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40 YEAR ANNIVERSARY
SAN ANTONIO BREAST CANCER SYMPOSIUM®
Henry B. Gonzalez Convention Center, San Antonio, Texas, USA
2017 DEC. 5-9

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Beneficência Portuguesa de São Paulo

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Phase Ib/II Study Evaluating Safety and Efficacy of Pembrolizumab and Trastuzumab in Patients with Trastuzumab-Resistant HER2-positive Advanced Breast Cancer: Results from the PANACEA Study (IBCSG 45-13/BIG 4-13/KEYNOTE-014)

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On behalf of the International Breast Cancer Study Group and Breast International Group

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Objetivo Primário do estudo:

- ✓ **Fase Ib:** determinar dose recomendada de pembrolizumabe em combinação com dose padrão de trastuzumabe.

- ✓ **Fase II:** Avaliar eficácia e segurança dessa combinação em pacientes com câncer de mama irressecável ou metastático que **expressam PD-L1**, HER-2 positivos, que **progrediram durante tratamento prévio baseado em trastuzumabe**.

Objetivo Secundário do estudo:

- ✓Fase II: Avaliar eficácia dessa combinação em pacientes com câncer de mama irressecável ou metastático **PD-L1 negativos**, HER-2 positivos, que progrediram durante tratamento prévio baseado em trastuzumabe.

Objetivo Exploratório:

- ✓Avaliar resultados de eficácia de acordo com níveis de TILs.

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

Análises estatísticas:

Design PD-L1 Positive Cohorts

- Phase Ib (3+3 dose escalation)
- Phase II
  - Primary endpoint: Objective response rate (ORR) by RECIST 1.1
  - ***Simon two-stage design (N=40): 85% power to compare ORR of 7% vs. 22% with one-sided, α=0.05; required ≥ 6 objective responses to reject null hypothesis***
  - Secondary endpoints
    - Progression-free survival (PFS), Disease control rate (DCR), Duration of response (DoR), Duration of disease control (DDC), Overall survival (OS)

Design PD-L1 Negative Cohort

- Single-stage design (N=15) to compare ORR of 1% vs. 20%
- Not worthy of further investigation if no objective responses observed

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%)

Baseline Characteristics

Characteristic N (%)	Phase ib PD-L1 positive; n = 6	Phase II PD-L1 positive; n = 40	Phase II PD-L1 negative; n = 12	Overall n = 58
Age yrs. median (range)	49 (38 - 57)	49 (28 - 72)	56.5 (43 - 61)	50.5 (28 - 72)
ER				
Negative	4 (66%)	23 (57.5%)	6 (50%)	33 (56.9%)
Positive (≥ 1%)	2 (33%)	17 (42.5%)	6 (50%)	25 (43.1%)
Prior trastuzumab-containing therapy	6 (100%)	40 (100%)	12 (100%)	58 (100%)
Additional anti-HER2 therapy				
No	1 (16.7%)	6 (15%)	0 (0%)	7 (12.1%)
Yes	5 (83.3%)	34 (85%)	12 (100%)	**51 (87.9%)**
T-DM1	4	29	9	42
Pertuzumab	3	10	4	17
Other	1	17	8	26
Prior chemotherapy (Anth/Taxane)	6 (100%)	40 (100%)	12 (100%)	58 (100%)
Mediam time from Dx met disease to enrolment; months (range)	15.5 (6 - 83.6)	40.8 (1.1 - 111)	71.5 (9.9 - 179.1)	40 (1.1 - 179.1)

Most Common AEs[1] at Least Possible Related; N = 58)

Adverse Event	Pts N (%)	G1	G2	G3	G4
Fatigue	12 (21%)	7	5		
Diarrhea	8 (14%)	6	2		
Arthalgia	8 (14%)	6	2		
Headache	6 (10%)	4	2		
Nausea	6 (10%)	6			
Dyspnoea	5 (9%)	2	1	1	1
Myalgia	5 (9%)	5			

No cardiac events reported
No DLTs in Phase Ib

Immune-related AEs

- ✓ Any grade, n = 11 (19.0%)
- ✓ Grade ≥ 3, n = 6 (10.3%)
- ✓ Led to discontinuation, n = 4 (6.9%)

Most common Immune AEs

- ✓ Any grade thyroid, n = 4 (6.9%)
- ✓ Pneumonitis
  - All grades, n = 4 (6.9%)
  - Grades ≥ 3, n = 2 (3.4%)

[1]Grade is reported as worst grade for patiente

Best Overall Response (RECIST 1.1)

