## SUPPLEMENTARY TABLES AND FIGURES

## TABLES

**Supplementary Table S1.** Treatment Duration and Follow -Up

| | Dose escalation | | | | Dose expansion | Pooled RDE | All patients |
|---|---|---|---|---|---|---|---|
| | 3.2 mg/kg (N=4) | 4.8 mg/kg (N=15) | 5.6 mg/kg (N=12) | 6.4 mg/kg (N=5) | 5.6 mg/kg (N=45) | 5.6 mg/kg (N=57) | All doses (N=81) |
| Treatment duration, median (range), months | 6.1 (2.8-28.3) | 5.6 (0.7-22.9) | 3.8 (0.7-18.6) | 9.7 (1.4-22.1) | 5.5 (0.7-11.8) | 5.5 (0.7-18.6) | 5.7 (0.7-28.3) |
| Follow-up after start of study treatment, median (range), months | 29.8 (29.3-31.8) | 20.6 (15.0-25.6) | 19.2 (17.9-19.9) | 27.7 (22.2-28.3) | 9.2 (5.2-12.7) | 10.2 (5.2-19.9) | 11.8 (5.2-31.8) |
| Patients remaining on treatment, n (%) | 0 | 0 | 2 (17) | 0 | 16 (36) | 18 (32) | 18 (22) |
| Discontinued treatment, n (%) | 4 (100) | 15 (100) | 10 (83) | 5 (100) | 29 (64) | 39 (68) | 63 (78) |
| Primary reason for discontinuation, n (%) | | | | | | | |
| Progressive disease (per RECIST 1.1)[a] | 3 (75) | 8 (53) | 8 (67) | 4 (80) | 14 (31) | 22 (39) | 37 (46) |
| Clinical progression[a] | 1 (25) | 2 (13) | 0 | 1 (20) | 6 (13) | 6 (11) | 10 (12) |
| Adverse event | 0 | 1 (7) | 1 (8) | 0 | 4 (9) | 5 (9) | 6 (7) |
| Withdrawal of consent | 0 | 3 (20) | 0 | 0 | 2 (4) | 2 (4) | 5 (6) |
| Investigator decision | 0 | 1 (7) | 0 | 0 | 1 (2) | 1 (2) | 2 (2) |
| Death | 0 | 0 | 1 (8) | 0 | 2 (4) | 3 (5) | 3 (4) |

[a] Assessed by investigator.

**Supplementary Table S2.** Safety Summary by Dose Group

| | Dose escalation | | | | Dose expansion |
|---|---|---|---|---|---|
| | 3.2 mg/kg (N=4) | 4.8 mg/kg (N=15) | 5.6 mg/kg (N=12) | 6.4 mg/kg (N=5) | 5.6 mg/kg (N=45) |
| Any TEAE | 4 (100) | 15 (100) | 12 (100) | 5 (100) | 45 (100) |
| Grade ≥3 TEAEs | 0 | 7 (47) | 8 (67) | 3 (60) | 34 (76) |
| TEAEs associated with death | 0 | 1 (7) | 1 (8) | 0 | 3 (7) |
| TEAEs associated with treatment discontinuation | 0 | 1 (7) | 1 (8) | 0 | 5 (11) |
| TEAEs associated with dose interruption | 1 (25) | 5 (33) | 1 (8) | 3 (60) | 20 (44) |
| TEAEs associated with dose reduction | 0 | 3 (20) | 2 (17) | 3 (60) | 10 (22) |
| Serious TEAEs | 1 (25) | 6 (40) | 5 (42) | 0 | 20 (44) |
| Treatment-related TEAEs | 4 (100) | 14 (93) | 12 (100) | 5 (100) | 43 (96) |
| Grade ≥3 TEAEs | 0 | 4 (27) | 5 (42) | 3 (60) | 26 (58) |
| TEAEs associated with death | 0 | 0 | 0 | 0 | 0 |
| Serious TEAEs | 0 | 3 (20) | 3 (25) | 0 | 9 (20) |

