PS12-12

ARC-2: Efficacy and Safety of Etrumadenant (AB928) + Pegylated Liposomal Doxorubicin (PLD) ± Eganelisib (IPI-549) in Participants with Metastatic Ovarian and Triple Negative Breast Cancer

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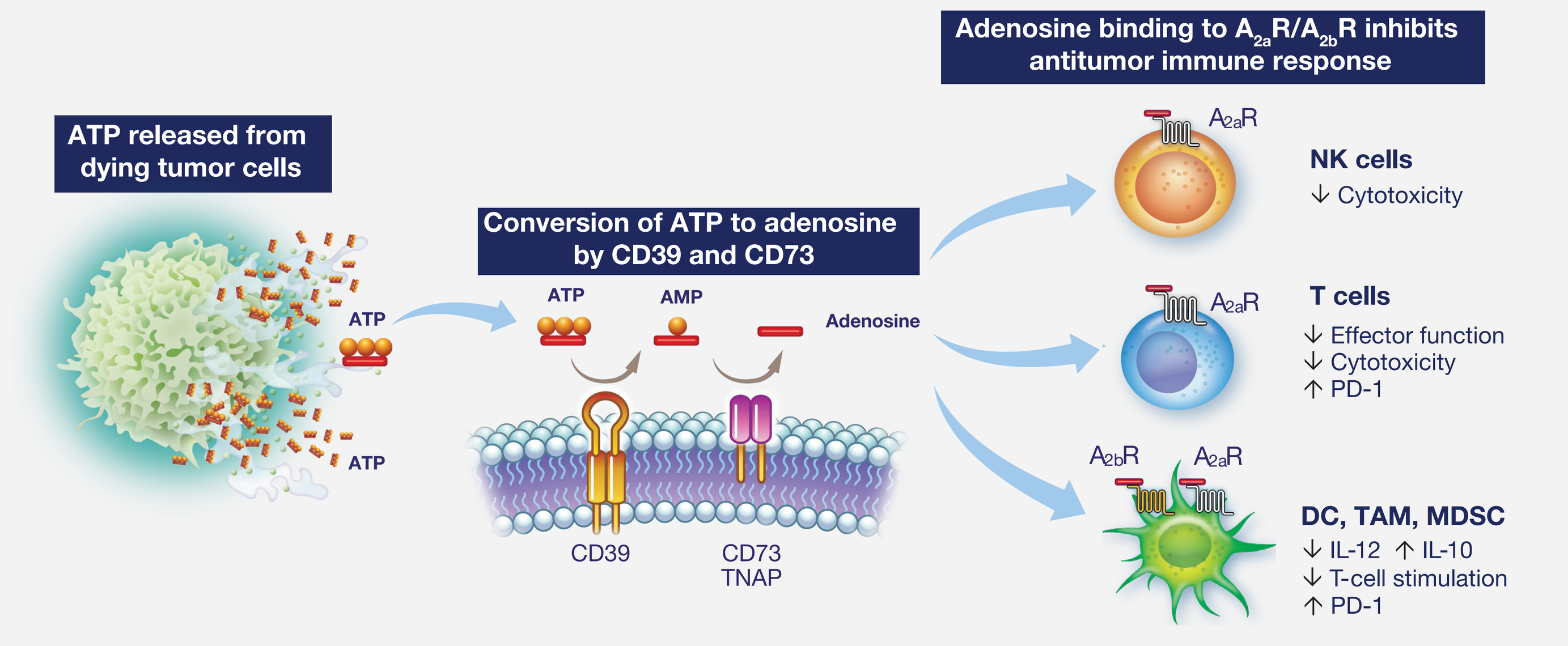
INTRODUCTION

