IV Simpósio Internacional de

IMUNO-ONCOLOGIA

O FUTURO DA ONCOLOGIA

27 E 28 DE JULHO – HOTEL PULLMAN VILA OLÍMPIA

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Câncer de Mama: perspectivas e limitações da imunoterapia

Dra. Juliana Martins Pimenta
Hospital BP e BP Mirante
Hospital Beneficência Portuguesa de São Paulo

Declaração de Conflito de Interesses

- De acordo com a Norma 1595/2000 do Conselho Federal de Medicina e com a RDC 96/2008 da ANVISA, declaro que:

  –Pesquisa Clínica: como médico investigador, participo de estudos patrocinados por: **MSD, Roche, Novartis**

  –Apresentações: como palestrante convidado, participo dos eventos de: **Roche, Astrazeneca, Amgen, Eisai, Novartis**

  –Consultoria: como membro de advisory boards, participo de reuniões com: **Roche, Novartis**

- Não possuo ações de quaisquer destas companhias farmacêuticas.

Câncer de mama

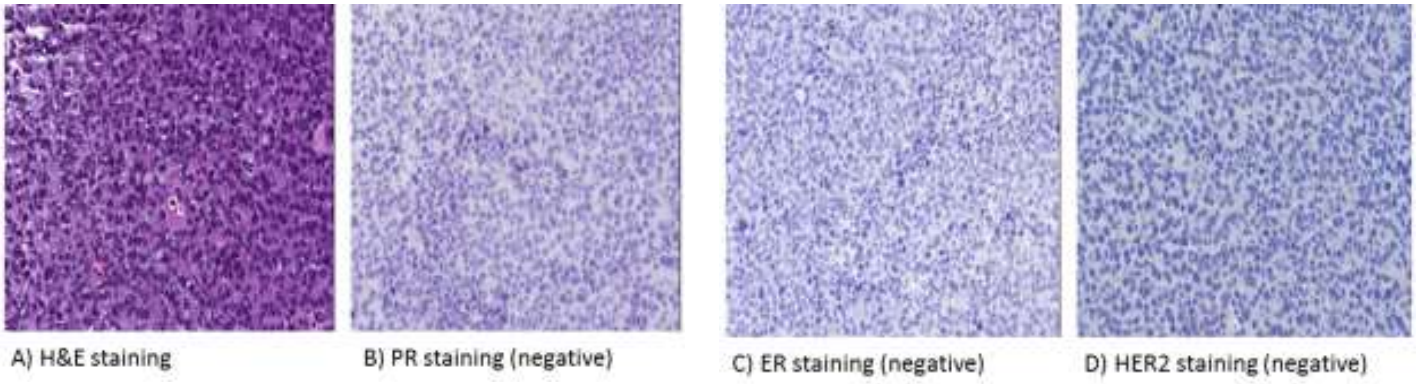
Apesar de grandes avanços no tratamento dessa neoplasia nos últimos anos, poucos avanços foram alcançados no subtipo triplo negativo...

Imunoterapia em Câncer de Mama

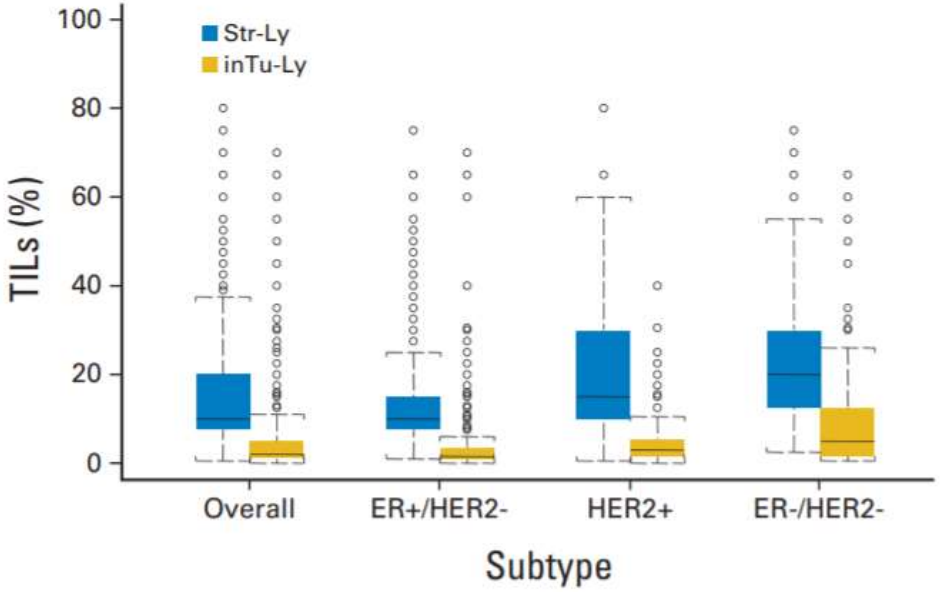
1. Introdução
2. Agentes únicos
3. Combinações com imunoterapia
4. Próximos passos
5. Conclusão

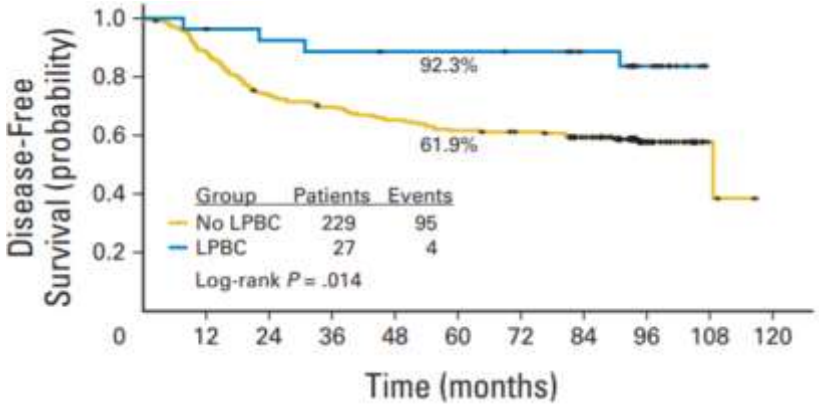
Câncer de mama triplo negativo (TNBC):

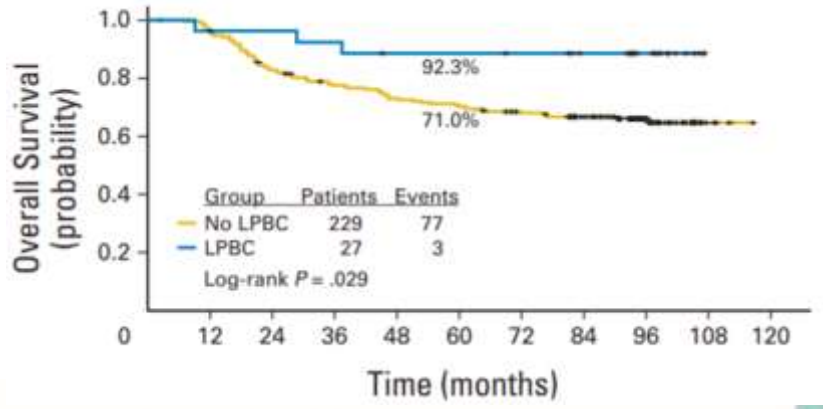
- Maior instabilidade cromossômica
- Maior número de mutações → maior capacidade imunogênica
- Maior expressão de PD-L1
- Maior infiltração por TILs



