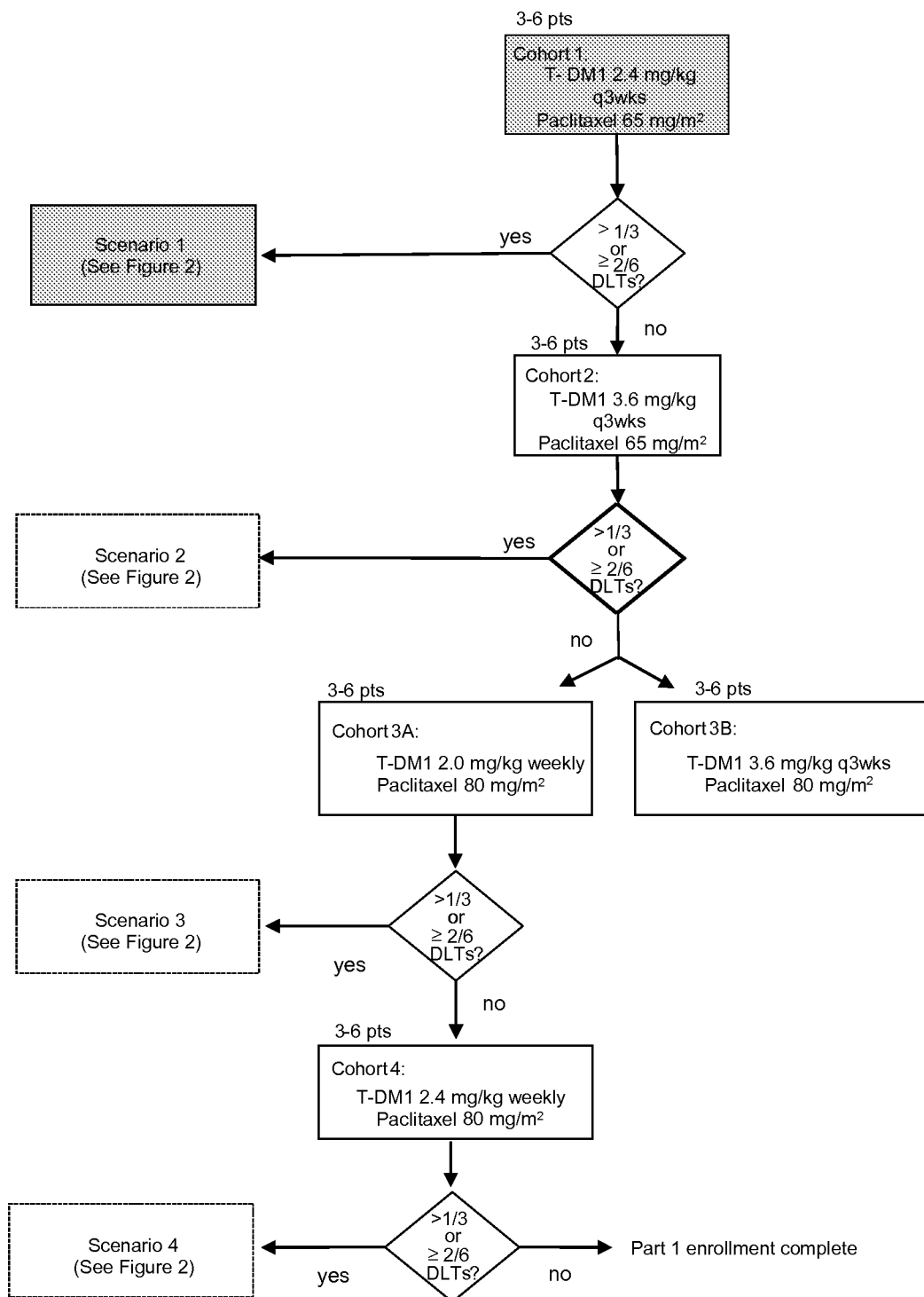


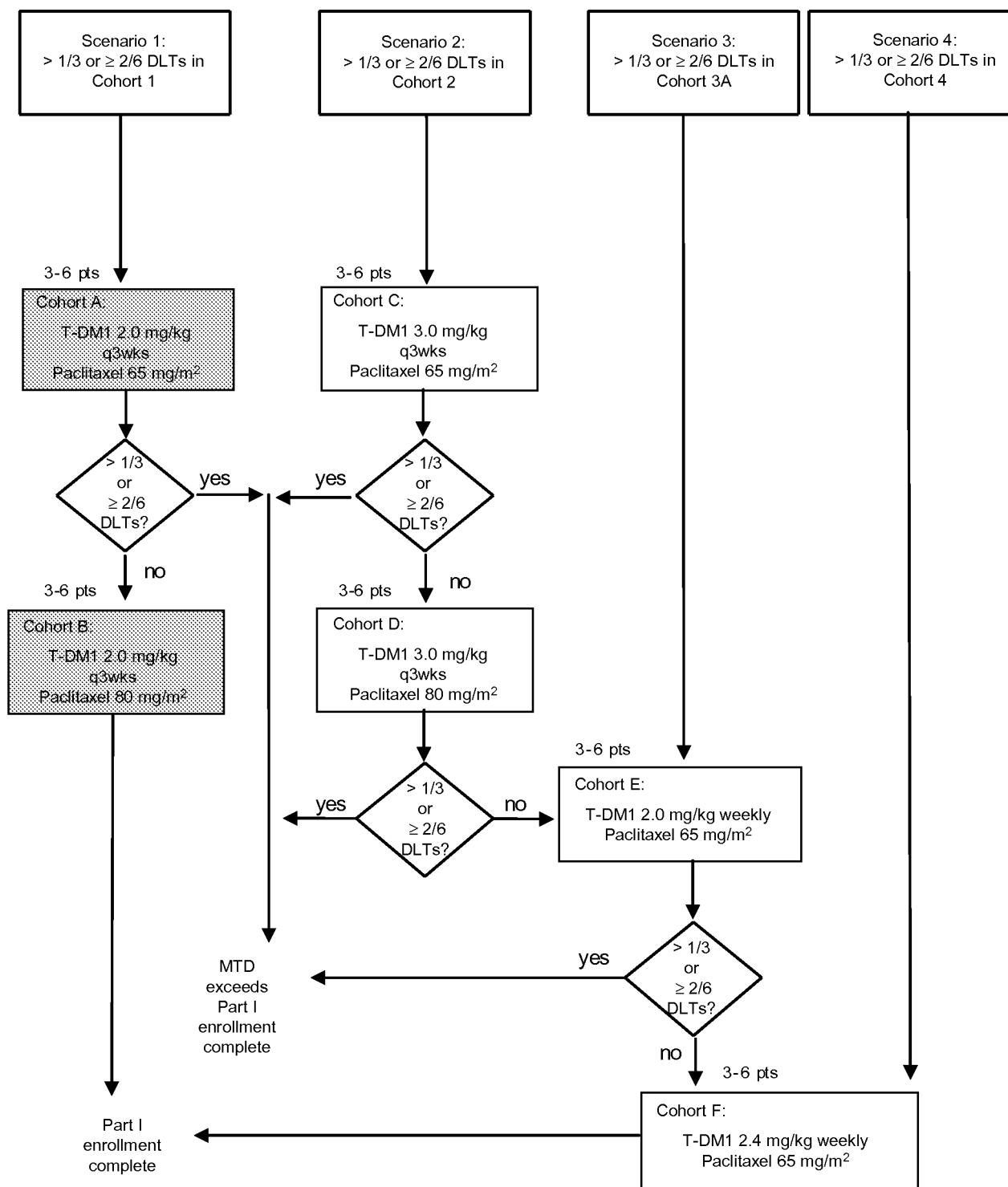
Figure 1
Study Schema for Study Part 1 (Dose Escalation)



DLT = dose-limiting toxicity; q3wks = every 3 weeks; T-DM1 = trastuzumab-MCC-DM1.

Note: All cohorts shaded in gray have been completed. All other cohorts were not explored.