The Adenosine Axis in Cancer

- Standard chemotherapy regimens may contribute to immunosuppression by elevating intratumoral levels of adenosine triphosphate (ATP) in the tumor microenvironment (TME) where the enzymes CD39 and CD73 convert ATP to adenosine[1,2] (**Figure 1**)
- By binding adenosine receptors 2a and 2b ($A_{2a}R$ and $A_{2b}R$) expressed on immune cells, adenosine promotes immunosuppression by inhibiting critical components of the antitumor immune response, ultimately enabling tumors to evade destruction[2]
- Additionally, $A_{2a}R$ signaling impairs the activation, proliferation, and cytotoxic activity of effector T cells[3]
- Initial research focused on $A_{2a}R$ as the most relevant adenosine receptor in cancer physiology; however, $A_{2b}R$ signaling mediates unique functions, such as dendritic cell activation and function[4]
- Thus, adenosine receptor blockade may be necessary to overcome adenosine-dependent immunosuppression and lead to enhanced therapeutic efficacy of some chemotherapeutic agents[2]

Figure 1. Critical Role of Adenosine Pathway in the Immunosuppressive Tumor Microenvironment


ATP released from dying tumor cells
ATP
Conversion of ATP to adenosine by CD39 and CD73
ATP
AMP
Adenosine
CD39
CD73
TNAP
Adenosine binding to A2aR/A2bR inhibits antitumor immune response
A2aR
NK cells
↓ Cytotoxicity
A2aR
T cells
↓ Effector function
↓ Cytotoxicity
↑ PD-1
A2bR
A2aR
DC, TAM, MDSC
↓ IL-12 ↑ IL-10
↓ T-cell stimulation
↑ PD-1

AMP, adenosine monophosphate; ATP, adenosine triphosphate; $A_{2a}R/A_{2b}R$, adenosine receptors 2a/2b; DC, dendritic cell; IL, interleukin; MDSC, myeloid-derived suppressor cell; NK, natural killer; PD-1, programmed cell death protein-1; TAM, tumor-associated macrophage; TNAP, tissue nonspecific alkaline phosphatase.

- Etrumadenant (AB928) is an orally bioavailable, small-molecule, selective dual antagonist of $A_{2a}R$ and $A_{2b}R$ that was specifically designed to block immunosuppressive effects associated with high adenosine concentration within the TME; it is the only adenosine receptor antagonist in active clinical trials that potently blocks $A_{2b}R$ in addition to $A_{2a}R$
- Currently, there are 4 ongoing global phase 1/1b disease-specific platform studies to assess safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary clinical activity of etrumadenant in combination with chemotherapy and/or anti–PD-1 antibody[5]
  - Based on dose escalation data from these studies, etrumadenant 150 mg once daily (QD) was selected as the recommended dose for expansion (RDE) based on PK, PK/PD correlation, and a well-tolerated safety profile of etrumadenant + chemo/immunotherapy

ARC-2 Study Rationale

- Standard treatment for advanced triple-negative breast cancer (TNBC) or ovarian cancer includes chemotherapy regimens with anthracycline drugs, such as pegylated liposomal doxorubicin (PLD); however, long-term survival for patients with either cancer type is poor and an unmet need remains for novel, efficacious treatment regimens[6,7]
- Genetic profiling of human tumors has shown that TNBC and ovarian cancer have high CD73 expression levels[8]
  - High CD73 expression levels correlate with poor prognosis in patients with TNBC or ovarian cancer[9]
  - Additionally, high levels of $A_{2b}R$ expression are associated with lower survival in TNBC[10]
- In the murine AT-3 mammary adenocarcinoma tumor model, etrumadenant + doxorubicin synergistically inhibited tumor growth[11]
- In addition, preclinical data illustrate crosstalk between phosphoinositide-3-kinase gamma (PI3Kγ) and adenosine signaling pathways; eganelisib (IPI-549), a PI3Kγ inhibitor, is thought to restore antitumor immunity by shifting tumor-associated macrophages to a less immunosuppressive phenotype and enhancing T cell costimulatory function[12]
- Thus, novel combinations of etrumadenant with PLD ± eganelisib potentially offer a nonredundant complementary approach to increase antitumor immune activation and improved anticancer therapy