Mol Cancer Ther. 2007;6(7):2065-2072 ; J Clin Oncol. 2013;31:(suppl; abstr 521) ; Neoplasia 8:190, 2006







In Tu-Ly: intratumoral lymphocytic infiltration
Str-Ly: stromal lymphocytic infiltration

Loi et al, J Clin Oncol 2013

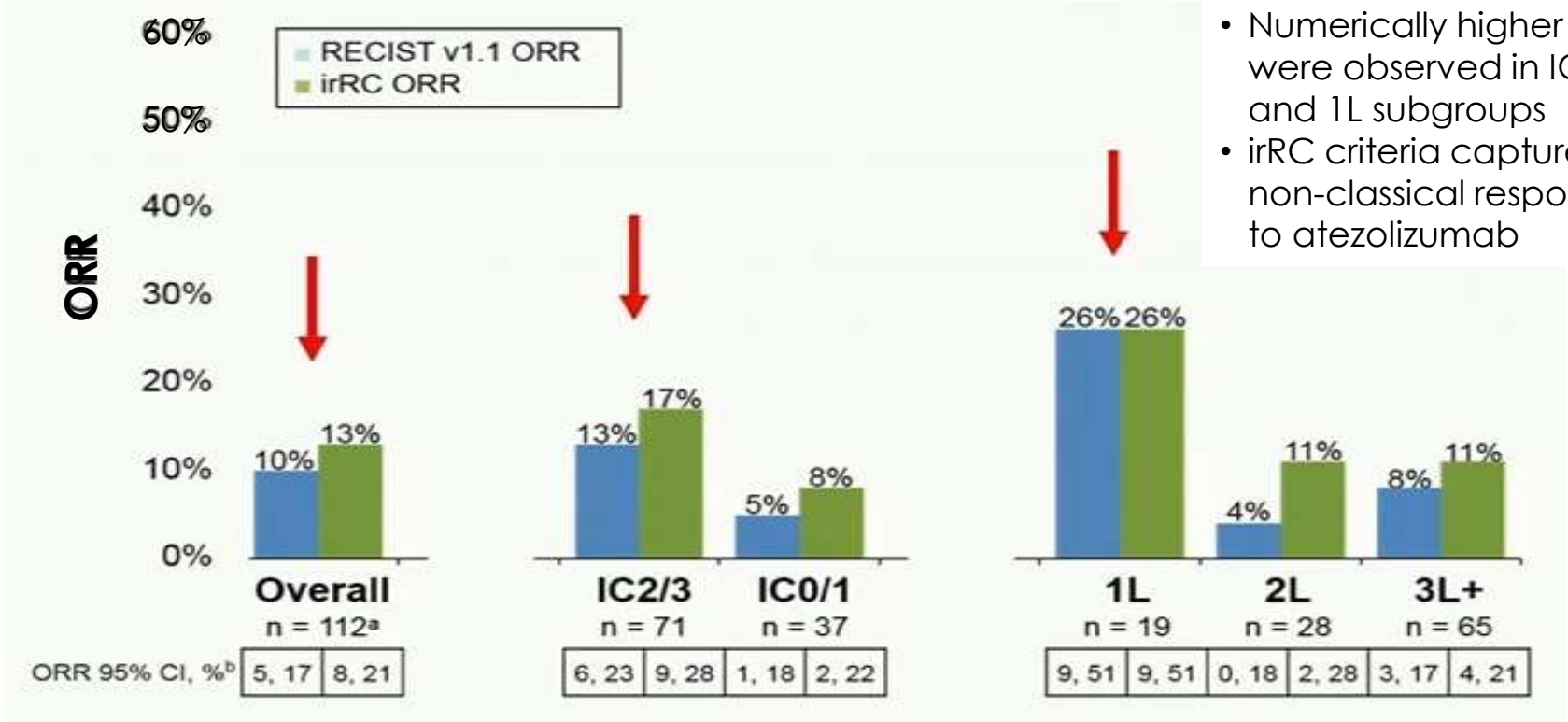
Taxas de Resposta com Checkpoint inhibitors agente único

Agent	Subtype	ORR	ORR (PD-L1+)
Pembrolizumab			
Keynote-012	TNBC	18.5%	18.5%
Keynote-028	ER+	12.0%	12.0%
Keynote-086-A	TNBC	4.7%	4.8%
Keynote-086-B (Frontiline, PD-L1+)	TNBC	23.0%	23.0%
Atezolizumab 1a			
All	TNBC	10.0%	13.0%
Frontline	TNBC	26.0%	NR
Avelumab	All	3.0%	16.7% (2/12)
Single agente (Javelin)	ER+	2.8%	NR
	HER2+	0%	NR
	TNBC	5.2% (3/58)	22.2% (2/9)

*Studies used diferente antibodies and cutoffs for determining PD-L1 positivity

Nanda et al, JCO 2016; Rugo et al, CCR 2018; Adams et al, ASCO 2017; Schmid et al, AACR 2017, Dirix et al, BRCT 2017

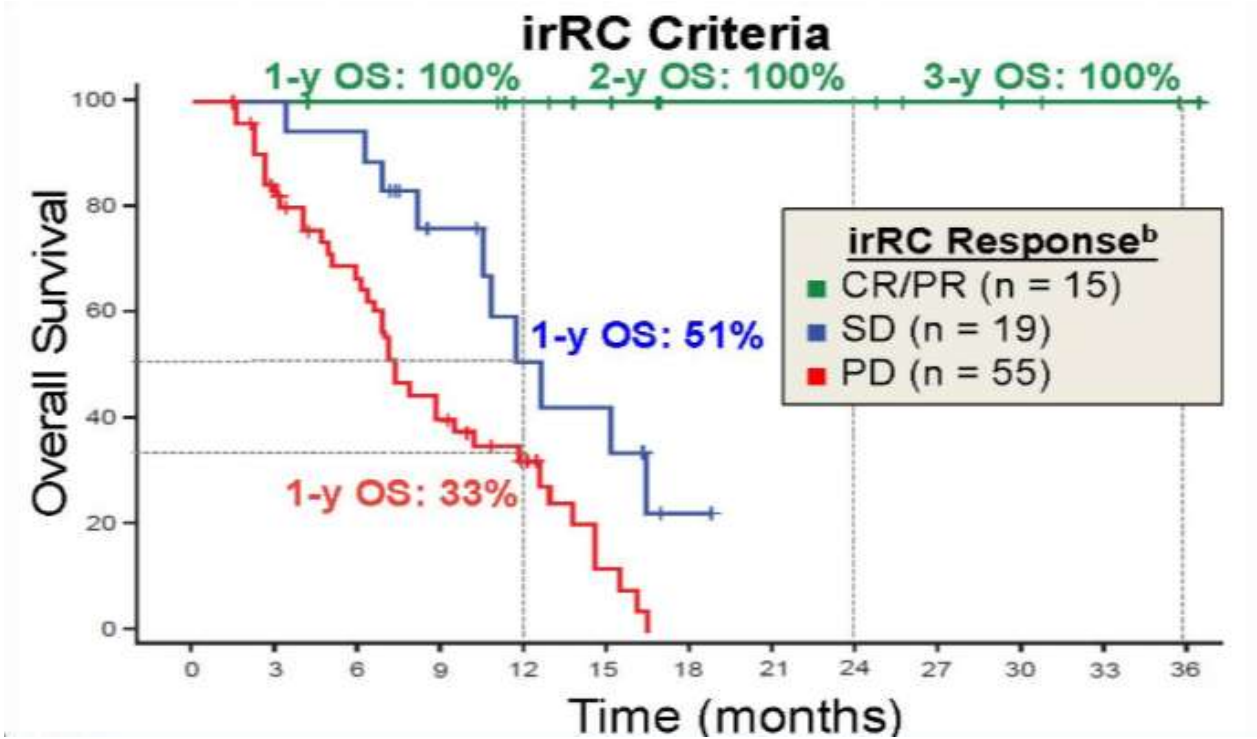
Atezolizumab (α-PD-L1)



