# EV-302: Exploratory Analysis of Nectin-4 Expression

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# EV

- Enfortumab-Fully human Mab –Nectin
- Vedotin –MMAE –microtubule poison
- DAR is 3.8:1

# EV trials

- EV 301:
- Post CTh/IO –Urothelial ca
- OS :9→12 months

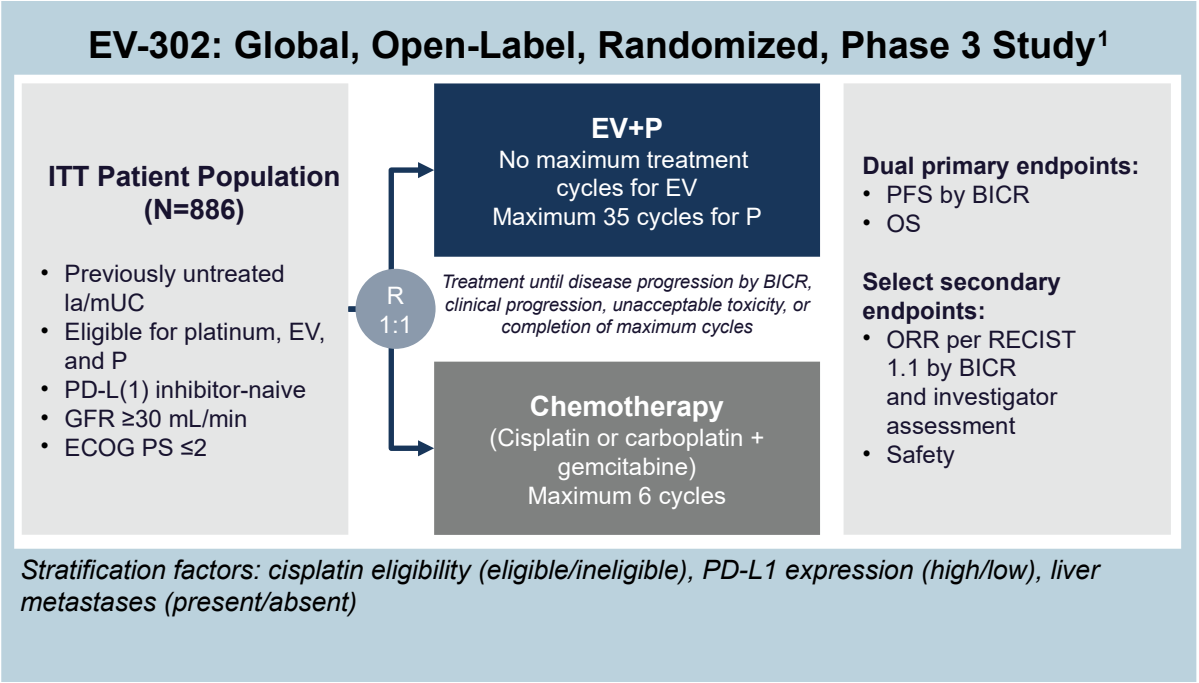
- EV 302
- Pembro EV vs Gem platinum
- PFS :6→12 months
- OS:16→32 months

# Background

- Nectin-4 –CAM -highly expressed on the surface of most UC cells
- Maintains Cytoskeleton
- IHC –H score
- 150-225 is the cutoff

Powles TB, et al. Presented at: ESMO Annual Meeting; September 13-17, 2024; Barcelona, Spain. 1966MO.