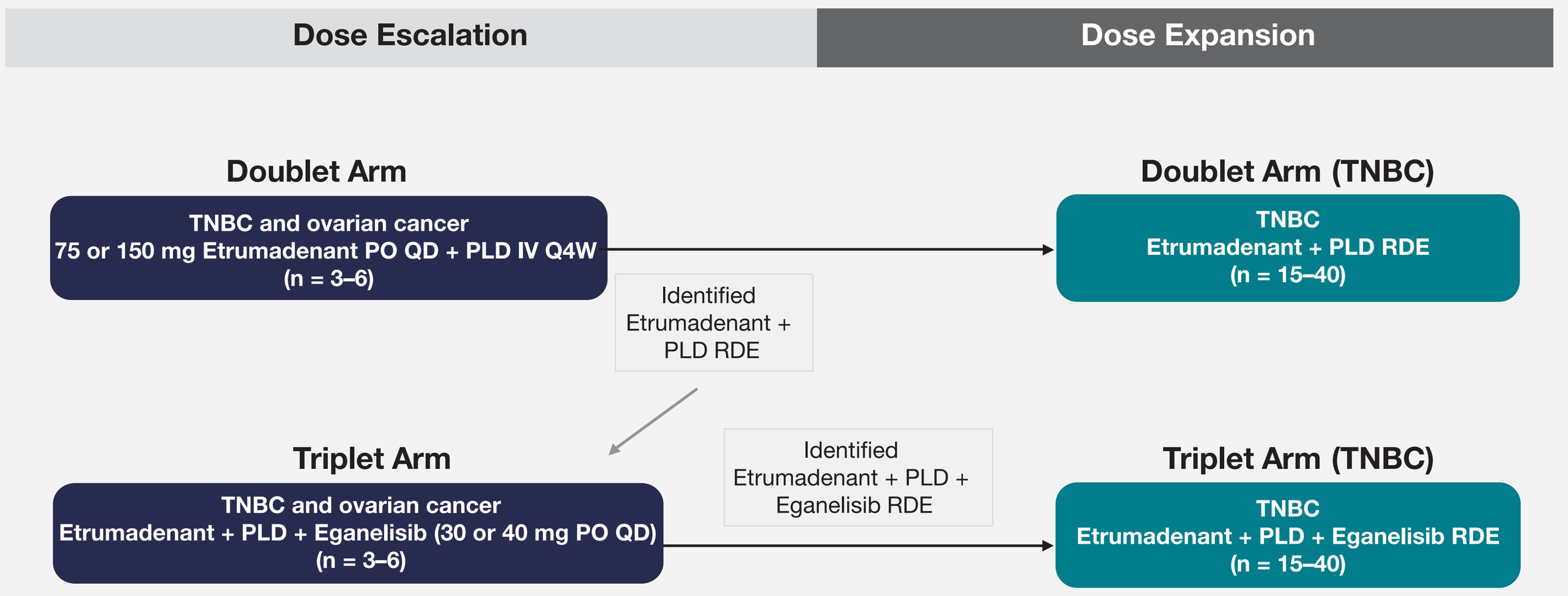
METHODS

Study Design

- ARC-2 (NCT03719326) is an ongoing, Phase 1/1b, open-label, dose-escalation, and dose-expansion study to evaluate the safety, tolerability, and clinical activity of etrumadenant + PLD ± eganelisib in patients with locally advanced or metastatic TNBC or ovarian cancer (**Figure 2**)
- The dose escalation stage was a standard 3+3 design consisting of 2 treatment arms:
  - **Doublet:** Etrumadenant (75 or 150 mg) administered orally (PO) once daily (QD) with a standard intravenous (IV) dose of PLD (40 mg/m²) once every 4 weeks
  - **Triplet:** Etrumadenant (at the RDE identified in doublet arm) + standard IV PLD administered with escalating doses of eganelisib (30 or 40 mg PO QD)
- The dose expansion stage includes study treatment at the RDE in TNBC-specific arms:
  - **Doublet (TNBC):** Etrumadenant (RDE) + PLD
  - **Triplet (TNBC):** Etrumadenant + eganelisib (RDE) + PLD

