

Peripheral Neuropathy with Teliso-V in c-Met–Protein Overexpressing NSCLC in LUMINOSITY: Clinical Characteristics and PROs

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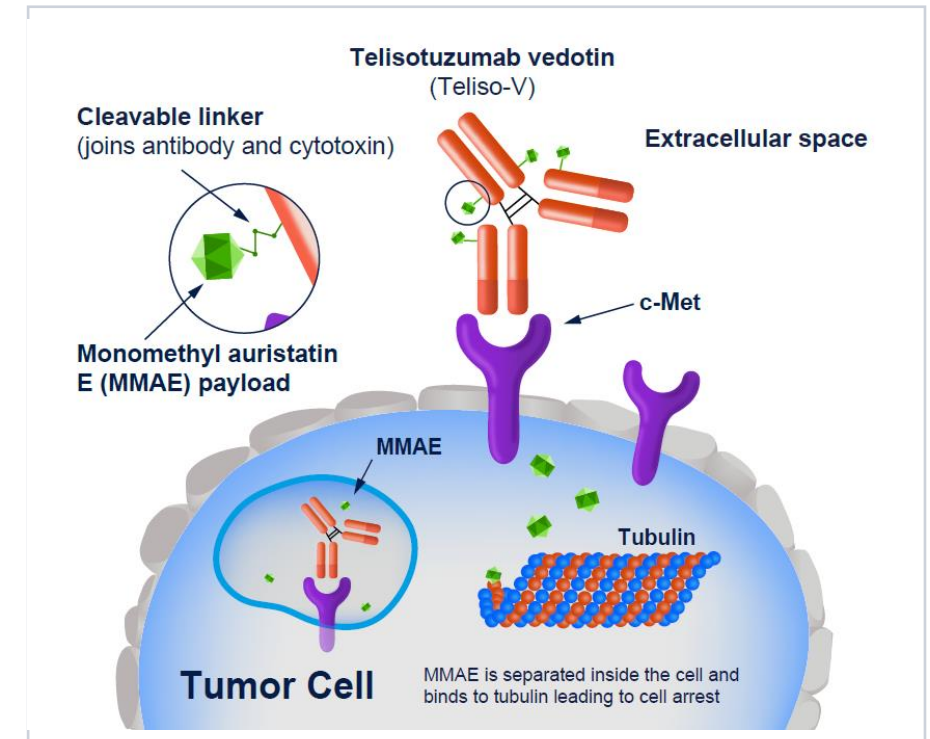
BACKGROUND

OBJECTIVES:

To assess the clinical characteristics and patient-reported outcomes (PROs), to evaluate exposure to telisotuzumab vedotin (Teliso-V) and describe management strategies in patients with epidermal growth factor receptor (*EGFR*) wildtype non-squamous non-small cell lung cancer (NSCLC) overexpressing c-Met, and peripheral neuropathy (PN) in the LUMINOSITY Phase 2 study

- c-Met protein overexpression (OE) has been associated with worse clinical outcomes in patients with *EGFR* wildtype non-squamous NSCLC and effective second-line treatment options remain limited following disease progression^{1,2}
- Teliso-V is a first-in-class c-Met protein-directed antibody-drug conjugate (ADC) comprising a humanized monoclonal antibody conjugated to the cytotoxic microtubule polymerization inhibitor monomethyl auristatin E (MMAE)³
 - Teliso-V received accelerated US Food and Drug Administration (FDA) approval for adult patients with locally advanced/metastatic non-squamous NSCLC with high c-Met protein OE (3+, ≥50%) as determined by an FDA-approved test who had received a prior systemic therapy based on the pivotal Phase 2 LUMINOSITY (NCT03539536) study⁴
- **PN is a known class effect of ADCs carrying microtubule-inhibitory payloads such as MMAE** and may adversely impact quality of life in patients with *EGFR* wildtype nonsquamous NSCLC⁵
- In LUMINOSITY, PN events treatment-related per investigator occurred in 40.7% of patients (Grade ≥3, 9.3%)⁶
- Herein, we present additional data on PN from the Phase 2 LUMINOSITY study, including baseline clinical characteristics, medical history, Teliso-V exposure, and medical management. Furthermore, we contextualize PROs specific to PN