# Study Design and Methods




## Exploratory Nectin-4 Biomarker Analysis

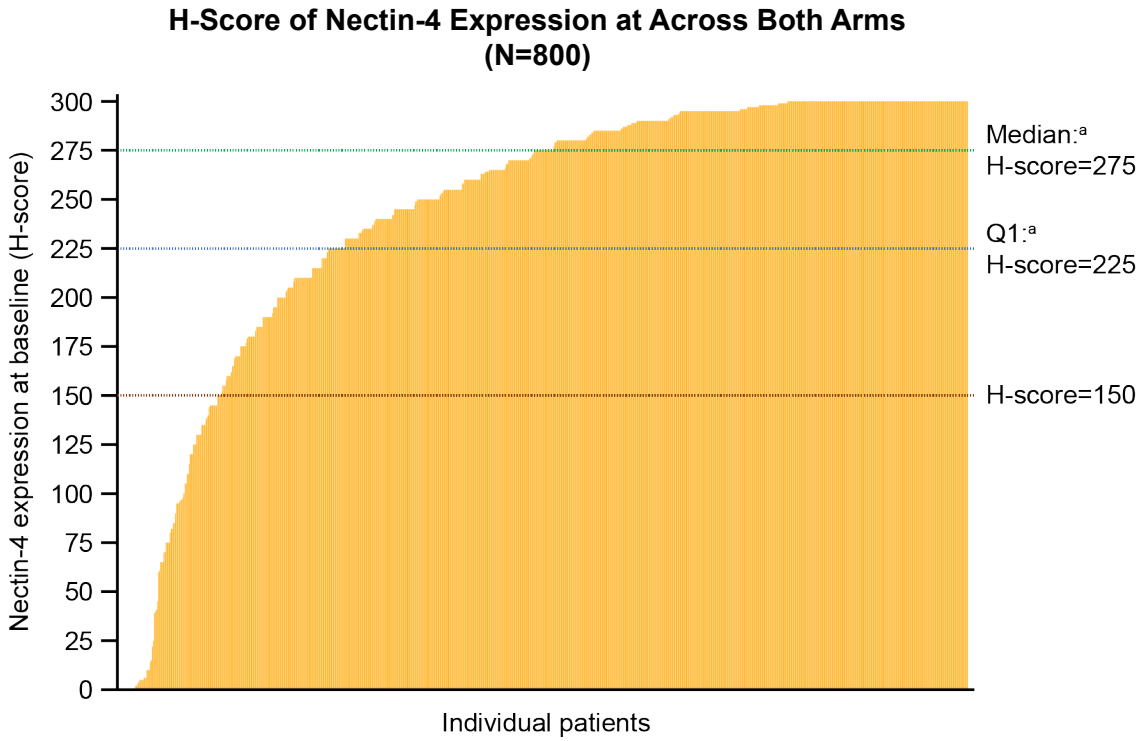
- Retrospective assessment of Nectin-4
- Available for 800 of 886 randomized patients (EV+P: n=394; chemotherapy: n=406)
- Clinical efficacy (PFS, OS, and ORR) was assessed in Nectin-4 expression subgroups

BICR, blinded independent central review; CAP, College of American Pathologists; CLIA, Clinical Laboratory Improvement Amendments; CPS, combined positive score; EV, enfortumab vedotin; GFR, glomerular filtration rate; IV, intravenous infusion; IHC, immunohistochemistry; ITT, intent-to-treat; la/mUC, locally advanced or metastatic urothelial cancer; P, pembrolizumab; Q3W, once every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.
[a]Nectin-4 expression in tumor samples was measured retrospectively by IHC using a validated assay with a Nectin-4 antibody (clone M22-321b41.1) as previously described.[2-4] [b]Fresh or archived tumor tissue was collected from either the primary or metastatic biopsies after completion of most recent prior systemic therapy. [c]PD-L1 expression was assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies).

1. Powles T, et al. *N Engl J Med*. 2024;390(10):875-888. 2. Rosenberg J, et al. *J Clin Oncol*. 2020;38(10):1041-1049. 3. O'Donnell P, et al. *J Clin Oncol*. 2023;41(25):4107-4117. 4. Klümper N, et al. *Clin Cancer Res*. 2023;29(8):1496-1505.

Powles TB, et al. Presented at: ESMO Annual Meeting; September 13-17, 2024; Barcelona, Spain. 1966MO.

# Distribution of Nectin-4 H-Scores Was Skewed Toward High Expression




| Variable | EV+P (n=394) | Chemotherapy (n=406) |
|---|---|---|
| **H-score,** median (IQR) | 280 (230-298) | 270 (215-297) |
| **Subgroup, H-score**, n (%) | | |
| <150 | 38 (9.6) | 50 (12.3) |
| ≥150 to <225 | 50 (12.7) | 56 (13.8) |
| ≥225 | 306 (77.7) | 300 (73.9) |
| **Patients with H-score 0,** n (%) | 3 (0.8) | 6 (1.5) |

**Data cutoff: 8 August 2023.**

EV, enfortumab vedotin; IQR, interquartile range; P, pembrolizumab.

