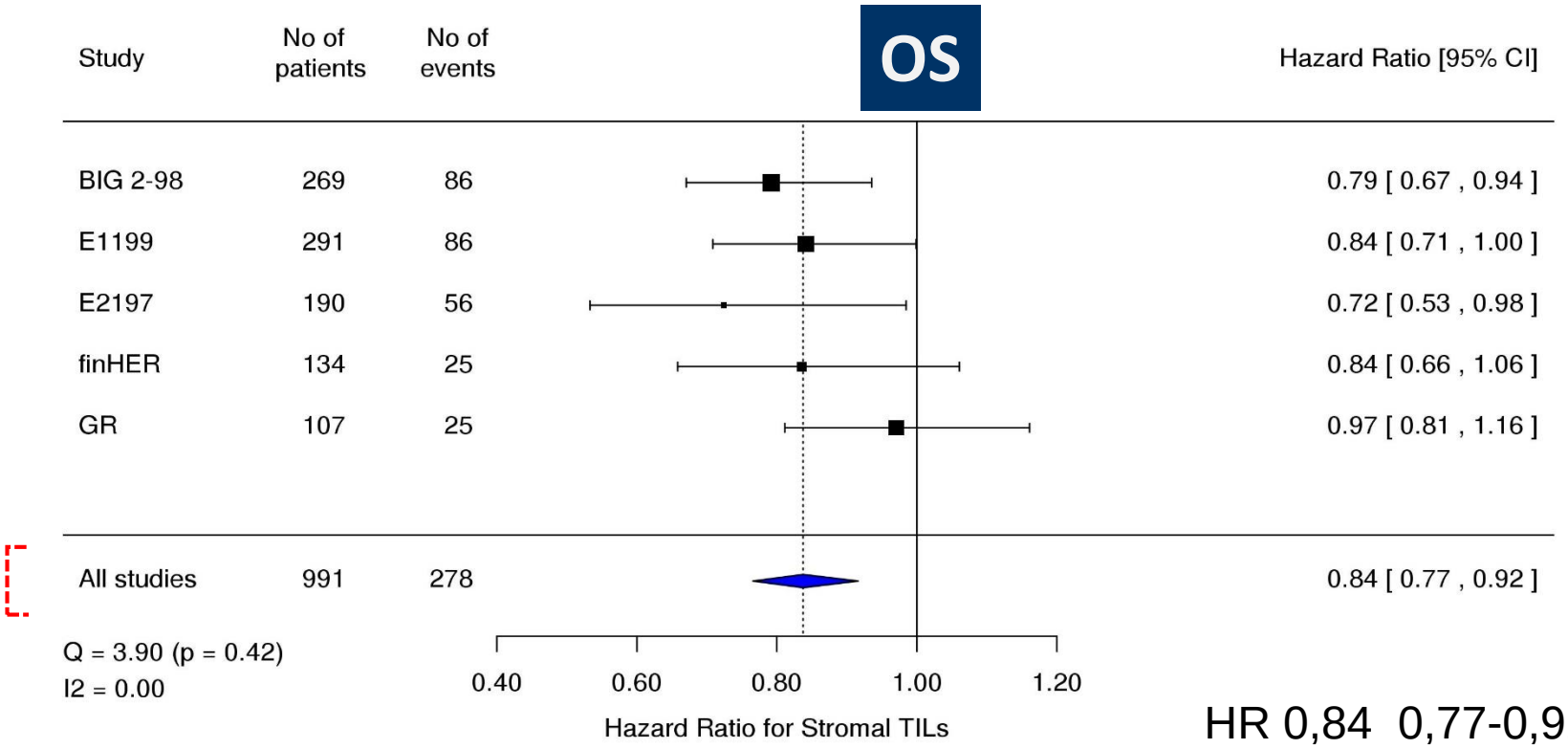
REGIONE DEL VENETO

Immunoterapia nel carcinoma mammario: risultati degli studi clinici

PierFranco Conte
DiSCOG, Università di Padova
IOV – Istituto Oncologico Veneto I.R.C.C.S.

Pooled individual patient data analysis of tumor infiltrating lymphocytes (TILs) in primary triple negative breast cancer (TNBC) treated with anthracycline-based chemotherapy

Sherene Loi, Damien Drubay, Sylvia Adams, Prudence A Francis, Heikki Joensuu, Maria Vittoria Dieci, Sunil Badve, Sandra Demaria, Robert Gray, Martine J Piccart, Pirkko-Liisa Kellokumpu-Lehtinen, Fabrice Andre, Carsten Denkert, Roberto Salgado, Stefan Michiels.



HR 0,84 0,77-0,92

Loi S, SABCS 2015

Immune checkpoint inhibitors in metastatic TNBC PDL1+/-

	Pembrolizumab	Atezolizumab	Avelumab
Phase	II	I	I
N	222	115	58
ORR	---	10%	5.2%**
ORR 1L	23.1%*	26%	---
ORR 2L+	4.7%	11%	---

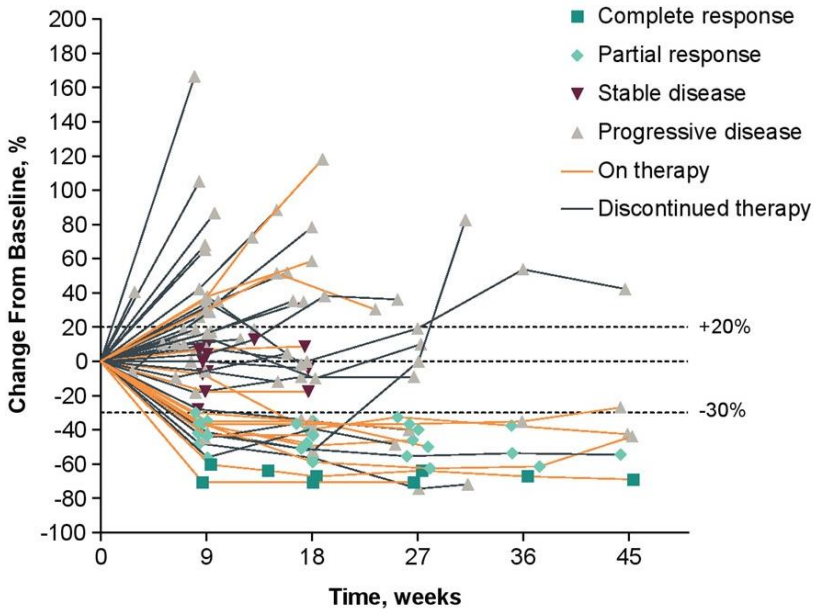
*All PD-L1+

**50% received ≥ 2 previous lines of anticancer treatment

Adams S, ASCO 2017; Schmid P, AACR 2017; Dirix L, BCRT 2018

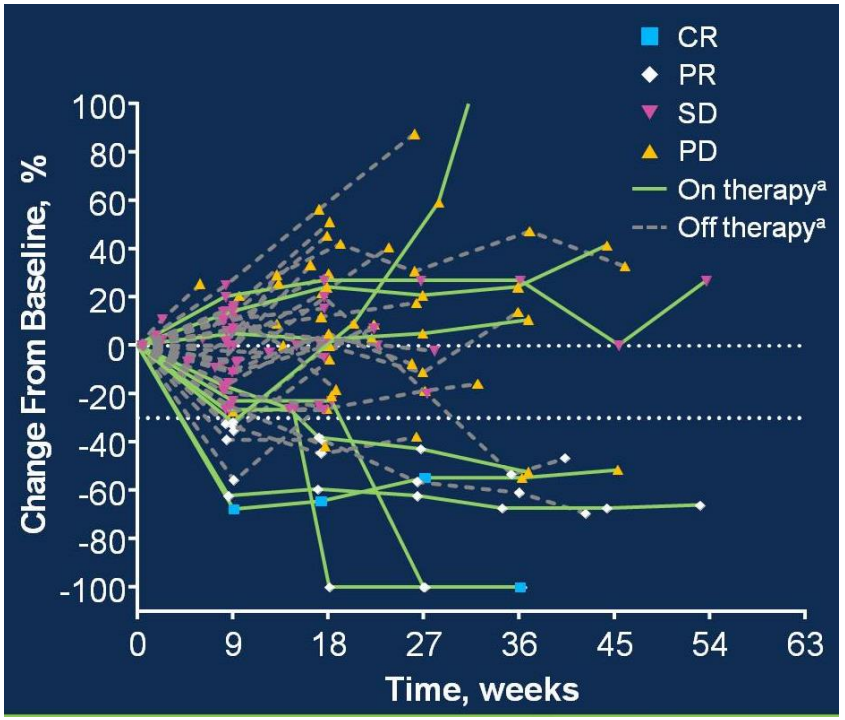
Immune checkpoint inhibitors in metastatic TNBC: durable responses