**Supplementary Table S3.** Clinical Activity by Dose Group as Assessed by BICR according to RECIST 1.1

| | Dose escalation | | | | Dose expansion | Pooled RDE with prior PBC |
|---|---|---|---|---|---|---|
| | 3.2 mg/kg (N=4) | 4.8 mg/kg (N=15) | 5.6 mg/kg (N=12) | 6.4 mg/kg (N=5) | 5.6 mg/kg (N=45) | 5.6 mg/kg (N=52) |
| Confirmed ORR, % (n) [95% CI] | 25 (1) [0.6-80.6] | 33 (5) [11.8-61.6] | 42 (5) [15.2-72.3] | 80 (4) [28.4-99.5] | 38 (17) [23.8-53.5] | 37 (19) [23.6-51.0] |
| Best overall response, n (%) | CR, 0<br>PR, 1 (25)<br>SD, 3 (75)<br>PD, 0<br>NE, 0 | CR, 0<br>PR, 5 (33)<br>SD, 5 (33)<br>PD, 2 (13)<br>NE, 3 (20) | CR, 0<br>PR, 5 (42)<br>SD, 4 (33)<br>PD, 2 (17)<br>NE, 1 (8) | CR, 0<br>PR, 4 (80)<br>SD, 1 (20)<br>PD, 0<br>NE, 0 | CR, 1 (2)<br>PR, 16 (36)<br>SD, 15 (33)<br>PD, 7 (16)<br>NE, 6 (13) | CR, 1 (2)<br>PR, 18 (35)<br>SD, 19 (37)<br>PD, 8 (15)<br>NE, 6 (12) |
| Disease control rate,[a] % (n) [95% CI] | 100 (4) [39.8-100] | 67 (10) [38.4-88.2] | 75 (9) [42.8-94.5] | 100 (5) [47.8-100] | 71 (32) [55.7-83.6] | 73 (38) [59.0-84.4] |
| Time to response, median (range), months | 5.5 (5.5-5.5) | 2.6 (1.2-5.4) | 1.4 (1.3-2.6) | 2.7 (1.2-4.2) | 2.7 (1.2-5.4) | 2.7 (1.2-5.4) |
| Duration of response, median (95% CI), months | 11.0 (NE-NE) | 5.6 (4.1-17.5) | 5.0 (3.0-7.0) | 8.0 (4.1-11.1) | NE (5.6-NE) | 7.0 (5.6-NE) |
| Progression-free survival, median (95% CI), months | 4.9 (2.8-16.5) | 5.4 (1.4-11.2) | 5.6 (1.4-8.3) | 11.0 (7.6-13.7) | 8.3 (4.7-NE) | 8.2 (4.4-NE) |
| Overall survival, median (95% CI), months | 12.4 (7.7-NE) | 16.8 (6.4-NE) | NE (4.4-NE) | 23.2 (11.5-NE) | 11.6 (8.2-11.6) | NE (11.6-NE) |

PBC, platinum-based chemotherapy.

[a] Disease control rate = rate of confirmed BOR of CR, PR, or SD.

**Supplementary Table S4.** Adverse Events of Any Causality Occurring in ≥15% of Patients

| TEAEs, n (%) | Pooled RDE 5.6 mg/kg (N=57) | All patients 3.2/4.8/5.6/6.4 mg/kg (N=81) |
|---|---|---|
| Fatigue | 37 (65) | 52 (64) |
| Nausea | 34 (60) | 49 (60) |
| Platelet count decreased/thrombocytopenia | 30 (53) | 40 (49) |
| Decreased appetite | 24 (42) | 32 (40) |
| Vomiting | 18 (32) | 30 (37) |
| Alopecia | 17 (30) | 26 (32) |
| Neutrophil count decreased/neutropenia | 20 (35) | 26 (32) |
| Anemia/hemoglobin decreased | 19 (33) | 24 (30) |
| Constipation | 17 (30) | 23 (28) |
| Hypokalemia | 12 (21) | 17 (21) |
| Diarrhea | 11 (19) | 16 (20) |
| Dyspnea | 11 (19) | 16 (20) |
| Cough | 10 (18) | 15 (19) |
| Aspartate aminotransferase increased | 7 (12) | 13 (16) |
| Dizziness | 9 (16) | 13 (16) |

**Supplementary Table S5.** Protocol Recommendations for Management of Suspected Interstitial Lung Disease

| Worst toxicity grade NCI-CTCAE v5.0 | **Schedule modification for HER3-DXd** |
|---|---|
| Grade 1 | The administration of HER3-DXd must be delayed. HER3-DXd can be restarted only if the event is fully resolved to grade 0:<br>• If resolved in ≤28 days from day of onset, maintain dose.<br>• If resolved in >28 days from day of onset, reduce dose 1 level.<br>Toxicity management:<br>• Monitor and closely follow up in 2 to 7 days for onset of clinical symptoms and pulse oximetry.<br>• Consider follow-up imaging in 1 to 2 weeks (or as clinically indicated).<br>• Consider starting systemic steroids (eg, at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks.<br>• If diagnostic observations worsen despite initiation of corticosteroids, follow grade 2 guidelines (if patient is asymptomatic, then patient should still be considered as having toxicity grade 1 even if steroid treatment is given). |
| Grade 2 | Permanently discontinue patient from HER3-DXd.<br>Toxicity management:<br>• Promptly start systemic steroids (eg, at least 1 mg/kg/day prednisone or equivalent) for a minimum of 14 days or until complete resolution of clinical symptoms and chest CT scan findings, followed by gradual taper over at least 4 weeks.<br>• Monitor symptoms closely.<br>• Reimage as clinically indicated.<br>• If worsening or no improvement in clinical or diagnostic observations in 5 days,<br>  ○ Consider increasing dose of steroids (eg, 2 mg/kg/day prednisone or equivalent); administration may be switched to IV (eg, methylprednisolone).<br>  ○ Reconsider additional workup for alternative etiologies. |

| | |
|---|---|
| | ○ Escalate care as clinically indicated. |
| Grade 3 or 4 | Permanently discontinue subject from HER3-DXd.<br><br>Toxicity management:<br><br>• Hospitalization required.<br><br>• Promptly initiate empiric high-dose methylprednisolone IV treatment (eg, 500 to 1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) for a minimum of 14 days or until complete resolution of clinical symptoms and chest CT findings, followed by gradual taper over at least 4 weeks.<br><br>• Reimage as clinically indicated.<br><br>• If still no improvement within 3 to 5 days,<br><br>  • Reconsider additional workup for alternative etiologies.<br><br>  • Consider other immunosuppressants and/or treat per local practice. |