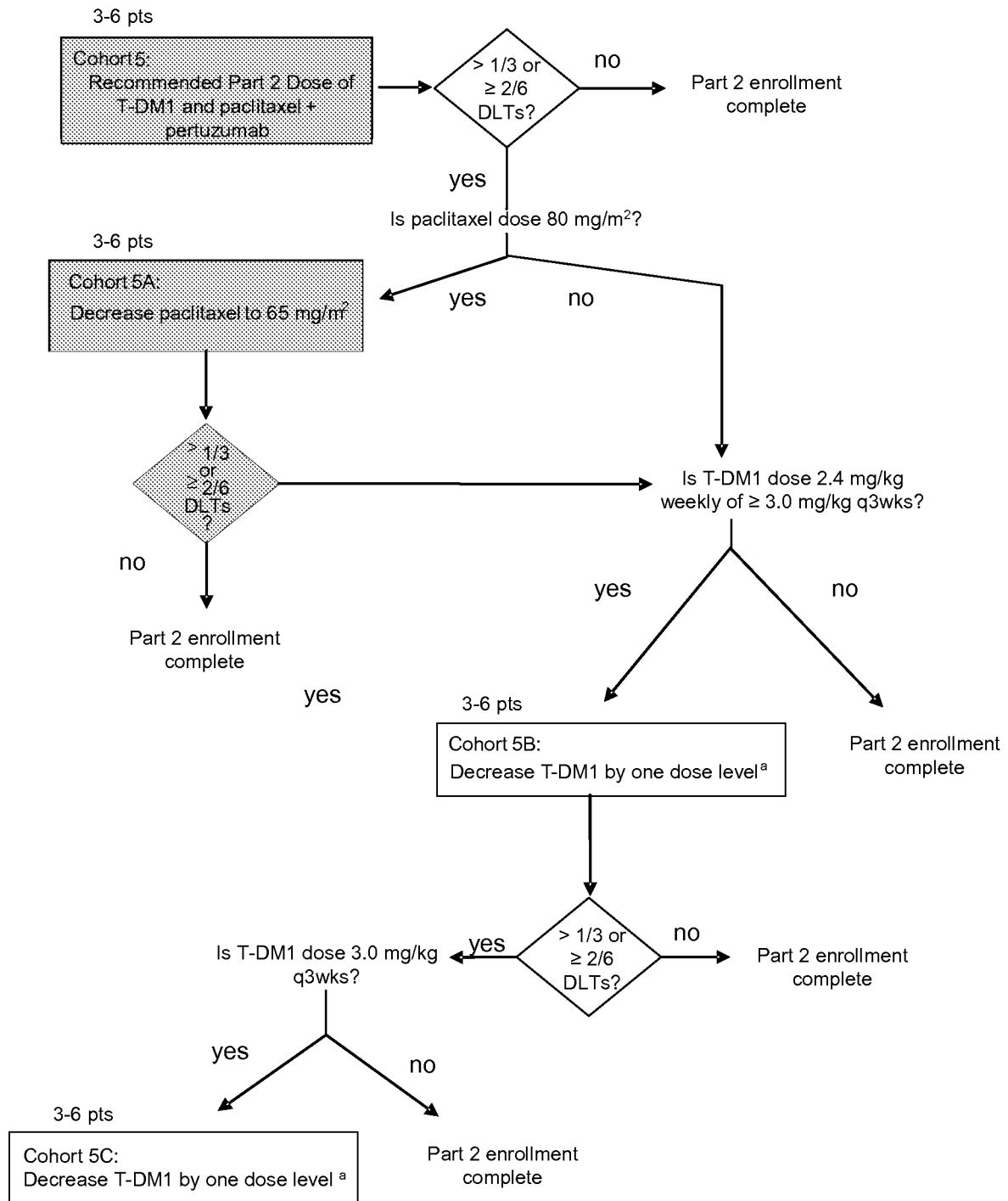
Figure 2
Alternative Scenarios for Study Part 1 (Dose Escalation)



DLT = dose-limiting toxicity; MTD = maximum tolerated dose; q3wks = every 3 weeks;
T-DM1 = trastuzumab-MCC-DM1.

Note: All cohorts shaded in gray have been completed. All other cohorts were not explored.