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

[1]DCR: CR, PR, or SD ≥ 6 months

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

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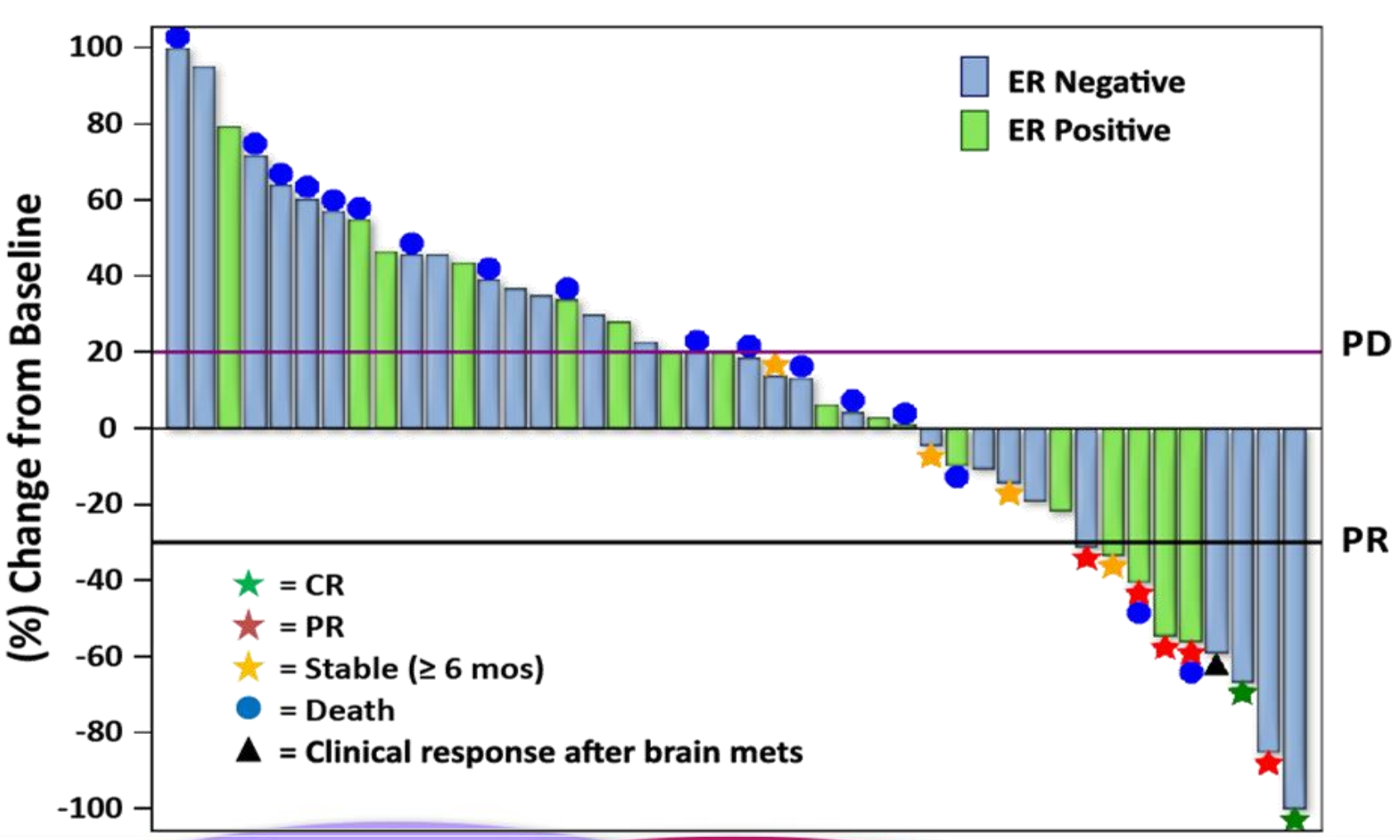
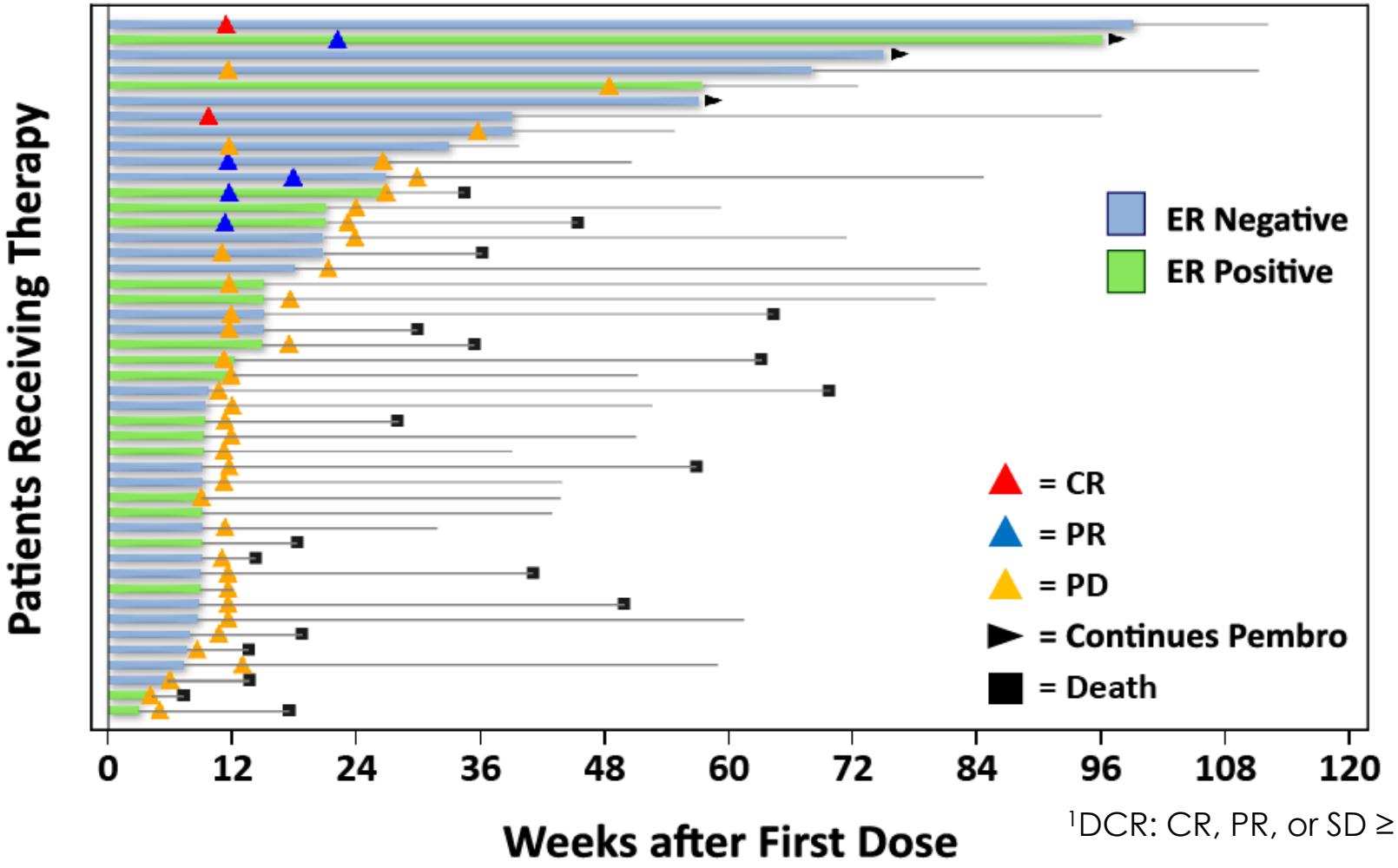
Maximum Change from Baseline in Target Lesions: PD-L1 Positive Cohort (N=44)