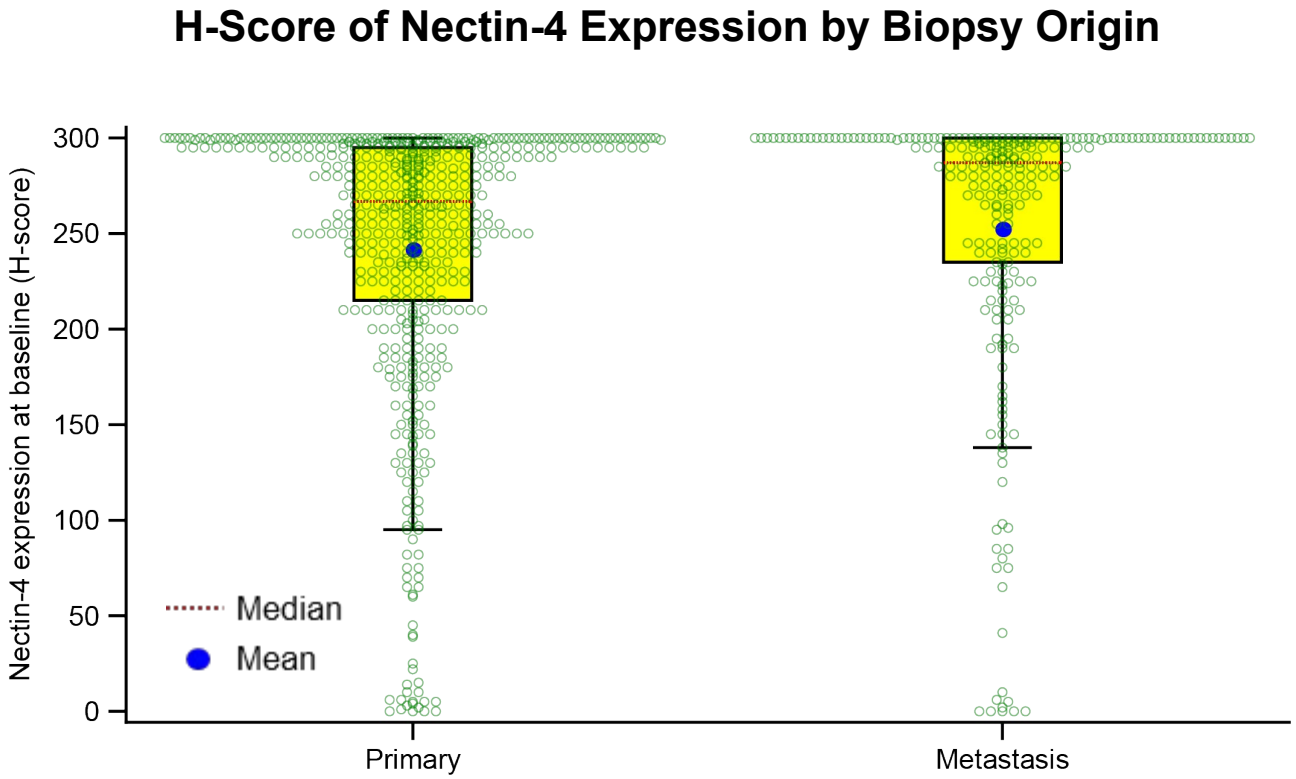
[a]Including all patients across both arms.

Powles TB, et al. Presented at: ESMO Annual Meeting; September 13-17, 2024; Barcelona, Spain. 1966MO.

# High Nectin-4 H-Scores Were Observed Regardless of the Biopsy Origin

| Biopsy origin (n) | H-score, median (IQR) |
|---|---|
| **Primary (n=554)** | 267 (215-295) |
| **Metastasis (n=246)** | 287 (235-300) |

The majority (69%) of biopsy samples submitted were of primary origin[a]




**Data cutoff: 8 August 2023.**

EV, enfortumab vedotin; IQR, interquartile range; la/mUC, locally advanced or metastatic urothelial cancer; P, pembrolizumab.

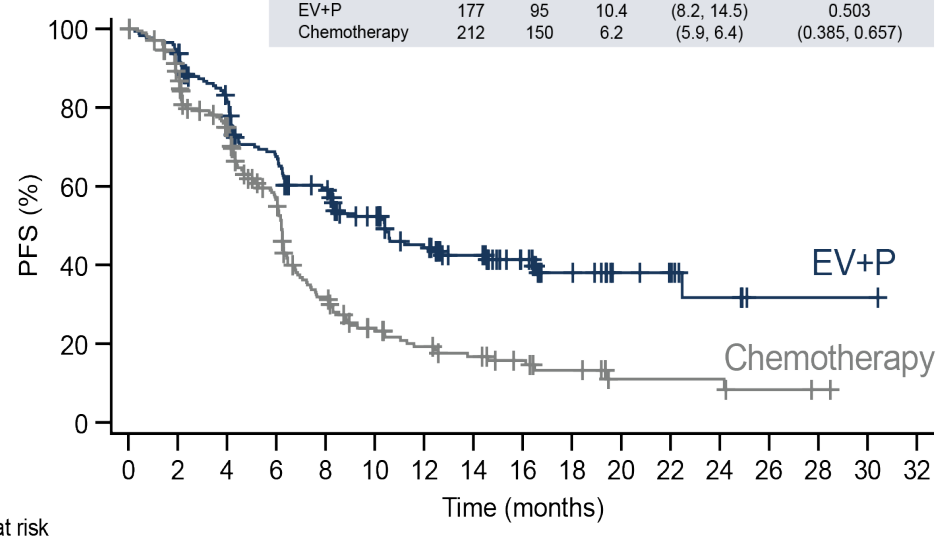
[a]These are not matched biopsies; one tumor tissue sample was submitted for each patient.

Powles TB, et al. Presented at: ESMO Annual Meeting; September 13-17, 2024; Barcelona, Spain. 1966MO.

