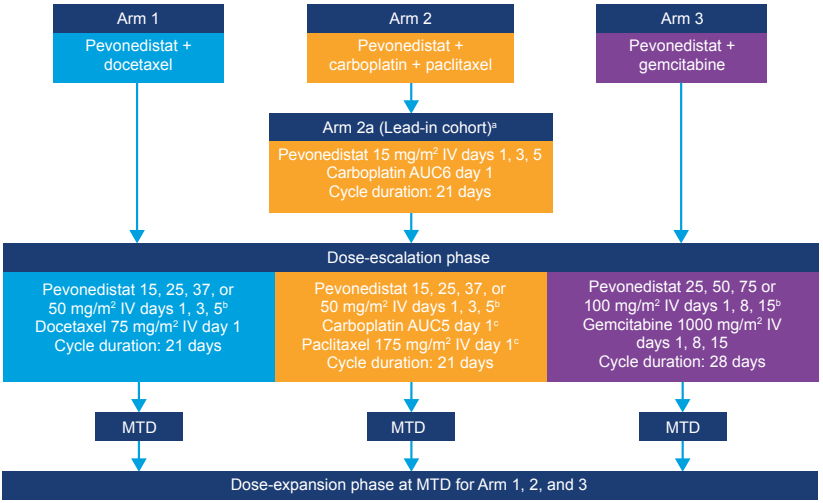
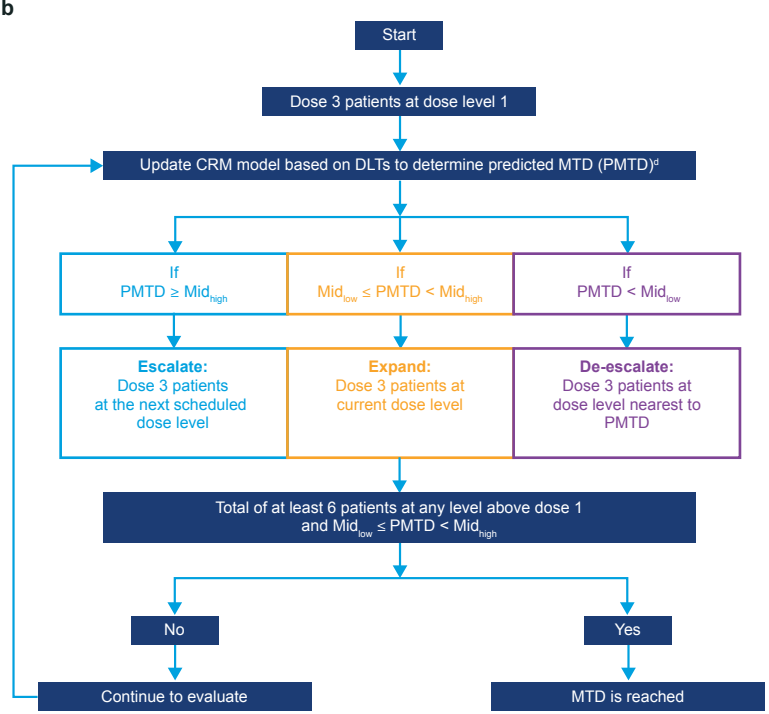
a


Arm 1
Pevonedistat + docetaxel
Arm 2
Pevonedistat + carboplatin + paclitaxel
Arm 3
Pevonedistat + gemcitabine
Arm 2a (Lead-in cohort)[a]
Pevonedistat 15 mg/m² IV days 1, 3, 5
Carboplatin AUC6 day 1
Cycle duration: 21 days
Dose-escalation phase
Pevonedistat 15, 25, 37, or 50 mg/m² IV days 1, 3, 5[b]
Docetaxel 75 mg/m² IV day 1
Cycle duration: 21 days
Pevonedistat 15, 25, 37, or 50 mg/m² IV days 1, 3, 5[b]
Carboplatin AUC5 day 1[c]
Paclitaxel 175 mg/m² IV day 1[c]
Cycle duration: 21 days
Pevonedistat 25, 50, 75 or 100 mg/m² IV days 1, 8, 15[b]
Gemcitabine 1000 mg/m² IV days 1, 8, 15
Cycle duration: 28 days
MTD
MTD
MTD
Dose-expansion phase at MTD for Arm 1, 2, and 3

b


Start
Dose 3 patients at dose level 1
Update CRM model based on DLTs to determine predicted MTD (PMTD)[d]
If PMTD ≥ Mid_high
If Mid_low ≤ PMTD < Mid_high
If PMTD < Mid_low
Escalate: Dose 3 patients at the next scheduled dose level
Expand: Dose 3 patients at current dose level
De-escalate: Dose 3 patients at dose level nearest to PMTD
Total of at least 6 patients at any level above dose 1 and Mid_low ≤ PMTD < Mid_high
No
Yes
Continue to evaluate
MTD is reached