METHODS

Figure 2. ARC-2 Study Design


Dose Escalation
Dose Expansion
Doublet Arm
TNBC and ovarian cancer
75 or 150 mg Etrumadenant PO QD + PLD IV Q4W
(n = 3–6)
Identified Etrumadenant + PLD RDE
Doublet Arm (TNBC)
TNBC
Etrumadenant + PLD RDE
(n = 15–40)
Triplet Arm
TNBC and ovarian cancer
Etrumadenant + PLD + Eganelisib (30 or 40 mg PO QD)
(n = 3–6)
Identified Etrumadenant + PLD + Eganelisib RDE
Triplet Arm (TNBC)
TNBC
Etrumadenant + PLD + Eganelisib RDE
(n = 15–40)

IV, intravenous; PLD, pegylated liposomal doxorubicin; PO, orally; Q4W, once every 4 weeks; QD, once daily; RDE, recommended dose for expansion; TNBC, triple-negative breast cancer.

ARC-2 Design Features

- Primary objective is safety and tolerability of etrumadenant combination therapy in patients with advanced or metastatic TNBC or ovarian cancer with secondary objectives that include clinical activity
- Eligible patients are adult females with histologically-confirmed, advanced or metastatic TNBC or ovarian cancer; ≥1 measurable lesion per RECIST v1.1; an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1; and must not have received a cumulative lifetime anthracycline dose ≥450 mg/m² **or** ≥200 mg/m² but <450 mg/m² with <50% ejection fraction
- For the dose escalation, any number of prior systemic therapies for advanced or metastatic TNBC or ovarian cancer is allowed
- For the dose expansion, patients are allowed ≤3 prior lines of therapy (including taxane and anthracycline regimens) for advanced or metastatic TNBC; for those who received prior (neo)adjuvant chemotherapy, if disease recurrence is <12 months after completion of therapy, this is considered first-line treatment
- Baseline archival tumor samples (≤6 months old for dose escalation; ≤24 months old for dose expansion) or on-treatment biopsies (if medically feasible) are collected from all patients
- Study treatment may continue until disease progression, unacceptable toxicity, consent withdrawal, or by the investigator's decision

Statistical Analysis

- Safety analyses included all patients who received ≥1 etrumadenant dose; summary statistics are shown for treatment-emergent adverse events (TEAEs), treatment-emergent serious AEs (TESAEs), AE severity, and relationship to study drugs
- Efficacy analyses included all patients who were enrolled and assigned to receive etrumadenant; clinical activity was assessed according to RECIST v1.1 criteria. Evaluable patients were those with ≥1 disease assessment or discontinued the study prior to any disease assessment

RESULTS

Patient Baseline Characteristics

- As of 11OCT2020, 32 patients have received etrumadenant as part of the doublet (n=19) or triplet regimens (n=13; **Table 1**)
  - 150 mg etrumadenant QD was selected as the RDE in combination with standard PLD based on PK, PK/PD correlation, and a well-tolerated safety profile in the dose escalation portion of the study
  - For similar reasons, 40 mg eganelisib QD was selected as the RDE in combination with 150 mg etrumadenant QD and standard PLD
- The number of prior therapies in the metastatic setting for patients in the dose escalation and dose expansion stages range from 0-11 (median=2) and 0-5 (median=1), respectively