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

Schmid et al. AACR 2017

Resposta a Checkpoint inhibitors associada com aumento de SG



Schmid et al. AACR 2017

Pembrolizumab (α-PD-1)

KEYNOTE-012:
Triple-Negative Breast Cancer Cohort

- Recurrent or metastatic ER⁻/PR⁻/HER2⁻ breast cancer
- ECOG PS 0-1
- PD-L1⁺ tumor[a]
- No systemic steroid therapy
- No autoimmune disease (active or history of)
- No active brain metastases

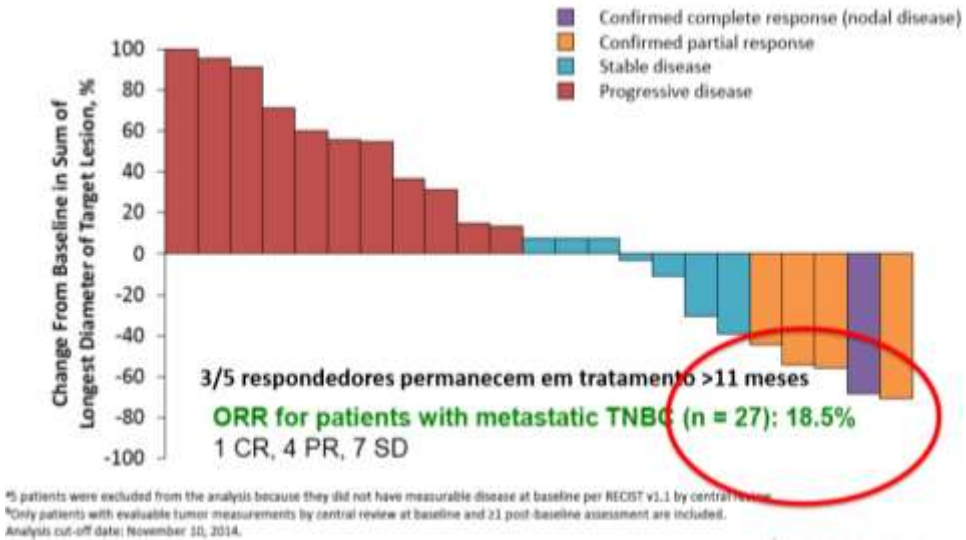
→ Pembro 10 mg/kg Q2W

- Complete response → Discontinuation permitted
- Partial response or Stable disease → Treat for 24 months or until progression or intolerable toxicity
- Confirmed progressive disease → Discontinue

- PD-L1 positivity: 58% of all patients screened had PD-L1-positive tumors
- Treatment: 10 mg/kg IV Q2W
- Response assessment: performed every 8 weeks per RECIST v1.1

Nanda R, et al. J Clin Oncol, 2016 May 2 [Epub ahead of print]

Keynote 012: pembrolizumab in TNBC Maximum percentage Target lesion Change from Baseline (RECIST v1.1, Central Review)[a,b]



Nanda. SABCS. 2014

Tipo de resposta	Pacientes avaliados quanto à resposta (N = 27)
Taxa de resposta global	18,5%
Resposta completa	1 (3,7)
Resposta parcial	4 (14,8)
Doença estável	7 (25,9)
Doença progressiva	13 (48,1)
Sem avaliação	2 (7,4)

J Clin Oncol 34:2460, 2016

Estudo JAVELIN, de fase Ib avaliou a atividade do avelumabe (anti-PD-L1)

- Dose de 10 mg/kg a cada 2 semanas em 168 pts com CA de mama (33,9% com TNBC) refratários a ≥ 1 linha de tratamento sistêmico
- Grupo que mais se beneficiou: TNBC com expressão de PD-L1 (RO: 44% em PD-L1+ *versus* 2,6% em PD-L1-)

Melhor resposta global, %	Todos os pacientes (N = 168)	Pacientes com TNBC (N = 58)
Resposta Completa	**0,6%**	**0%**
Resposta Parcial	**4,2%**	**8,6%**
Doença Estável	23,3%	22,4%
Doença Progressiva	63,1%	65,5%
Não avaliado	8,9%	3,4%
Taxa de resposta objetiva (ORR)	4,8%	8,6%
DCR	28,0%	31,0%

Dirix et al, BRCT 2017

KEYNOTE-086 - fase II

60% das pts eram PD-L1+ Pembrolizumabe 200 mg q3w por até 2 anos

Study design - KEYNOTE-086 Cohort A

Patients

- Age ≥18 years
- Centrally confirmed mTNBC[a]
- ≥1 prior systemic treatment for mTNBC with documented PD on/after most recent therapy
- ECOG PS 0-1
- LDH <2.5 x ULN
- Tumor biopsy sample for TNBC status and PD-L1 evaluation
- No radiographic evidence of CNS metastases
- Measurable disease per RECIST v1.1 by central review

N = 170

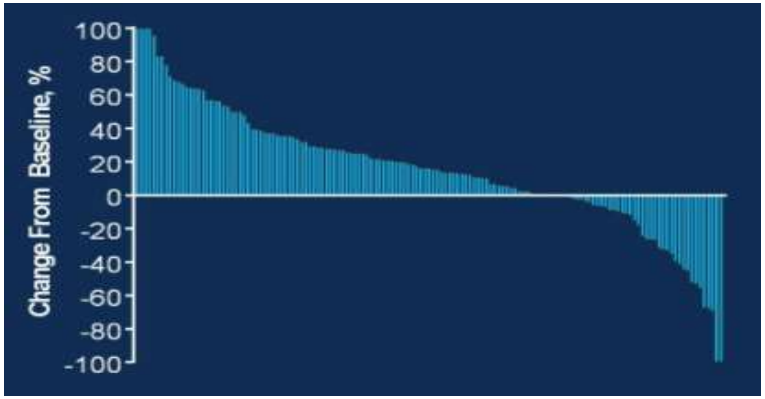
Pembrolizumab 200 mg IV Q3W for 2 years or until PD, intolerable toxicity, patient withdrawal, or investigator decision