# Consistent PFS Benefit With EV+P in Both <275 and ≥275 Nectin-4 H-Score Subgroups

## Nectin-4 H-score <275[a]

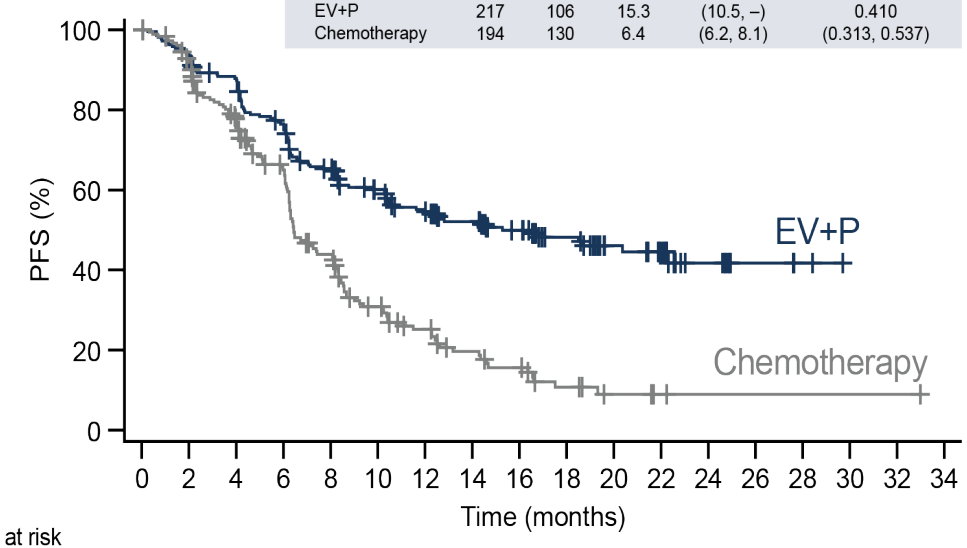
| | N | Events | Median (months) | 95% CI | Stratified HR (95% CI) |
|---|---|---|---|---|---|
| EV+P | 177 | 95 | 10.4 | (8.2, 14.5) | 0.503 |
| Chemotherapy | 212 | 150 | 6.2 | (5.9, 6.4) | (0.385, 0.657) |




| No. at risk | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EV+P | 177 | 165 | 138 | 111 | 94 | 72 | 54 | 40 | 28 | 19 | 11 | 9 | 5 | 1 | 1 | 1 |
| Chemotherapy | 212 | 178 | 142 | 97 | 51 | 33 | 24 | 19 | 14 | 10 | 4 | 4 | 4 | 2 | 1 | |

## Nectin-4 H-score ≥275[a]

| | N | Events | Median (months) | 95% CI | Stratified HR (95% CI) |
|---|---|---|---|---|---|
| EV+P | 217 | 106 | 15.3 | (10.5, –) | 0.410 |
| Chemotherapy | 194 | 130 | 6.4 | (6.2, 8.1) | (0.313, 0.537) |




| No. at risk | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EV+P | 217 | 202 | 186 | 159 | 132 | 111 | 97 | 80 | 66 | 47 | 29 | 21 | 10 | 4 | 2 | |
| Chemotherapy | 194 | 166 | 129 | 96 | 63 | 40 | 29 | 20 | 15 | 8 | 4 | 2 | 1 | 1 | 1 | 1 |

**Data cutoff: 8 August 2023.**

EV, enfortumab vedotin; P, pembrolizumab; PFS, progression-free survival.

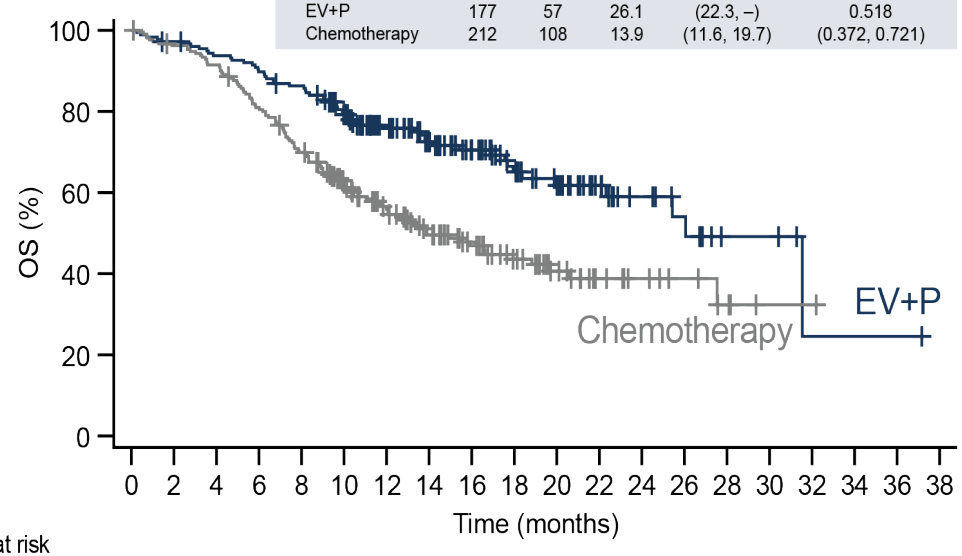
[a]The median Nectin-4 H-score was 275 across patients in both arms.