KEYNOTE-086
Cohort B



Pembrolizumab single agent in TNBC PD-L1+, 1st line

KEYNOTE-086
Cohort A

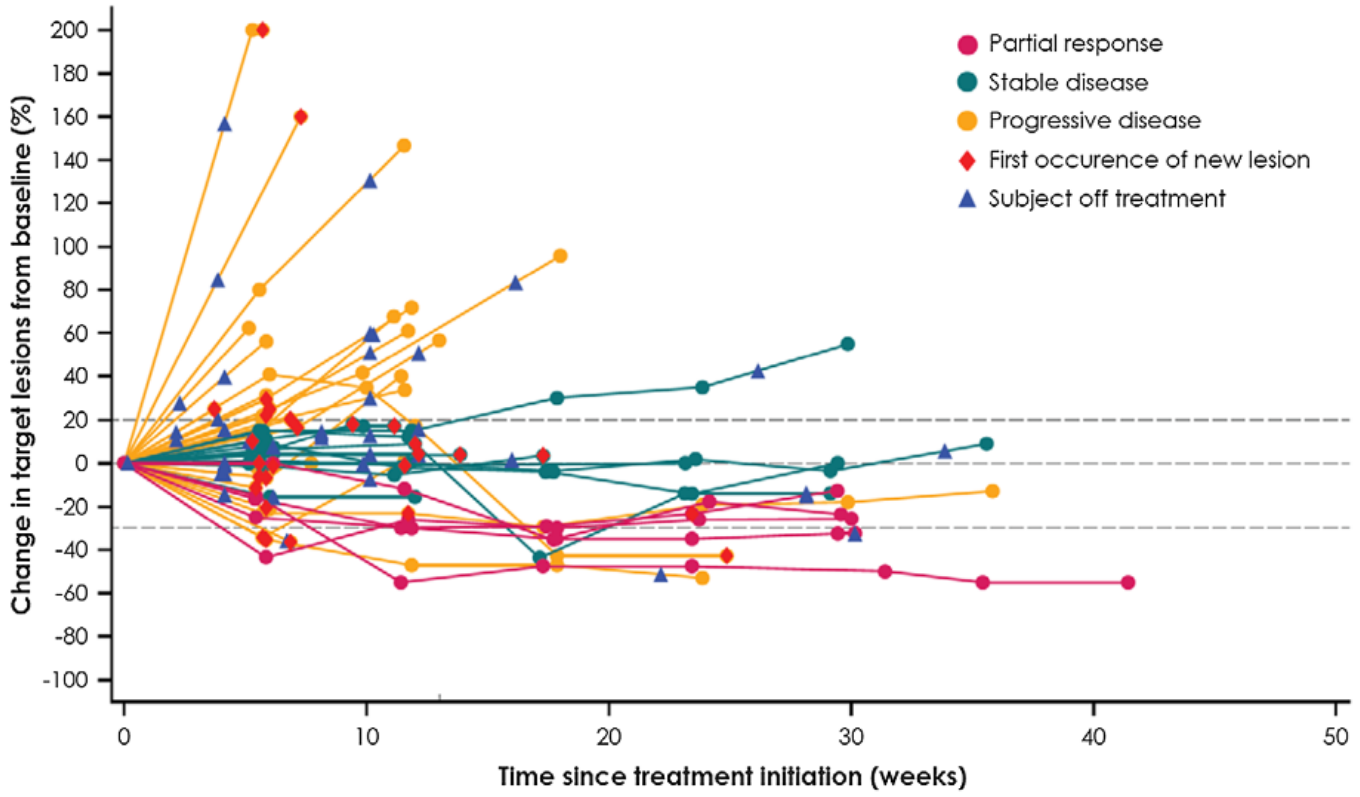


Pembrolizumab single agent in TNBC PD-L1+/-, 2+ line

Adams S, ASCO 2017

Immune checkpoint inhibitors in metastatic TNBC: durable responses

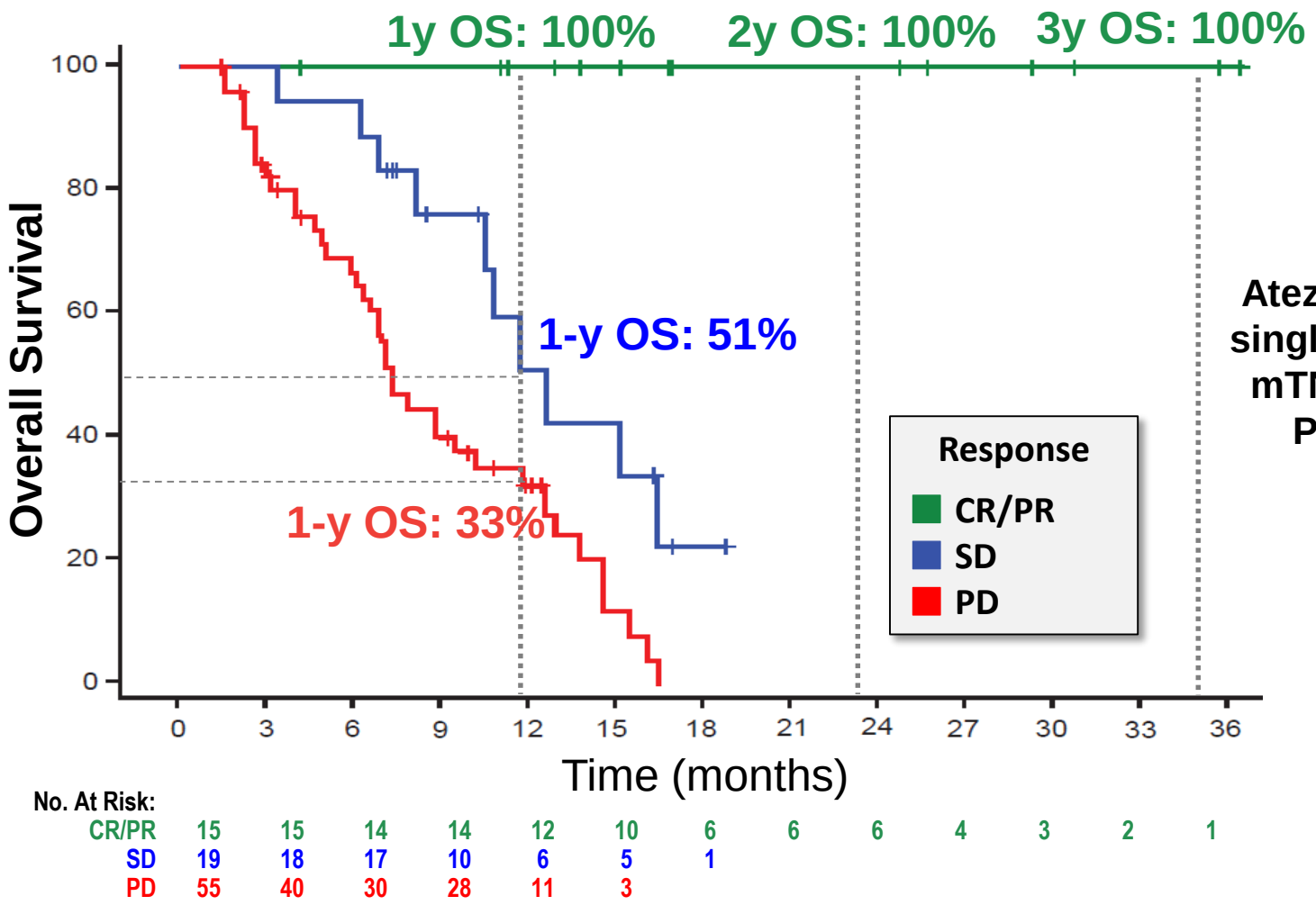
Javelin 1b - AVELUMAB



Percent change in target lesions from baseline in 46 evaluable patients with TNBC with baseline tumor assessment and ≥ 1 post-baseline assessment

Dirix L, BCRT 2018

OS according to best response



Atezolizumab single agent in mTNBC ≥1L, PDL1+/-

Median OS follow-up (range) was 15.2 mo (0.4+ to 36.7) in all patients, 17.0 mo (0.43+ to 36.7) in IC2/3 patients and 12.8 mo (0.8+ to 16.9) in IC0/1 patients.