Protocol-specified follow-up

- Primary endpoints: ORR[b] and safety
- Secondary endpoints[b]: DOR, DCR,[c] PFS, OS

KEYNOTE-086 - fase II

ORR, n (%) [95% CI]	8 (4.7) [2.3-9.2]
DCR, n(%) [95% CI]	13 (7.6) [4.4-12.7]
Best overall response, n (%)	
Complete response	1 (0.6)
Partial response	7 (4.1)
Stable disease	35 (20.6)
Progressive disease	103 (60.6)
Not evaluable	5 (2.9)
Not able to be assessed	19 (11.2)



Kaplan-Meier estimate of OS

J Clin Oncol 35, 2017 (suppl; abstr 1008)

Estudo de fase Ib (ASCO 2016) avaliou a combinação de atezolizumbe com nab-paclitaxel em pts com TNBC tratadas com ≤ 3 linhas

- 24 pts avaliáveis (87% já haviam recebido tratamento com taxanos previamente)
- *Endpoints* primários: segurança e tolerabilidade
- Atezo 800 mg (D1,15) e nab-pac 125 mg/m² (D1,8,15) a cada 4 semanas
- Após nab-pac descontinuado, manutenção de atezo permitida

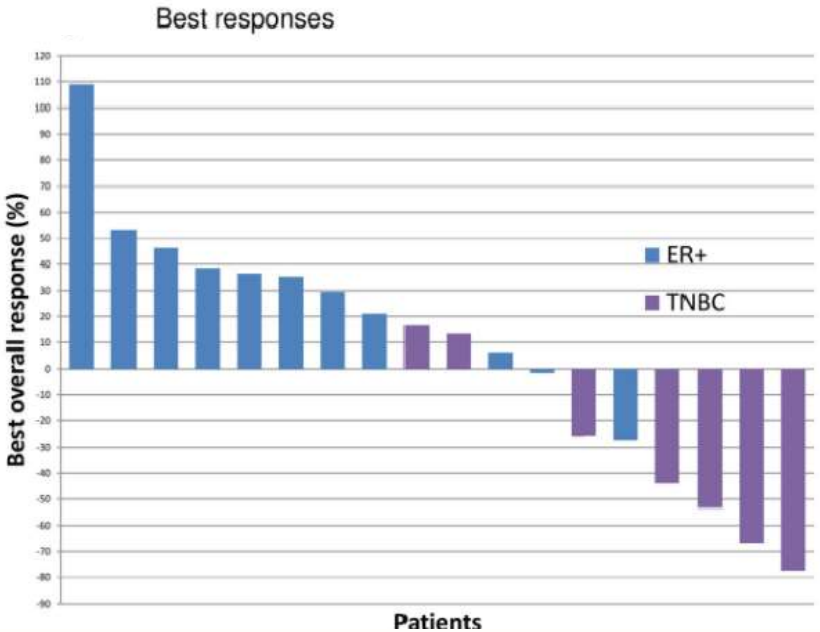
Best Overall Response	1L (n=9)	2L (n=8)	3L+ (n=7)	All patients (n=24)
ORR (95% CI)	67% (30, 93)	25% (3, 65)	29% (4, 71)	42% (22, 63)
CR	11%	0	0	4%
PR	78%	75%	43%	67%
SD	11%	25%	29%	21%
PD	0	0	29%	8%

J Clin Oncol 34, 2016 (suppl; abstr 1009)

TNBC e RE+ metastático

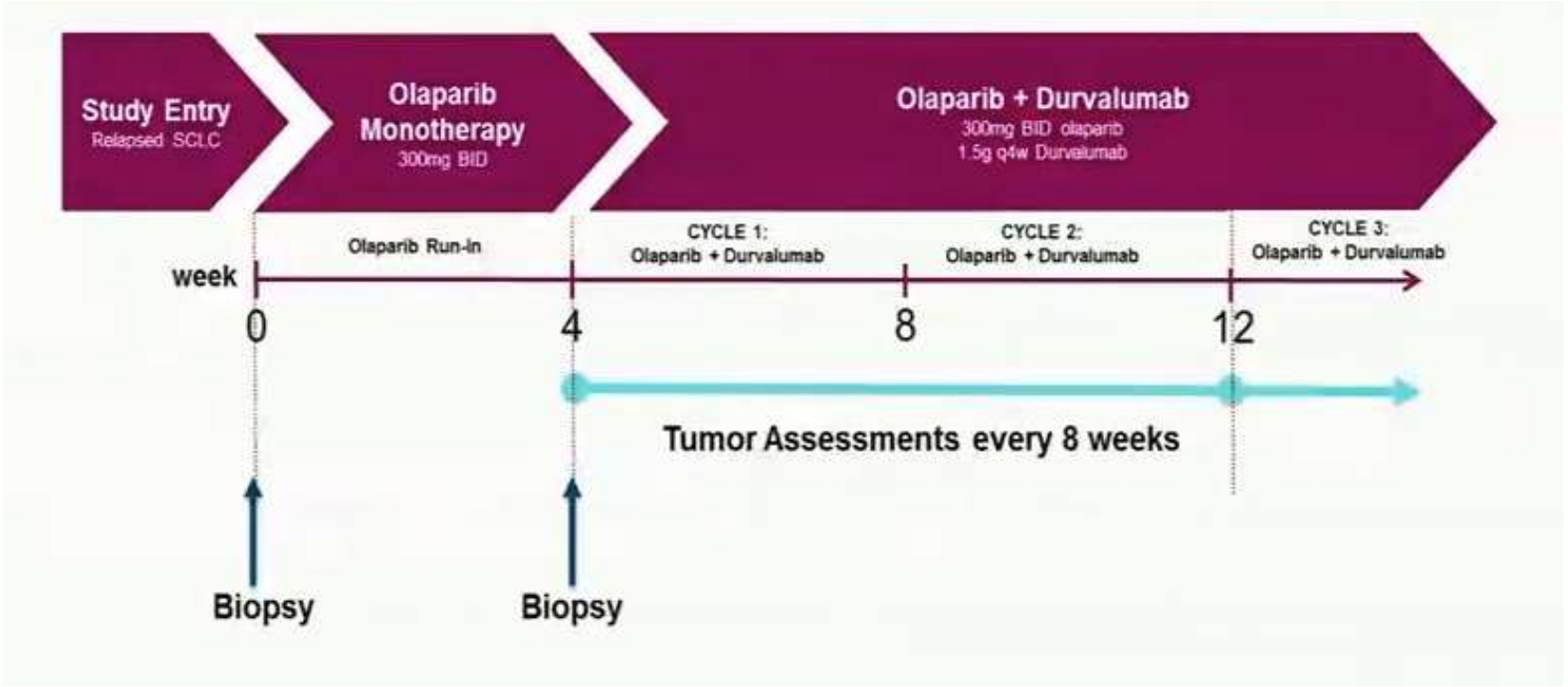
- Durvalumabe 1500 mg + Tremelimumabe 75 mg EV mensal x 4 doses seguido de Durvalumabe 750 mg q2w até completar 1 ano