Powles TB, et al. Presented at: ESMO Annual Meeting; September 13-17, 2024; Barcelona, Spain. 1966MO.

# Consistent OS Benefit with EV+P in Both <275 and ≥275 Nectin-4 H-Score Subgroups

## Nectin-4 H-score <275[a]

| | N | Events | Median (months) | 95% CI | Stratified HR (95% CI) |
|---|---|---|---|---|---|
| EV+P | 177 | 57 | 26.1 | (22.3, –) | 0.518 |
| Chemotherapy | 212 | 108 | 13.9 | (11.6, 19.7) | (0.372, 0.721) |

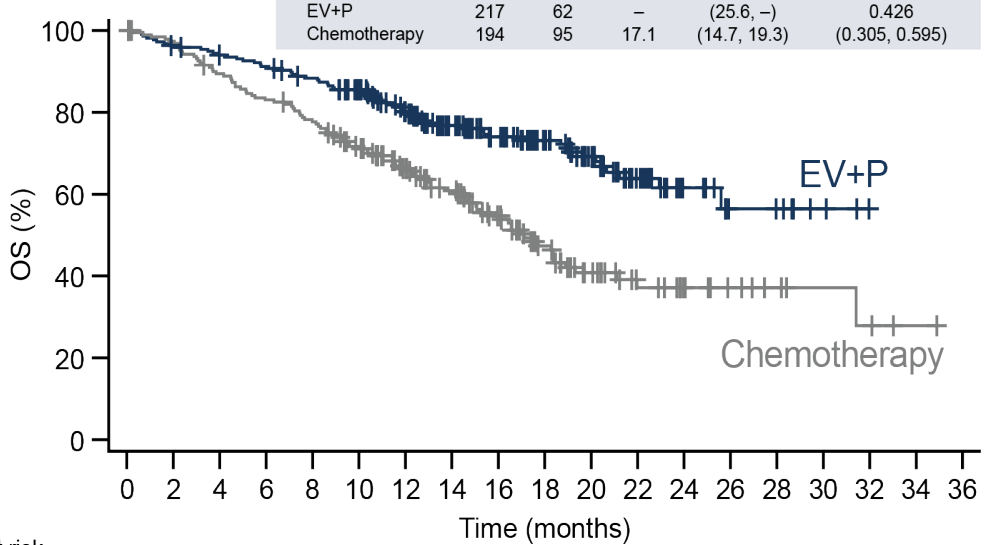



No. at risk

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EV+P | 177 | 171 | 164 | 157 | 150 | 128 | 102 | 81 | 64 | 46 | 36 | 24 | 15 | 11 | 4 | 4 | 1 | 1 | 1 |
| Chemotherapy | 212 | 202 | 192 | 169 | 145 | 114 | 87 | 66 | 50 | 36 | 24 | 15 | 10 | 7 | 4 | 1 | 1 | | |

## Nectin-4 H-score ≥275[a]

| | N | Events | Median (months) | 95% CI | Stratified HR (95% CI) |
|---|---|---|---|---|---|
| EV+P | 217 | 62 | – | (25.6, –) | 0.426 |
| Chemotherapy | 194 | 95 | 17.1 | (14.7, 19.3) | (0.305, 0.595) |




No. at risk

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EV+P | 217 | 208 | 201 | 195 | 186 | 169 | 144 | 121 | 103 | 81 | 59 | 35 | 17 | 8 | 7 | 3 | | |
| Chemotherapy | 194 | 184 | 168 | 156 | 145 | 126 | 103 | 86 | 65 | 46 | 30 | 19 | 13 | 9 | 6 | 4 | 3 | 1 |

