Poster 1023

BEGONIA: Phase 1b/2 study of durvalumab (D) combinations in locally advanced/metastatic triple-negative breast cancer: Initial results from Arm 1, D + paclitaxel, and Arm 6, D + trastuzumab deruxtecan (T-DXd)

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Introduction

- Chemotherapy together with immune checkpoint inhibitors can improve outcomes versus chemotherapy alone in patients with programmed death ligand-1 positive (PD-L1+) metastatic triple-negative breast cancer (TNBC); however, many still have poor clinical outcomes.[1,2]
- Preliminary clinical studies of durvalumab, an anti–PD-L1 antibody, combined with chemotherapy or a PARP inhibitor suggest that durvalumab combinations may provide additional benefit in treating TNBC.[3,4]
- T-DXd is an antibody-drug conjugate consisting of an anti-HER2 antibody, a cleavable linker, and a topoisomerase I inhibitor.
- T-DXd was recently approved for previously treated metastatic HER2-positive breast cancer, and it provided durable responses in patients with HER2-low–expressing breast cancer in a Phase Ib study.[5,6]
- BEGONIA (NCT03742102) is an ongoing 2-part, multicenter, multiarm, open-label platform study evaluating safety and efficacy of durvalumab + paclitaxel (D+P) and durvalumab with or without paclitaxel (P) combined with novel therapies as first-line (1L) treatment for metastatic TNBC.

Objectives

- Determine initial safety, tolerability, and efficacy of the combination of durvalumab with other therapies of known, or potential, efficacy in patients with metastatic TNBC enrolled in Part 1 of the BEGONIA study.
- Here we present preliminary results from Arm 1, D+P, and Arm 6, D+T-DXd.

Methods

- The first 6 patients treated with D+T-DXd were evaluated for dose-limiting toxicities (DLTs), with additional patients enrolled if D+T-DXd was tolerated.
- Tumors were assessed every 8 weeks for D+P or every 6 weeks for D+T-DXd per Response Evaluation Criteria in Solid Tumors (RECIST 1.1).
- HER2-low expression was determined by local testing and defined as immunohistochemistry (IHC) score 1+ or 2+ and in situ hybridization (ISH) negative or untested.
- PD-L1 expression was assessed retrospectively by IHC using an SP263-based assay.
- An exploratory analysis using an area-based scoring algorithm was employed. PD-L1 expression was defined as the proportion of the tumor area populated by tumor cells or immune cells with membranous PD-L1 staining.[a]
- A sample was considered positive if it demonstrated ≥5% PD-L1 expression.
- Study arms were noncomparable due to differing eligibility criteria, treatment periods, and data maturity.

Interactive poster · Plain language summary · Supplemental material

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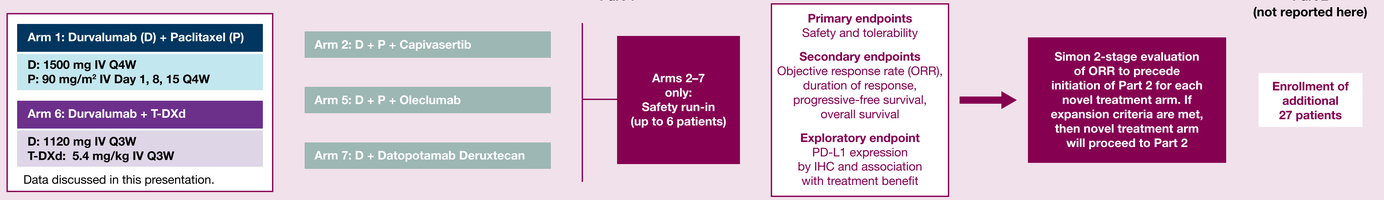
BEGONIA Study Design

Eligibility criteria

- Unresectable locally advanced or metastatic Stage IV TNBC
- No prior treatment for Stage IV TNBC
- ≥12 months since taxane therapy for early-stage disease
- Eastern Cooperative Oncology Group performance status of 0–1
- Measurable disease per RECIST 1.1
- No autoimmune, inflammatory illnesses

Additional Arm 6 criteria

- HER2-low–expressing (IHC 2+/ISH–, IHC 1+/ISH–, or IHC 1+/ISH untested; per local testing), estrogen receptor (ER)-negative, and progesterone receptor (PR)-negative tumors
- No ongoing pulmonary disorders



Results and Interpretation

Arm 1: Durvalumab + Paclitaxel

- As of the data cutoff of September 2020, 23 patients received D+P with 7 still on treatment.
  - 2 patients discontinued D+P due to an adverse event (AE).
  - 16 discontinued due to disease progression.
  - 2 of these patients discontinued for >1 reason.
- Median (range) follow-up time was 16.6 (8.5–19.8) months.