N=44 as excludes 2 patients without follow-up measurements of target lesions

▲ brain met not detected at screening in a patient with PR

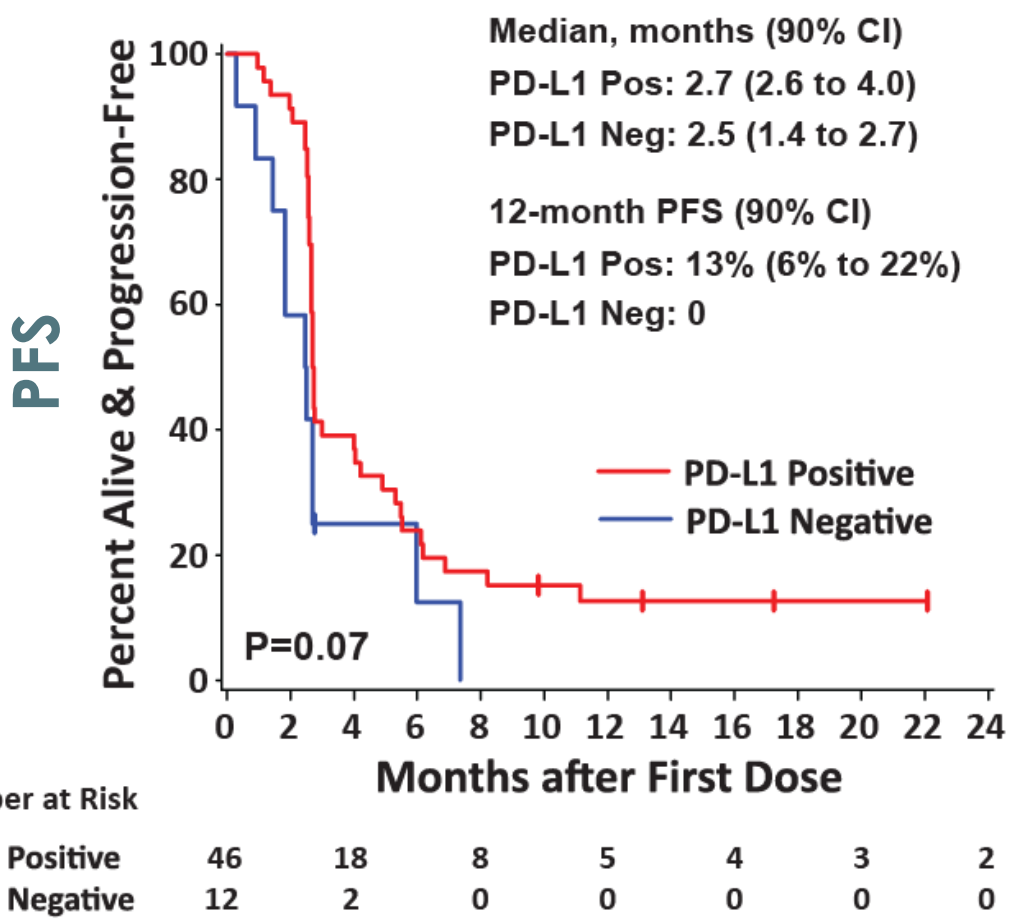
Disease Control: PD-L1 Positive Cohorts

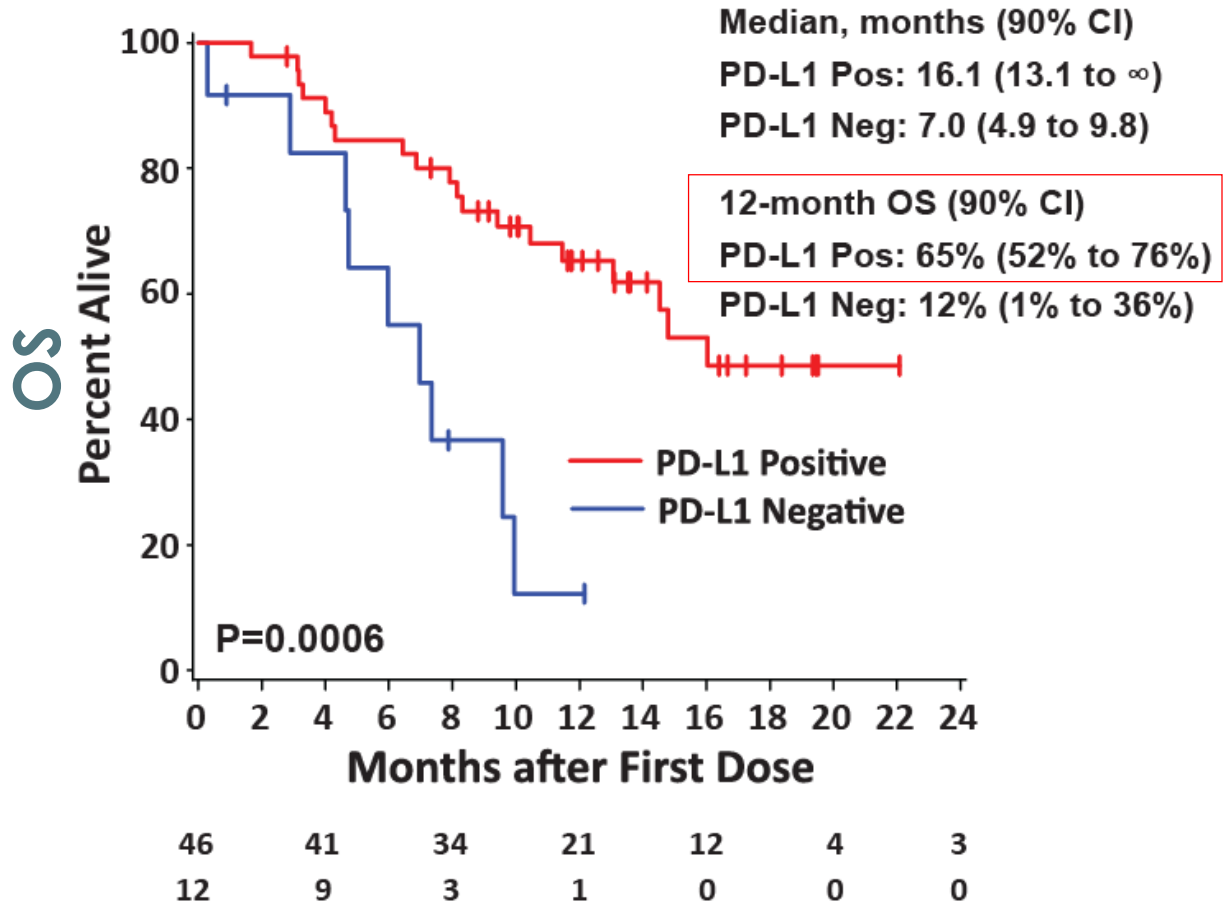


- ✓ **Median duration of disease control[1]: 11.1 months (90% CI: 6.2 -∞)**
- ✓ Median DoR[2]: 3.5 months (90% CI: 2.7 - ∞)
- ✓ Mean DoR[2]: 10 months (90% CI: 2.7-23.1)
- ✓ **Five patients (10.8%) continue with no progression at time of reporting**