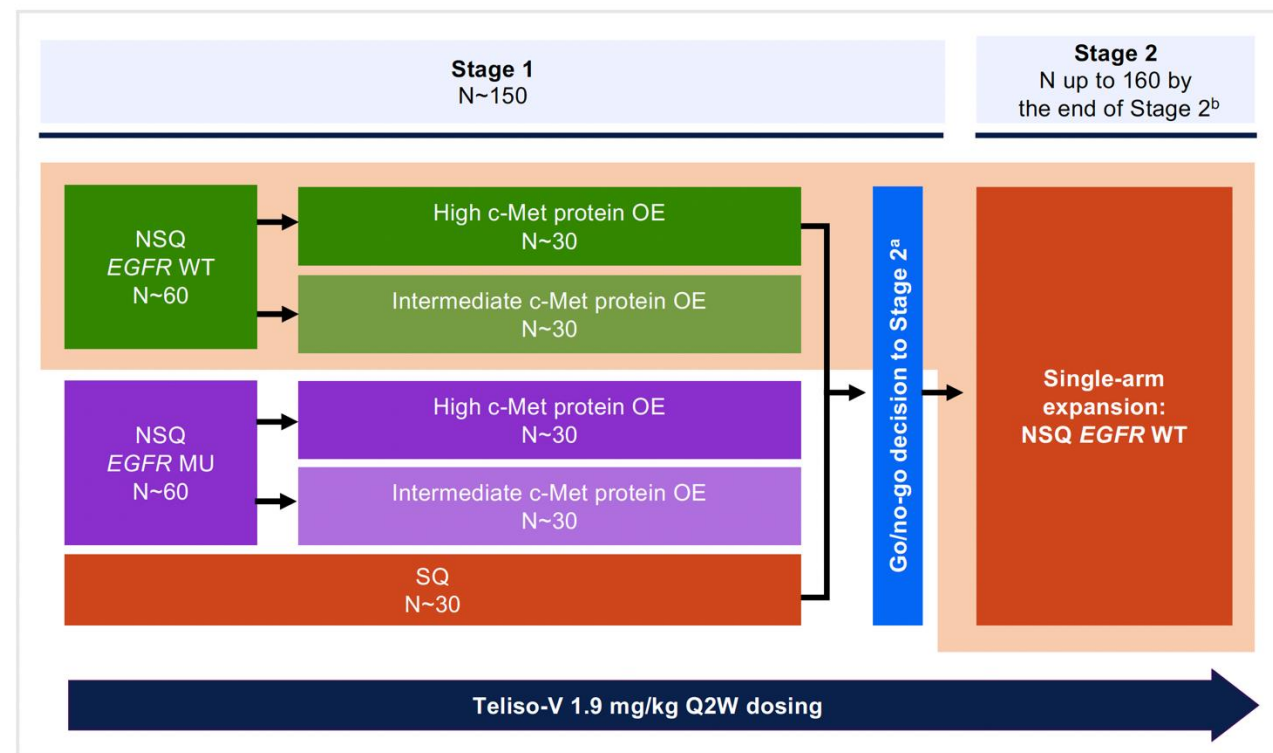
Teliso-V Mechanism of Action



METHODS

- Adult patients (≥ 18 years) with locally advanced/metastatic c-Met protein–overexpressing non-squamous *EGFR* wildtype NSCLC who received prior therapy were treated with Teliso-V monotherapy 1.9 mg/kg every 2 weeks
- c-Met protein OE was assessed by an immunohistochemistry clinical trial assay for MET (SP44; Roche Diagnostics) and defined as $\geq 25\%$ tumor cells with 3+ staining intensity
 - *High c-Met protein OE*: $\geq 50\%$ tumor cells with 3+ staining intensity (3+, $\geq 50\%$)
 - *Intermediate c-Met protein OE*: 25%–49% tumor cells with 3+ staining intensity (3+, 25%–49%)
- Adverse events on PN were reported using Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms Analyses based on Standardized MedDRA Queries (SMQ narrow)
- **This analysis includes the safety population with first occurrence of treatment-emergent per SMQ PN Grade ≥ 2 vs PN Grade < 2 (asymptomatic Grade 1 or absence of PN Grade 0)**
- The **EORTC QLQ-CIPN20**, a validated instrument that captures PROs, was used to **contextualize sensory versus motor symptoms in relation to PN events**. Higher QLQ-CIPN20 scores reflect worse PN