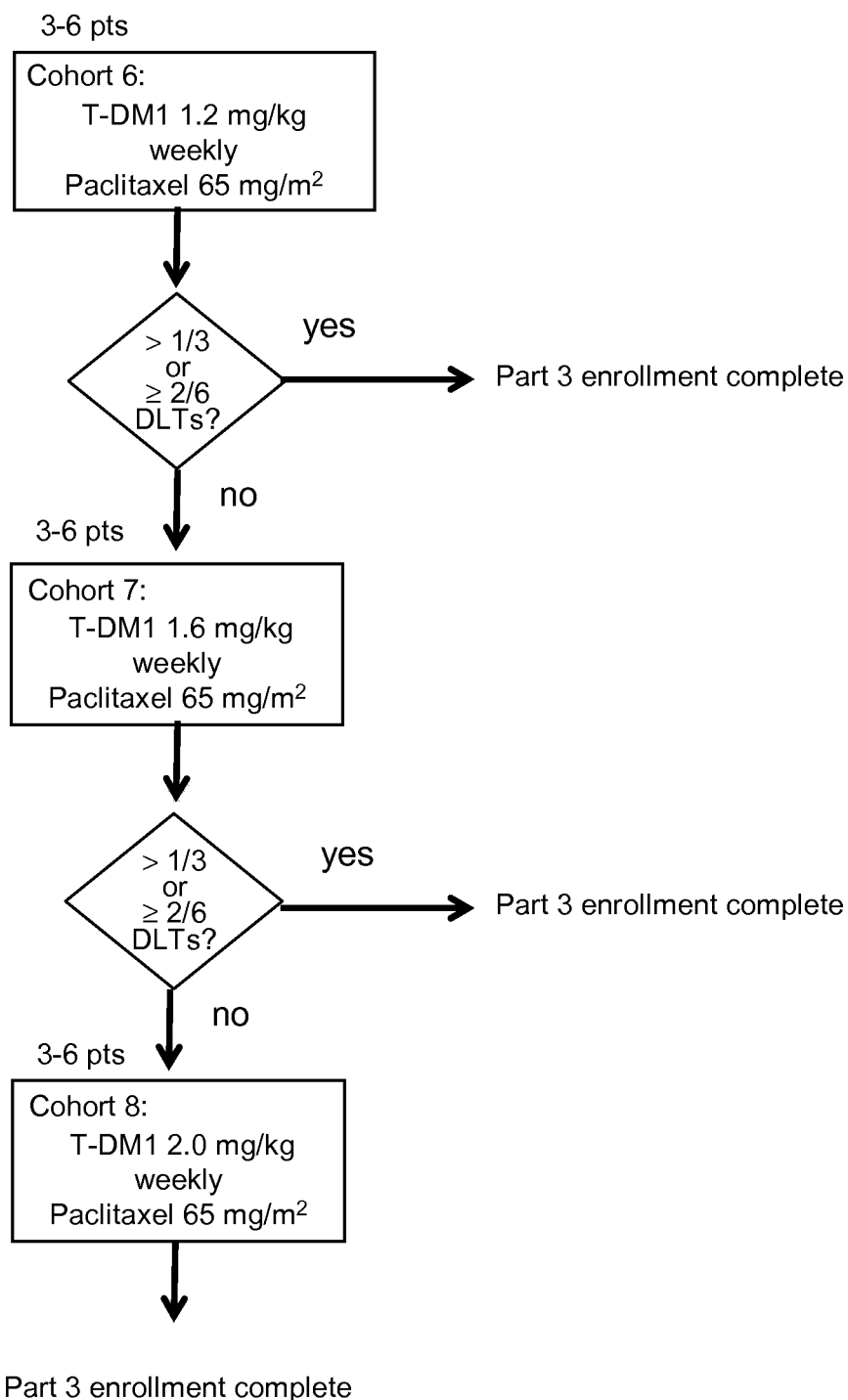
Figure 3
Study Schema for Study Part 2 (Addition of Pertuzumab)



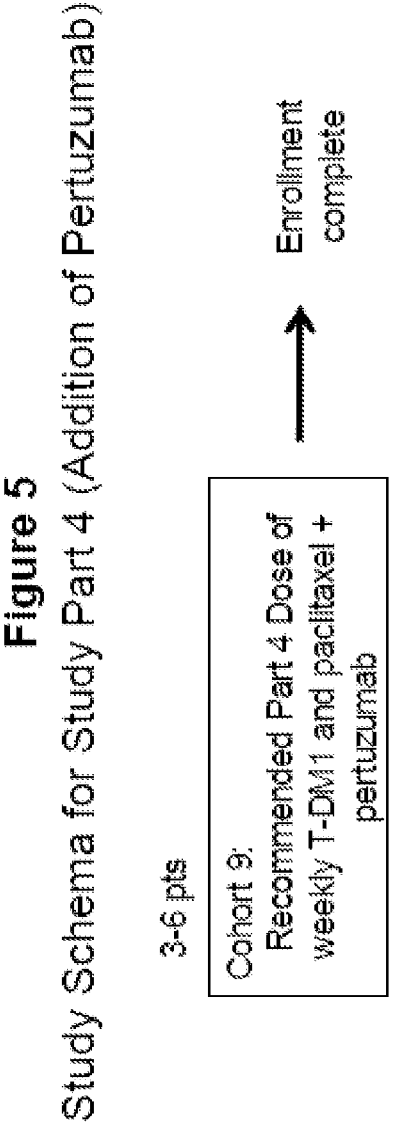
DLT = dose-limiting toxicity; q3wks = every 3 weeks; T-DM1 = trastuzumab-MCC-DM1.