[1]DCR: CR, PR, or SD ≥ 6 months, [2] timing from first restaging at 12 weeks

PFS and OS by PD-L1 Status





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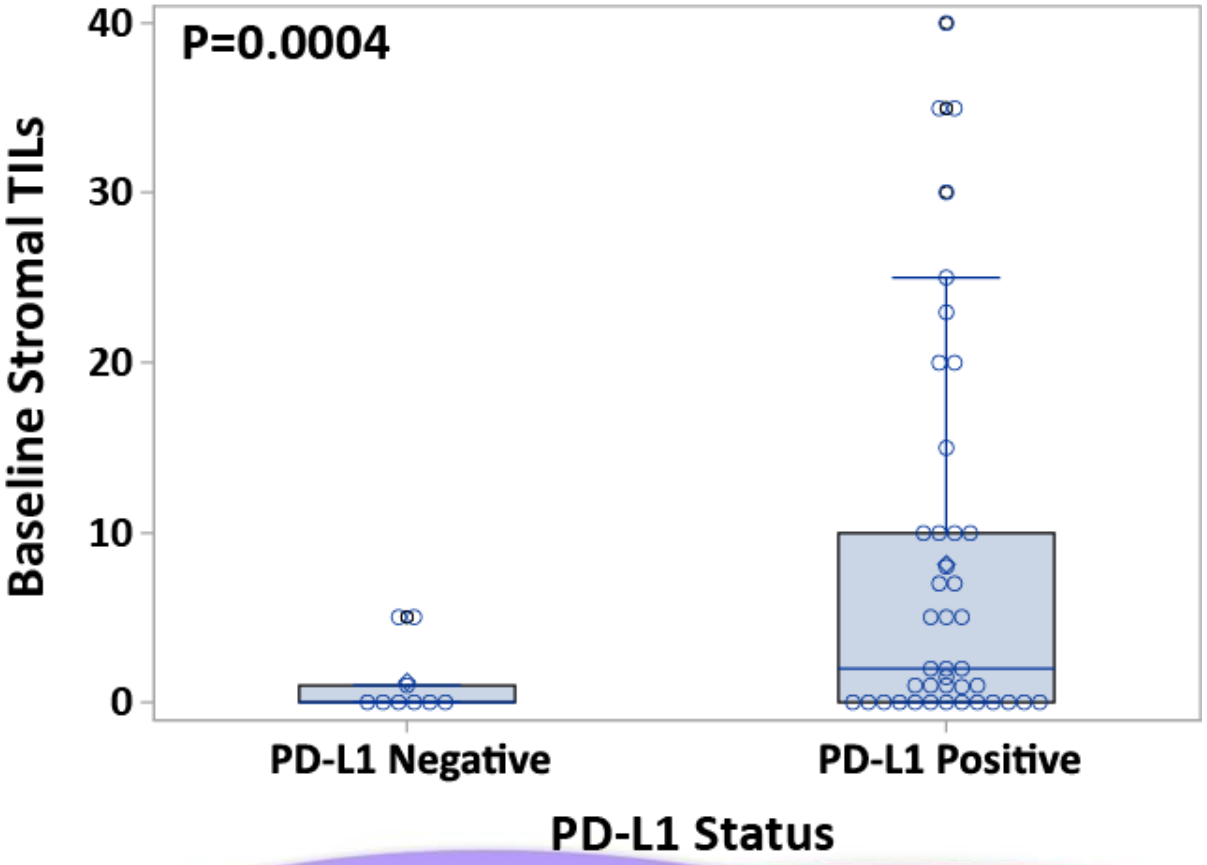
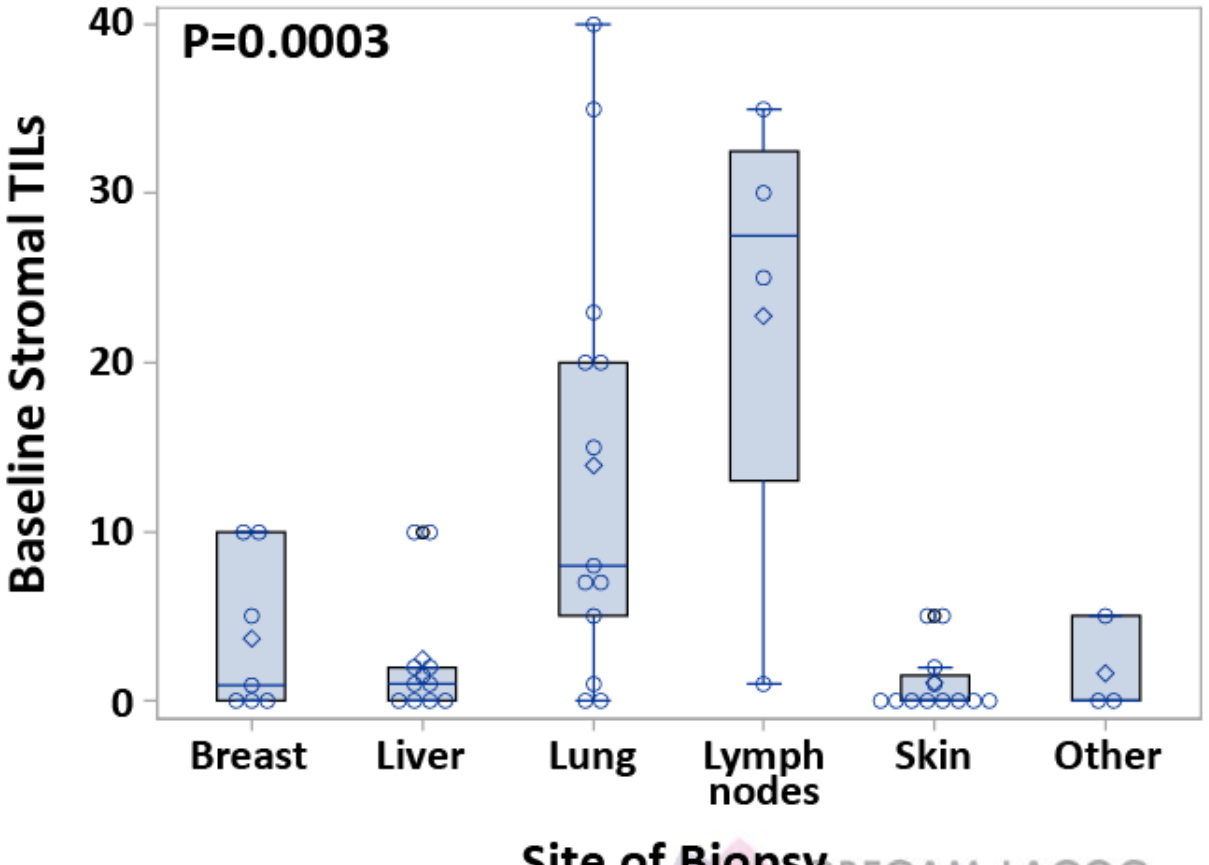
sTILs by PD-L1 Status and Site of Biopsy