**Data cutoff: 8 August 2023.**

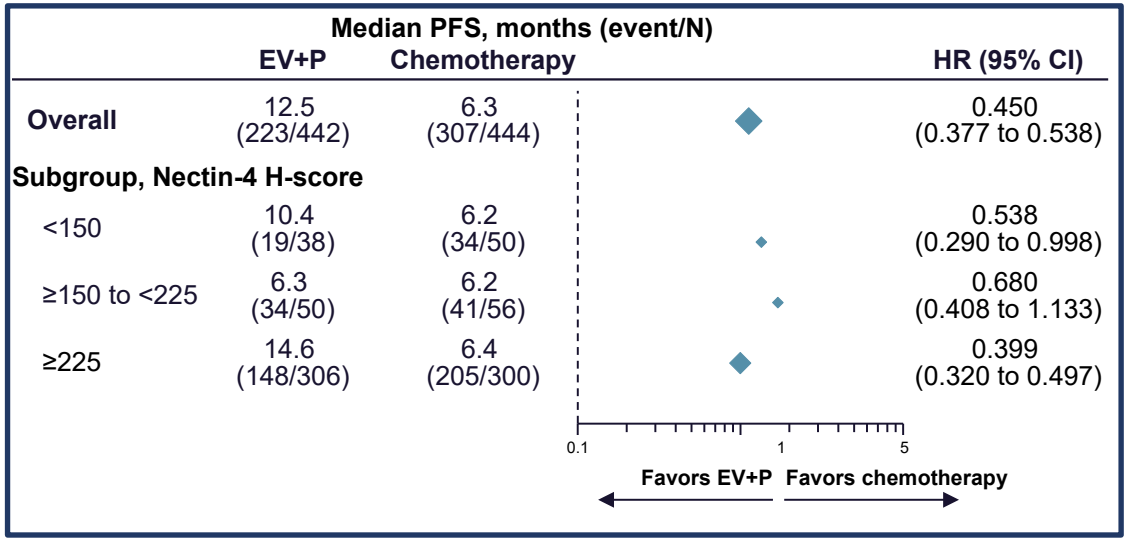
EV, enfortumab vedotin; OS, overall survival; P, pembrolizumab.

[a]The median Nectin-4 H-score was 275 across patients in both arms.

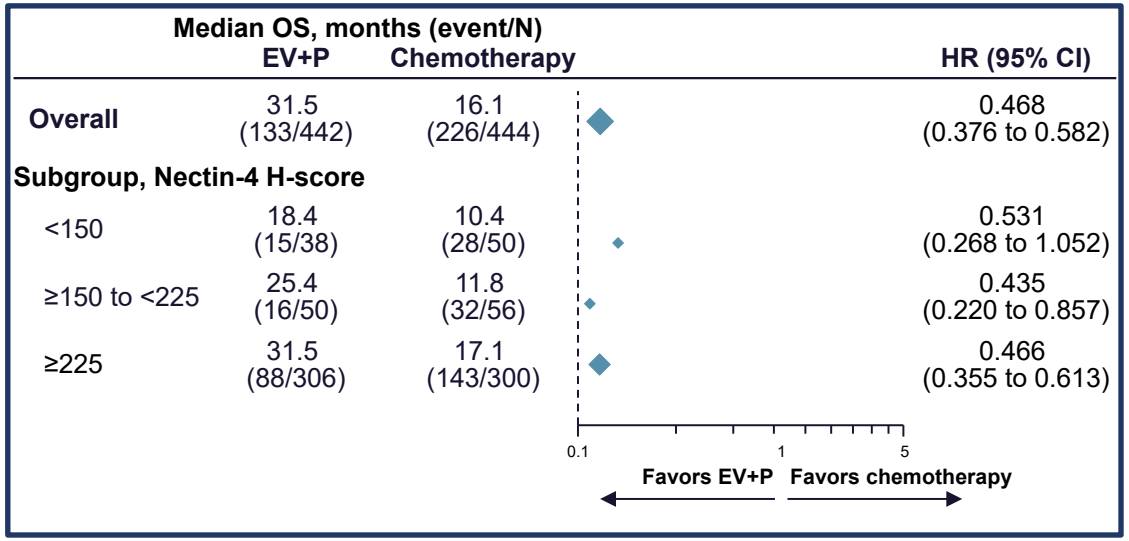
Powles TB, et al. Presented at: ESMO Annual Meeting; September 13-17, 2024; Barcelona, Spain. 1966MO.

# Consistent PFS and OS Benefit with EV+P Across Nectin-4 H-Score Subgroups

## PFS




## OS




***The size of diamonds is relative to the size of the population in each subgroup.***

**Data cutoff: 8 August 2023.**

EV, enfortumab vedotin; OS, overall survival; P, pembrolizumab; PFS, progression-free survival.