Schmid P, et al. AACR 2017

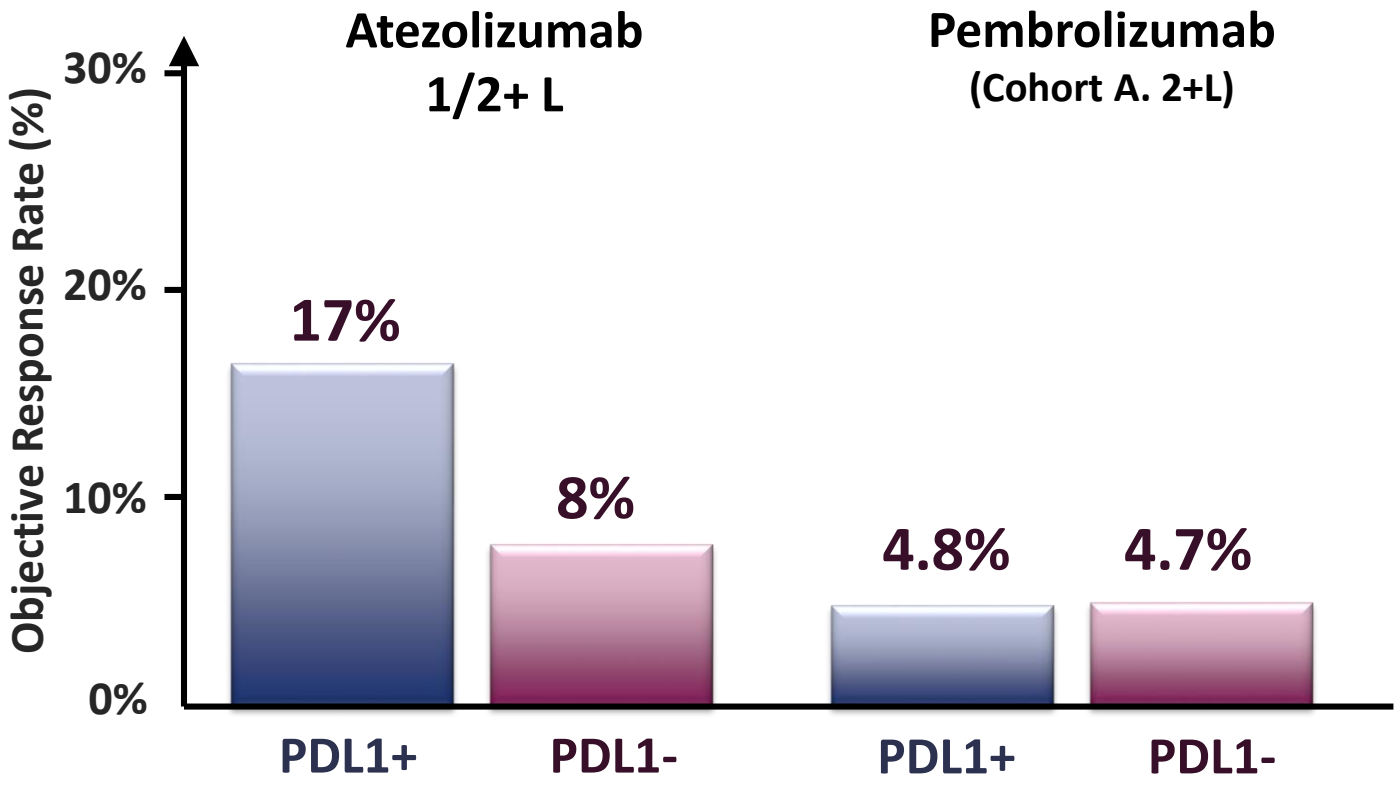
How to move forward in TNBC

- Optimize patients selection
- Combinations
  - Chemotherapy
  - Immune-attractants

- Move to the adjuvant/neoadjuvant setting

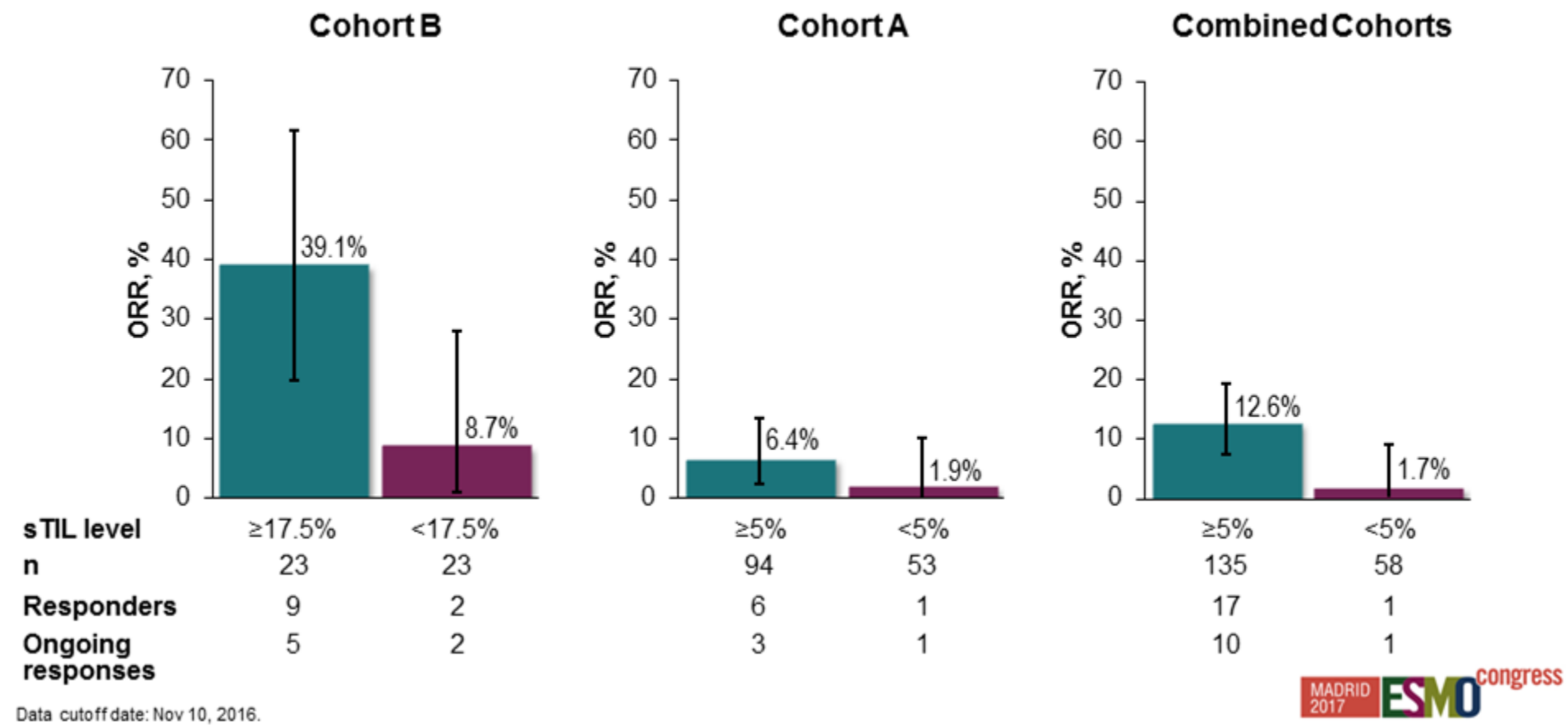
PD-L1 expression and response to single agent immune checkpoint inhibitor

Anti-PD-L1/PD-1 single agent in mTNBC ≥1L, PDL1+/-



Schmid P, et al. AACR 2017; Adams S, et al ASCO 2017, Loi, ESMO 2017

KEYNOTE-086: TILs and ORR



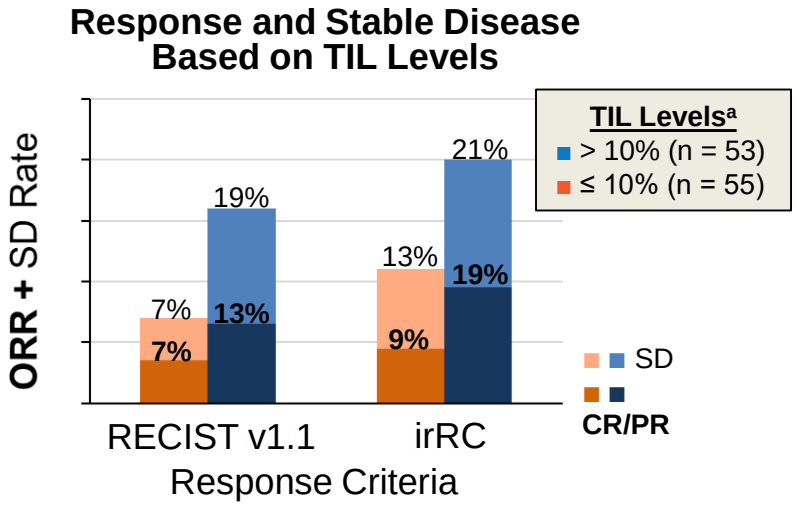
Data cutoff date: Nov 10, 2016.

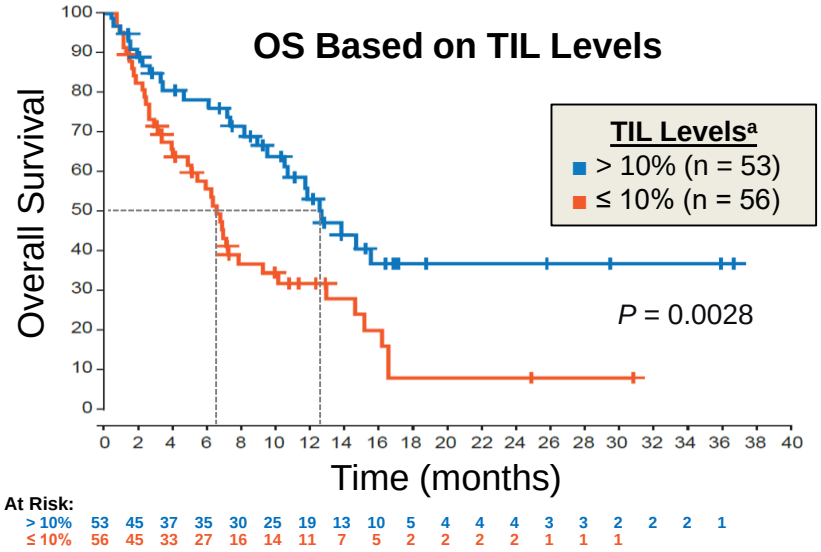
MADRID 2017 ESMO congress

Loi S, ESMO 2017

ORR and OS by TILs – Atezolizumab single agent for mTNBC

- Median TIL infiltration (% tumor area) in tumors from enrolled patients defined the cutoff used for analysis