**Supplementary Table S6.** Pharmacokinetic Properties of Released MAAA-1181a (HER3-DXd Payload) and MAAA-1181a Conjugated Antibody for All Dose Groups (N=81[a]; data are mean [SD])

| MAAA-1181a conjugated antibody | Dose escalation (frozen liquid formulation) | | | | Dose expansion (lyophilized powder formulation) |
|---|---|---|---|---|---|
| | 3.2 mg/kg (N=4) | 4.8 mg/kg (N=9) | 5.6 mg/kg (N=10) | 6.4 mg/kg (N=5) | (5.6 mg/kg; N=28) |
| $C_{max}$, ug/mL | 72.6 (9.7) | 105 (22.4) | 130 (28.9) | 141 (24.1) | 121 (20.7) |
| $AUC_{last}$, ug•day/mL | 227 (71.5) | 424 (148) | 597 (175) | 572 (93.8) | 515 (142) |
| Tmax, h | 2.67 (1.16) | 2.49 (1.45) | 1.57 (0.06) | 1.57 (0.07) | 2.71 (1.33) |
| $AUC_{inf}$, ug•day/mL | 232 (74.6) | 450 (175) | 666 (217) | 649 (109) | 556 (174) |
| $t_{1/2}$, days | 3.64 (1.14) | 4.90 (1.06) | 6.73 (1.54) | 6.95 (2.46) | 5.60 (1.32) |
| CL, mL/day/kg | 15.3 (6.44) | 12.2 (4.30) | 9.47 (3.92) | 10.3 (1.97) | 10.9 (3.03) |
| Vss, mL/kg | 62.2 (8.08) | 69.4 (17.6) | 71.9 (15.5) | 90.9 (19.6) | 72.9 (12.9) |

| Released MAAA-1181a | Dose escalation (frozen liquid formulation) | | | | Dose expansion (lyophilized powder formulation) |
|---|---|---|---|---|---|
| | 3.2 mg/kg (N=4) | 4.8 mg/kg (N=10) | 5.6 mg/kg (N=10) | 6.4 mg/kg (N=3) | (5.6 mg/kg; N=30) |
| $C_{max}$, ng/mL | 13.9 (7.6) | 13.3 (3.3) | 21.7 (8.0) | 21.7 (6.4) | 22.5 (7.6) |
| $AUC_{last}$, ng•day/mL | 24.2 (10.2) | 31.5 (8.5) | 47.4 (10.4) | 46.4 (9.2) | 48.3 (17.8) |
| $T_{max}$, h | 3.66 (0.15) | 3.53 (0.14) | 3.75 (0.62) | 3.49 (0.02) | 3.66 (0.71) |
| $AUC_{inf}$, ng•day/mL | 24.5 (10.2) | 29.9 (7.2; n=8) | 51.1 (10.0; n=8) | 52.8 (8.8; n=2) | 49.1 (18.6; n=27) |
| $t_{1/2}$, days | 4.38 (0.77) | 4.46 (0.86; n=8) | 5.80 (1.22; n=8) | 5.91 (0.29; n=2) | 4.95 (1.08; n=27) |

$AUC_{inf}$, area under the concentration vs time curve from time zero extrapolated to infinity; $AUC_{last}$, area under the concentration vs time curve from time zero to the time of the last quantifiable concentration; CL, weight-adjusted total body clearance; $t_{1/2}$, terminal elimination half-life; $T_{max}$, time of observed $C_{max}$; Vss, volume of distribution at steady state.

[a] Although patients with missing data points were not automatically excluded from this analysis, not all patients had sufficient PK data points to warrant inclusion.

**Supplementary Table S7.** Geometric Mean Ratios of Cycle 1 PK Parameters for Lyophilized Powder Drug Product (Dose-Expansion Cohort 1) and Frozen Liquid Drug Product (Dose Escalation) of HER3-DXd at 5.6 mg/kg Q3W[a]

