

Avanços no tratamento com imunoterapia do câncer de mama triplo negativo metastático

Romualdo Barroso-Sousa

Oncologista Clínico, Head de Pesquisa em Oncologia e
Líder Nacional de Câncer de Mama - DASA Oncologia



Disclosures

R.BS reported receiving speaker bureau fees from AstraZeneca, Daichi-Sankyo, Eli Lilly, Pfizer, Novartis, Merck, and Roche. He has also served as a consultant/advisor for AstraZeneca, Daichi-Sankyo, Eli Lilly, Libbs, Pfizer, Roche, Merck and has received support for attending medical conferences from Astrazeneca, Roche, Eli Lilly, Daichi-Sankyo, and Merck.

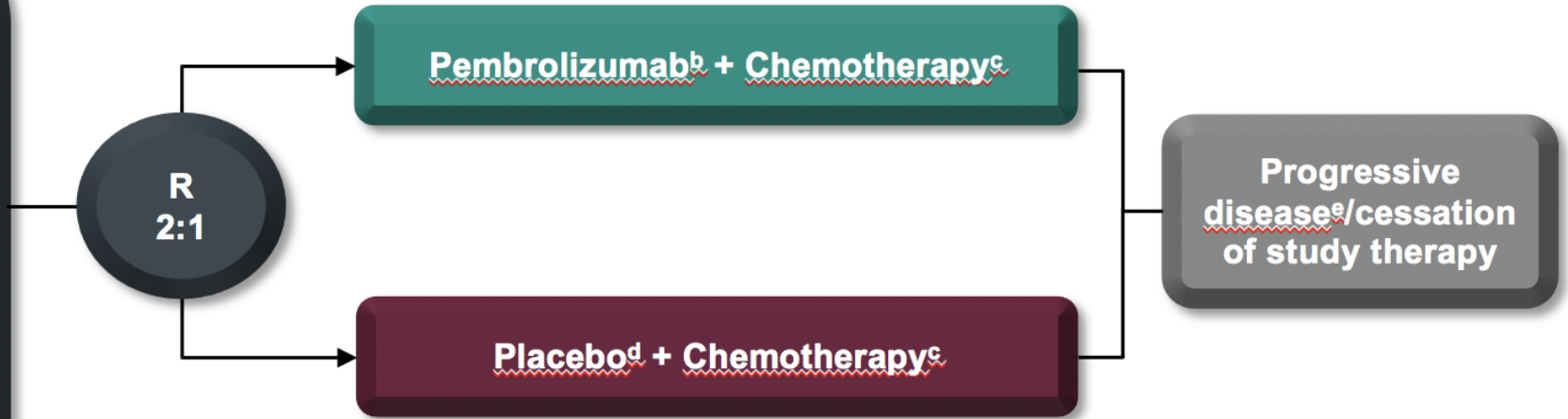
IMPassion130, IMPassion131 and KN-355

| | IMPASSION130 | IMPASSION131 | KEYNOTE-355 |
|---------------------------------------|---|--|---|
| Population | De novo IV or metastatic recurrent disease > 12 m from the end of CT | De novo IV or metastatic recurrent disease > 12 m from the end of CT | De novo IV or metastatic recurrent disease > 6 m from the end of CT |
| CT backbone | Nab-paclitaxel | Paclitaxel | Paclitaxel, Nab-paclitaxel ou Carboplatin + Gemzar |
| PD-L1 clone/IO | SP142 Ventana (Atezo) | SP142 Ventana (Atezo) | 22C3 DAKO (Pembro) |
| Progression-free survival (HR) | 0.63 PD-L1+ immune cells | 0.82 (not significant) PD-L1+ immune cells | 0.65 CPS \geq 10 |
| Overall survival (HR) | Clinically significant $\Delta = 7$ months (not statistically significant) | No benefit | 0.73 CPS \geq 10 |

KEYNOTE-355 Study Design (NCT02819518)

Key Eligibility Criteria

- Age ≥ 18 years
- Central determination of TNBC and PD-L1 expression^a
- Previously untreated locally recurrent inoperable or metastatic TNBC
- De novo metastasis or completion of treatment with curative intent ≥ 6 months prior to first disease recurrence
- ECOG performance status 0 or 1
- Life expectancy ≥ 12 weeks from randomization
- Adequate organ function
- No systemic steroids
- No active CNS metastases
- No active autoimmune disease



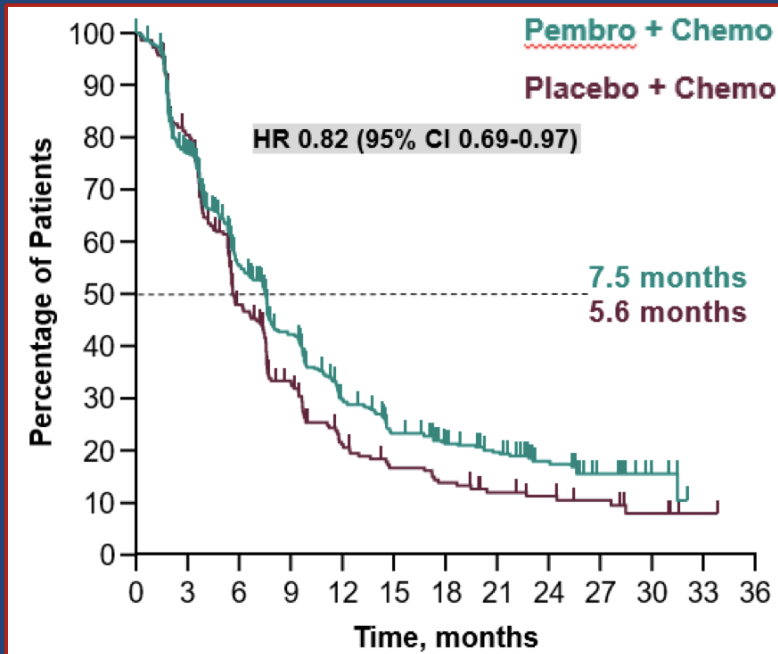
Stratification Factors:

- Chemotherapy on study (taxane or gemcitabine-carboplatin)
- PD-L1 tumor expression (CPS ≥ 1 or CPS < 1)
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes or no)

^aBased on a newly obtained tumor sample from a locally recurrent inoperable or metastatic site (an archival tumour sample was used with permission from the study sponsor if a new tumor biopsy was not obtainable). ^bPembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W). ^cChemotherapy dosing regimens are as follows: Nab-paclitaxel 100 mg/m² IV on days 1, 8, and 15 every 28 days; Paclitaxel 90 mg/m² IV on days 1, 8, and 15 every 28 days; Gemcitabine 1000 mg/m²/carboplatin AUC 2 on days 1 and 8 every 21 days. ^dNormal saline. ^eTreatment may be continued until confirmation of progressive disease.

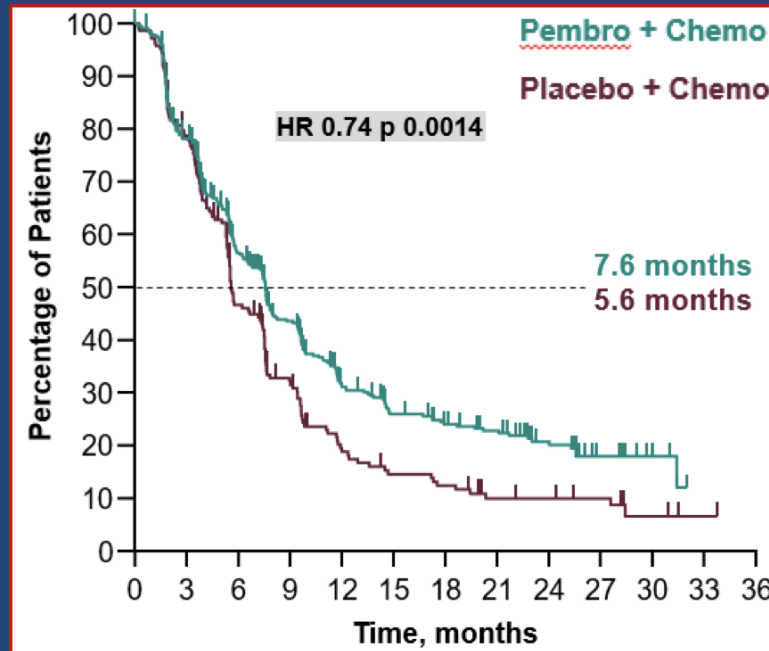
KEYNOTE 355: Progression-free survival

ITT



Statistical significance was not tested due to the prespecified hierarchical testing strategy