Table 1. Patient Demographics and Characteristics

Parameter	Dose Escalation				Dose Expansion		All Patients (N=32)
	Doublet		Triplet		Doublet (TNBC)	Triplet (TNBC)	
			150 mg Etruma + PLD		150 mg Etruma + PLD		
	75 mg Etruma + PLD (n=3)	150 mg Etruma + PLD (n=6)	30 mg Eganelisib (n=3)	40 mg Eganelisib (n=3)	– (n=10)	40 mg Eganelisib (n=7)	
Age, mean (SD), years	58.0 (15.6)	65.2 (11.3)	68.7 (7.6)	68.3 (11.5)	61.0 (9.9)	62.1 (13.8)	63.2 (11.2)
White, n (%)	2 (67)	5 (83)	3 (100)	3 (100)	8 (80)	6 (86)	27 (84)
Disease, n (%)							
Ovarian cancer	3 (100)	4 (67)	3 (100)	1 (33)	0	0	11 (34)
TNBC	0	2 (33)	0	2 (67)	10 (100)	7 (100)	21 (66)
Prior therapies for metastatic disease, n (%)							
0	0	1 (17)	0	1 (33)	2 (20)	1 (14)	5 (16)
1	0	2 (33)	2 (67)	0	5 (50)	3 (43)	12 (37)
2	1 (33)	1 (17)	0	0	0	3 (43)	5 (16)
3+	2 (67)	2 (33)	1 (33)	2 (67)	3 (30)	0	10 (31)
Any prior anthracycline[a], n (%)	3 (100)	3 (50)	0	2 (67)	5 (50)	2 (29)	15 (47)
Any prior immunotherapy[a], n (%)	1 (33)	4 (67)	0	0	3 (30)	2 (29)	10 (31)

[a] Regardless of treatment setting; includes exposure in the neoadjuvant/adjuvant settings, if applicable. Etruma, etrumadenant; PLD, pegylated liposomal doxorubicin; SD, standard deviation; TNBC, triple-negative breast cancer.

RESULTS

Safety Analyses

- As of 11OCT2020, no dose limiting toxicities have been reported in any treatment arm
- As shown in **Table 2**, the most common TEAEs regardless of dose or regimen were fatigue (13/32; 41%), anemia (11/32; 34%), stomatitis (10/32; 31%), constipation (10/32; 31%), and nausea (9/32; 28%)
- Across arms, 24/32 (75%) of patients reported TEAEs that were deemed at least possibly related to etrumadenant
  - 8/32 (25%) patients reported Grade 3 events: fatigue (n=2), anemia (n=1), pruritis (n=1), rash (n=1), rash maculopapular (n=1), aspartate aminotransferase increased (n=1), mucosal inflammation (n=1), neuropathy peripheral (n=1), syncope (n=1), white blood cell count decreased (n=1), and neutrophil count decreased (n=1)
- Regardless of dose or regimen, 4 patients had TESAEs; for 2 patients, these TESAEs were study treatment-related:
  - One patient in the doublet (TNBC) arm (150 mg etrumadenant + PLD) experienced Grade 2 mucosal inflammation that was considered related to etrumadenant and PLD; no action was taken with study treatment and the event resolved with supportive care
  - One patient with ovarian cancer in the doublet arm (75 mg etrumadenant + PLD) had Grade 4 pleural effusion that was considered related to PLD, resulting in etrumadenant interruption and PLD withdrawal; the event resolved after an aspiration procedure and the patient resumed single-agent etrumadenant treatment
- One patient with ovarian cancer in the triplet arm (150 mg etrumadenant + PLD + 30 mg eganelisib), who had a current history of peripheral neuropathy at the time of treatment initiation, experienced Grade 3 peripheral neuropathy related to all drugs in the triplet regimen; the event was not resolved and as a result of the event, the patient discontinued study treatment