Table 1. Patient and disease characteristics

Characteristic	N=23
Age, median (range), years	52 (30–63)
No prior treatment	6 (26.1)
Prior cytotoxic chemotherapy	17 (73.9)
Taxane	14 (60.9)
Anthracycline	15 (65.2)
Platinum compound	4 (17.4)
Visceral metastases	17 (73.9)
Lymph node metastases	16 (69.6)

n (%) unless otherwise stated. See **Supplemental Table 1** for additional baseline characteristics.

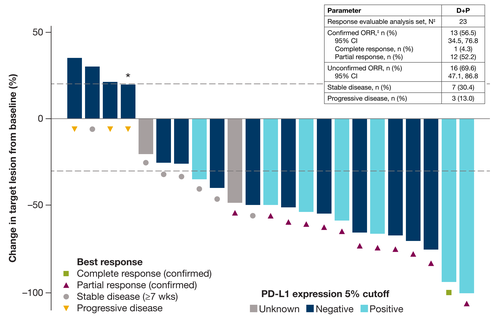
- Grade 3/4 AEs were mainly hematologic; the most frequent was decreased neutrophil count (n=4, 17.4%) (**Suppl. Table 2**).
- **Suppl. Table 3** reports additional safety data.

Table 2. Safety summary (N=23)

	n (%)
Any AE	22 (95.7)
Common AEs (≥20% patients, any grade)	
Alopecia	14 (60.9)
Peripheral sensory neuropathy	13 (56.5)
Nausea	10 (43.5)
Rash	9 (39.1)
Fatigue, neutrophil count decreased	8 (34.8) each
Peripheral edema	7 (30.4)
Hypothyroidism, myalgia	6 (26.1) each
ALT increased, nail discoloration, pruritus	5 (21.7) each
Any Grade 3/4 AE	10 (43.5)
Any SAE	1 (4.3)
Any treatment-related AE	22 (95.7)
Any AESI for durvalumab	11 (47.8)
AE leading to death	0
AE leading to dose interruption	13 (56.5)
Any durvalumab dose delay	7 (30.4)

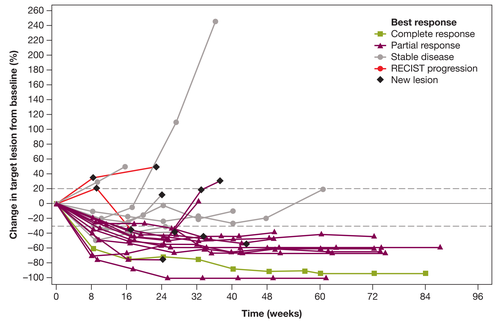
AESIs for durvalumab include diarrhea/colitis, pneumonitis/interstitial lung disease, endocrinopathies, hepatitis/transaminase increase, nephritis/blood creatinine increase, pancreatitis/serum lipase and amylase increase, rash/dermatitis, myocarditis, myositis/polymyositis, neuropathy/neuromuscular toxicity, and other less frequent inflammatory responses. AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; SAE, serious adverse event.

Figure 1. Best change from baseline of target tumor size†



- In this small population, responses occurred for both PD-L1–positive (confirmed ORR 6/7 [85.7%]) and –negative (confirmed ORR 6/14 [42.9%]) groups (**Figure 1, Suppl. Figure 1**).

Figure 2. Change from baseline in target tumor size over time



- A total of 7/13 (53.8%) patients remained in response at the time of data cutoff
- **Suppl. Table 4** reports additional efficacy data.

Arm 6: Durvalumab + T-DXd

- As of the data cutoff of March 2021, 21 patients received D+T-DXd with 19 still on treatment.
  - 2 discontinued D+T-DXd, 1 due to Grade 3 pneumonitis and the other due to dyspnea (T-DXd discontinued) and disease progression (durvalumab discontinued).
- Median (range) follow-up time was 3.6 (0-9) months.

Table 3. Patient and disease characteristics

Characteristic	N=21
Age, median (range), years	58 (35–81)
No prior treatment	4 (19.0)
Prior cytotoxic chemotherapy	15 (71.4)
Taxane	11 (52.4)
Anthracycline	15 (71.4)
Platinum compound	7 (33.3)
Visceral metastases	17 (80.9)
Lymph node metastases	12 (57.1)

n (%) unless otherwise stated. Full analysis set (N=21) includes all patients who received study treatment. See **Supplemental Table 5** for additional baseline characteristics.

- No DLTs were observed during the safety run-in.
- Common AEs were of low grade and consistent with those previously reported for durvalumab[7] and T-DXd[5,6] single agents.
- Grade 3/4 AEs were mainly hematologic; the most frequent was neutropenia (n=4, 19.0%) (**Suppl. Table 6**).