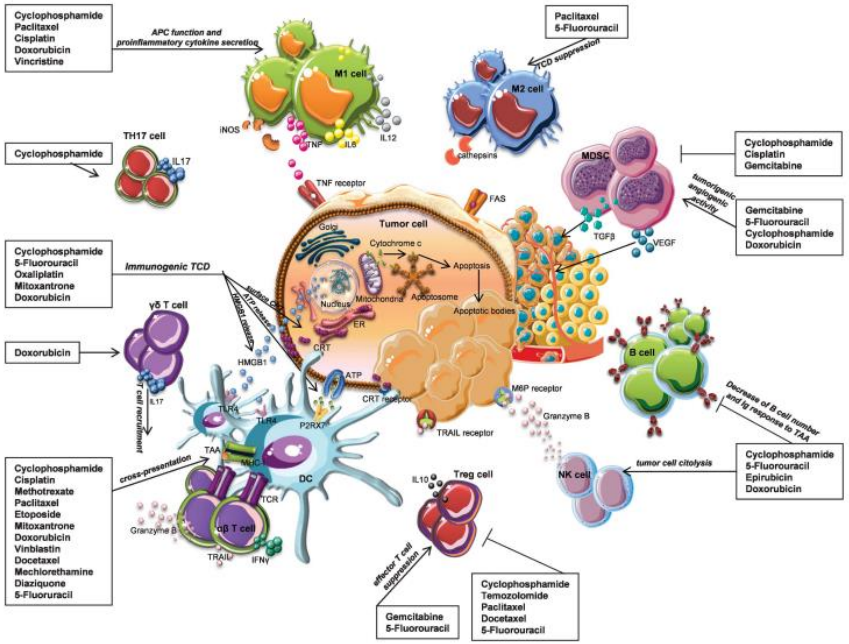


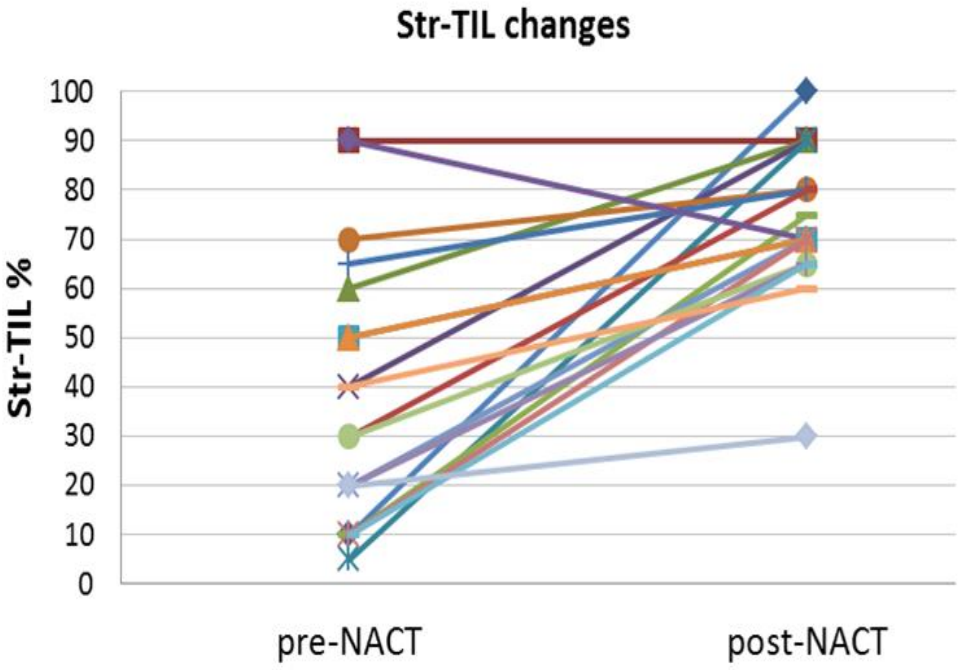
- Higher ORR and longer OS were seen with higher baseline TIL infiltration
- Similar results were observed with CD8 infiltration

	≤ 10% TILs (n = 53)	> 10% TILs (n = 56)
mOS (95% CI)	6.6 mo (4.9, 10.2)	12.6 mo (10.5, NA)

Schmid P, et al. AACR 2017
Phase Ia Atezolizumab in TNBC

Chemotherapy as a trigger for immune activation

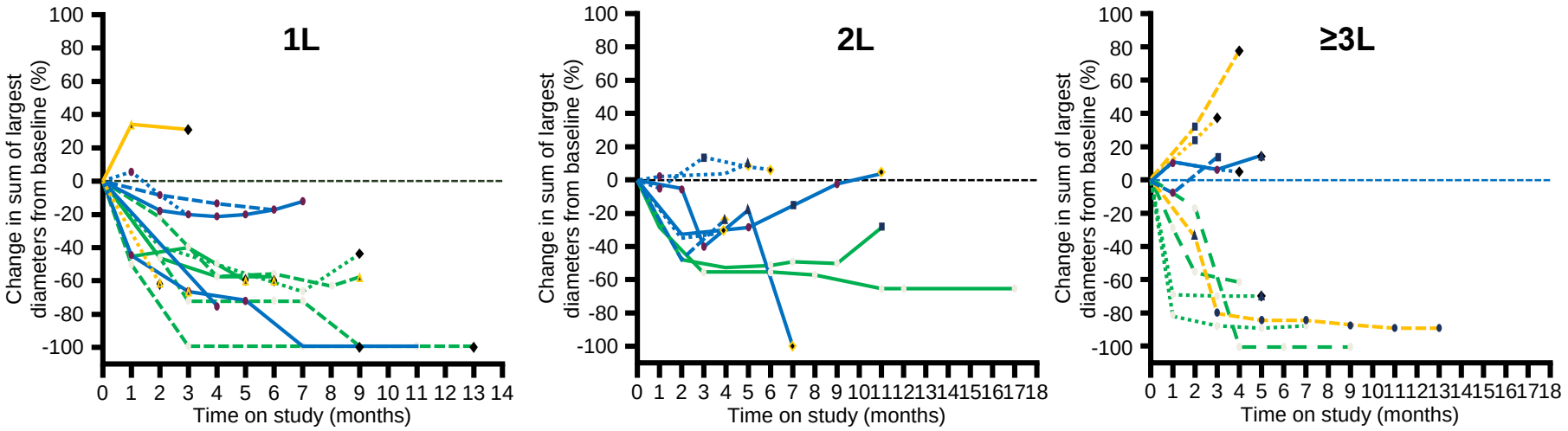




Bracci L, et al. *Cell Death Differ 2014*

Dieci MV, et al. *Ann Oncol*. 2014

Nab-paclitaxel + Atezolizumab for mTNBC PD-L1+/-



	1L n=13	2L n=9*	3L+ n=10†
Confirmed ORR (95% CI)*	46% (19–75)	22% (3–60)	40% (12–74)
SD	39%	67%	30%
PD	15%	0	30%
DCR	85%	89%	70%

*Investigator-assessed confirmed response rate. †One tissue missing/unevaluable.1L, first line; 2L, second line; 3L, third line; CI, confidence interval; CR, complete response; DCR, disease control rate; IC, tumour-infiltrating immune cell; ORR, objective response rate; PD-L1, programmed death-ligand 1; PR, partial response; PD, progressive disease; SD, stable disease

Adams S, et al. ASCO 2016

A-BRAYE-TRIAL

Sponsor: DiSCOG - UNIPD
PI: P. Conte

Stratum A: Adjuvant
High-risk TNBC pts (≥4 metastatic axillary lymph nodes) who received curative intent surgery and completed adjuvant chemotherapy

Stratum B: Post-neoadjuvant
TNBC pts treated with neoadjuvant chemotherapy and with residual invasive breast cancer in the breast and/or in the axilla at surgery (except from ypT1micN0, ypT1micN0i+, ypT0N0i+)

R

Avelumab for 1 year

Observation

Randomization 1:1 (after RT, if indicated) balanced for adjuvant and post-neoadjuvant patients.