Table 2. Treatment-Emergent Adverse Events

Parameter, n (%)	Dose Escalation				Dose Expansion		All Patients (N=32)
	Doublet		Triplet		Doublet (TNBC)	Triplet (TNBC)	
			150 mg Etruma + PLD		150 mg Etruma + PLD		
	75 mg Etruma + PLD (n=3)	150 mg Etruma + PLD (n=6)	30 mg Eganelisib (n=3)	40 mg Eganelisib (n=3)	– (n=10)	40 mg Eganelisib (n=7)	
Any TEAE	3 (100)	6 (100)	3 (100)	3 (100)	9 (90)	7 (100)	31 (97)
Grade ≥3	3 (100)	4 (67)	1 (33)	2 (67)	3 (30)	4 (57)	17 (53)
Any TESAE	2 (67)	1 (17)	0	0	1 (10)	0	4 (13)
Grade ≥3	2 (67)	1 (17)	0	0	1 (10)	0	4 (13)
Etruma-related TEAEs	2 (67)	4 (67)	2 (67)	3 (100)	7 (70)	6 (86)	24 (75)
Grade ≥3	0	2 (33)	1 (33)	1 (33)	1 (10)	3 (43)	8 (25)
Etruma-related TESAEs	0	0	0	0	1 (10)	0	1 (3)
Grade ≥3	0	0	0	0	0	0	0