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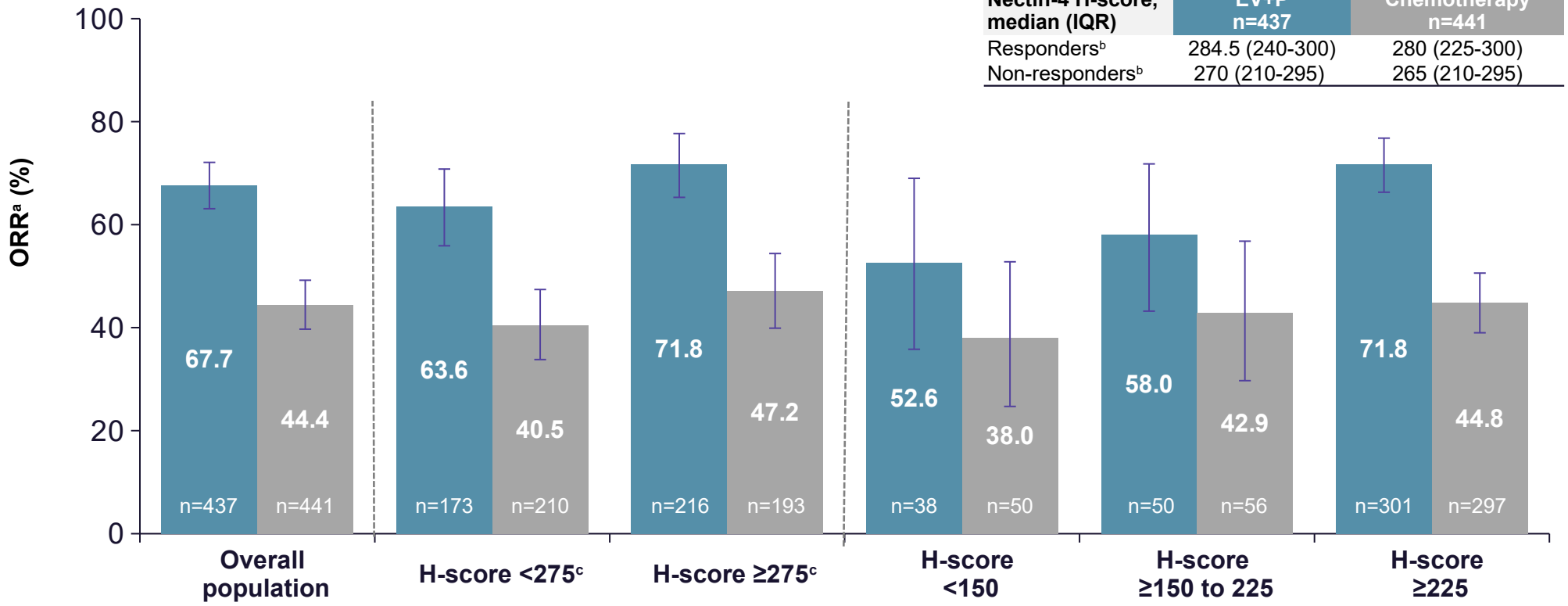
# Consistent ORR Benefit with EV+P Across All Nectin-4 Subgroups

| Nectin-4 H-score, median (IQR) | EV+P n=437 | Chemotherapy n=441 |
|---|---|---|
| Responders[b] | 284.5 (240-300) | 280 (225-300) |
| Non-responders[b] | 270 (210-295) | 265 (210-295) |




**Data cutoff: 8 August 2023.**

CR, complete response; EV, enfortumab vedotin; IQR, interquartile range; ORR, objective response rate; P, pembrolizumab; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

[a]Best overall response according to RECIST 1.1. CR or PR were confirmed with repeat scans ≥28 days after initial response. [b]With Nectin-4 expression data available. [c]The median Nectin-4 H-score was 275 across patients in both arms.

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# Nectin-4 and PD-L1 Expression Distribution

| | EV+P (N=442) | | Chemotherapy (N=444) | |
|---|---|---|---|---|
| | **PD-L1 Low** (CPS <10)[a] n=184 | **PD-L1 High** (CPS ≥10)[a] n=254 | **PD-L1 Low** (CPS <10)[a] n=185 | **PD-L1 High** (CPS ≥10)[a] n=254 |
| **Nectin-4 H-score,** n (%) | | | | |
| **<275**[b] | 70 (15.8) | 107 (24.2) | 86 (19.4) | 126 (28.4) |
| **≥275**[b] | 97 (21.9) | 120 (27.1) | 84 (18.9) | 109 (24.5) |
| Missing | 17 (3.8) | 27 (6.1) | 15 (3.4) | 19 (4.3) |

**Data cutoff: 8 August 2023.**

CPS, combined positive score; EV, enfortumab vedotin; P, pembrolizumab; PD-L1, programmed death ligand 1.

[a]CPS was calculated by the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100; PD-L1 low was defined as CPS <10, and PD-L1 high was defined as CPS ≥10.

[b]The median Nectin-4 H-score was 275 across patients in both arms.

