Patritumab Deruxtecan (HER3-DXd) In Previously Treated Patients With Advanced *EGFR*-Mutated (*EGFR*m) NSCLC: Updated Safety Results From HERTHENA-Lung01

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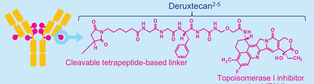
BACKGROUND

- Tolerable therapies are needed for previously treated patients with advanced *EGFR*-mutated NSCLC
- Patritumab deruxtecan (HER3-DXd) is an antibody-drug conjugate (**Figure 1**) that showed meaningful efficacy and a manageable safety profile in the phase 2 HERTHENA-Lung01 trial (NCT04619004)[1]

Figure 1 HER3-DXd Structure and Attributes

HER3-DXd is an ADC composed of 3 parts[2-5]:
- A fully human anti-HER3 IgG1 mAb (patritumab)
- A topoisomerase I inhibitor payload (DXd)
- A tetrapeptide-based cleavable linker that covalently bonds the other 2 components



Payload mechanism of action: topoisomerase I inhibitor[2,5,a]	
High potency of payload[2,5,a]	
High drug to antibody ratio ≈8[2,3,a]	
Payload with short systemic half-life[3,4,a,b]	
Stable linker-payload[3,5,a]	
Tumor-selective cleavable linker[2-5,a]	
Bystander antitumor effect[3,7,a]	

- Here we present further details of the safety profile of HER3-DXd in patients with previously treated, advanced *EGFR*-mutated NSCLC based on follow-up data for 6 months beyond the primary analysis of HERTHENA-Lung01

Figure 2 Study Design

Patient population
- Advanced *EGFR*-mutated NSCLC
- Progression on most recent systemic therapy
- Prior EGFR TKI and prior platinum-based chemotherapy (amended protocol required prior osimertinib)
- Inactive or previously treated asymptomatic brain metastases allowed
- Pretreatment tumor tissue required

→ **HER3-DXd 5.6 mg/kg IV Q3W (N=225)**

Primary endpoint
- cORR by BICR

Key secondary endpoint
- DOR by BICR

Primary data cutoff: 21 November 2022
Snapshot data cutoff: 18 May 2023 (additional 6 months of follow-up)

CONCLUSION

- HER3-DXd demonstrated a manageable and tolerable safety profile, consistent with previous reports
- The majority of hematologic and GI TEAEs were transient and occurred in early treatment cycles
- No new safety signals were observed

METHODS

- Patients with advanced *EGFR*-mutated NSCLC (N=225) previously treated with EGFR TKI therapy and platinum-based chemotherapy received HER3-DXd 5.6 mg/kg intravenously once every 3 weeks (**Figure 2**)
- Patients with any underlying pulmonary disorder at screening (eg, pulmonary emboli within 3 months prior to study enrollment, severe asthma, severe COPD, restrictive lung disease, pleural effusion) were excluded

RESULTS

- At the snapshot data cutoff (18 May 2023), patients with previously treated, advanced *EGFR*-mutated NSCLC (N=225) (**Table 1**) had received HER3-DXd 5.6 mg/kg for a median of 5.5 months (range, 0.7-23.7 months)
  - Relative dose intensity, median (range), was 97.4% (57.1%-107.8%) (**Table 2**)
  - 224 patients (99.6%) had any-grade TEAEs; 147 (65.3%) had grade ≥3 TEAEs (**Table 2**)
- 14 patients (6.2%) had centrally adjudicated treatment-related ILD (**Table 3**); 2 of these events occurred during the 6-month additional follow-up
  - The median time to onset of adjudicated treatment-related ILD was 70.5 days (range, 9-474 days), and the median duration of ILD with outcomes of resolved (n=10) was 40.0 days (range, 6-207 days)
  - Among patients without prior immunotherapy (n=135), 5 (3.7%) had an ILD event (3 grade 2, 1 grade 3, 1 grade 5); among patients with prior immunotherapy (n=90), 9 (10.0%) had an ILD event (1 grade 1, 5 grade 2, 3 grade 3)
- The most common TEAEs were nausea (66.2%), thrombocytopenia (43.6%; grouped PT), and decreased appetite (42.2%) (**Figure 3**)
  - The most common grade ≥3 TEAEs were thrombocytopenia (20.9%; grouped PT), neutropenia (19.1%; grouped PT), and anemia (15.1%; grouped PT)
  - 88.9% of patients had a GI TEAE (SOC of GI disorders), 8.0% were grade ≥3
- TEAEs associated with dose interruption, dose reduction, and discontinuation occurred in 41.3%, 22.2%, and 8.4% of patients, respectively (**Table 2; Figure 4**)