	All pts (n = 18)	TNBC (n = 7)	ER+ (n = 11)
PR	3	3	0
SD ≥ 6 months	1	1	0
PD	14	3*	11
ORR	17%	43%	0%



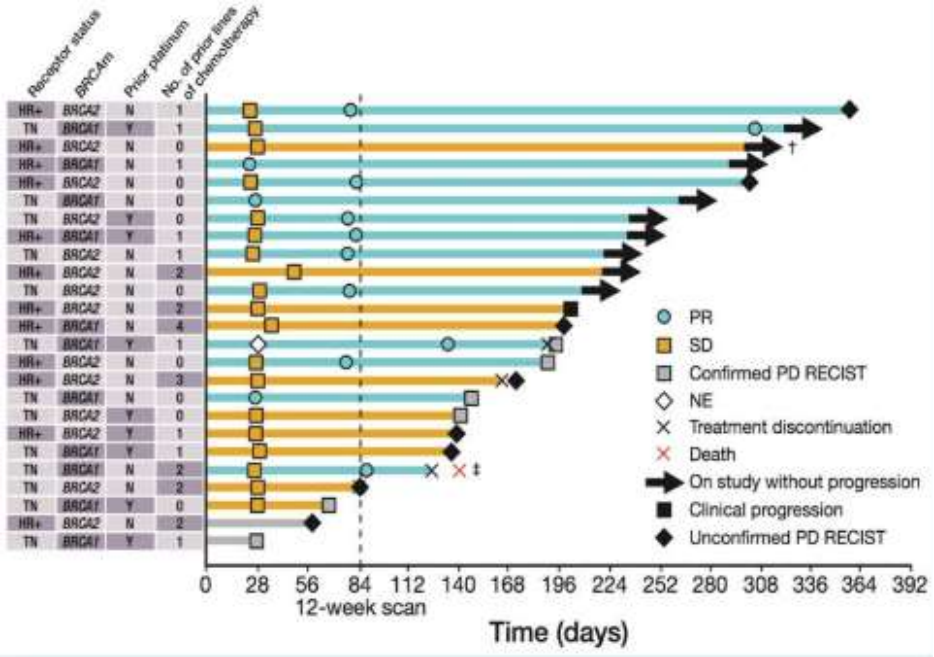
J Clin Oncol 35, 2017 (suppl; abstr 3052)

Mediola: Olaparibe + Durvalumabe



Domcheck et al, SABCS 2017

Mediola: Olaparibe + Durvalumabe



Best Response by Line of Chemotherapy				
Response	1L	2L	3L	4L
CR	0	0	0	0
PR	6	6	1	0
SD	2	2	2	2
PD	1	1	2	0
Total #	9	9	5	2
ORR	6/9=67%	6/9=67%	1/5=20%	0/2=0%

12/25 (48%) com controle de doença aos 7 meses
Resposta independente do status de RH e tipo de mutação de BRCA

Domcheck et al, SABCS 2017

TOPACIO Phase 2 Design

Objective: Evaluate niraparib and anti-PD-1 combination therapy in metastatic TNBC patients

Phase 2

Recommended Phase 2 Dose
Niraparib 200 mg orally daily + Pembrolizumab 200 mg IV every 21 days (21 day cycle)

Endpoint Assessment

Primary Endpoint	**Objective response Rate (ORR) by RECIST 1.1**
Secondary Endpoint	**Progression-free survival (PFS) Duration of Response (DOR)**

Statistical Plan

Hypothesis	**Null: ORR ≤ 15%**
Power to reject null with N=48 patients (alpha = 10%, two-sided	**82% - assuming true ORR = 30% 94% - assuming true ORR = 35%**

*ER and PR < 1% per ASCO/CAP guidelines
#Prior amendment up to 3 prior lines of cytotoxic therapy for advanced disease
**Prior amendment had no restriction on platinum for inclusion or exclusion criteria

Key Inclusion criteria

- TNBC (ER-negative, PR-negative, and HER-2 negative)*
- Disease recurrence or progression following neoadjuvant/adjuvante therapy
- ≤ 2 prior lines of cytotoxic treatment for advanced disease (not including neoadjuvant/adjuvante therapies or targeted smaill molecules)#
- Prior platinum allowed in metastatic setting if no progression documented while on or within 8 weeks of last platinum**

Key Exclusion Criteria

- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or PARP inhibitor

Response Assessments

- Scans every 9 weeks

Vinayak et al, ASCO 2018

Best Overall Response and Objective Response Rate (ORR)

Response	Response Rate, n (%) Efficacy Evaluable (N = 46)*
Complete Response (CR)	3 (7%)
Partial response (PR)**	10 (22%)
Stable Disease (SD)	10 (22%)
Progressive Disease (PD)	23 (50%)
ORR (CR + PR)	13 (28%)
DCR (CR + PR + SD)	23 (50%)

9 Patients still on treatment

- 2 Cr
- 6 PR
- 1 SD

*9 pts did nothave evaluable post-baseline tumor assessments and were not included in the evaluable population (6 pts discontinued due to AE; 1 due to clinical progression and 2 for other reasons).
** Responses include both confirmed and unconfirmed; DCR: Disease Control Rate; Data as of April 02, 2018