LUMINOSITY Study Design (NCT03539536)



^aGo/no-go decision was based on the Bayesian posterior probability of success, defined as the posterior probability of the ORR exceeding 25%; if this fell below 0.10, the group was considered futile; if this went above 0.70, the group was expanded. ^bAfter completion of global Stage 2 enrollment, a China extension cohort of up to 12 patients dosing at 1.9 mg/kg was added.

EGFR, epidermal growth factor receptor; EORTC, European Organization for Research and Treatment of Cancer; MedDRA, Medical Dictionary for Regulatory Activities; Mut, mutated; NSQ, non-squamous; OE, overexpression; PN, peripheral neuropathy; PRO, patient-reported outcomes; Q2W, every 2 weeks; QLQ-CIPN20, Quality of Life Questionnaire–Chemotherapy-Induced Peripheral Neuropathy 20-Item Scale; SMQ, Standardized MedDRA Queries; SQ, squamous; Teliso-V, telisotuzumab vedotin; WT, wildtype.

RESULTS - Demographics

Baseline Clinical Characteristics PN Grade ≥2 vs PN Grade <2

Characteristic	PN Grade ≥2 (n=52)	PN Grade <2 (n=116)
Median age , years (range)	66 (47–83)	64 (33–82)
≥65 years, n (%)	32 (62)	52 (45)
Sex , n (%)		
Male	41 (79)	76 (66)
Female	11 (21)	40 (34)
Median weight , kg (range)	76 (50–115)	64 (39–97)
BMI , n (%)		
25–29	21 (40)	28 (24)
≥30	7 (13)	8 (7)
Race , n (%)		
White	34 (65)	76 (66)
Asian	17 (33)	38 (33)
Black or African American	1 (2)	2 (2)
Baseline ECOG PS , n (%)		
0	17 (33)	31 (27)
1	35 (67)	84 (72)
Tobacco use , n (%)		
Former	38 (73)	67 (58)
Never	5 (10)	32 (28)
Current	9 (17)	17 (15)
Alcohol use , n (%)		
Never	19 (37)	50 (43)
Current	17 (33)	28 (24)
Former	5 (10)	23 (20)
Unknown	11 (21)	15 (13)
Number of metastatic sites , n (%)		
0	2 (4)	1 (<1)
1	19 (37)	30 (26)
2	31 (60)	85 (73)
Brain metastases , n (%)		
No	42 (81)	90 (78)
Yes	10 (19)	26 (22)
Prior radiation therapy , n (%)		
No	25 (48)	57 (49)
Yes	27 (52)	59 (51)
Prior platinum-based chemotherapy , n (%)		
Platinum-based chemotherapy	51 (98)	110 (95)
Platinum-based chemotherapy + ICI	43 (83)	87 (75)
c-Met protein OE , n (%)		
High	23 (44)	61 (53)

- As of the data cutoff of 21 February 2024, 168 patients had received at least 1 dose of Teliso-V
- Of those, PN Grade ≥2 was observed in 31% (52/168)
- **PN Grade ≥2 vs PN Grade <2** was more common in patients:
 - **≥65 years and in males**
 - Who had a **higher median body weight and obesity (BMI)**
 - With **former smoking status**
 - With **alcohol usage**

Data cutoff date: 21 February 2024.

ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; OE, overexpression; PN, peripheral neuropathy; Teliso-V, telisotuzumab vedotin.