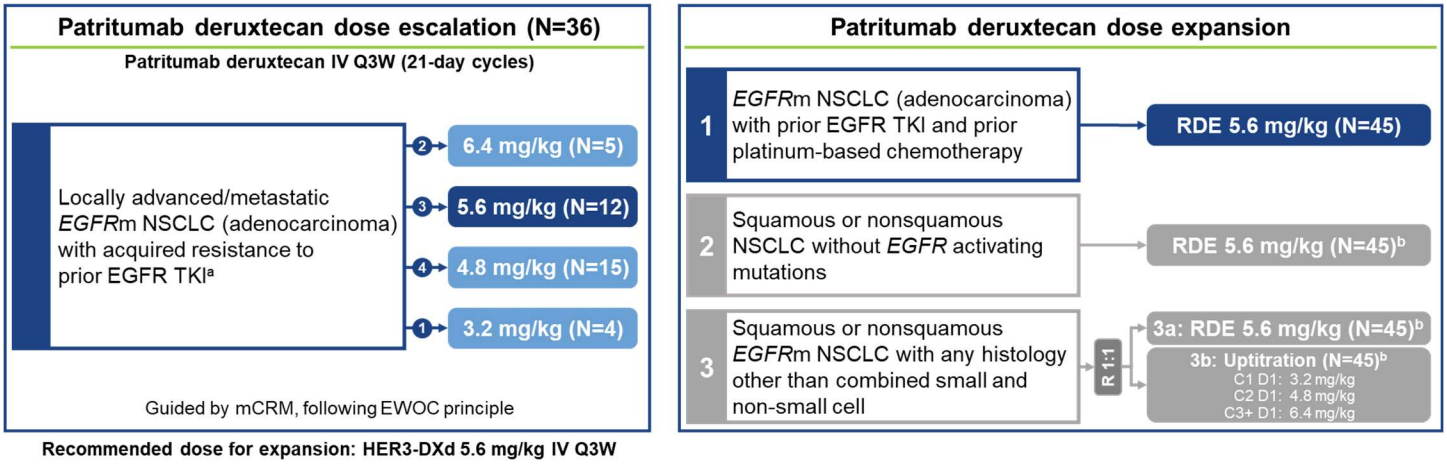
| Analyte | PK parameters | Lyo-DP geometric means (N=14) | FL-DP geometric means (N=10) | Ratio of geometric means (Lyo/FL) (%) | 90% CI for the ratio of geometric means (%) |
|---|---|---|---|---|---|
| MAAA-1181a conjugated antibody | $C_{max}$ (µg/mL) | 122.62 | 127.22 | 96.4 | 83.6, 111.1 |
| | $AUC_{last}$ (d•µg/mL) | 534.54 | 571.61 | 93.5 | 77.6, 112.7 |
| | $AUC_{0\text{-}21d}$ (d•µg/mL) | 535.06 | 572.98 | 93.4 | 77.4, 112.6 |
| Released payload MAAA-1181a | $C_{max}$ (ng/mL) | 21.80 | 20.28 | 107.5 | 79.5, 145.4 |
| | $AUC_{last}$ (d•ng/mL) | 46.17 | 46.30 | 99.7 | 82.0, 121.2 |
| | $AUC_{0\text{-}21d}$ (d•ng/mL) | 44.77 n=12 | 48.11 n=8 | 93.0 | 75.0, 115.4 |

$AUC_{0\text{-}21d}$, area under the serum concentration-time curve from 0 to 21 days; CI, confidence interval; FL-DP, frozen liquid drug product; lyo-DP, lyophilized powder drug product; max, maximum; min, minimum.

[a] Patients in the dose escalation 5.6 mg/kg group (frozen liquid formulation) and dose-expansion Cohort 1 (5.6mg/kg; lyophilized powder formulation), who were dosed on or before December 19, 2019, were included in a PK comparability summary. The analysis was generated using only PK-evaluable patients who had all PK data points at predose, end of infusion, at 2, 4, and 8 hours post-infusion, and on Day 8, Day 15, Day 21 after the end of infusion.

## FIGURES

**Supplementary Figure S1.** Study design. The dose escalation part and the dose expansion Cohorts 1 and 3 enrolled patients with *EGFR* activating mutations. The current paper reports data for patients in dose escalation and dose expansion cohort 1, including efficacy data for the pooled population of patients receiving the RDE. Cohorts 2 and 3 of the dose expansion part will be reported separately.



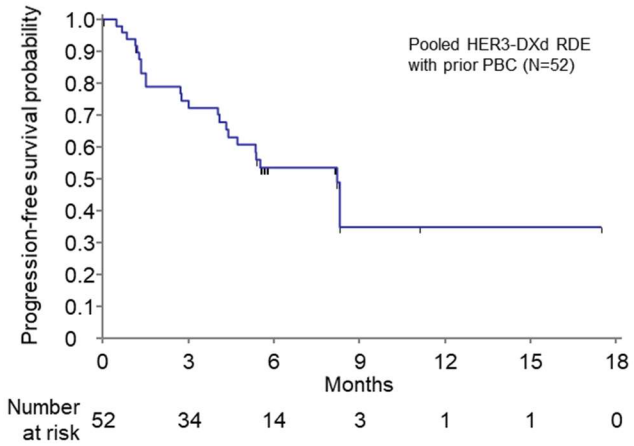

*EGFR*m NSCLC, NSCLC with *EGFR* activating mutations; mCRM, modified continual reassessment method.

[a] Per Jackman criteria.

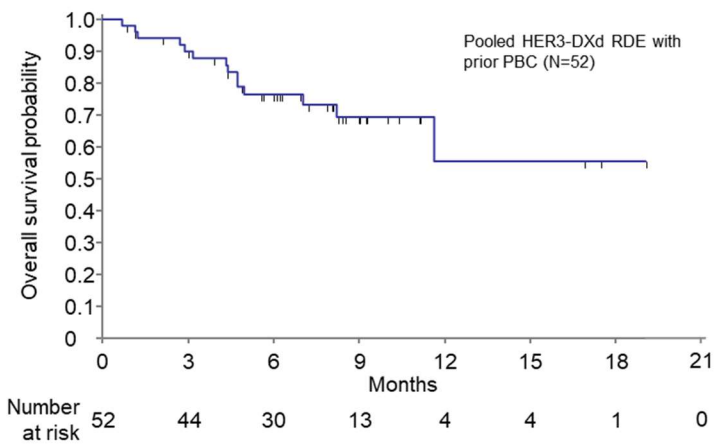
[b] Planned enrollment.