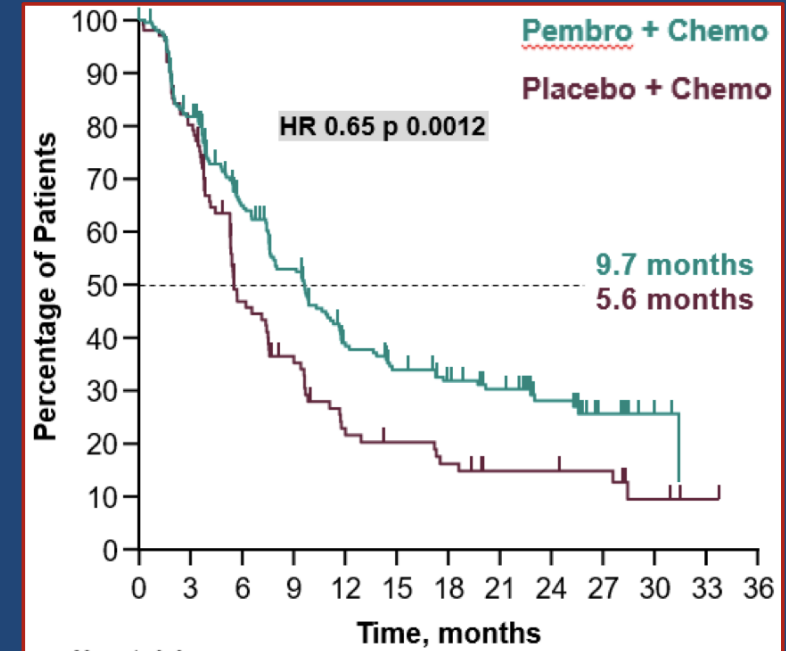
PD-L1 CPS ≥ 1



Prespecified *P* value boundary of 0.00111 not met

75% of pts

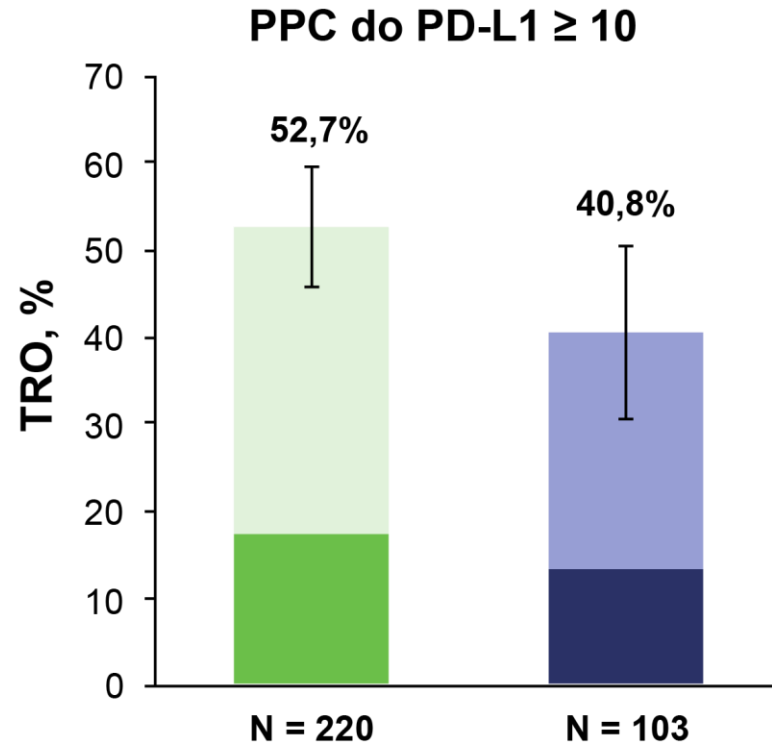
PD-L1 CPS ≥ 10



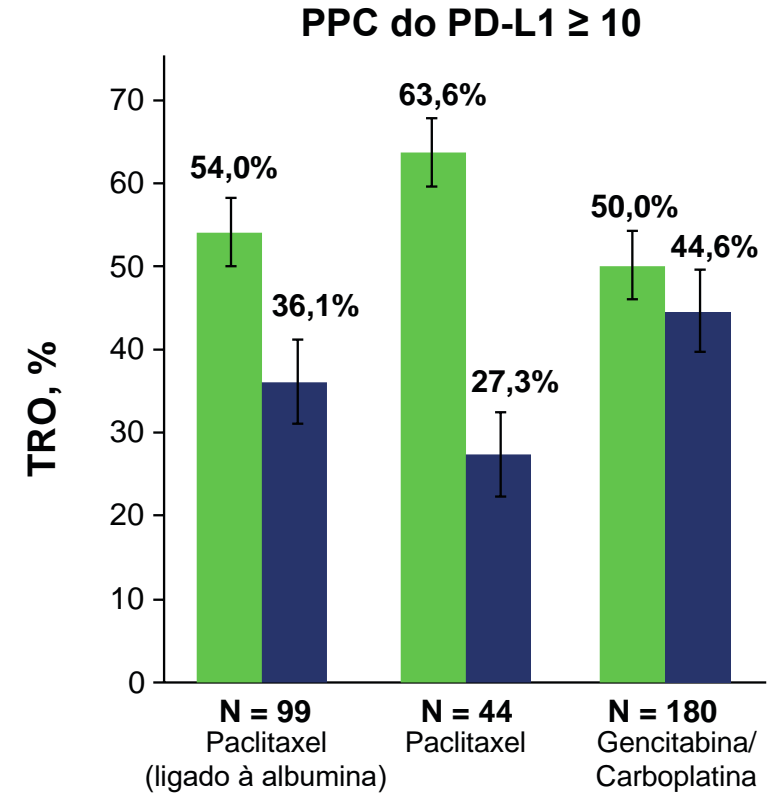
Prespecified *P* value boundary of 0.00411 met

38% of pts

Taxa de resposta objetiva



Data do corte de dados: 15 de junho de 2021



Pembrolizumabe + quimioterapia ■ **Placebo + quimioterapia** ■

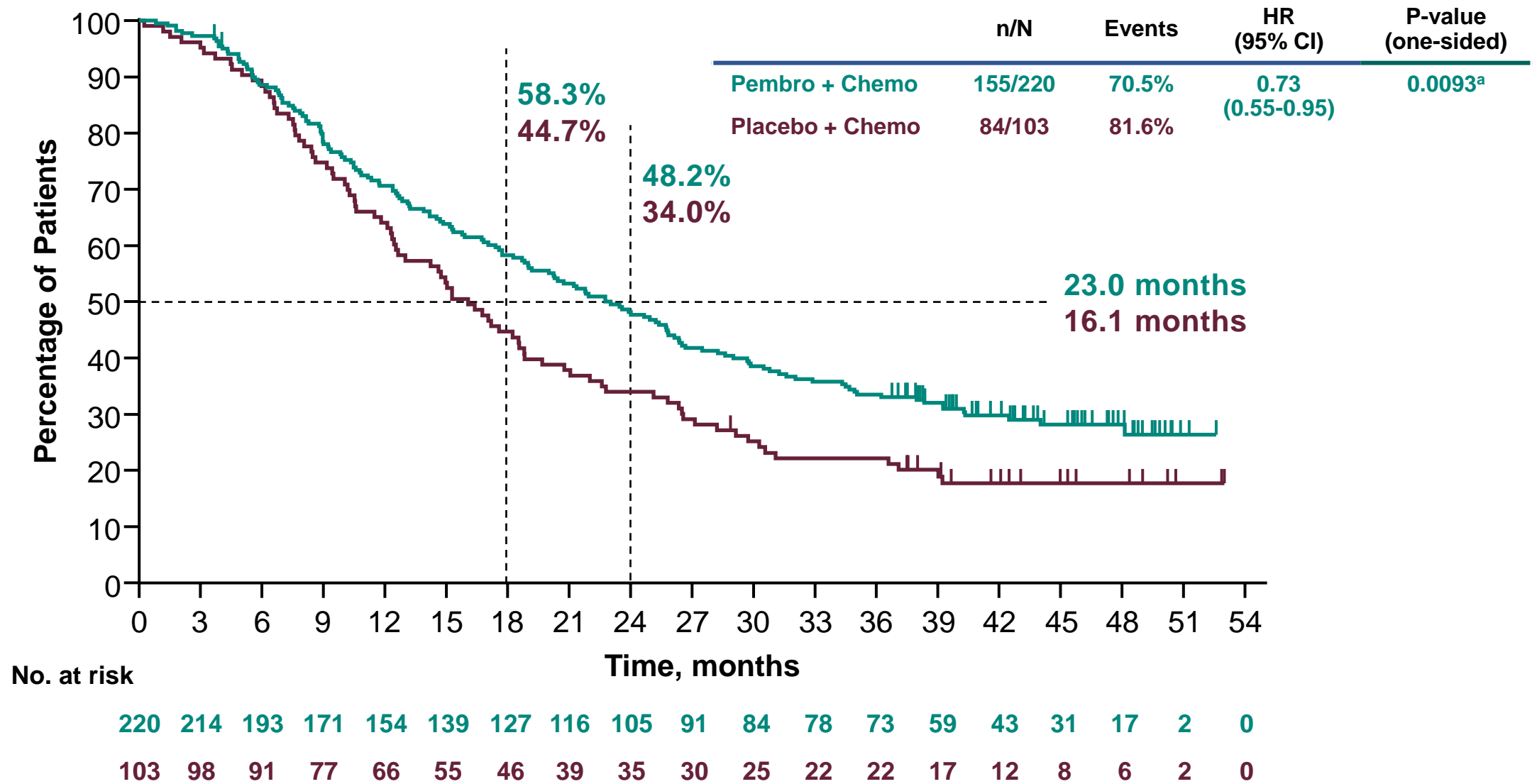
TCD: taxa de controle da doença; TRO: taxa de resposta objetiva.

Adaptado de Hugo R et al.^{1,2}

1. Rugo HS, Schmid P, Cescon DW, et al. Additional efficacy endpoints from the phase 3 KEYNOTE-355 study of pembrolizumab plus chemotherapy vs placebo plus chemotherapy as first-line therapy for locally recurrent inoperable or metastatic triple-negative breast cancer. Abstract presented at: the 2020 San Antonio Breast Cancer Symposium Virtual Meeting; December 8-11, 2020. Abstract GS3-01.