RESULTS – Medical History and Teliso-V Exposure

Medical History PN Grade ≥2 vs PN Grade <2

Characteristic, n (%)	PN Grade ≥2 (n=52)	PN Grade <2 (n=116)
Metabolism and nutrition disorders		
Diabetes UNS	6 (12)	20 (17)
Neurological symptoms		
Demyelination	2 (4)	0
Dysesthesia	0	1 (1)
Hypoesthesia	0	1 (1)
Neuralgia	3 (6)	3 (3)
Paresthesia	1 (2)	4 (3)
Peripheral neuropathy	4 (8)	2 (2)
Peripheral sensory neuropathy	1 (2)	1 (1)
Endocrine disorders		
Hypothyroidism	6 (12)	4 (3)
Primary hypothyroidism	0	1 (1)
Autoimmune hypothyroidism	0	1 (1)
Autoimmune thyroiditis	1 (2)	1 (1)
Graves' disease	2 (4)	0
Blood and lymphatic system disorders		
Vitamin B12 deficiency	0	1 (1)
Musculoskeletal and connective tissue disorders		
Rheumatoid arthritis	3 (6)	0
Systemic lupus erythematosus	0	1 (1)
Skin and subcutaneous tissue disorders		
Psoriasis	2 (4)	1 (1)

- The **prevalence of neurologic symptoms** reported in medical history was higher in the PN Grade ≥2 group than in the PN Grade <2 group
- Endocrine disorders and hypothyroidism** in particular, were more frequent in patients with PN Grade ≥2 compared with those with PN Grade <2, respectively. However, in this study diabetes was more frequently seen in patients with PN Grade <2 compared to patients with PN Grade ≥2

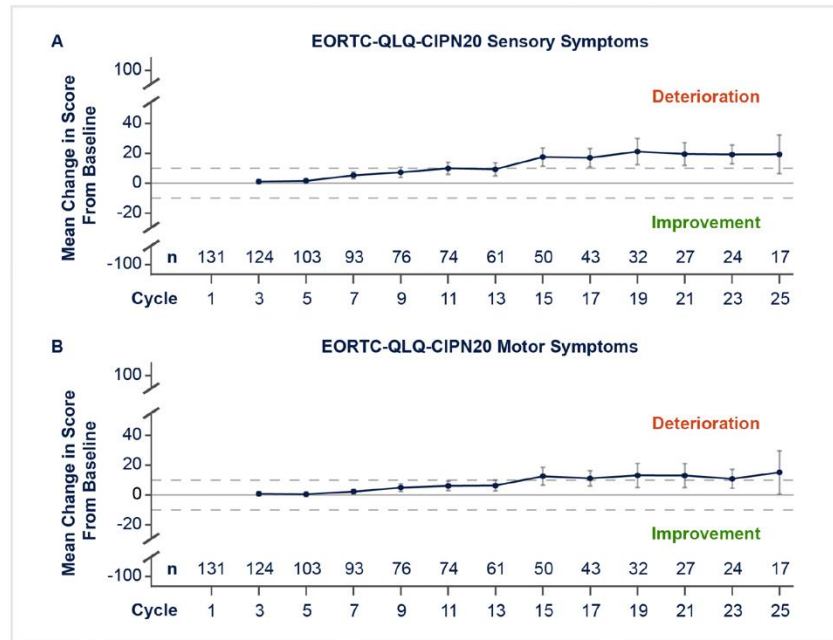
Teliso-V Exposure and PN Grade ≥2 vs PN Grade <2 in Patients With c-Met OE

Exposure	PN Grade ≥2 (n=52)	PN Grade <2 (n=116)
Median number of cycles	18	6
Median total cumulative dose, mg (range)	30.7 (6.6–95.2)	11.4 (1.9–64.6)
Median duration of treatment, months	9	2
Dose reductions, n (%)	36 (69)	10 (9)
Dose interruptions n (%)	34 (65)	33 (28)