Table 1 Patient Demographics and Clinical History

Baseline characteristics		HER3-DXd 5.6 mg/kg (N=225)
Age, median (range), years		64 (37-82)
Female, n (%)		132 (58.7)
Asian, n (%)		105 (46.7)
BMI, median (range), kg/m^2		22.8 (14.9-42.6)
Smoking history, n (%)	Never	144 (64.0)
	Ever	81 (36.0)
History of GI disorders, n (%)[a]		16 (7.1)
History of hematologic disorders, n (%)[b]		6 (2.7)
ECOG performance status, n (%)	0/1	73 (32.4)/149 (66.2)
	2[c]	3 (1.3)
Time since initial NSCLC diagnosis, median (range), months		41.0 (9.1-224.7)
Sum of target lesion diameters at baseline (BICR), median (range), mm		68 (11-248)
History of CNS metastasis, n (%)		115 (51.1)
Brain metastasis at baseline (BICR), n (%)		72 (32.0)
Liver metastasis at baseline (BICR), n (%)		75 (33.3)
EGFR-activating mutations, n (%)[d]	Ex19del	142 (63.1)
	L858R	82 (36.4)
No. of prior lines of systemic therapy (in the locally advanced/metastatic setting)	Median (range)	3 (1-11)[e]
	2 prior lines, n (%)	58 (25.8)
	>2 prior lines, n (%)	165 (73.3)
Prior anticancer systemic therapy regimens, n (%)	Prior EGFR TKI therapy	225 (100.0)
	Prior third-generation EGFR TKI	209 (92.9)
	Prior platinum-based chemotherapy	225 (100.0)
	Prior immunotherapy	90 (40.0)
Prior thoracic radiation therapy		43 (19.1)

[a]Patients with a medical history of SOC GI disorders. [b]Patients with a medical history of SOC blood and lymphatic system disorders. [c]These patients had ECOG performance status of 0 or 1 at screening. [d]1 patient had both Ex19del and L858R mutations. [e]2 patients had 1 prior line of therapy.

Table 2 Summary of Safety Profile

Safety summary	HER3-DXd 5.6 mg/kg (N=225)
Study drug exposure	
Treatment duration, median (range), months	5.5 (0.7-23.7)
Dose intensity, median (range), mg/kg/cycle	5.45 (3.2-6.0)
Relative dose intensity, median (range), %	97.4 (57.1-107.8)
TEAEs	
Any TEAE, n (%)	224 (99.6)
Associated with treatment discontinuation	19 (8.4)
Associated with treatment dose reduction	50 (22.2)
Associated with treatment dose interruption	93 (41.3)
Grade ≥3 TEAE, n (%)	147 (65.3)
Treatment-related TEAE, n (%)	215 (95.6)
Associated with death[a]	4 (1.8)
Grade ≥3	104 (46.2)
Serious TEAE	36 (16.0)

[a]Pneumonitis, GI perforation, pneumonia, respiratory failure (n=1 each)

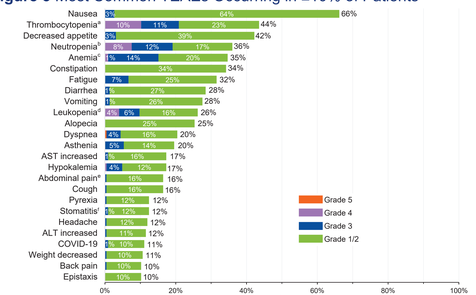
RESULTS (continued)

Table 3 ILD Adjudication for HER3-DXd 5.6 mg/kg (N=225)