2. Hugo RS, Cortes J, Cescon DW, et al. KEYNOTE-355: Final results from a randomized, double-blind phase III study of first-line pembrolizumab + chemotherapy vs placebo + chemotherapy for metastatic TNBC. *Ann Oncol.* 2021;32(suppl_5): S1283-S1346.

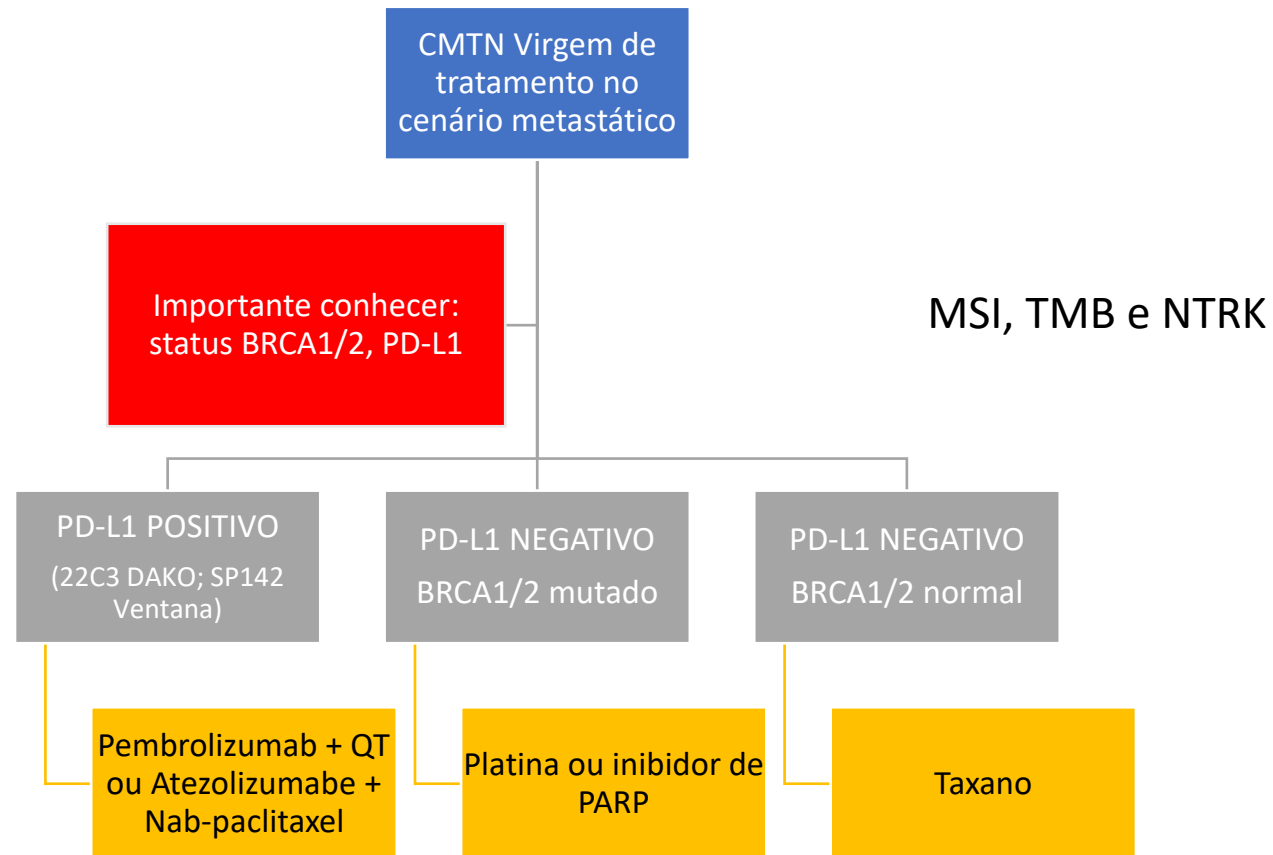
Overall Survival: PD-L1 CPS ≥ 10



^aPrespecified *P* value boundary of 0.0113 met.

Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff: June 15, 2021.

Algoritmo padrão de tratamento do CMTN metastático



2a linha e após: Sacituzumab Govitecano ou Trastuzumabe-deruxtecano (se HER2 low)
3a linha e após: ou quimioterapia

Como melhorar esses desfechos ou aumentar o número de pacientes beneficiados?

- Combinação com outras imunoterapias?
- Combinação com ADCs?
- Melhor seleção dos pacientes?

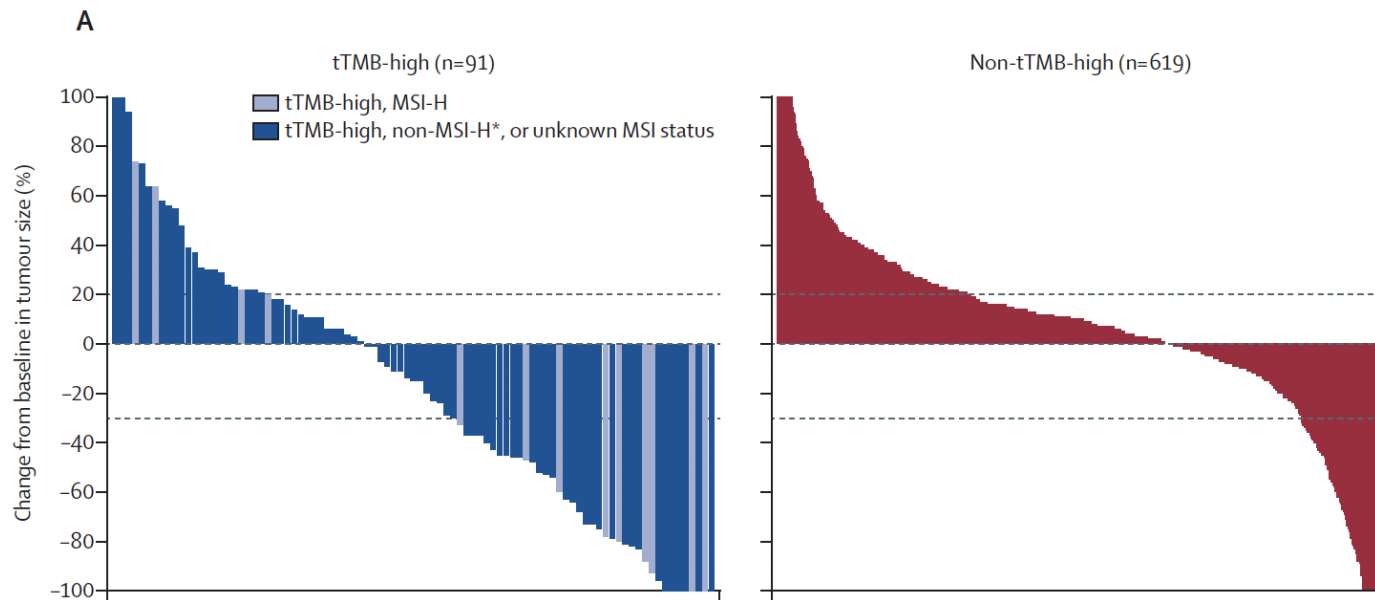
FDA approval of Pembrolizumab of TMB-H tumors

Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study



Aurélien Marabelle, Marwan Fakih, Juanita Lopez, Manisha Shah, Ronnie Shapira-Frommer, Kazuhiko Nakagawa, Hyun Cheol Chung, Hedy L Kindler, Jose A Lopez-Martin, Wilson H Miller Jr, Antoine Italiano, Steven Kao, Sarina A Piha-Paul, Jean-Pierre Delord, Robert R McWilliams, David A Fabrizio, Deepti Aurora-Garg, Lei Xu, Fan Jin, Kevin Norwood, Yung-Jue Bang