Co-primary endpoints: 1. DFS in all-comers; 2. DFS in PD-L1+ patients
Secondary endpoints: OS, Safety, Biomarkers

n=335 (for the 1st co-primary endpoint)

First patient in: June 2016

A-BRAVE-TRIAL

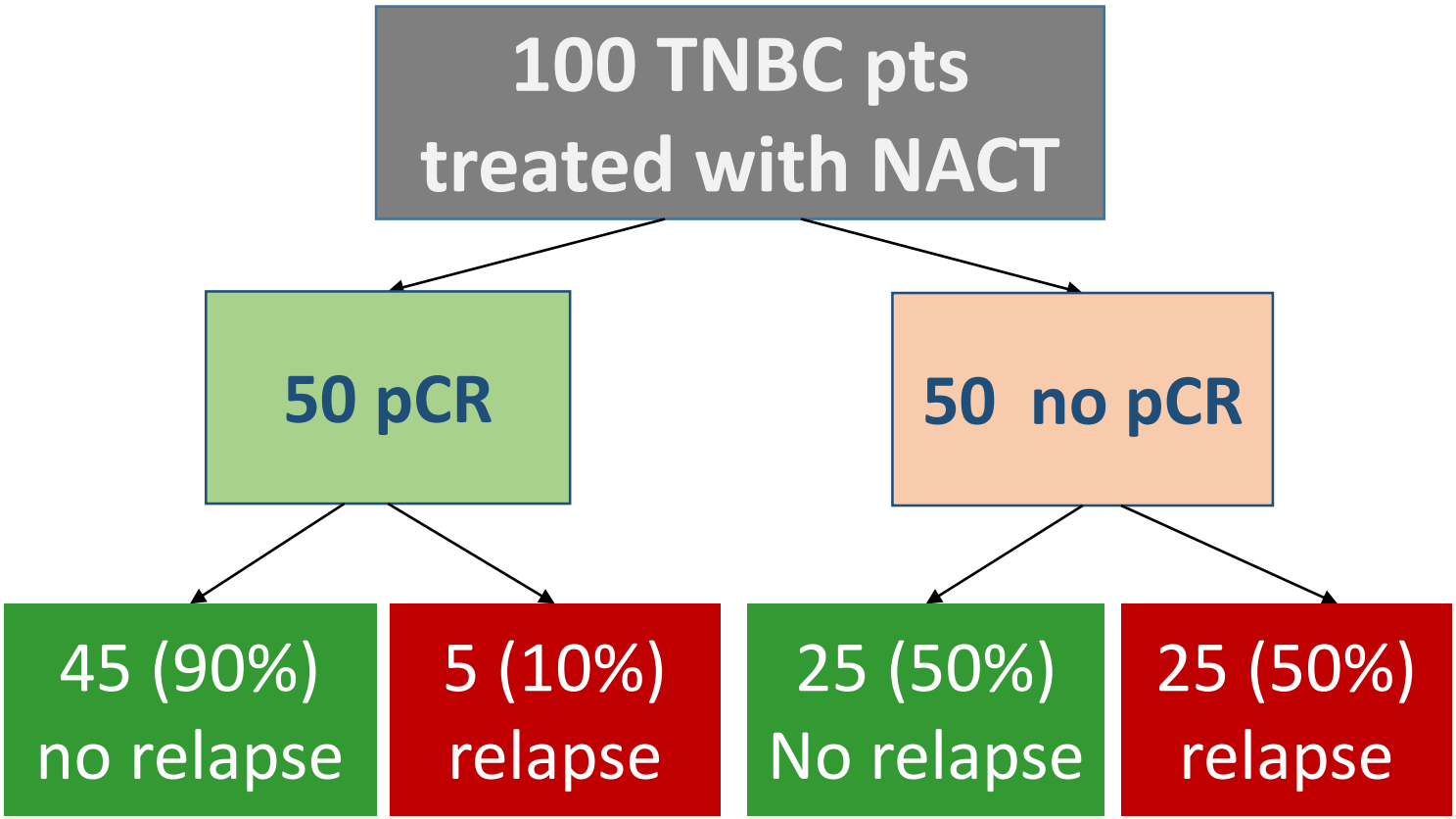
AMENDMENT, v2.0: main changes

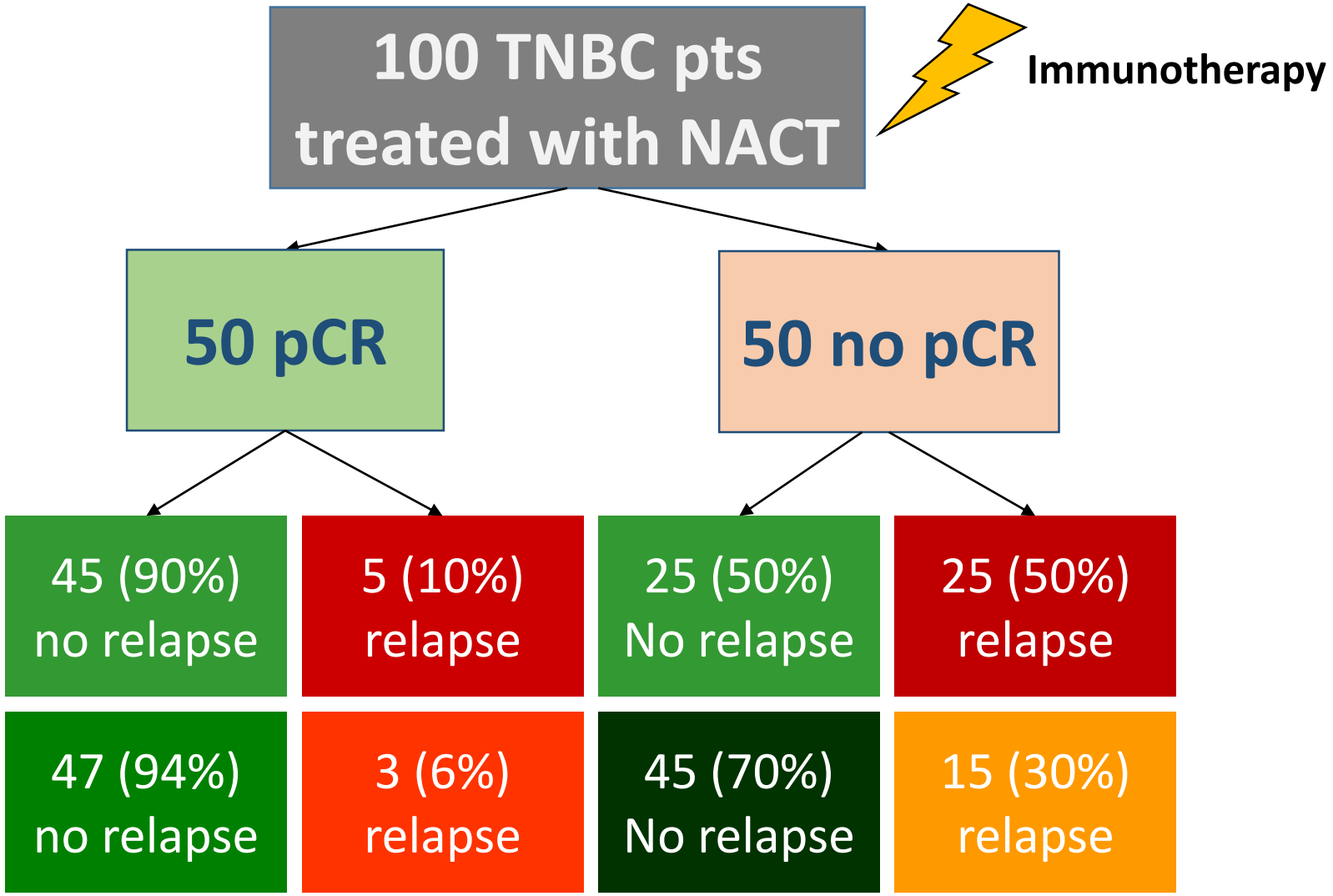
- For **Stratum A Adjuvant:**

  inclusion criteria relative to Stage have been expanded to also include patients with

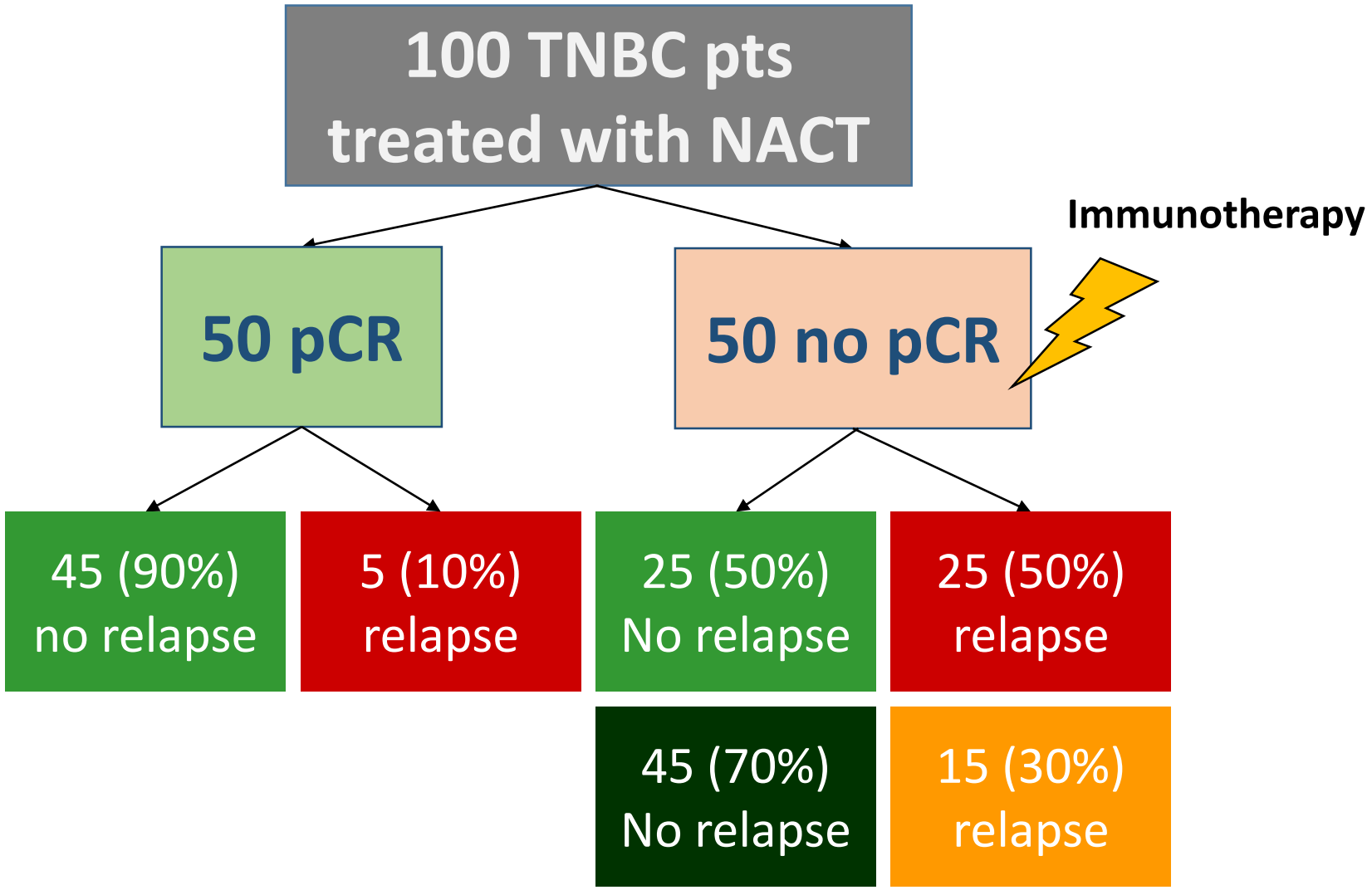
  - **1 to 3 positive nodes and pT >2 cm**
  - **N0 and pT >5 cm**