**Supplementary Figure S2.** PFS as assessed by BICR and OS in patients treated with HER3-DXd at 5.6 mg/kg according to prior treatment. Kaplan-Meier plot of PFS (A) and OS (B) for patients with prior platinum-based chemotherapy (N=52); Kaplan-Meier plot of PFS (C) and OS (D) for patients with prior platinum-based chemotherapy and osimertinib (N=44).

A




B

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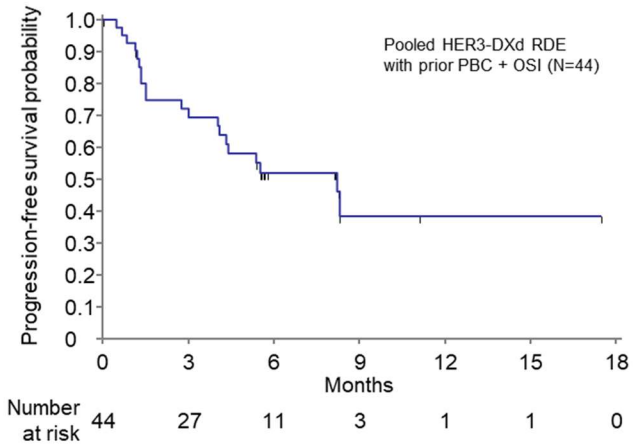


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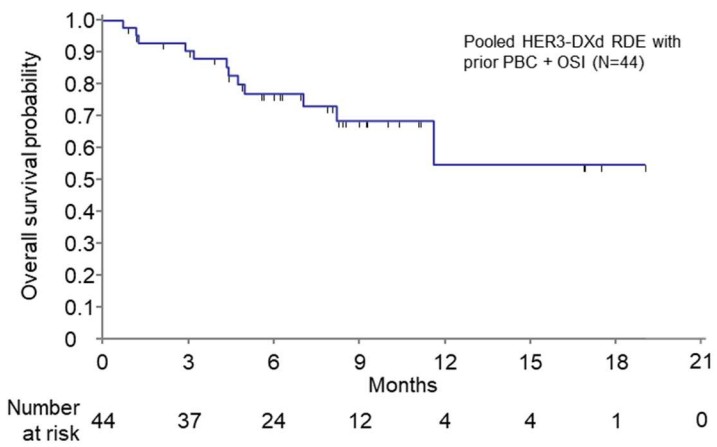
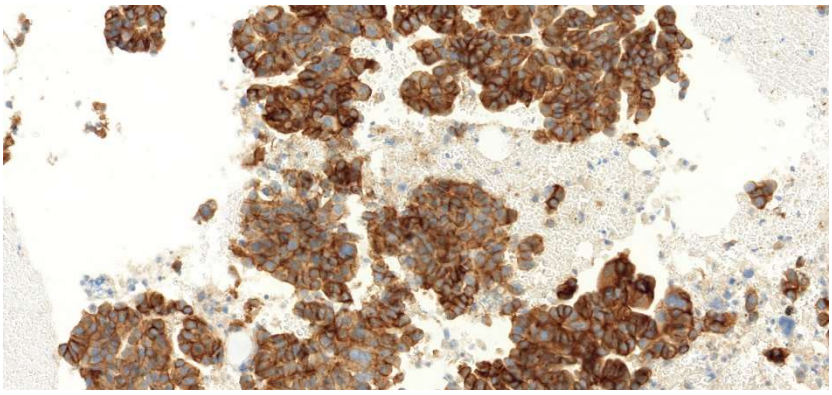


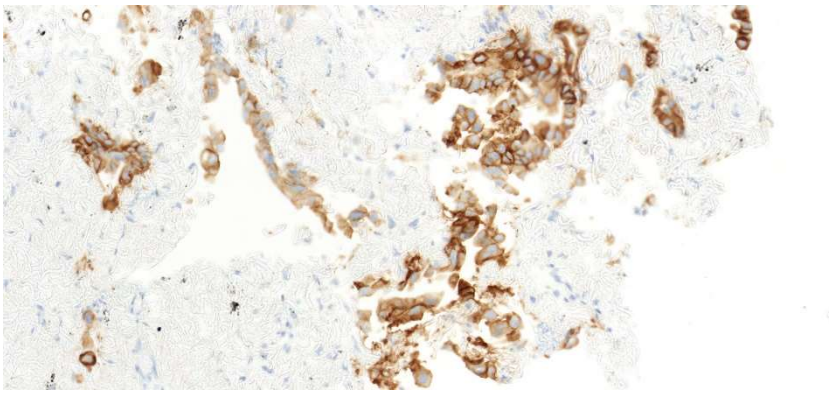

PBC, platinum-based chemotherapy; OSI, osimertinib.

**Supplementary Figure S3.** Representative examples of IHC staining showing membrane H-scores that are: (A) high, H-score 245; (B) medium (due to localized strong staining), H-score 180; (C) medium (due to widespread medium staining), H-score 175; and (D) low, H-score 2.