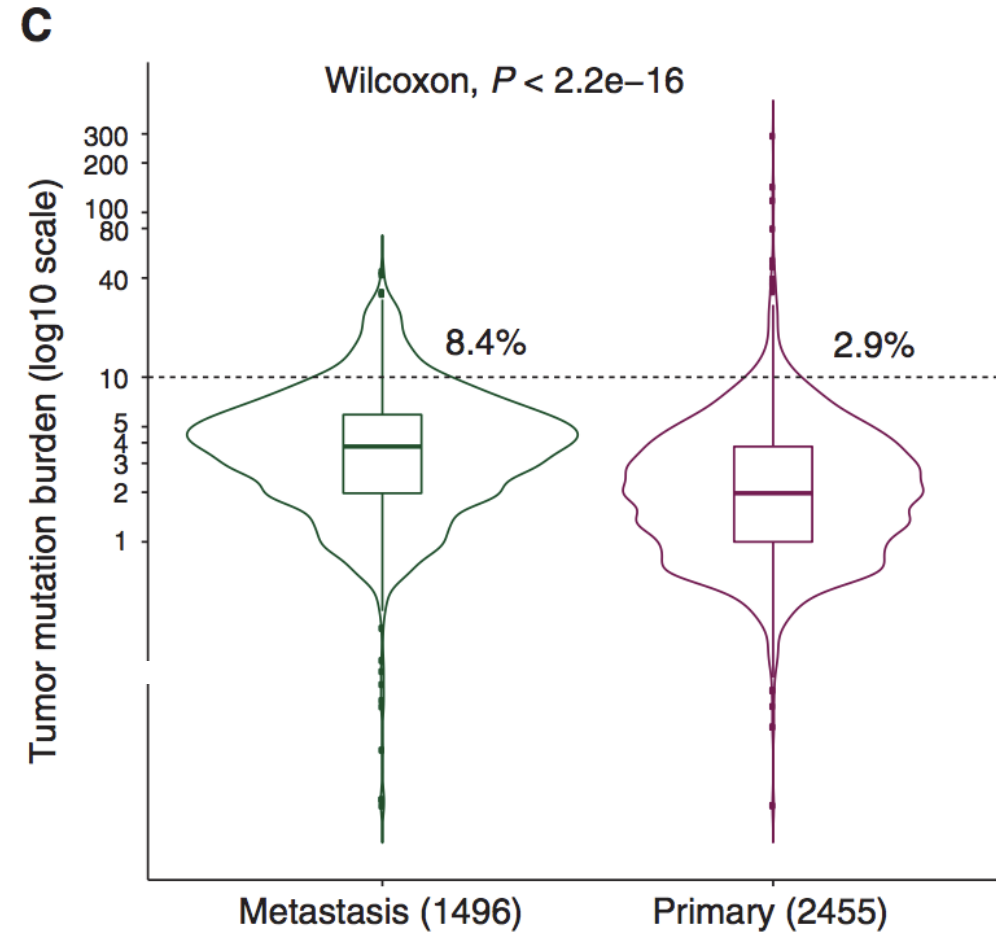
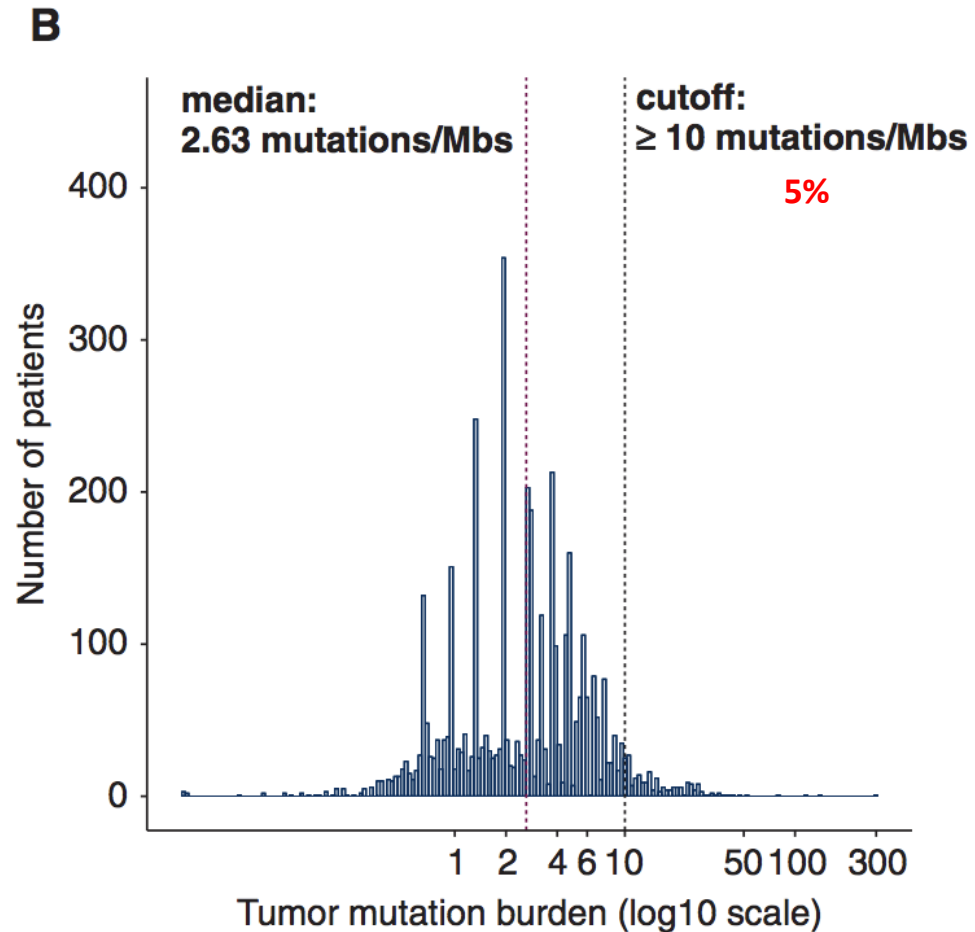
Lancet Oncol 2020



| Tumour types§ | Safety population (n=105)* | Efficacy population | |
|----------------------------------|----------------------------|-------------------------|-----------------------------|
| | | tTMB-high group (n=102) | Non-tTMB-high group (n=688) |
| (Continued from previous column) | | | |
| Anal | 14 (13%) | 14 (14%) | 75 (11%) |
| Biliary | 0 | 0 | 63 (9%) |
| Cervical | 16 (15%) | 16 (16%) | 59 (9%) |
| Endometrial | 15 (14%) | 15 (15%) | 67 (10%) |
| Mesothelioma | 1 (1%) | 1 (1%) | 84 (12%) |
| Neuroendocrine | 5 (5%) | 5 (5%) | 82 (12%) |
| Salivary | 3 (3%) | 3 (3%) | 79 (11%) |
| Small-cell lung | 34 (32%) | 34 (33%) | 42 (6%) |
| Thyroid | 2 (2%) | 2 (2%) | 78 (11%) |
| Vulvar | 15 (14%) | 12 (12%) | 59 (9%) |

- Objective response of 29%
- No patients with MBC included

Prevalence of high TMB among breast cancers



Pembrolizumab in Patients With Metastatic Breast Cancer With High Tumor Mutational Burden: Results From the Targeted Agent and Profiling Utilization Registry (TAPUR) Study



Ajjai S. Alva, MD¹; Pam K. Mangat, MS²; Elizabeth Garrett-Mayer, PhD²; Susan Halabi, PhD³; Damien Hansra, MD⁴; Carmen J. Calfa, MD⁵; Maged F. Khalil, MD⁶; Eugene R. Ahn, MD⁷; Timothy L. Cannon, MD⁸; Pamela Crilley, DO⁹; Julie G. Fisher, MD¹⁰; Derrick S. Haslem, MD¹¹; Sagun Shrestha, MD¹²; Kaitlyn R. Antonelli, BA²; Nicole L. Butler, MPH²; Sasha L. Warren, MS²; Andrew L. Rygiel, MPH²; Shamika Ranasinghe, MS²; Suanna S. Bruinooge, MPH²; and Richard L. Schilsky, MD²

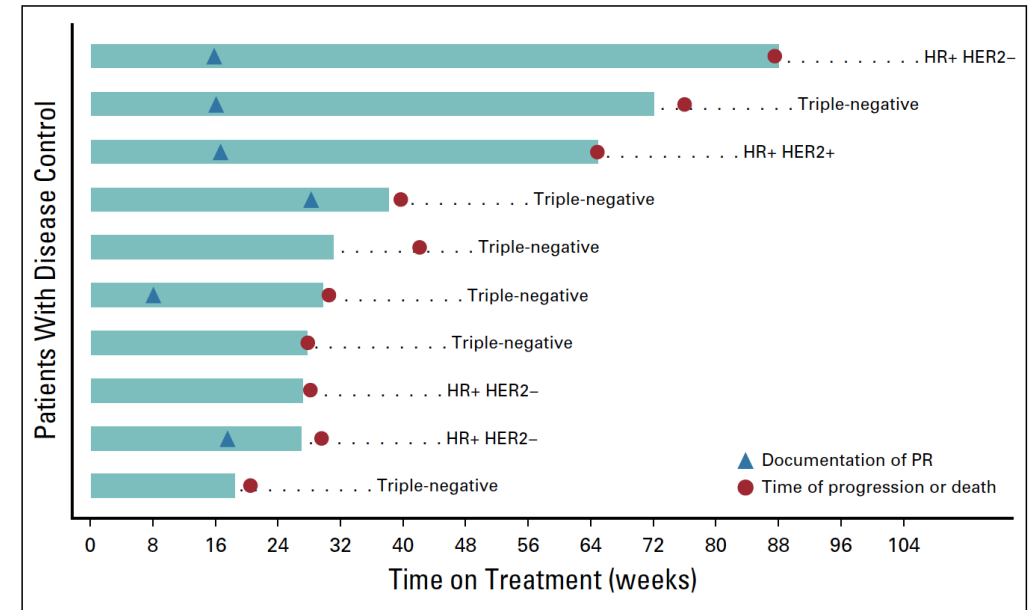
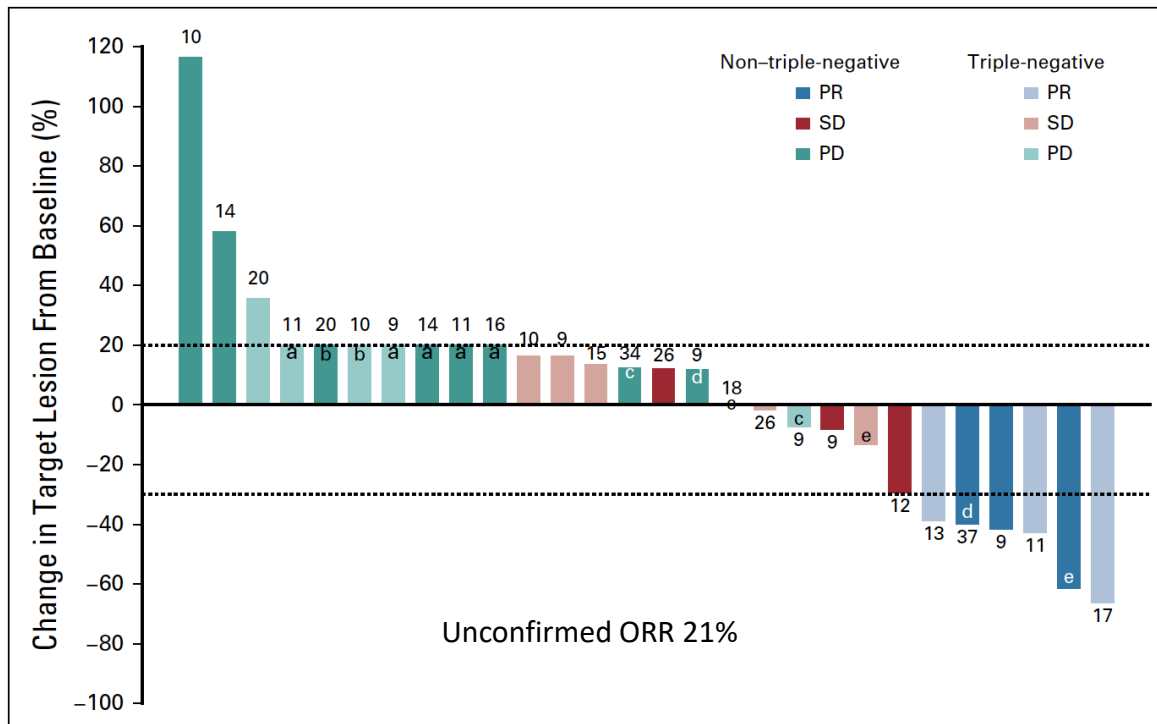