- Completion of RT (for patients for whom it is indicated) is no longer an inclusion criteria: **concomitant avelumab and radiotherapy allowed.**


100 TNBC pts
treated with NACT
50 pCR
50 no pCR
45 (90%)
no relapse
5 (10%)
relapse
25 (50%)
No relapse
25 (50%)
relapse



Assuming a RR of relapse of 0.60 in all patients, number of relapses will decrease from 30 to 18 (Δ= 12). NNT: 100/12 = 8,3



Assuming a RR of relapse of 0.60, number of relapses will decrease from 25 to 15 (Δ= 10).

NNT: 50/10 = 5

A-BRAVE-TRIAL

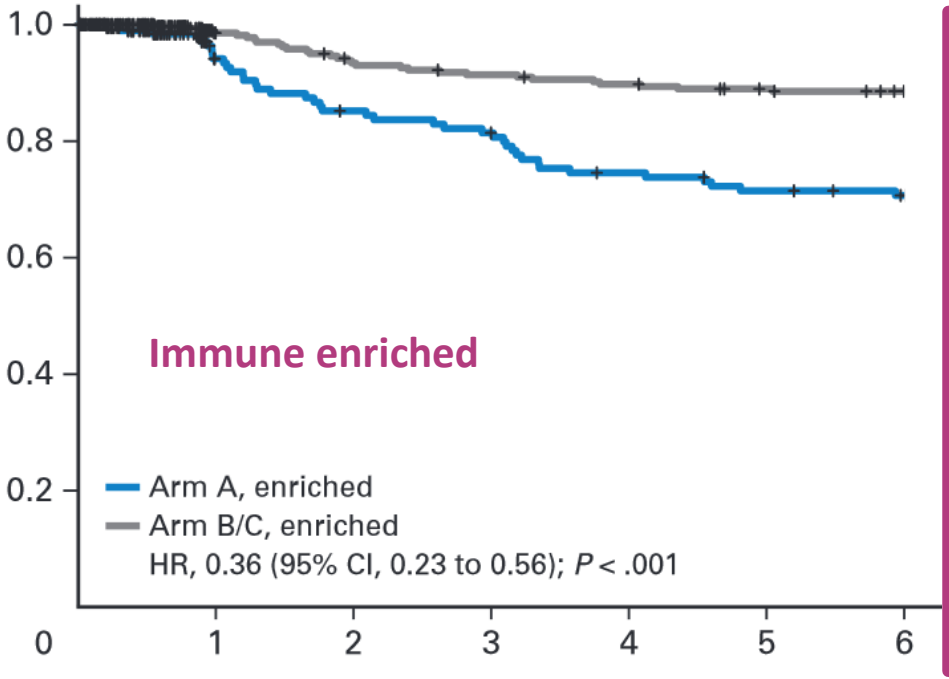
Trial Status

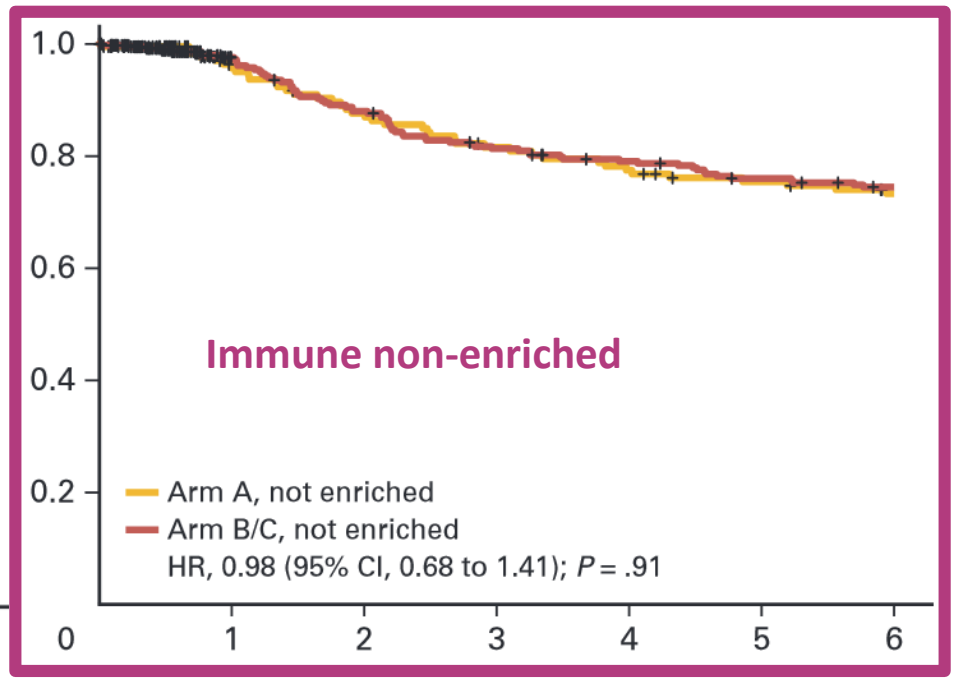
- 47 activated centers:
  - 31 actively recruiting
  - 40 amendment 1, v2.0 approved

- 83 patients enrolled

- Amendment 2, v3.0 planned
- To be opened with amendment 2 v3.0
- 8 additional italian centers
- 10 UK centers