A



B



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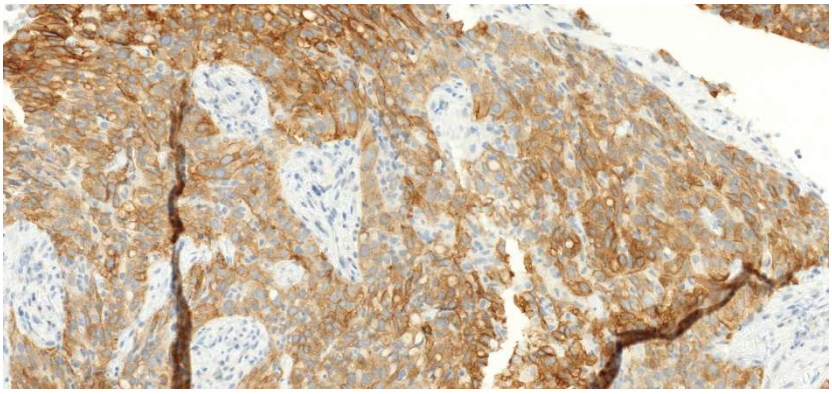
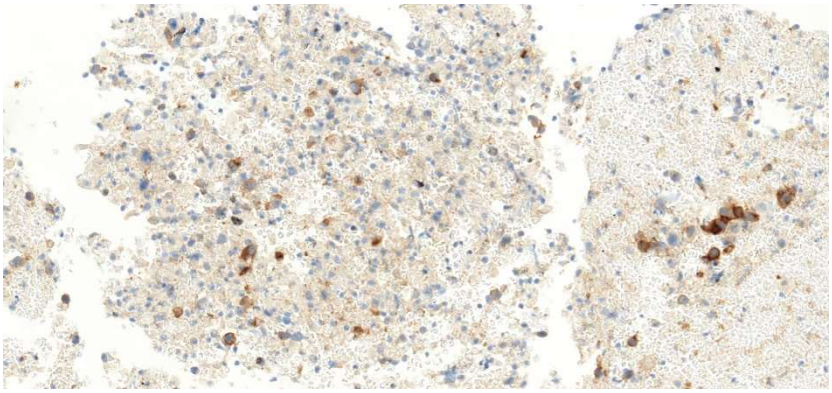
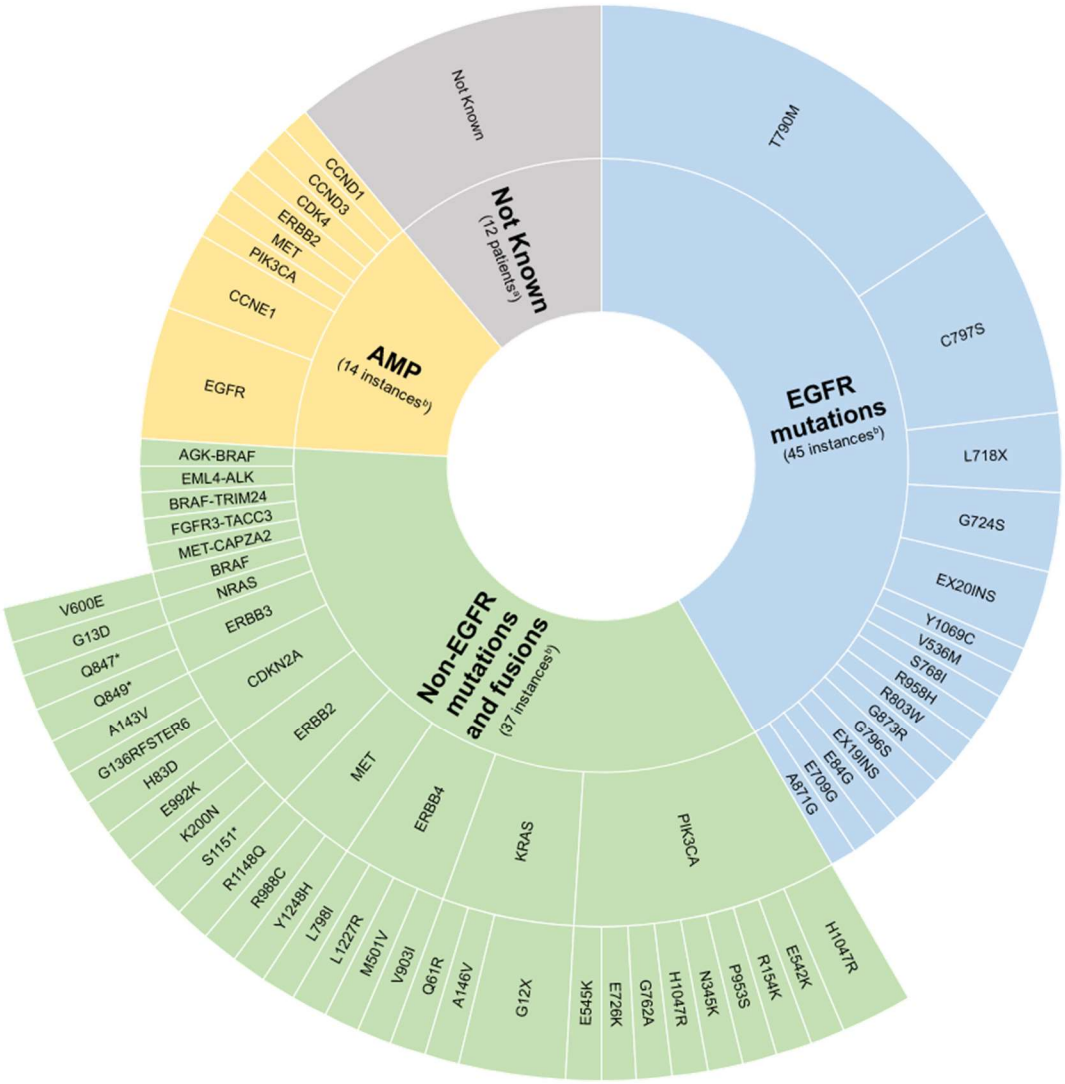


D



**Supplementary Figure S4.** Presence of resistance-associated genomic alterations detected in tumor tissue or blood ctDNA collected prior to study treatment in patients receiving HER3-DXd 5.6 mg/kg (N=57). The chart depicts each instance of a detected known genomic alteration. The category of “Not Known” represents instances of individual patients who had no detected known genomic alteration.