Vinayak et al, ASCO 2018

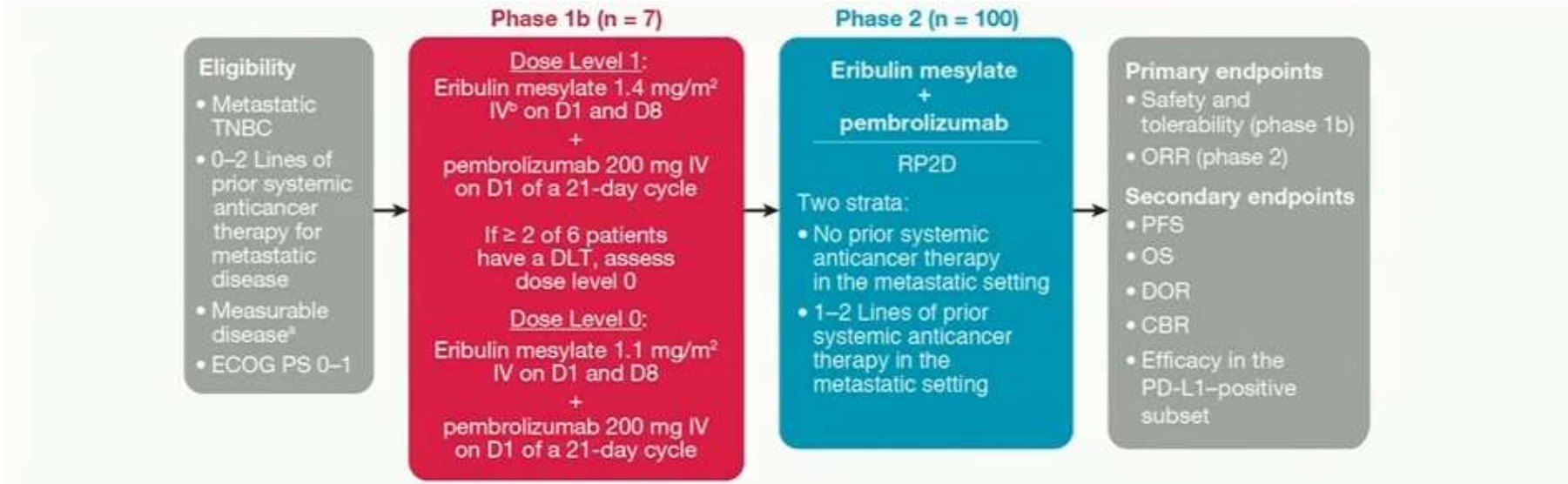
Biomarker-Selected Populations

Efficacy Evaluable Patients	ORR (CR + PR)	DCR (CR + PR + SD)
tBRCAmut patients (n = 15)	9 (60%)	12 (80%)
HRRmut + tBRCAmut (n = 20)	11 (55%)	16 (80%)
PD-L1 positive patients (n = 25)	9 (36%)	13 (52%)

Overall response Rate in all evaluable (biomarker-unselected) patients (N = 46); ORR 28%, DCR = 50%

Vinayak et al, ASCO 2018

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.

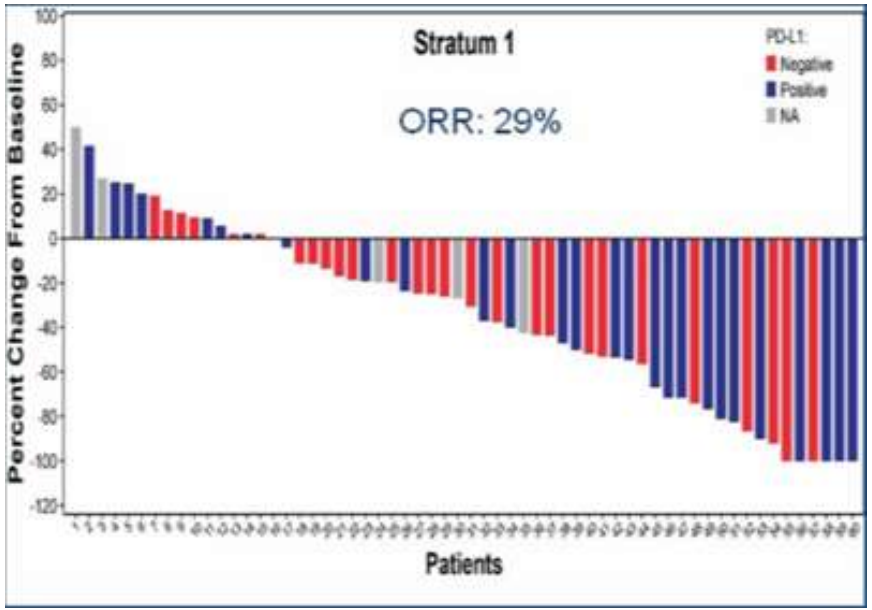
[a]≥ 1 Lesion of ≥ 10 mm in long-axis diameter (nonlymph node) or ≥ 15 mm in short-axis diameter (lymph node) serially measurable by RECIST v1.1. Lesions that have had radiotherapy must show subsequent radiographic evidence of increased size to be deemed a target lesion.

[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.

Tolaney S, et al. SABCS 2017

Eribulina mais Pembrolizumabe (n=107)



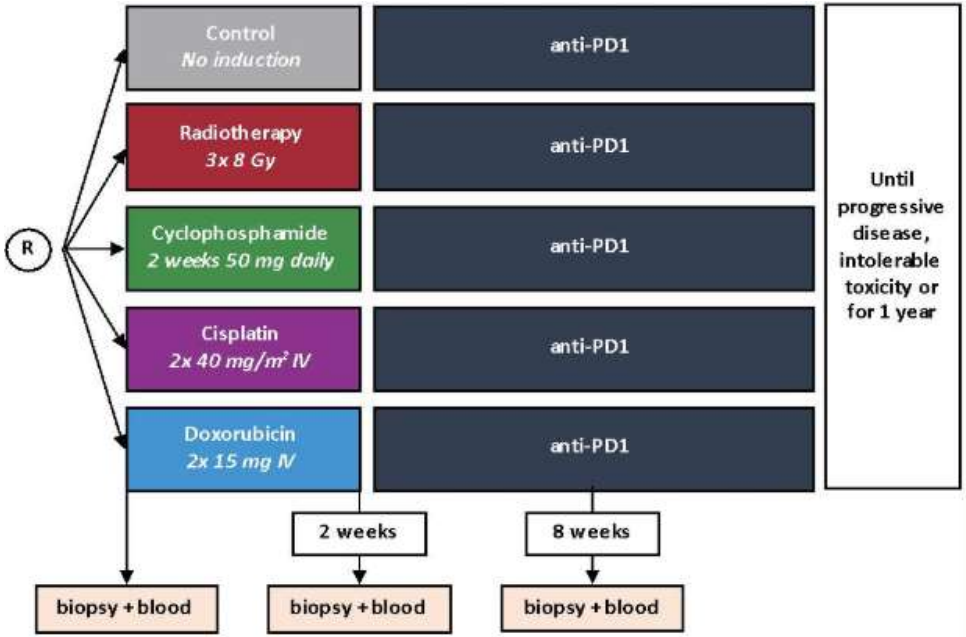
	Evaluable Analysis Set		
	Stratum 1 (n = 65)	Stratum 2 (n = 41)	Total (n = 106)
Objective Response Rate (CR + PR), n (%) (95% CI)	19 (29.2) (18.6–41.8)	9 (22.0) (10.6–37.6)	28 (26.4) (18.3–35.9)
CR, n (%)	1 (1.5)	2 (4.9)	3 (2.8)
PR, n (%)	18 (27.7)	7 (17.1)	25 (23.6)
CBR (CR + PR + durable SD [duration ≥ 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)

PFS mediana: 4,2 meses, SG 17,7 meses

Tolaney S, et al. SABCS 2017

TONIC Trial:Tratamento de indução + Nivolumabe (N=66)

Design stage I



- Non-comparative design
- 5 cohorts with n=10 with paired biopsies
- **Endpoits1** ORR, CBR, safety, PFS, OS
- **Translational endpoints:** increase in signatures associated with anti-PD1 response, T cells