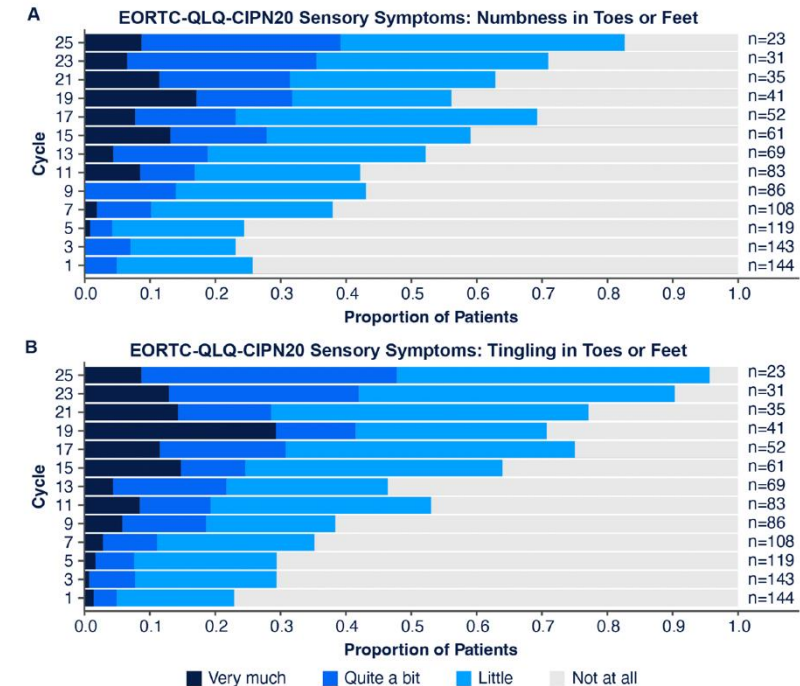
- Patients who experienced **PN Grade ≥2** received a **median number of Teliso-V treatment cycles 3 times greater** (n=18) than those with PN Grade <2 (n=6), which is also reflected in the median duration of Teliso-V exposure
- Despite more frequent dose reductions** in patients with PN Grade ≥2 than in patients with PN Grade <2, the **median total cumulative dose was still higher in patients with PN Grade ≥2** vs patients with PN Grade <2

RESULTS – EORTC QLQ-CIPN20 Scores

EORTC QLQ-CIPN20: PN Scores Sensory and Motor Symptoms^a



EORTC QLQ-CIPN20: Patient-Reported PN Sensory Symptoms From Toes or Feet/Lower Extremity^b



- The EORTC QLQ-CIPN20 measure had a **completion rate of 85.7%** and a completion rate >70% up to Cycle 45
- Patient self-reported sensory symptom and motor symptom scores did not cross the threshold for clinically meaningful deterioration until Cycle 15**
- Median time to deterioration was shorter for sensory vs motor symptoms indicating that **PN sensory symptoms emerged earlier in patients than motor symptoms (sensory: 4.8 months [95% CI, 4.1–6.5]; motor: 6.6 months [95% CI, 5.6–7.4])**

- Patients were requested to evaluate sensory symptoms such as “Tingling toes or feet” and “Numbness in toes or feet” using the QLQ-CIPN20 questionnaire
- The figures show the proportion of patients that rated each sensory symptom event (“not at all”, “a little”, “quite a lot”, and “very much”) over time
- As expected, as the number of cycles increased, the sample size decreased and a higher proportion of patients reported more pronounced symptoms

CONCLUSIONS

PN is a known class effect of ADCs carrying microtubule-inhibitory payloads. In the LUMINOSITY Phase 2 study, PN Grade ≥ 2 was more common with longer treatment duration and a higher median total cumulative dose, likely reflecting ongoing clinical benefit as well as the cumulative nature of this toxicity as previously reported

Among patients with NSCLC treated with Teliso-V who experienced PN Grade ≥ 2 , baseline clinical characteristics observed more often included age ≥ 65 years, high body weight, smoking status, prior platinum-based chemotherapy and their medical history more frequently described neurologic symptoms

Time to deterioration in PN was shorter with QLQ-CIPN20-reported sensory symptoms than motor symptoms, and neither sensory symptom nor motor symptom scores crossed the threshold for clinically meaningful deterioration until Cycle 15

Although patients who experienced PN Grade ≥ 2 had more dose interruptions and reductions, they had longer treatment exposure and higher median cumulative dose. Previously published clinical pharmacology analyses of the 1.9 mg/kg dose of Teliso-V support this, showing that the positive exposure–safety relationships can be managed in clinical practice through dose modifications and/or reductions

Overall, in patients with locally advanced or metastatic c-Met protein overexpressing–NSCLC treated with Teliso-V, assessment of baseline characteristics and prior medical history together with early identification and proactive management of PN may help reduce symptom burden

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