Any study treatment d/c due to TEAEs	2 (67)	0	1 (33)	0	2 (20)	1 (14)	6 (19)
Deaths due to TEAEs	0	0	0	0	0	0	0
TEAEs in >20% of patients							
Fatigue	1 (33)	4 (67)	1 (33)	2 (67)	5 (50)	0	13 (41)
Anemia	3 (100)	3 (50)	1 (33)	2 (67)	2 (20)	0	11 (34)
Stomatitis	1 (33)	1 (17)	0	1 (33)	3 (30)	4 (57)	10 (31)
Constipation	0	4 (67)	1 (33)	1 (33)	2 (20)	2 (29)	10 (31)
Nausea	0	1 (17)	0	1 (33)	6 (60)	1 (14)	9 (28)
Palmar-plantar erythrodysesthesia syndrome	0	1 (17)	0	1 (33)	3 (30)	3 (43)	8 (25)
Rash	0	1 (17)	0	0	3 (30)	4 (57)	8 (25)
Pruritus	1 (33)	1 (17)	0	1 (33)	2 (20)	2 (29)	7 (22)
Cough	1 (33)	2 (33)	0	0	3 (30)	1 (14)	7 (22)

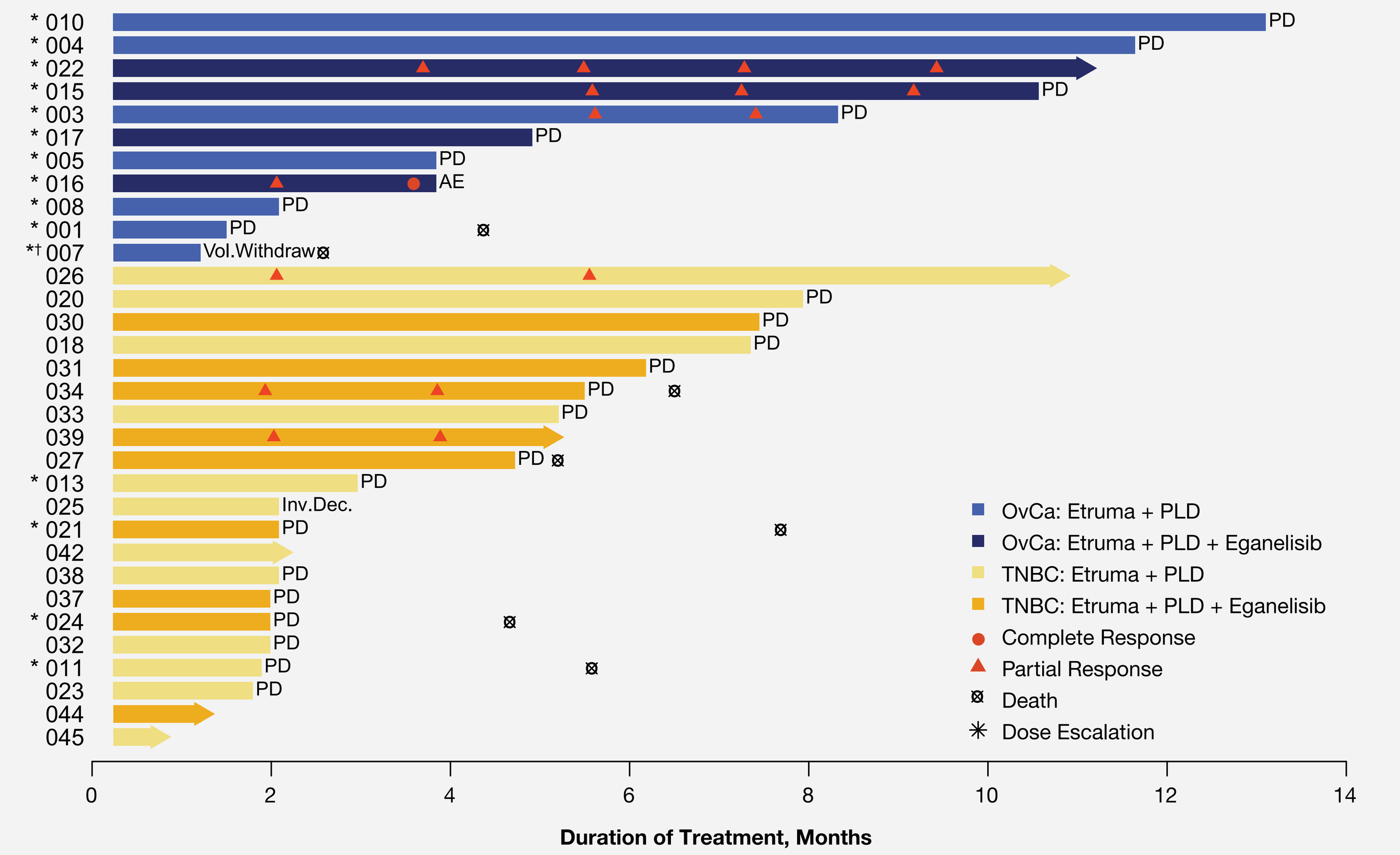
d/c, discontinuation; Etruma, etrumadenant; PLD, pegylated liposomal doxorubicin; QD, once daily; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