Stromal TILs Median 1%, Mean 4.8%, IQR 0-5%, all < 1 yr old biopsies from metastatic lesions

Baseline sTILs by PD-L1 status

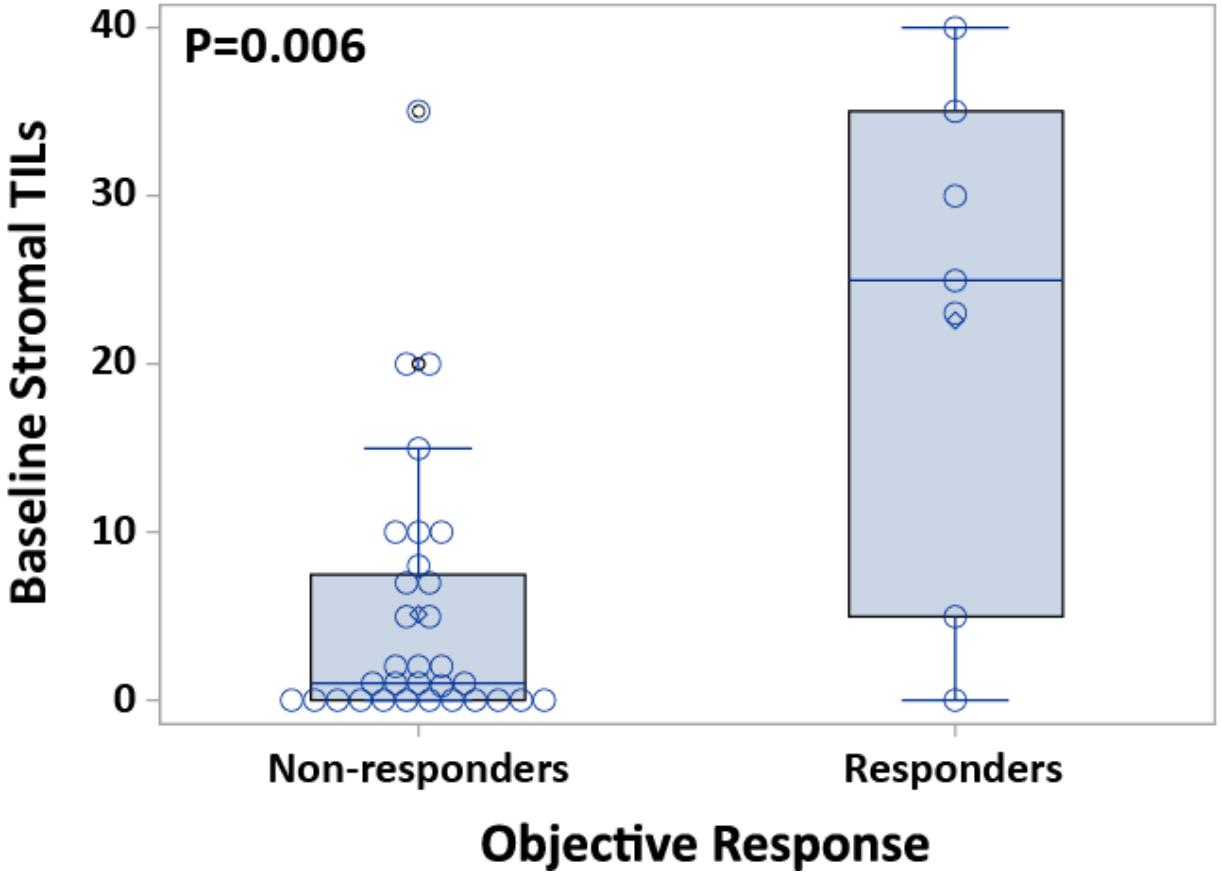