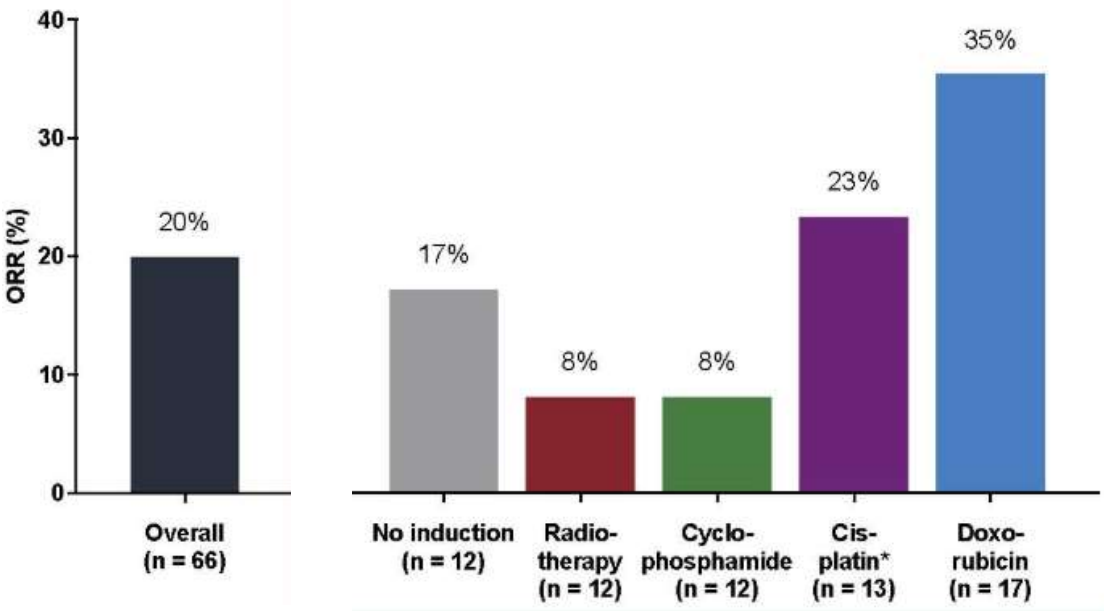
Simon's 2-stage design

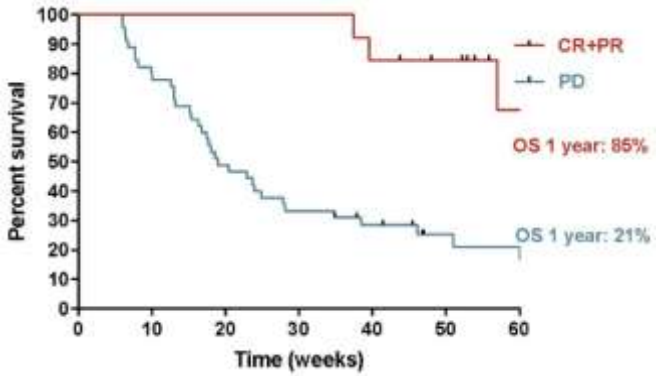
- Early discontinuation of cohort with n=10 if ≤ 30% of the patients responds3
- **'pick the winner'** expand cohort to stage II, based on clinical and translational endpoints

nivolumab 3mg/kg, every 2 weeks, for 1 year or until progression (RECIST) or until intolerable toxicity.
1. measured from randomization start nivolumab, according RECIST and RECIST (seymor et al. Lancet Oncol 2017), 3. minimax design, alpha 0.15, power 0.85, p = 0.3, r1/01 = 3/10, r/n 11/27

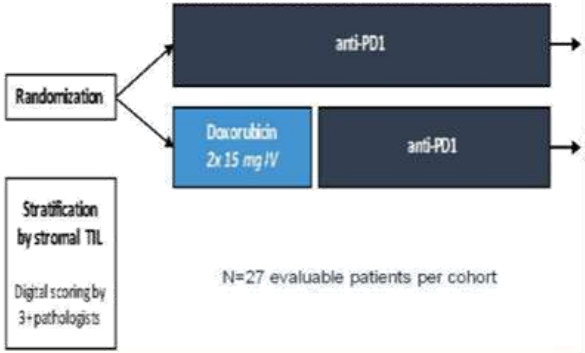
Kok et al, ASCO 2018

TONIC Trial:Tratamento de indução + Nivolumabe (N=66)



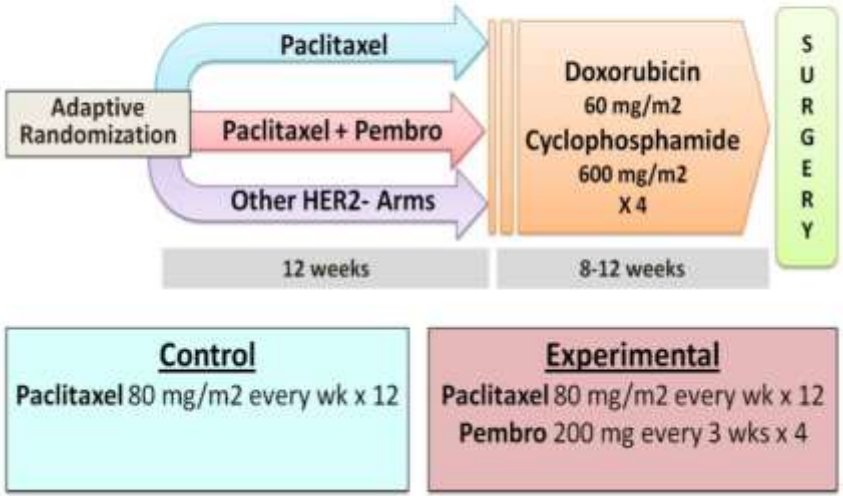


TONIC Stage II



Kok et al, ASCO 2018

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

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.

Nanda et al, ASCO 2017

Study Design: PANACEA
IBCSG 45-13/BIG 4-13/KEYNOTE-014

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

PD-L1 +

Phase Ib
Pembrolizumab 2mg/kg and 10mg/kg IV + trastuzumab Q3W

Phase II
Pembrolizumab 200mg IV + trastuzumab Q3W

PD-L1 -

Phase II
Pembrolizumab 200mg IV + trastuzumab Q3W

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

Loi et al. SABCS 2017

Enrollment and Disposition

Median follow-up: 13.6 months

146 patients screened
68 (53.5%) PD-L1 - positive
Feb. 2015- April 2017
11 sites, 5 countries

Ineligible as HER2 negative (10.6%)

Enrolled 58 (39.7% of screened)

- 6 Phase Ib PD-L1 positive
- 40 Phase II PD-L1 positive
  - 41% ER pos
  - 59% ER neg
- 12 PD-L1 negative
  - 50% ER pos
  - 50% ER neg

- On treatment: 3 (5%)
- Discontinued
  - PD: 46 (84%)
  - Death from PD: 1 (2%)
  - AE: 6 (10%)
  - Withdrew consent: 1 (2%)
  - Patient deterioration: 1 (2%)