Clinical Activity

- As of 11OCT2020, 5 patients with TNBC and 1 patient with ovarian cancer remained on active treatment; 3 patients are receiving the doublet regimen, 3 are receiving the triplet regimen (**Figure 3**)
- Of 18 evaluable patients treated with the doublet regimen:
  - 2 patients (1 TNBC, 1 ovarian) achieved a partial response (PR) and 9 had stable disease (SD) as a best response
- Of 12 evaluable patients treated with the triplet regimen:
  - 1 patient achieved a complete response (CR; ovarian), 4 had a PR (2 ovarian, 2 TNBC), and 4 had SD as a best response
- Regardless of treatment setting, 10 patients received a prior treatment regimen that included immunotherapy or matched placebo
  - 9 of 10 patients have completed ≥1 on-study disease evaluation
  - 2 of these 9 patients achieved a PR (both confirmed): 1 with ovarian cancer (003) and 1 with TNBC (034)
- Regardless of treatment setting, 15 patients received a prior treatment regimen that included an anthracycline
  - 14 of 15 patients have completed ≥1 on-study disease evaluation
  - 8 patients achieved SD, including 1 with ovarian cancer (004) who received the doublet regimen for >11 months

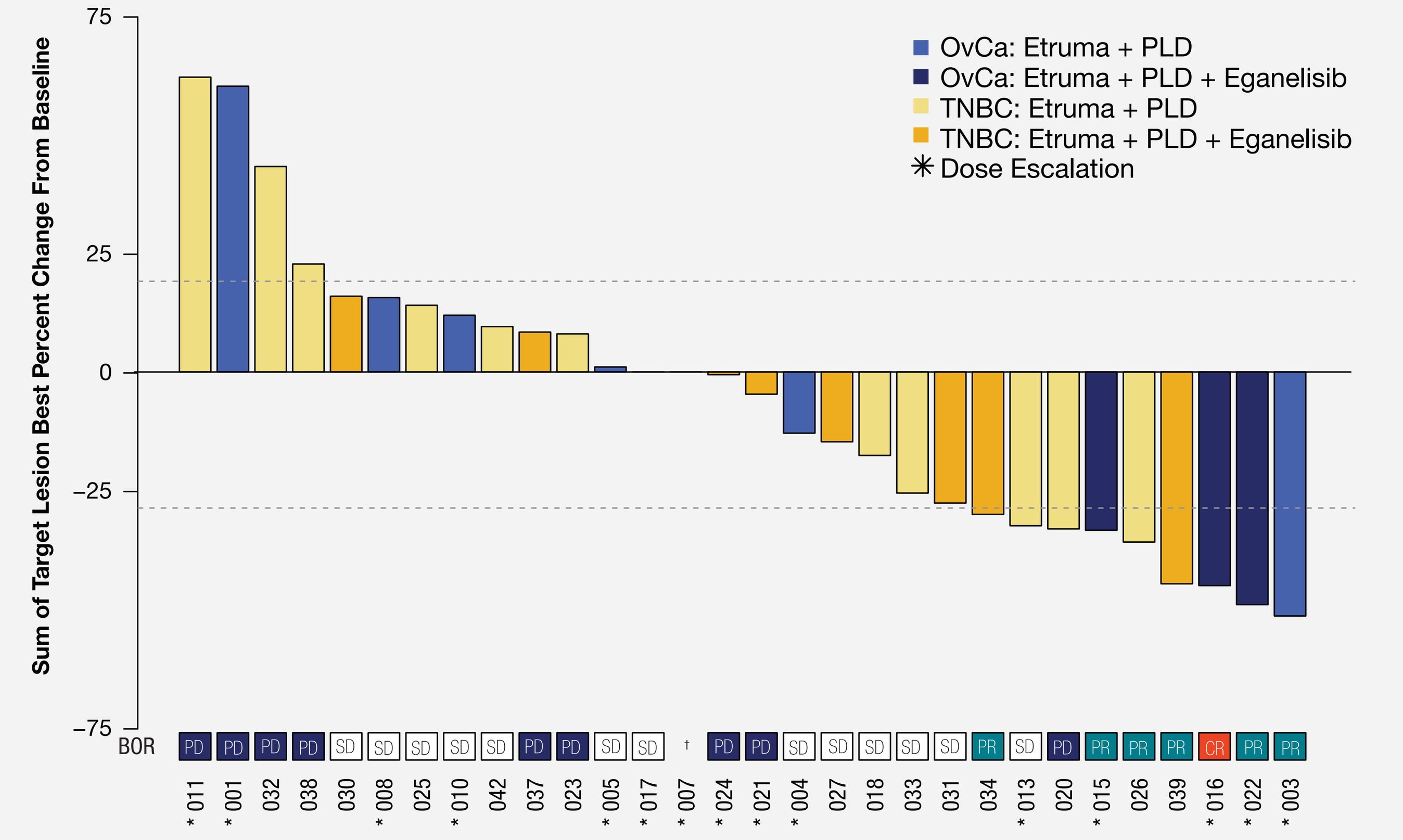
RESULTS

Figure 3. Time on Treatment and RECIST v1.1 Response



AE, adverse event; Etruma, etrumadenant; Inv.Dec., discontinuation due to investigator decision; OvCa, ovarian cancer; PD, progressive disease; PLD, pegylated liposomal doxorubicin; TNBC, triple-negative breast cancer.

Figure 4. Waterfall Plot of Best Percent Change from Baseline in Sum of Target Lesions



† Patient withdrew prior to first disease assessment. BOR, best overall response; CR, complete response; Etruma, etrumadenant; OvCa, ovarian cancer; PD, progressive disease; PLD, pegylated liposomal doxorubicin; PR, partial response; SD, stable disease; TNBC, triple-negative breast cancer.

CONCLUSIONS

- Etrumadenant + PLD ± eganelisib has been well tolerated without significant evidence of additive toxicity in patients with advanced TNBC or ovarian cancer
- Doublet and triplet combination therapy regimens were both associated with clinical benefit, including in late-line patients who had disease progression after prior immunotherapy or anthracycline treatment; these encouraging results warrant further exploration
- Enrollment of patients with TNBC is proceeding in the doublet and triplet dose expansion arms
- Across the etrumadenant program, extensive tissue/blood biomarker characterization is ongoing

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