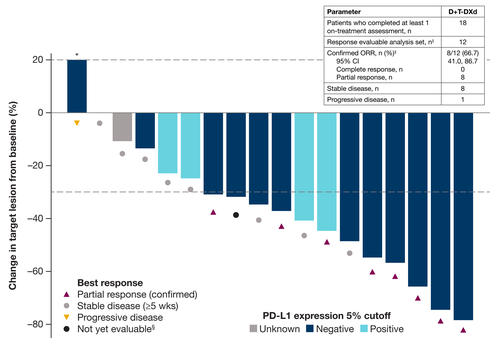
Table 4. Safety summary (N=21)

	n (%)
Any AE	21 (100)
Common AEs (≥20% patients, any grade)	
Nausea	16 (76.2)
Fatigue	11 (52.4)
Alopecia, neutropenia, anemia, constipation	6 (28.6) each
Decreased appetite, hypothyroidism, hypokalemia	5 (23.8) each
Any Grade 3/4 AE	8 (38.1)
Any SAE	5 (23.8)
Any treatment-related AE	20 (95.2)
Any AESI for durvalumab	11 (52.4)
Any AESI for T-DXd	2 (9.5)
AE leading to death	0
AE leading to dose interruption	7 (33.3)
Any durvalumab dose delay	9 (42.9)
Any T-DXd dose delay	9 (42.9)
T-DXd dose reduction	5 (23.8)

AESIs for T-DXd include pneumonitis/interstitial lung disease and left ventricular ejection fraction decrease. A list of AESIs for durvalumab is shown in **Table 2**. AEs, adverse events; AESI, adverse event of special interest; SAE, serious adverse event.

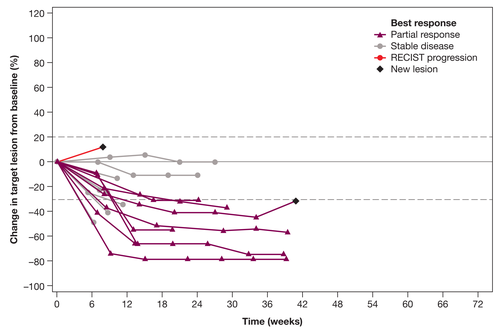
- 2 cases of pneumonitis were observed (Grade 2 and Grade 3) and both were treated with steroids.
  - Grade 3 pneumonitis led to the patient discontinuing D+T-DXd.
  - Grade 2 pneumonitis led to the patient discontinuing T-DXd only.
- 1 additional discontinuation of T-DXd alone occurred and was due to thrombocytopenia.
- 1 case of troponin increase was nonserious, with no change in ejection fraction.
- **Suppl. Table 7** reports additional safety data.

Figure 3. Best change from baseline of target tumor size†



- Local testing of HER2 expression successfully identified patients with HER2 IHC1+ and HER2 IHC2+/ISH– tumors, who benefit from this treatment combination.
- In this small group of patients, responses were observed in both PD-L1–positive (confirmed ORR 1/1 [100%]) and –negative (confirmed ORR 7/10 [70.0%]) groups (**Figure 3, Suppl. Figure 2**).

Figure 4. Change from baseline in target tumor size over time



- A total of 7/8 (87.5%) patients remained in response at the time of data cutoff.
- **Suppl. Table 8** reports additional efficacy data.

Conclusions
Arm 1: Durvalumab + Paclitaxel

- Acceptable safety/tolerability profile and demonstrates a response rate (confirmed ORR 56.5%) consistent with published data for 1L TNBC IO/taxane combination studies.
  - This was also consistent for patients with positive PD-L1 expression.
- Responses were observed regardless of PD-L1 expression (5% cutoff).
- Responses were durable with 53.8% of patients remaining in response for 12 months.

Conclusions
Arm 6: Durvalumab + T-DXd

- Shows promising early efficacy signal in 1L metastatic HER2-low/ER-negative/PR-negative breast cancer: confirmed ORR 8/12 (66.7%) patients in the response evaluable set.
  - Responses were observed regardless of PD-L1 expression (5% cutoff).
  - Local HER2 testing demonstrates benefit in both the HER2 1+ and HER2 2+/ISH– groups.
  - Responses were durable, with 87.5% remaining in response at time of data cutoff.
- Demonstrates a tolerable safety profile that is consistent with the known profile of the 2 agents individually.
  - Grade 3/4 AE rate was low at 8/21 (38.1%) and 2 cases of pneumonitis (Grade 2, Grade 3) were observed.
  - Overall safety assessment is limited by short follow-up and treatment duration to date.

Footnotes

[a]Optimal scoring algorithms and cutoffs for PD-L1 expression that are relevant to durvalumab treatment for metastatic TNBC have not yet been established.†Dotted lines indicate thresholds for partial response (PR; –30%) and progressive disease (PD; 20%). ‡If the best percentage change from baseline of target lesions cannot be calculated due to progression, withdrawal, or death, the value is imputed at +20%. §Number of patients that had the opportunity to complete at least 2 on-treatment disease assessments or have PD or death. ‖Patient had nonevaluable nontarget lesions at baseline and a sum of adjusted diameters of 117, which dropped to 80 at the first visit. The overall visit response was PR.

Acknowledgments

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