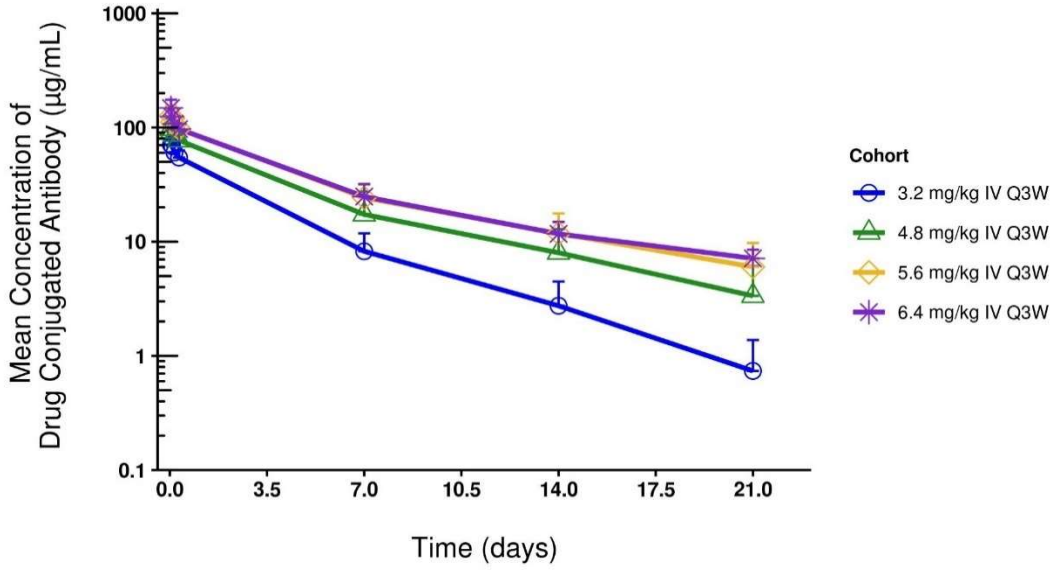

AMP, amplifications.

[a] Although it is possible that any of the patients had 1 or more additional unknown resistance-associated genomic alterations, the category of “Not Known” only represents instances of individual patients (n=12) who had no detected known genomic alteration.

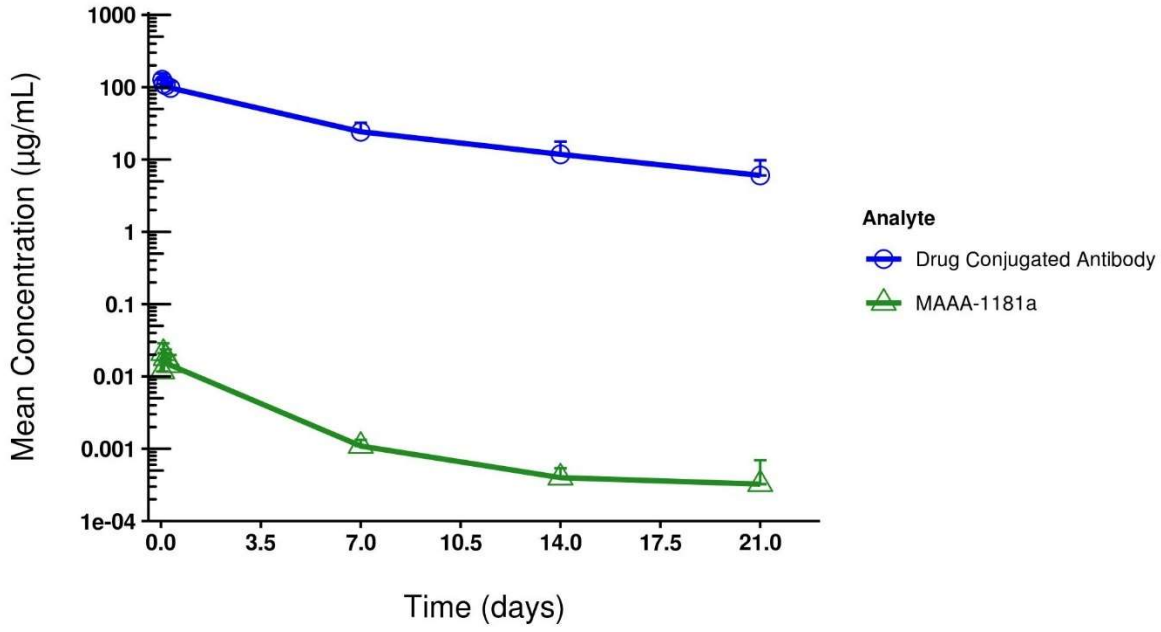
[b] The total instances of known resistance-associated genomic alterations detected (n=96) was larger than the number patients with known genomic alterations (n=45) because more than 1 genomic alteration was sometimes present in a single patient (**Figure 1**).