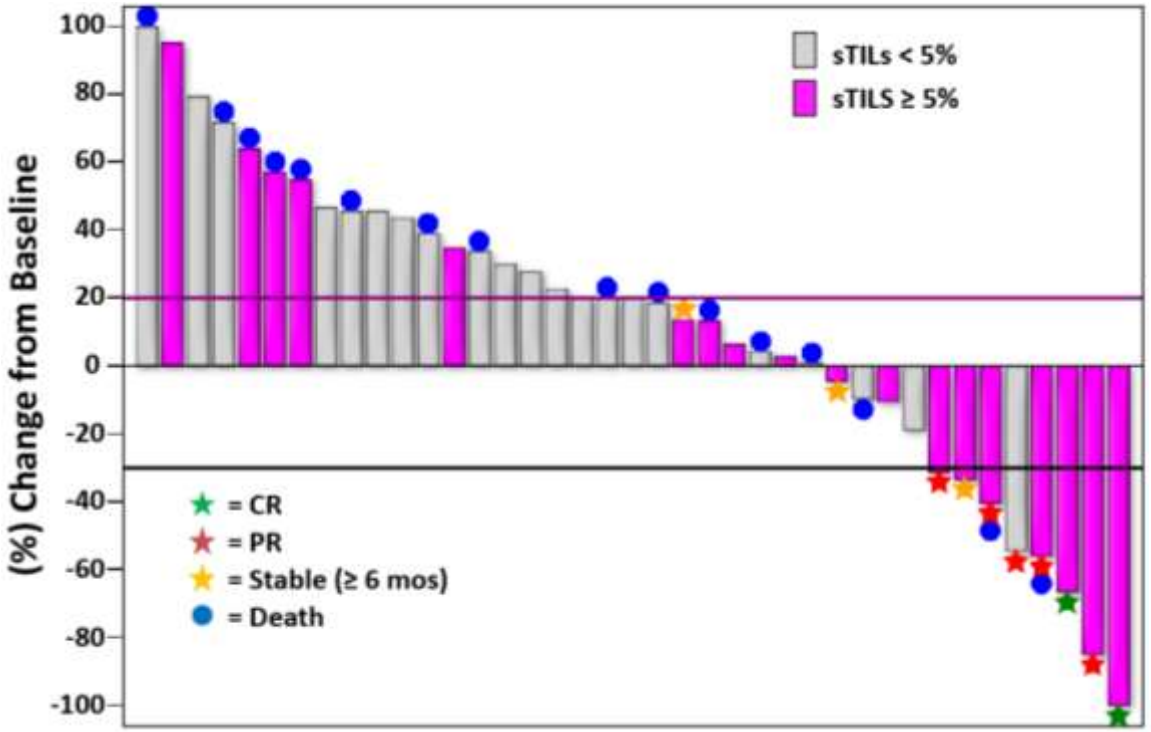
Best Overall Response (RECIST 1.1)

	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]** [1]DCR: CR, PR, or SD ≥ 6 months

Overall PD-L1 + cohort **ORR 15.2% [7-27]** **DCR 24% [14-36]** [1]DCR: CR, PR, or SD ≥ 6 months

sTILs ≥ 5% as Potential Predictive Marker: PD-L1 Positive Cohort



sTILs ≥ 5%: 41% of PD-L1 positive cohort

For sTILs ≥ 5% v. sTILs < 5%

ORR

✓ **39% vs. 5%**

- Sensitivity: 85.7%;
- Specificity: 61.8%
- NPV: 95.5%; PPV: 31.6%

DCR

• **47% vs. 5%**

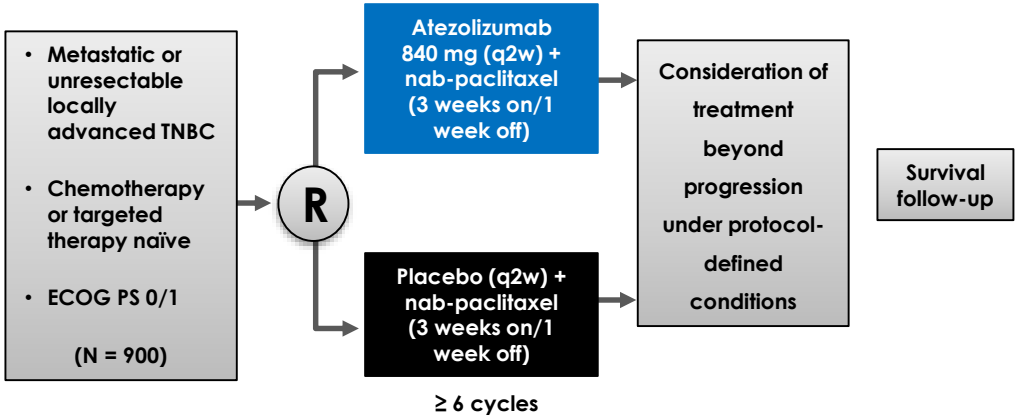
- Sensitivity: 90.0%;
- Specificity: 67.7%
- NPV: 95.5%; PPV: 47.4%

Media Release

Phase III IMpassion130 study showed Roche's Tecentriq plus Abraxane significantly reduced the risk of disease worsening or death in people with metastatic triple negative breast cancer

- **First Phase III immunotherapy study to demonstrate a statistically significant improvement in progression-free survival (PFS) in the intention-to-treat (ITT) and PD-L1 positive first-line metastatic triple negative breast cancer (TNBC) populations**
- **Encouraging overall survival (OS) benefit for PD-L1 positive population at interim analysis**
- **Data will be submitted to health authorities globally, including the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA)**

Basel, 2 July 2018 - Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that the Phase III IMpassion130 study met its co-primary endpoint of progression-free survival (PFS). Results demonstrated that the combination of Tecentriq® (atezolizumab) plus chemotherapy (Abraxane® [albumin-bound paclitaxel; *nab*-paclitaxel]), as an initial (first-line) treatment, significantly reduced the risk of disease worsening or death (PFS) in the intention-to treat and PD-L1 positive population with metastatic or unresectable locally advanced triple negative breast cancer (TNBC). Overall survival (OS) is encouraging in the PD-L1 positive population at this interim analysis, and follow up will continue until the next planned analysis.



Co-primary endpoints: PFS and OS

- **First Phase III immunotherapy study to demonstrate a statistically significant improvement in progression-free survival (PFS) in the intention-to-treat (ITT) and PD-L1 positive first-line metastatic triple negative breast cancer (TNBC) populations**
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Conclusão

Conclusão

- Checkpoint Inhibitor agentes únicos são geralmente bem tolerados.
- Taxa de resposta no subtipo triplo negativo com agente único variando entre 4,7 e 26%.
- Biomarcadores ideais ainda a serem definidos.
- Melhores respostas com administração precoce.

Conclusão

- Combinações com imunoterapia também em geral bem toleradas.
- Estudos com associação de imunoterapia + iPARP e imunoterapia + quimioterapia com resultados promissores.
- Muitos outros estudos incluindo neoadjuvância e adjuvância em andamento.

Conclusão

Estudo de fase 3 positivo:

Phase III IMpassion130 study showed Roche's Tecentriq plus Abraxane significantly reduced the risk of disease worsening or death in people with metastatic triple negative breast cancer

Aguardamos maiores informações ainda esse ano!

IV Simpósio Internacional de
IMUNO-ONCOLOGIA
O FUTURO DA ONCOLOGIA
27 E 28 DE JULHO – HOTEL PULLMAN VILA OLÍMPIA

Obrigada