Baseline sTILs by site of biopsy

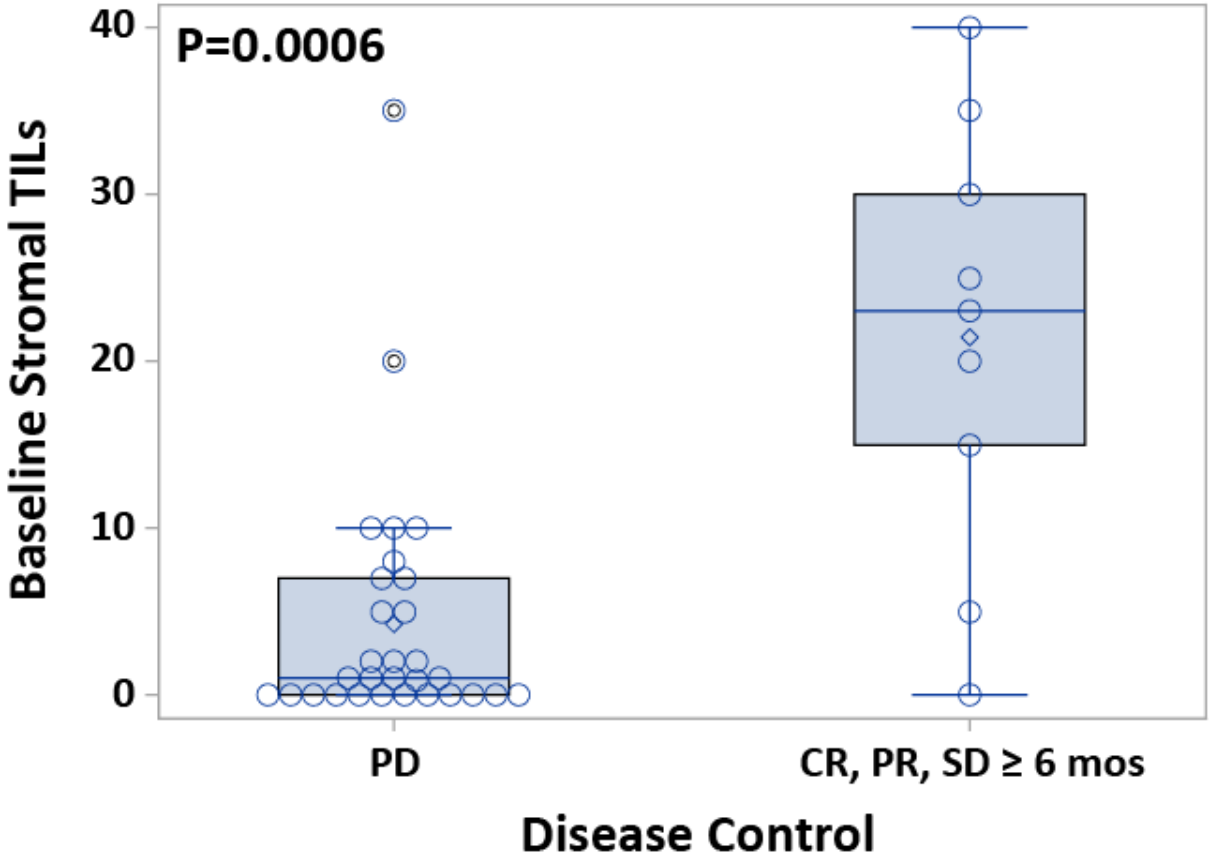


Higher sTILs Associated with Better Response and Disease Control: PD-L1 Positive Cohorts