**Supplementary Figure S5.** PK profile of HER3-DXd. (A) Cycle 1 mean (SD) serum concentration- time profile of MAAA-1181a conjugated antibody at doses of 3.2, 4.8, 5.6, and 6.4 mg/kg IV Q3W. (B) Cycle 1 mean (SD) serum concentration-time curve of MAAA-1181a conjugated antibody and released MAAA-1181a at a dose of 5.6 mg/kg Q3W.

**A**

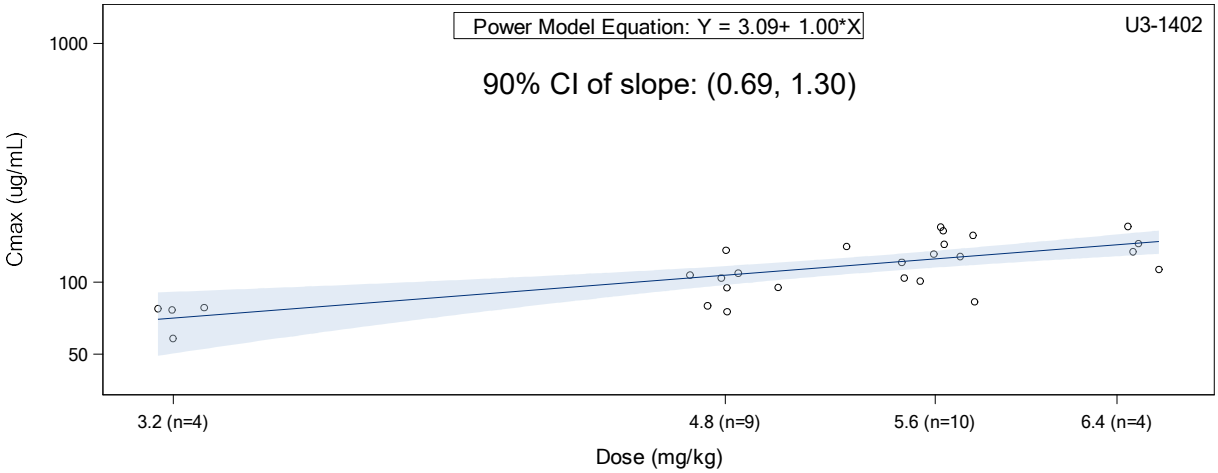



**B**



**Supplementary Figure S6.** Analysis of the dose proportionality of MAAA-1181a conjugated antibody for (A) $AUC_{last}$ and (B) $C_{max}$.

**A**

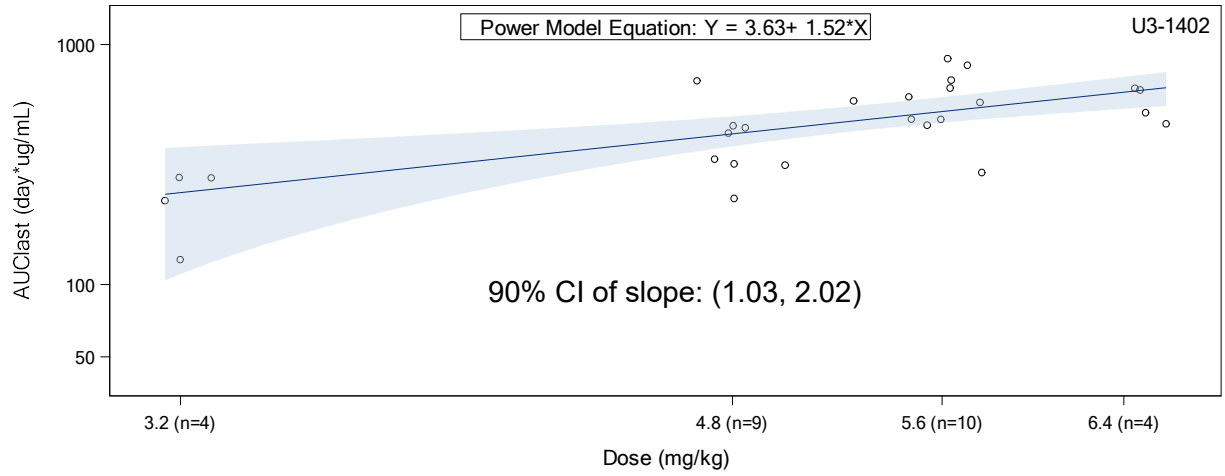



Subjects from dose escalation part dosed at 3.2, 4.8, 5.6 and 6.4 mg/kg are included. The straight line is the Power Model regression line. The shade is 90% confidence band.

Power Model: Y = alpha + beta * X, where Y = logarithm of the PK parameters Cmax, AUClast, and AUC0-21d, X = logarithm of actual dose taken.

n : number of subjects within each planned dose.

**B**




Subjects from dose escalation part dosed at 3.2, 4.8, 5.6 and 6.4 mg/kg are included. The straight line is the Power Model regression line. The shade is 90% confidence band.

Power Model: Y = alpha + beta * X, where Y = logarithm of the PK parameters Cmax, AUClast, and AUC0-21d, X = logarithm of actual dose taken.

n : number of subjects within each planned dose.