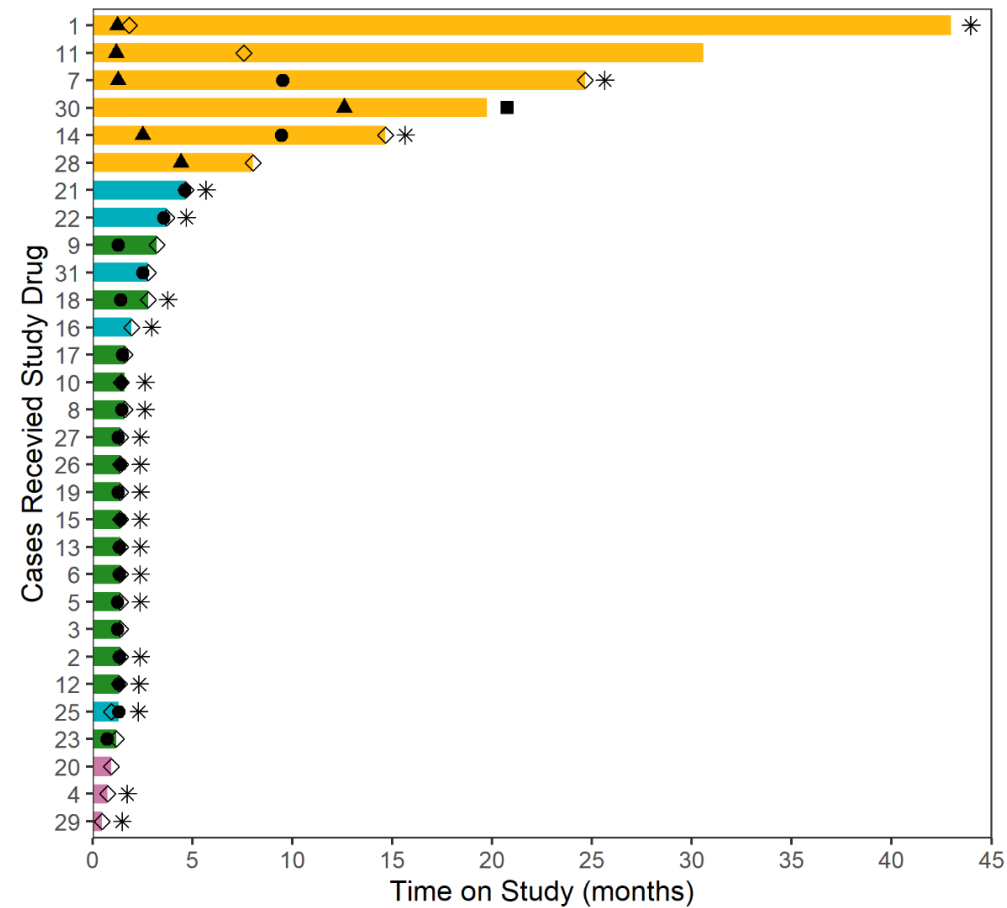
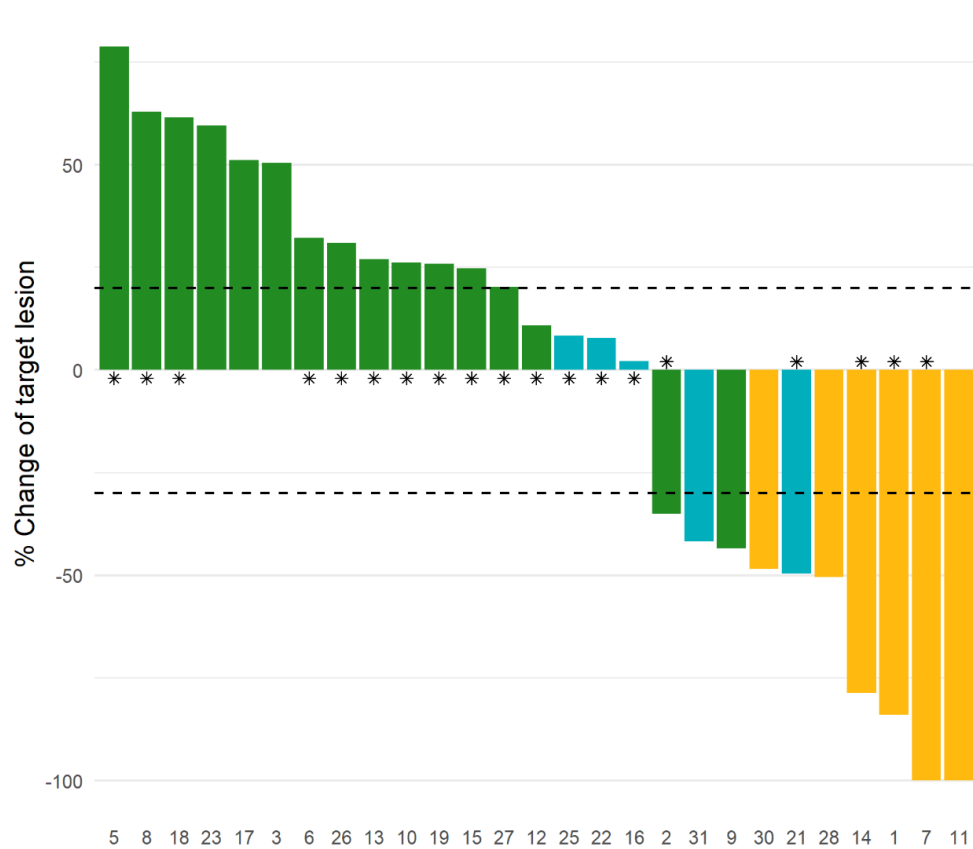
FIG 1. Time on treatment in 10 patients with SD or OR. HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OR, objective response; PR, partial response; SD, stable disease.

NIMBUS: A phase II study of Nivolumab plus Ipilimumab in Metastatic hypermutated HER2-negative Breast cancer

Romualdo Barroso-Sousa¹, Tianyu Li², Sangeetha Reddy³, Leisha A. Emens⁴, Beth Overmoyer², Edward T Richardson III², Paulina Lange², Molly K Dilullo², Victoria Attaya², Jeffrey Kimmel², Eric P. Winer², Elizabeth A. Mittendorf², Nabihah Tayob² and Sara M. Tolaney².

¹Hospital Sirio-Libanês, Brasília, Brazil; ²Dana-Farber Cancer Institute, Boston, MA; ³University of Texas Southwestern Medical Center, Houston, TX; ⁴University of Pittsburgh Medical Center, Pittsburgh, PA