Worst ILD grade per investigator	Patients with suspected ILD	Adjudicated not ILD	Grade after adjudication (all adjudicated ILD were treatment related)					
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total ILD
Any grade, n	22							
Grade 1	8	2	1	4	0	0	1	6
Grade 2	3	0	0	2	1	0	0	3
Grade 3	5	1	0	2	2	0	0	4
Grade 4	3	2	0	0	1	0	0	1
Grade 5	3	3	0	0	0	0	0	0
	Total adjudicated ILD, n (%)		**1 (0.4)**	**8 (3.6)**	**4 (1.8)**	**0**	**1 (0.4)**	**14 (6.2)**

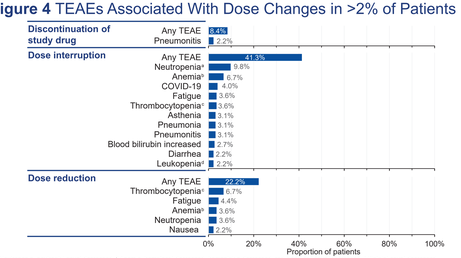
Treatment for adjudicated ILD by grade per investigator	Outcome of ILD treatment per investigator: Recovered/ resolved	Recovering/ resolving	Not recovered/ not resolved
Corticosteroids (n=13)			
Grade 1; n=5	4 (80)	1 (20)	0
Grade 2; n=3	3 (100)	0	0
Grade 3; n=4	2 (50)	0	2 (50)
Grade 4; n=1	1 (100)	0	0
Grade 5; n=0	0	0	0
Corticosteroids + antibiotics (n=5/13)			
Grade 1; n=0	0	0	0
Grade 2; n=2	2 (100)	0	0
Grade 3; n=2	2 (100)	0	0
Grade 4; n=1	1 (100)	0	0
Grade 5; n=0	0	0	0

Figure 3 Most Common TEAEs Occurring in ≥10% of Patients



[a]Platelet count decreased, thrombocytopenia. [b]Neutropenia, neutrophil count decreased. [c]Anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased. [d]Leukopenia, white blood cell count decreased. [e]Abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper. [f]Aphthous ulcer, mouth ulceration, oral mucosa erosion, oral mucosal blistering, stomatitis.

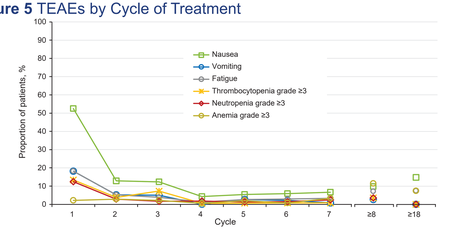
Figure 4 TEAEs Associated With Dose Changes in >2% of Patients



[a]Neutropenia, neutrophil count decreased. [b]Anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased. [c]Platelet count decreased, thrombocytopenia. [d]Leukopenia, white blood cell count decreased.

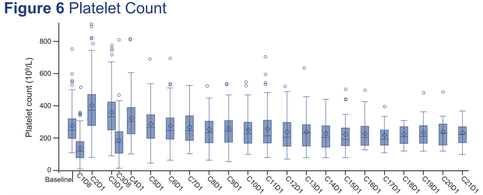
- The incidence of TEAEs of nausea and vomiting generally decreased over the course of treatment (**Figure 5**)
- The incidence of grade ≥3 thrombocytopenia and neutropenia peaked at cycle 1 and decreased in later cycles (**Figure 5**)
  - The incidence of grade ≥3 anemia was consistently low over the course of treatment
- The median platelet count showed a drop at cycle 1 day 8, followed by an increase at cycle 2 day 1, tapering to zero change from baseline (**Figure 6**)
  - The median changes from baseline for neutrophil count and hemoglobin level were close to zero over the course of treatment (**Figure 7**)
- Hematologic TEAEs were transient and managed by dose modifications and routine clinical practice (**Table 4**)

Figure 5 TEAEs by Cycle of Treatment



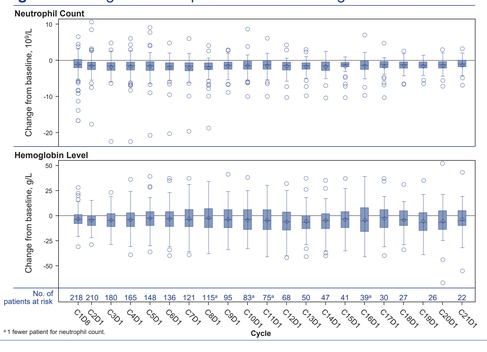
No. of patients at risk: 225 210 179 165 148 135 121 113 27

Figure 6 Platelet Count



No. of patients at risk: 218 210 180 165 148 136 121 115 95 83 75 68 50 47 41 39 30 27 26 22

Figure 7 Change in Neutrophil Count and Hemoglobin Level



[a]1 fewer patient for neutrophil count.