Immune correlates and benefit from adjuvant Trastuzumab: N9831

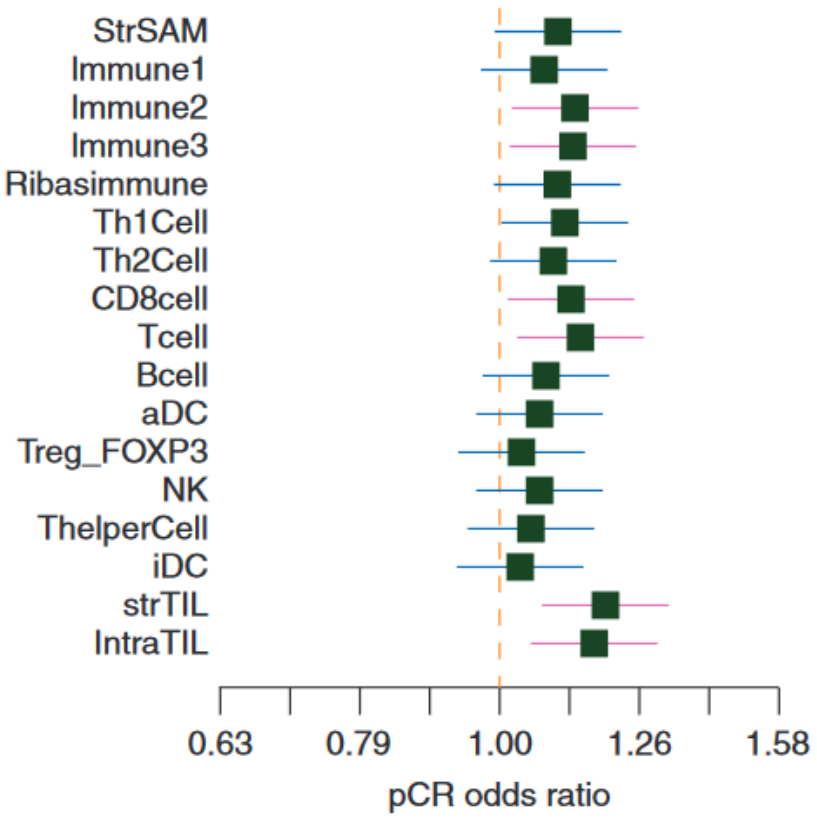




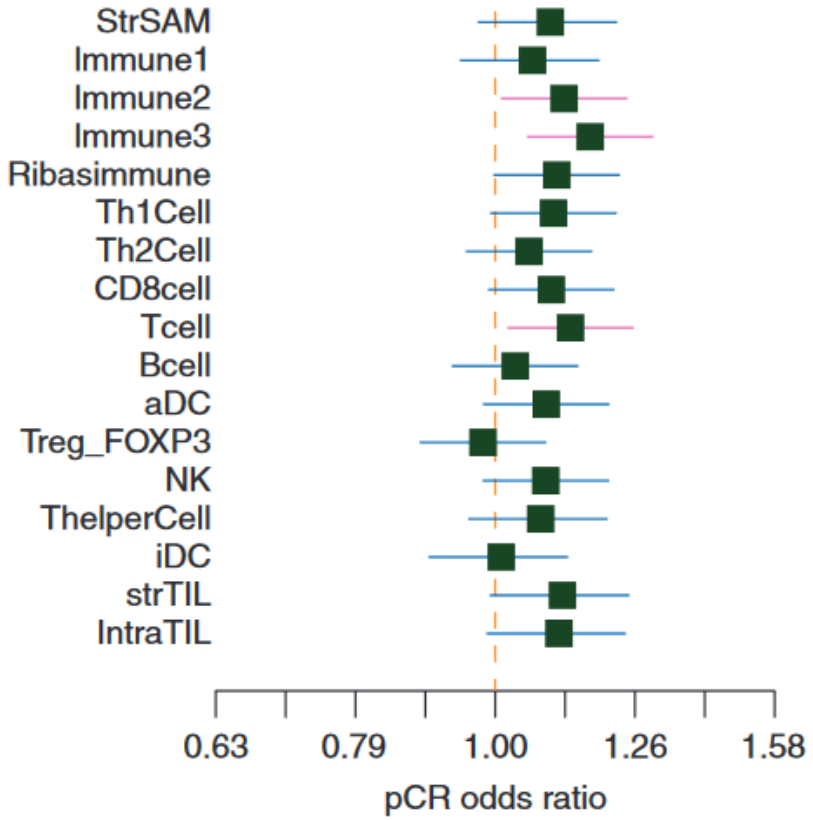
Perez EA, JCO 2015

CherLOB - Immune parameters and PAM50 subtypes: association with pCR

Univariate analysis



Corrected for PAM50



Dieci MV, Ann Oncol 2016

PANACEA Study:
Pembrolizumab + Trastuzumab in Trastuzumab-Resistant HER2+ ABC

- Centrally confirmed HER2+
- ECOG 0-1
- Tumor biopsy sample <1 yr
- Measurable disease RECIST 1.1
- No limit of prior systemic treatment
- Documented PD on trastuzumab or TDM-1

PD-L1+ → **Phase Ib**
Pembrolizumab 2 mg/kg and 10 mg/kg IV + trastuzumab q3w

Phase II
Pembrolizumab 200 mg IV + trastuzumab q3w

PD-L1- → **Phase II**
Pembrolizumab 200 mg IV + trastuzumab q3w

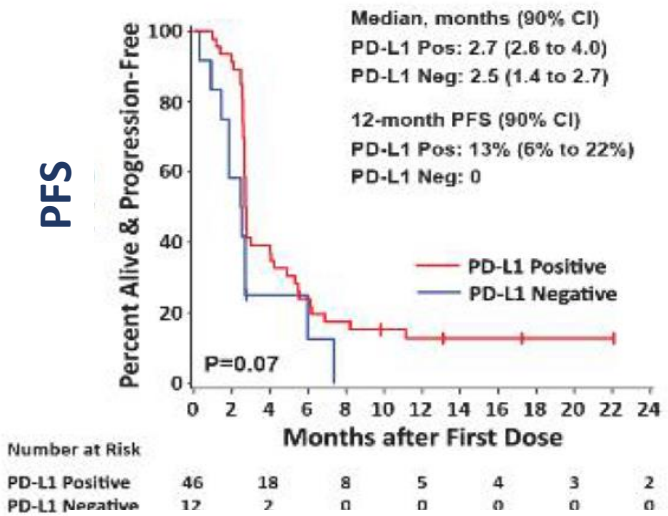
Protocol specified follow-up. Treatment until progression, toxicity, patient withdrawal, investigator decision, or maximum 2 years

	PD-L1 Positive Phase Ib, n=6	PD-L1 Positive Phase II, n=40	PD-L1 Negative Phase II, n=12
ORR n (%) [90%CI]	1 (17%) [1-58]	6 (15%) [7-29]	0 (0%) [0-18]
DCR[1] n (%) [90%CI]	1 (17%) [1-58]	10 (25%) [14-49]	0 (0%) [0-18]
Best overall response, n (%)			
Complete Response	1 (17%)	1 (2.5%)	-
Partial Response	-	5 (12.5%)	-
Stable Disease	-	7 (17.5%)	2 (16.7%)
Progressive Disease	5 (83%)	25 (62.5%)	9 (75.0%)
Not Evaluable	-	2 (5.0%)	1 (8.3%)
Overall PD-L1 + cohort	ORR 15.2% [7-27]	DCR 24% [14-36]	

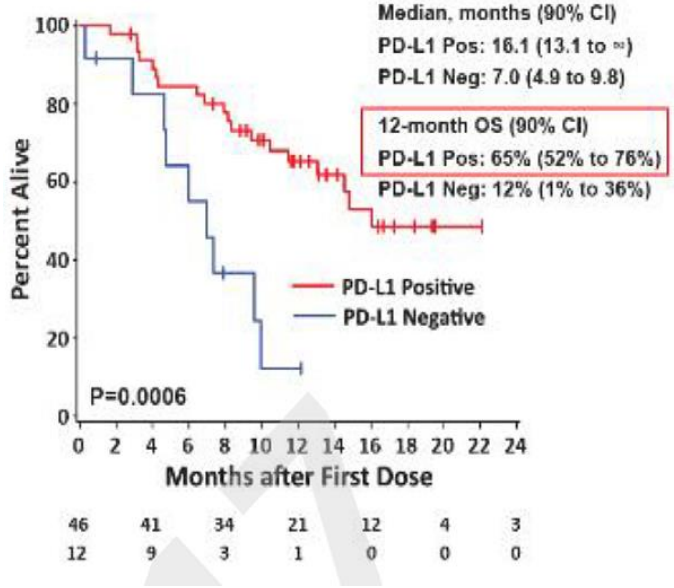
Loi S, et al. *Cancer Res.* 2017;77(13 Suppl): Abstract GS2-06.