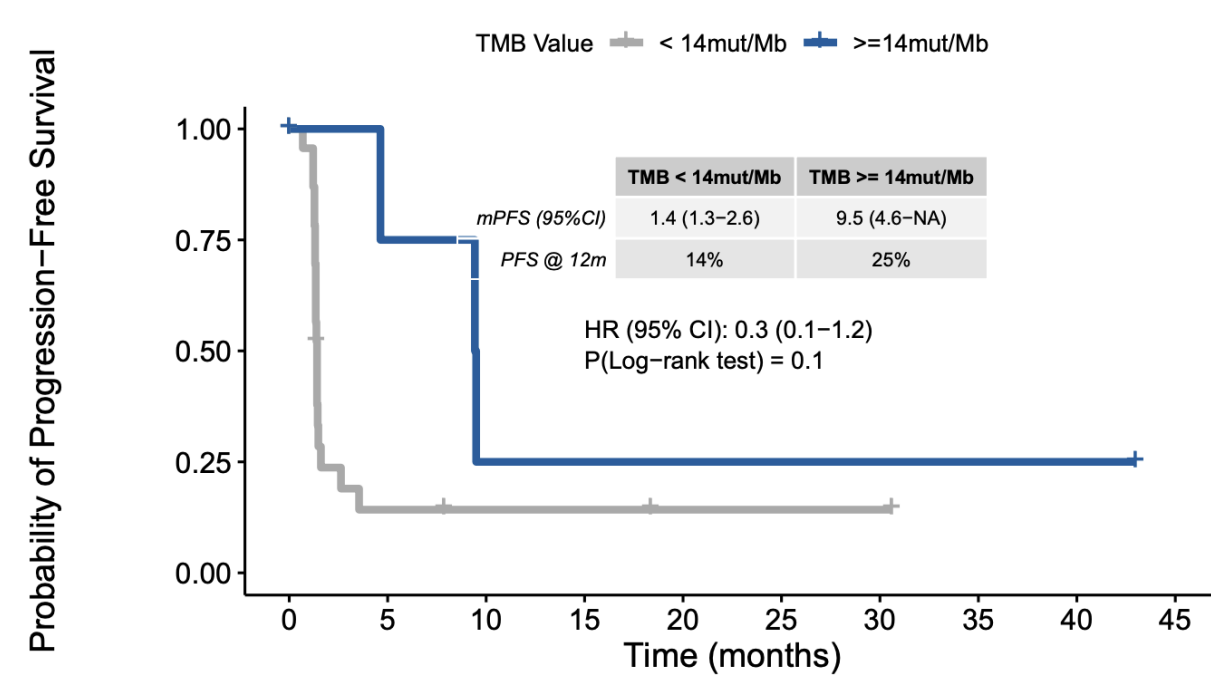
Outcomes



Exploratory analysis

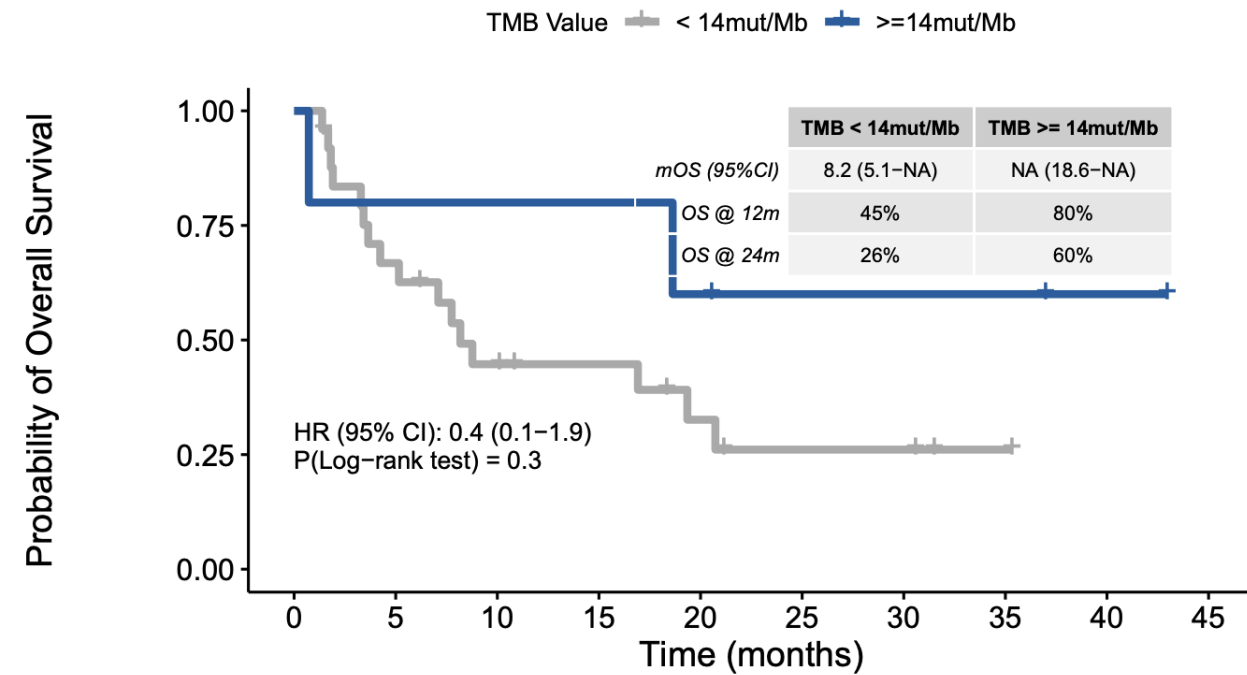
| | Objective response | No response | Total | P value |
|---------------------|--------------------|-------------|--------|---------|
| Subtype | n = 5 | n = 25 | n = 30 | 0.6 |
| TNBC, n (%) | 2 (22) | 7 (78) | n = 9 | |
| HR+, n (%) | 3 (14) | 18 (86) | n = 21 | |
| PD-L1 status | n = 6 | n = 23 | n = 25 | 1.0 |
| Negative, n (%) | 5 (20.8) | 19 (79.2) | n = 24 | |
| Positive, n (%) | 1 (20) | 4 (80) | n = 5 | |
| Stromal TIL | n = 5 | n = 23 | n = 28 | 0.3 |
| <10, n (%) | 2 (11) | 17 (89) | n = 19 | |
| ≥ 10, n (%) | 3 (33) | 6 (67) | n = 9 | |
| TMB (Mut/Mb) | n = 5 | n = 25 | n = 30 | 0.04 |
| <14, n (%) | 3 (12) | 23 (92) | n = 25 | |
| ≥14, n (%) | 3 (60) | 2 (40) | n = 5 | |

Median PFS and OS according to TMB



Number at risk

| | | | | | | | | | | |
|------------|----|---|---|---|---|---|---|---|---|---|
| < 14mut/Mb | 25 | 3 | 2 | 2 | 1 | 1 | 1 | 0 | 0 | 0 |
| >=14mut/Mb | 5 | 3 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 |



Number at risk

| | | | | | | | | | | |
|------------|----|----|----|---|---|---|---|---|---|---|
| < 14mut/Mb | 25 | 16 | 10 | 8 | 5 | 3 | 3 | 1 | 0 | 0 |
| >=14mut/Mb | 5 | 4 | 4 | 4 | 3 | 2 | 2 | 2 | 1 | 0 |

Ongoing analysis

- Genomic assays (FM tissue and blood)
- Gut microbiome

Combinações com ADCs

Trastuzumab Deruxtecan (T-DXd) + Durvalumab (D) as First-line (1L) Treatment for Unresectable Locally Advanced/Metastatic Hormone Receptor-negative (HR-), HER2-low Breast Cancer: Updated Results from BEGONIA, a Phase 1b/2 Study

SABCS 2022

BEGONIA Study Design

Eligibility criteria

- Unresectable locally advanced or metastatic Stage IV TNBC
- Eastern Cooperative Oncology Group performance status of 0-1
- No prior treatment for Stage IV disease
- Measurable disease per RECIST v1.1
- ≥12 months since taxane therapy for early-stage disease
- No autoimmune, inflammatory illnesses
- Adequate organ and marrow function

Additional criteria for T-DXd + durvalumab arm

- HER2-low tumor expression (per local testing; IHC 2+/ISH- or IHC 1+)
- and hormone receptor-negative tumors
- No ongoing pulmonary disorders

Treatment arms*

| | |
|-------------------------------|-----------------------------------|
| Arm 1: D + Paclitaxel (P) | Arm 5: D + P + Oleclumab |
| Arm 2: D + P + Capivasertib | Arm 7: D + Datopotamab Deruxtecan |
| Poster PD11-09 | |
| Arm 6: T-DXd + durvalumab (D) | |
| T-DXd: 5.4 mg/kg IV Q3W | |
| Durvalumab: 1120 mg IV Q3W | |

Part 1

| | |
|---|---|
| Arms 2-7 only: Safety run-in (up to 6 patients) | Simon 2-stage evaluation of ORR to precede initiation of Part 2 for each novel treatment arm. If expansion criteria are met, then novel treatment arm may proceed to Part 2 |
| Primary endpoints | Safety and tolerability |
| Secondary endpoints | ORR, DoR, PFS, OS |

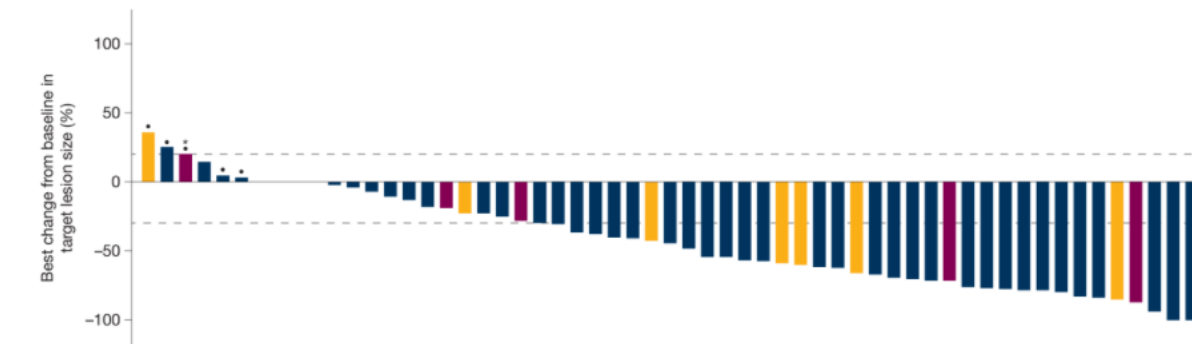
Part 2 Expansion

| | |
|---|--------------------|
| Enrollment of additional 27 patients in the novel treatment arm | |
| Primary endpoint | ORR |
| Secondary endpoints | PFS, DoR, PFS6, OS |

Primary endpoint Association of PD-L1 and HER2 expression with treatment response

*Arms 3 and 4, D + P + selumetinib and D + P + darvatrisen, were removed from the protocol prior to enrolling patients.