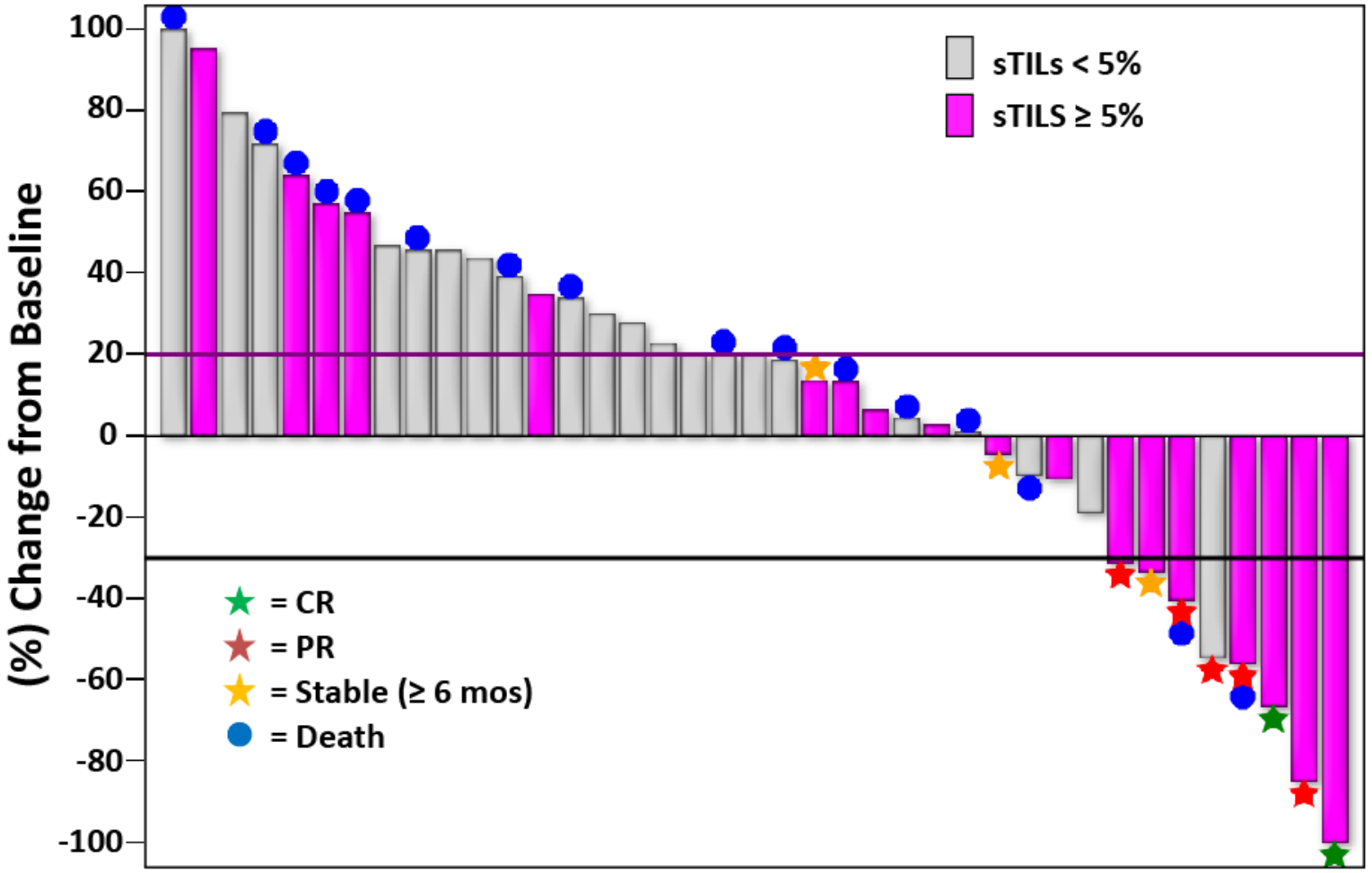
Baseline sTILs and ORR



Baseline sTILs and DCR



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%

Conclusão

- ✓ Estudo atingiu seu objetivo primário no grupo de pacientes PD-L1 positivo (Taxa de resposta 15%, Taxa de controle de doença 25%).
- ✓ Não houve respostas no grupo PD-L1 negativo.
- ✓ Níveis de linfócitos T infiltrantes no estroma ≥ a 5% associado a maior resposta (Taxa de resposta 39%, Taxa de controle de doença 47%).

Conclusão

- ✓ Controle de doença duradouro para pacientes respondedores com a combinação.
- ✓ Doença HER-2 positiva metastática previamente politratada é pouco imunogênica, a maioria das pacientes com baixos TILs nas lesões metastáticas.

Obrigada

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