PANACEA Study: Outcome by PD-L1+ and by TIL

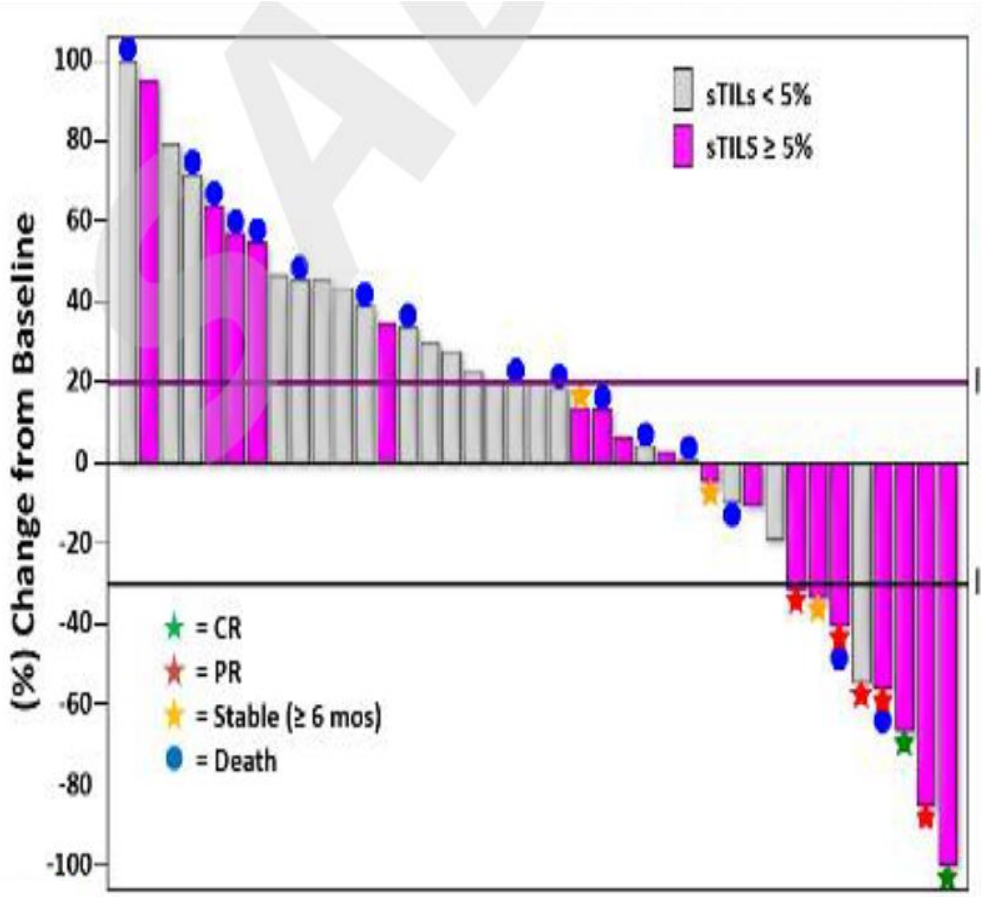
PFS



OS



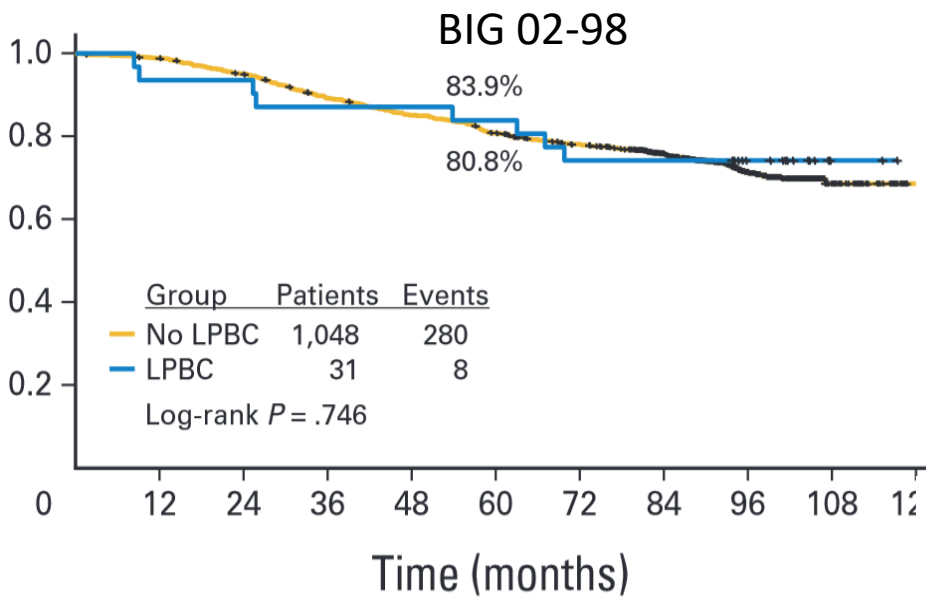
PD-L1+ cohort



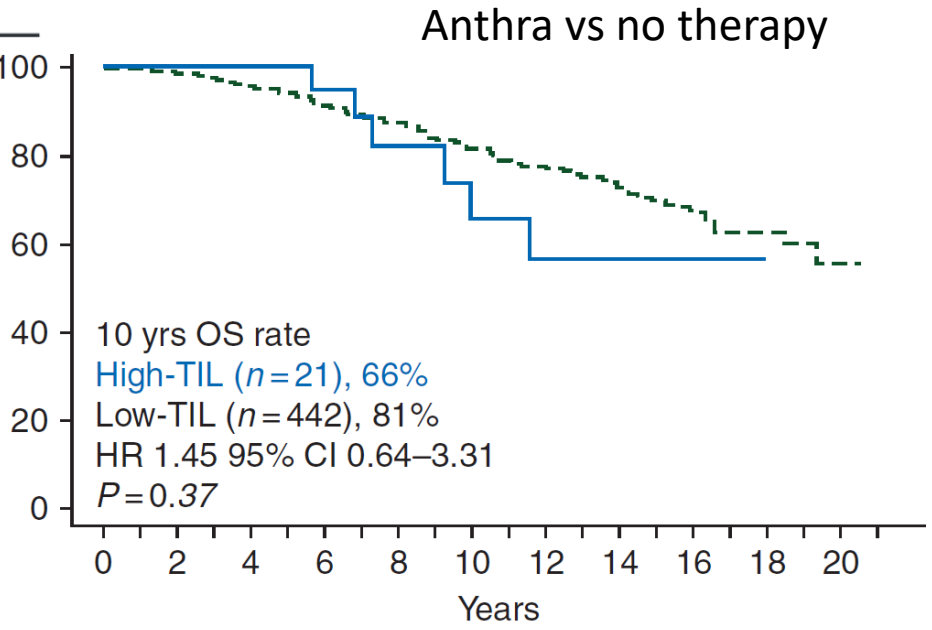
high stromal TILs → **PREDICTIVE** marker ?

Loi S et al, SABCS 2017

Prognostic role of TILs in HR+/HER2- early BC



Loi S, JCO 2013



Dieci MV, Ann Oncol 2015

The immune system and hormone-receptor positive breast cancer: Is it really a dead end?

Maria Vittoria Dieci [a,b,*], Gaia Griguolo [a,b], Federica Miglietta [b], Valentina Guarneri [a,b]

[a] Dept. of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy
[b] Division of Medical Oncology 2, Istituto Oncologico Veneto IRCCS, Padova, Italy

2016

	TNBC	HER2+	HR+/HER2-
Mechanisms of tumor-immune cells interaction	Neoantigens/Neopeptides RAS/MAPk activation as immune escape mechanism [97]	Oncogene addiction	Estrogen-mediated modulation of local immunity/inflammation
Methods for evaluation of clinically relevant immune markers	More comprehensive functional assessment: IHC markers, gene expression, RNASeq, combined scores General TILs		
Standard treatments contributing to the modulation of the immune milieu	CT and RT: immunogenic cell death	anti-HER2 moAB: ADCC TKIs: possible interference with immunesuppressive oncogene-mediated pathways	TAMOXIFEN: Th1 to Th2 (estrogen-independent); M2 to M1 TAMs (estrogen-dependent); TGFβ induction AIs: Foxp3+ depletion*

Pembrolizumab HR+/HER2-

% PD-L1+/screened	19%
PD-L1 cut-off	≥1% tumor cells or any stromal staining
Evaluable pts	25 (PD-L1+)
Median Nb of prior therapies	9 (3-15)
ORR	3 (12%)
CR	0
PR	3 (12%)
CBR ≥ 24 wks	5 (20%)
PD	15 (60%)
Median duration of response	12 m. (7.4-15.9)

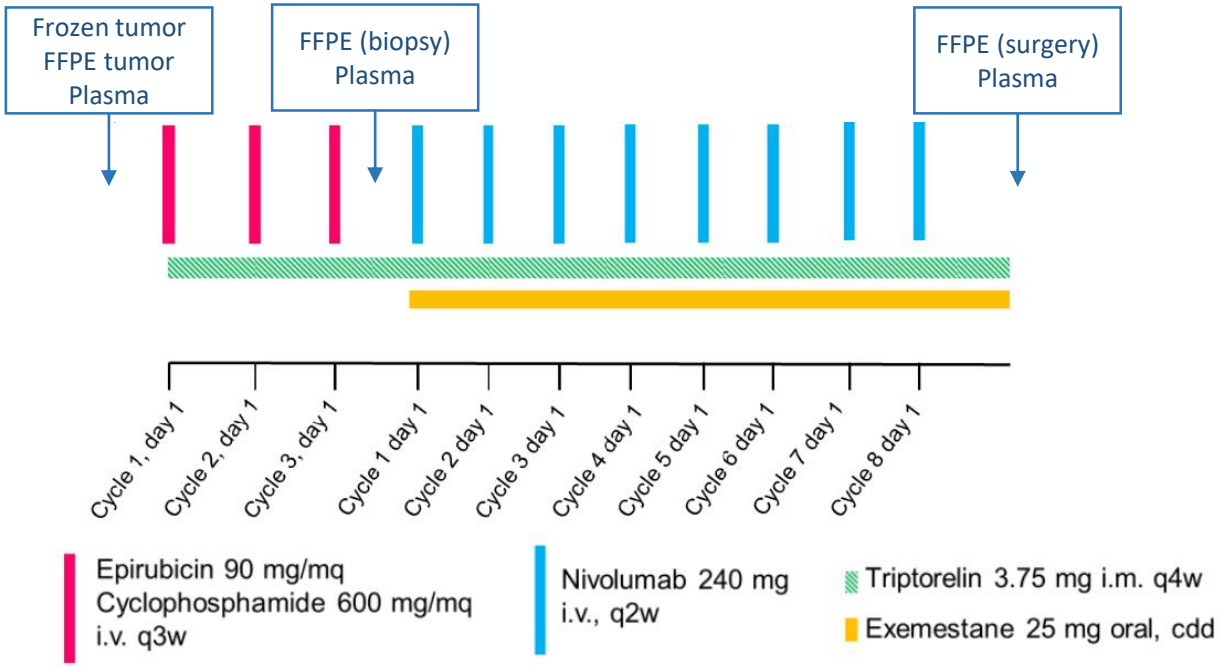
Rugo H, Clin Cancer Res 2018

STUDY DESIGN

Sponsor: University of Padova
PI: P.Conte
Financial Support: BMS

ENGAGING THE IMMUNE SYSTEM TO IMPROVE THE EFFICACY OF NEOADJUVANT CHEMO-ENDOCRINE THERAPY FOR PREMENOPAUSAL LUMINAL B BREAST CANCER PATIENTS.

Luminal B (HR+/HER2-, G3 or Ki67 >20%) premenopausal stage II-IIIA BC patients



Population: n=48
Primary endpoint: pCR
Secondary endpoints: OR, molecular response (Ki67), PEPI score, conservative surgery rate, safety, biomarkers

1° patient in october 2017 – 3 active centers – 7 pts enrolled