Figure 1. Best change from baseline of target lesion size



HER2 local status-ISH: - - - - -
HER2 local status-IHC: 1+ 2+ 1+ 1+ 2+ 2+ 2+ 2+ 1+ 1+ 2+ 2+ 2+ 2+ 1+ 2+

Dotted reference lines at -30% and 20% indicate thresholds for partial response and 1% if the best percentage change from baseline of target lesions cannot be calculated due to

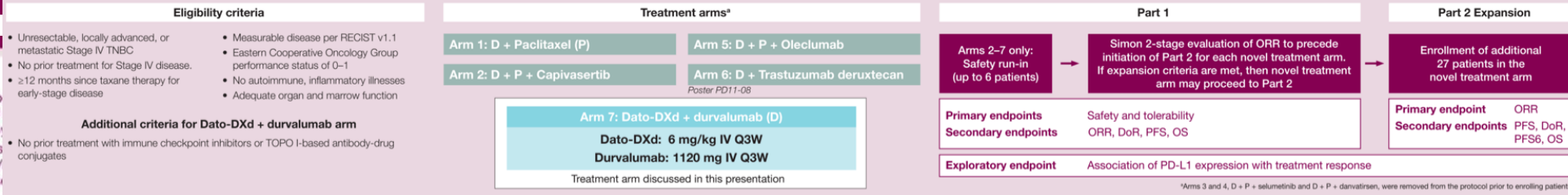
Conclusions

- For patients with HR-, HER2-low a/mBC, T-DXd in combination with durvalumab in the 1L setting shows a tolerable and manageable safety profile consistent with the known profile of individual agents.
- These updated results further demonstrate promising efficacy (response rate, durability of response, and PFS) of T-DXd + durvalumab in 1L HR-, HER2-low mBC.
 - Responses were observed in patients with HER2 IHC 1+ and IHC 2+/ISH- as well as with PD-L1-high and PD-L1-low tumors.
- Results for T-DXd + durvalumab in the 1L setting from BEGONIA, as well as previously reported Phase 3 results of T-DXd alone in the second-line or greater setting, support additional studies of these treatments in 1L HR-, HER2-low mBC.

Datopotamab Deruxtecan (Dato-DXd) + Durvalumab (D) as First-line (1L) Treatment for Unresectable Locally Advanced/Metastatic Triple-negative Breast Cancer (a/mTNBC): Updated Results from BEGONIA a Phase 1b/2 Study

SABCS 2022

BEGONIA Study Design



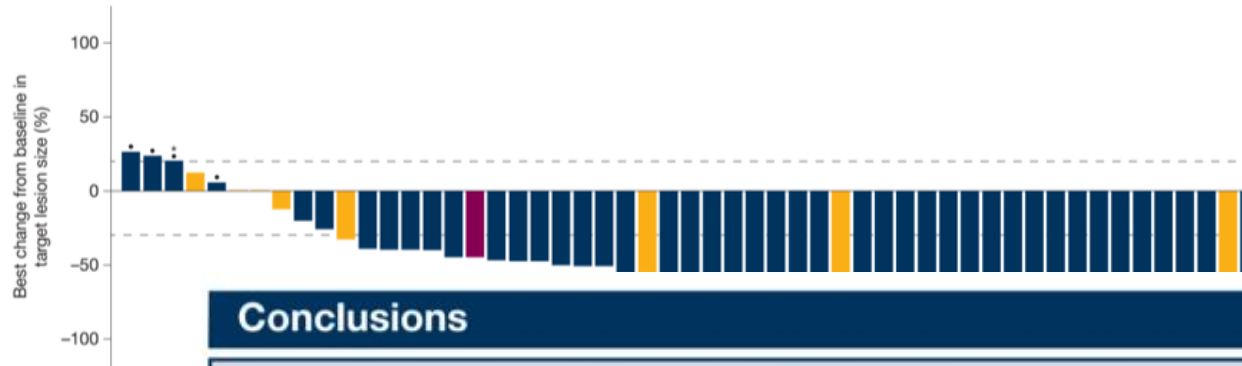
Introduction

- Patients with a/mTNBC have limited treatment options and a poor prognosis (objective response rate [ORR] of 37%, median duration of response of 3.5 months and median overall survival [OS] of 15.5 months with 1L chemotherapy).
- Combining immune checkpoint inhibitors with 1L chemotherapy modes outcomes but only in programmed cell death ligand-1 (PD-L1)-high a/mTNBC, emphasizing a critical unmet need for patients with PD-L1-low disease further improving outcomes in PD-L1-high disease.^{2,3}
- BEGONIA (NCT03742102) is an ongoing 2-part, open-label platform study evaluating safety and efficacy of durvalumab, an anti-PD-L1 antibody, with other novel therapies in 1L a/mTNBC, including Dato-DXd.⁴
- Dato-DXd is an antibody-drug conjugate consisting of a humanized anti-HER2 antibody covalently linked to a highly potent topoisomerase I inhibitor via a stable, tumor-selective, tetrapeptide-based cleavable linker.^{5,6}
- Early data from BEGONIA Arm 7 of durvalumab in combination with Dato-DXd were presented at ESMO Breast 2022 (n=29) and showed promising results.

Objective

- To report an update on safety, tolerability, and efficacy results as well as additional patients of the Dato-DXd + durvalumab combination in BEGONIA.

Figure 1. Best change from baseline of target lesion size



Conclusions

- In this updated analysis with a median of 7 months follow-up, the combination of Dato-DXd + durvalumab in 1L a/mTNBC demonstrated a tolerable and manageable safety profile.
- A compelling high response rate, with 4 patients having complete response, was observed with Dato-DXd + durvalumab.
- Although subgroups were small, responses were observed in PD-L1-high and PD-L1-low tumors.
- While maturity is low, response durability is promising; longer follow-up will further inform efficacy results, including PFS.
- Further investigation of Dato-DXd + durvalumab is warranted in this patient population.

Combinações com ADCs

- TROPION-BREAST 03

- Datopotamabe + Durvalumabe vs QT + pembrolizumabe

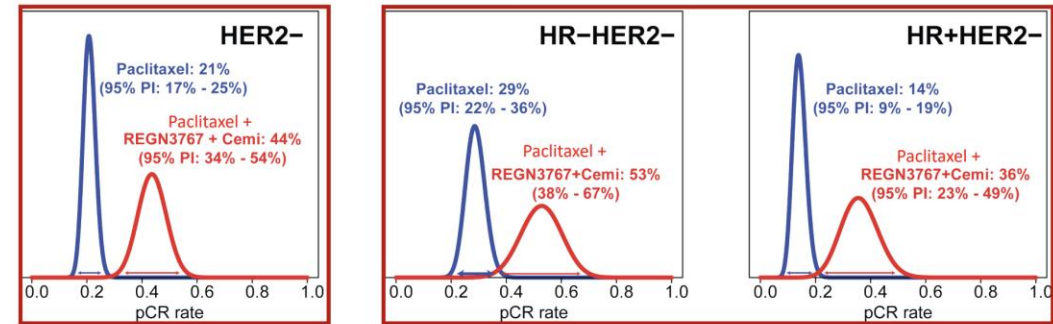
- ASCENT 04

- Sacituzumabe + Pembrolizumabe vs QT + Pembrolizumabe

Efficacy Analysis

Combinações com outras imunoterapias

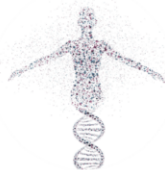
- ANTI-LAG3



| Signature | Estimated pCR Rate (95% Probability Interval) | | Probability Pac + REGN3767 + Cemi Superior to Control | Predictive Probability of Success in Phase 3 (relative to Control) |
|-----------|---|-----------------|---|--|
| | Pac + REGN3767 + Cemi (n=76) | Control (n=350) | | |
| HER2- | 44% (34% - 54%) | 21% (17% - 25%) | >0.999 | 0.955 |
| HR-HER2- | 53% (38% - 67%) | 29% (22% - 36%) | 0.999 | 0.915 |
| HR+HER2- | 36% (23% - 49%) | 14% (9% - 19%) | >0.999 | 0.940 |

Pac + REGN3767 + Cemiplimab graduated in all 3 eligible biomarker signatures by demonstrating increased pCR

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Evaluation of anti-PD-1 Cemiplimab plus anti-LAG-3 REGN3767 in Combination with Paclitaxel in Early-Stage, High-Risk HER2-negative Breast Cancer: Results from the Neoadjuvant I-SPY 2 TRIAL

Claudine Isaacs, Rita Nanda, Christina Yau, Jo Chien, Megna Trivedi, Erica Stringer-Reasor, Christos Vakilavass, Judy Boughey, Amy Sanford, Anne Wallace, Amy Clark, Alexandra Thomas, Kathy Albain, Laura Kennedy, Tara Sanft, Kevin Kalinsky, Heather Han, Williams N, Mili Arora, Anthony Elias, Carla Falkson, Smita Asare, Ruixiao Lu, Maria Pitsiouni, Amy Wilson, Jane Perlmutter, Hope S Rugo, Richard Schwab, Frasier Symmans, Nola Hylton, Laura Van 't Veer, Douglas Yee, Angela DeMichele, Don Berry, Laura Esserman

on behalf of the I-SPY 2 TRIAL Consortium

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Immune-Related Adverse Events (irAEs)