^a Per the T-DM1 dose-reduction guidelines in Table 6.

Note: All cohorts shaded in gray have been completed. All other cohorts were not explored.

Figure 4**Study Schema for Study Part 3 (Dose Escalation)**

DLT = dose-limiting toxicity; T-DM1 = trastuzumab-MCC-DM1.



T-DM1 • trastuzumab-MCC-DM1.

Dosing, SAEs and DLTs and Best Responses

Part/Cohort	Dosing	SAEs ^a	DLTs ^b	Best Response
Part 1. T-DM1 q3w + paclitaxel weekly				
Cohort 1 (n=5) (no patient ongoing)	T-DM1 2.4 mg/kg + Paclitaxel 65 mg/m ²	Grade 2 vomiting and Grade 3 dehydration (n=1)	Grade 3 dehydration due to Grade 2 Vomiting (n=1); Grade 3 AST/ALT (n=1)	2 PR (1 confirmed) 1 SD 2 PD
Cohort A (n=3) (1 patient ongoing)	T-DM1 2 mg/kg + Paclitaxel 65 mg/m ²	Grade 3 Cellulitis and Grade 3 muscular weakness (n=1); Grade 3 intervertebral disc protrusion (n=1); Grade 3 hypersensitivity (n=1)	None	2 confirmed PRs 1 SD
Cohort B (n=6) (4 patients ongoing)	T-DM1 2 mg/kg + Paclitaxel 80 mg/m ²	None	Grade 3 Neutropenia (n=1)	2 PR (1 confirmed) 2 SD 2 PD
Part 2. T-DM1 q3w + paclitaxel weekly = pertuzumab 420 mg q3w				
Cohort5 (n=4) (3 patients ongoing)	T-DM1 2 mg/kg + Paclitaxel 80 mg/m ²	Grade 3 pneumonia (n=1) Grade 4 thrombocytopenia (n=1)	Grade 3 neutropenia (n=1) Grade 4 thrombocytopenia (n=1)	4 PR (3 confirmed)
Cohort 5A (n=3) (3 patients ongoing)	T-DM1 2 mg/kg + Paclitaxel 65 mg/m ² + Pertuzumab 420 mg	Grade 3 deep vein thrombosis (n=1)	None	1 confirmed PR 2 SD
Part 3. T-DM1 weekly + paclitaxel weekly				
Cohort 6 (n=3) (3 patients ongoing)	T-DM1 1.2 mg/kg + Paclitaxel 65 mg/m ²	None	None	2 unconfirmed PR 1 SD

SAE = serious AE; DLT = dose-limiting toxicity; AST = aspartate aminotransferase; ALT = alanine aminotransferase; PR = partial response; SD = stable disease;

PD = progressive disease

^aSAEs were collected on case report forms and were described in the study protocol, under NCI-CTC v.3.

^bThe study definition of DLTs included any Grade >3 non-hematologic adverse event; Grade >3 elevation of serum bilirubin, hepatic transaminases (ALT or AST), or alkaline phosphatase (ALP) lasting >72 hours; Grade 2 hepatic transaminase levels at baseline (<5 x the upper limit of normal [ULN]) as a result of liver or bone metastases, a hepatic transaminase or ALP level >10 x ULN; Grade >4 thrombocytopenia; Grade >4 neutropenia lasting >72 hours or accompanied by a fever, any subjectively intolerable toxicity felt by the investigator to be related to T-DM1, paclitaxel, or pertuzumab; any treatment-related toxicity prompting a dose delay or modification of T-DM1 during the DLT observation period, such as prompting a dose reduction at Cycle 2, Day 1: any treatment-related toxicity prompting more than one weekly paclitaxel dose delay or any weekly paclitaxel dose modification during the DLT observation period. For Parts 1 and 2, a dose delay of weekly paclitaxel during the DLT observation period was considered a DLT.