- Platelet transfusions for thrombocytopenia were received by 20 patients (8.9%) (**Table 4**)
  - No patients discontinued treatment due to thrombocytopenia
  - Two patients (0.9%) experienced grade ≥3 bleeding events (unrelated to treatment) within ±14 days of a grade ≥3 decreased platelet count
- Granulocyte colony-stimulating factor was used to manage neutropenia in 23 patients (10.2%) (**Table 4**)
  - Febrile neutropenia occurred in 7 patients (3.1%; all grade ≥3) of whom 4 (1.8%) were treated with granulocyte colony-stimulating factor
  - Two patients (0.9%) experienced grade ≥3 infections (unrelated to treatment) within ±14 days of grade ≥3 neutropenia
- Red blood cell transfusions for anemia were received by 28 patients (12.4%) (**Table 4**)
  - Treatment discontinuation was associated with anemia in 1 patient (0.4%)
- Most patients with adjudicated ILD events (n=14; all of which were adjudicated to be treatment related) received corticosteroids (n=13 [93%]); 5 (36%) also received antibiotics (**Table 3**)
  - Among the 13 patients treated with corticosteroids, per investigator, 10 had recovered/resolved, 1 was recovering, and 2 had not recovered
  - Among the 10 patients who recovered/resolved (per investigator), 4 discontinued HER3-DXd (grades by investigator/adjudication, 2/2, 2/3, 3/2, and 4/3), 1 had a dose reduction (grade 1/2), 4 had a dose interruption (grades, 1/2, 1/2, 1/5, and 3/3), and 1 did not have any dose modifications for ILD (grade 2/2)
  - One patient with adjudicated grade 1 ILD did not receive corticosteroids and was recovering/resolving, per investigator

Table 4 Timing and Management of Hematologic TEAEs

Hematologic Event	HER3-DXd 5.6 mg/kg (N=225)
Thrombocytopenia (grouped PT; grade ≥3)	
Time to onset, median (range), days	8.0 (7-243)
Duration, median (range), days	12.5 (4-20)
Patients receiving platelet transfusion for thrombocytopenia within 28 days of onset, n (%)	20 (8.9)
Grade ≥3 bleeding events within ±14 days of grade ≥3 platelet count decrease, n (%)	2 (0.9)
Gastrointestinal hemorrhage	1 (0.4)
Hemothorax	1 (0.4)
Neutropenia (grouped PT; grade ≥3)	
Time to onset, median (range), days	21.0 (8-299)
Duration, median (range), days	7.0 (3-37)
Patients treated with granulocyte colony-stimulating factor for neutropenia within 28 of onset including febrile neutropenia, n (%)	23 (10.2)
Neutropenia	21 (9.3)
Febrile neutropenia	4 (1.8)
Grade ≥3 neutropenic infection within ±14 days of grade ≥3 neutrophil count decrease, n (%)	2 (0.9)
Sepsis	1 (0.4)
Septic shock	1 (0.4)
Anemia (grouped PT; grade ≥3)	
Time to onset, median (range), days	98.5 (3-462)
Duration, median (range), days	13.0 (2-247)
Patients receiving red blood cell transfusion for anemia with 28 days of onset, n (%)	28 (12.4)

ABBREVIATIONS

ADC, antibody-drug conjugate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BICR, blinded independent central review; BMI, body mass index; C, cycle; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; cORR, confirmed objective response rate; D, day; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; GI, gastrointestinal; HER3, human epidermal growth factor receptor 3; Ig, immunoglobulin; ILD, interstitial lung disease; IV, intravenous; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; PT, preferred term; Q3W, every 3 weeks; SOC, system organ class; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor.

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CONFLICT OF INTEREST

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