40 (53%) patients in REGN3767 + Cemi arm experienced irAE

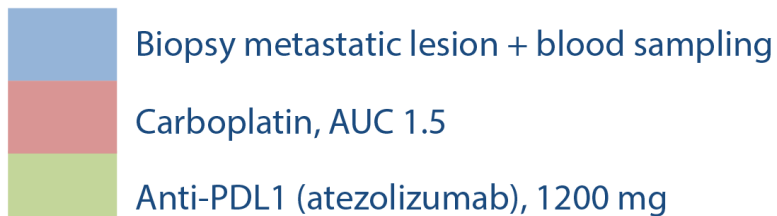
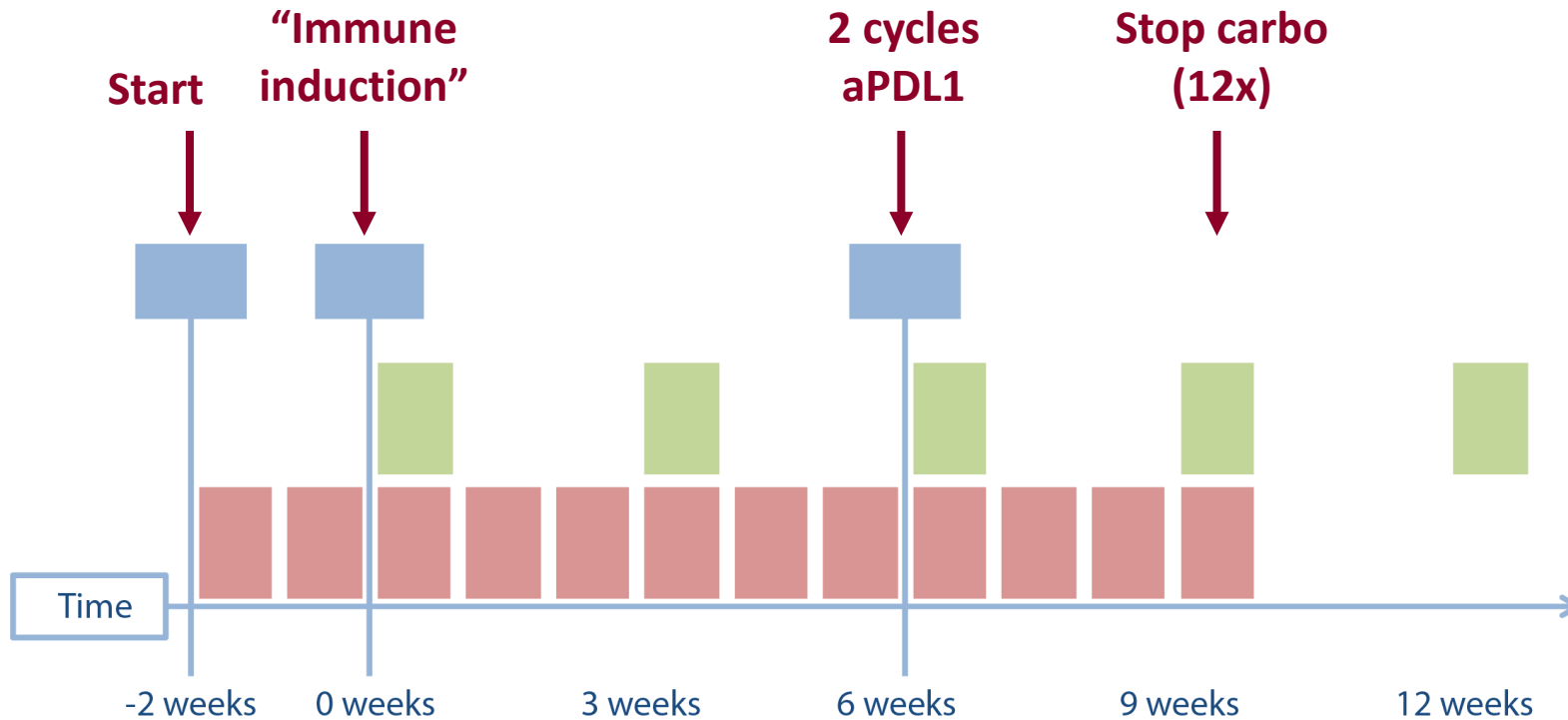
| irAE | Grade 1/2 | Grade 3 | All Grade |
|------------------------------------|-----------|---------|-----------|
| Hypothyroidism | 24 (32%) | 0 (0%) | 24 (32%) |
| Adrenal insufficiency/Hypophysitis | 10 (12%) | 6 (5%) | 16 (21%) |
| Type 1 diabetes mellitus | 0 | 3 (4%) | 3 (4%) |
| Autoimmune hepatitis | 0 | 2 (3%) | 2 (3%) |
| Pneumonitis | 2 (3%) | 0 (0%) | 2 (3%) |
| Renal failure acute | 1 (1%)* | 1 (1%) | 2 (3%) |

1 case of arthritis (G3)
 1 case of immune-related Rash maculo-papular (G3)
 1 case of thyroiditis (G2)
 No Grade 4+ irAEs

Based on available data as of October 15th, 2022

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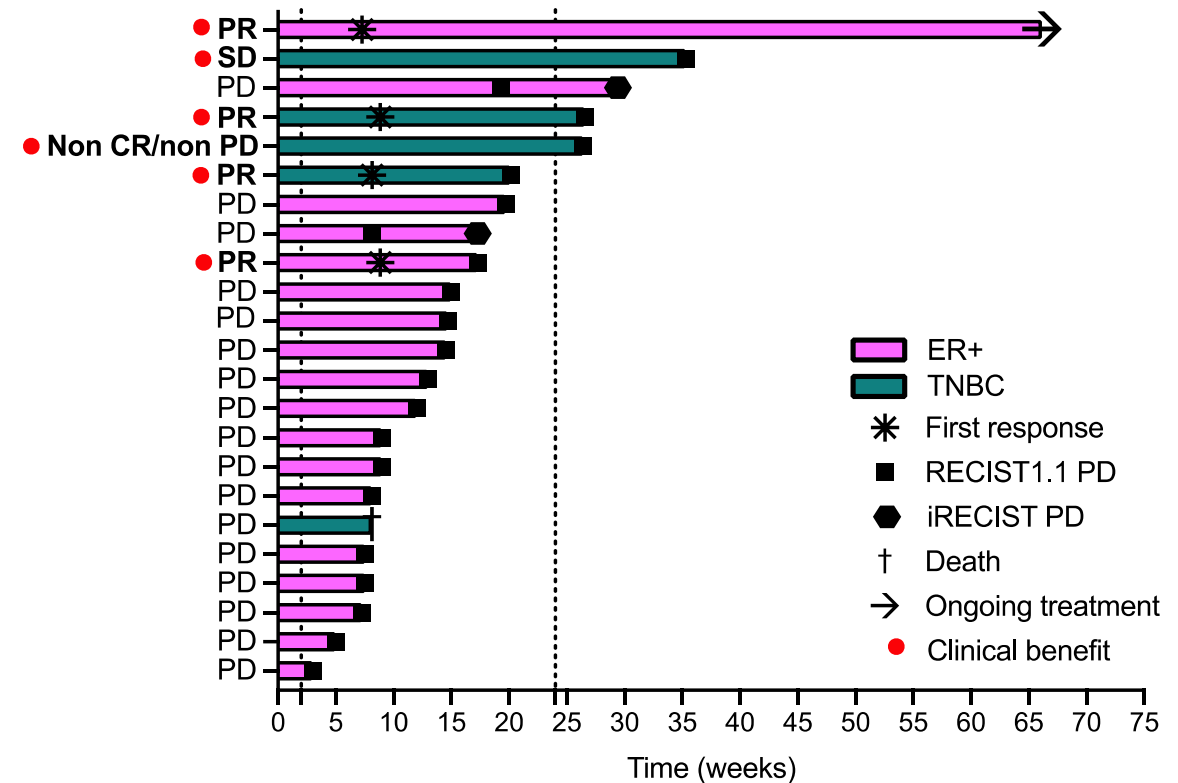
aPDL1 + induction with platinum: GELATO-trial



- Endpoint: clinical benefit rate (CR+PR+SD > 6m)
- Simon's 2-stage design with 3/22 (14%) in first stage considered a success

Efficacy aPDL1 plus carboplatin induction

| | |
|---|---------|
| N = 23 evaluable patients | |
| Best overall response (RECIST 1.1), no (%) | |
| Complete response (CR) | 0 (0) |
| Partial response (PR)* | 4 (19) |
| Stable disease (SD) or non-CR/non-PD | 2 (10) |
| Progressive disease (PD) | 15 (71) |
| Objective response rate (CR+PR) | 17% |
| Clinical benefit rate (CR+PR+SD>6 months) | 26% |



Conclusões

- A combinação de imunoterapia com novos ADCs é promissora, com a expectativa de ser tornar o novo padrão de tratamento em alguns anos
- Combinação com novas imunoterapias está sendo investigada
- O CUTOFF para utilizar o TMB como biomarcador preditivo de resposta não está estabelecido
- Mais estudos são necessários para a melhor compreensão dos mecanismos de evasão da imunidade no cancer de mama – far beyond immune checkpoint inhibitors!

barroso.romualdo@gmail.com



@DrRBarroso

Obrigado