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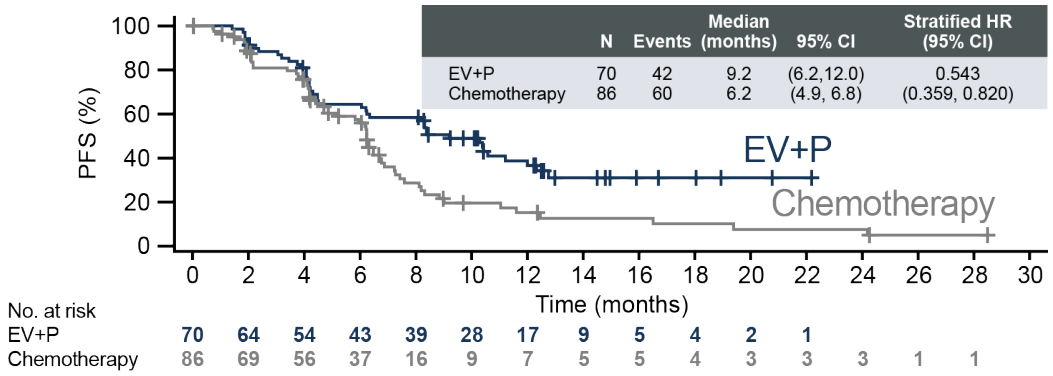
# Consistent PFS Benefit with EV+P Across Nectin-4 and PD-L1 Subgroups

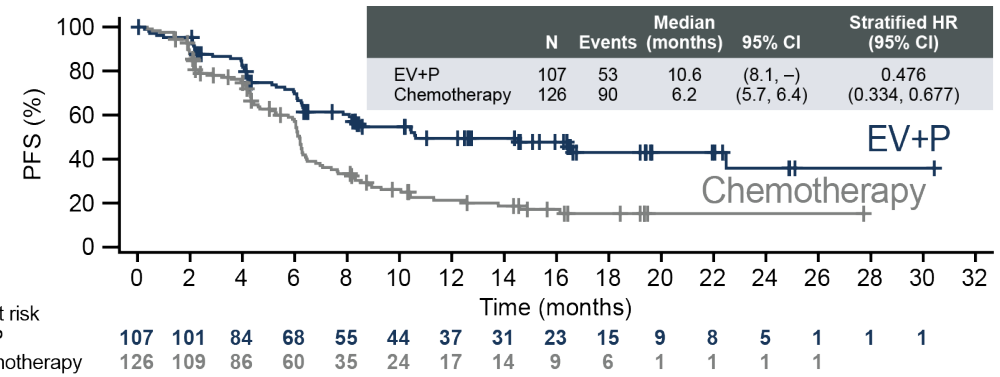
Nectin-4 **H-score <275**[a] / PD-L1 **Low**[b]




| | N | Events | Median (months) | 95% CI | Stratified HR (95% CI) |
|---|---|---|---|---|---|
| EV+P | 70 | 42 | 9.2 | (6.2,12.0) | 0.543 |
| Chemotherapy | 86 | 60 | 6.2 | (4.9, 6.8) | (0.359, 0.820) |

| No. at risk | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EV+P | 70 | 64 | 54 | 43 | 39 | 28 | 17 | 9 | 5 | 4 | 2 | 1 | | | |
| Chemotherapy | 86 | 69 | 56 | 37 | 16 | 9 | 7 | 5 | 5 | 4 | 3 | 3 | 3 | 1 | 1 |

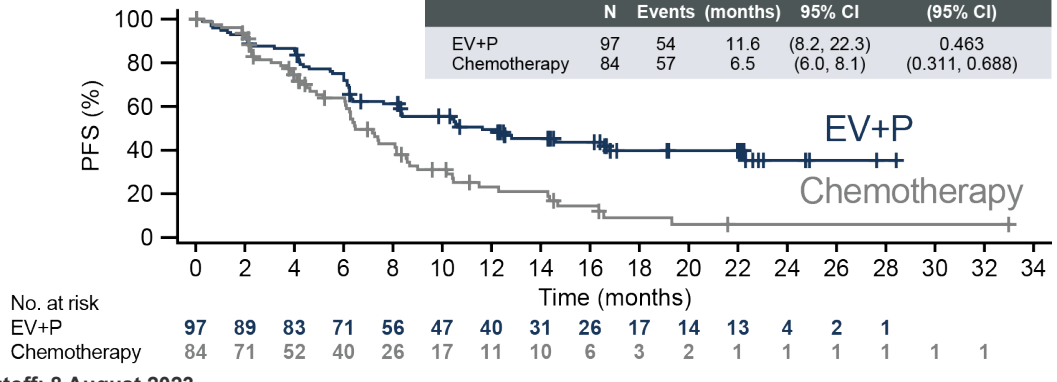
Nectin-4 **H-score <275**[a] / PD-L1 **High**[c]




| | N | Events | Median (months) | 95% CI | Stratified HR (95% CI) |
|---|---|---|---|---|---|
| EV+P | 107 | 53 | 10.6 | (8.1, –) | 0.476 |
| Chemotherapy | 126 | 90 | 6.2 | (5.7, 6.4) | (0.334, 0.677) |

| No. at risk | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EV+P | 107 | 101 | 84 | 68 | 55 | 44 | 37 | 31 | 23 | 15 | 9 | 8 | 5 | 1 | 1 | 1 |
| Chemotherapy | 126 | 109 | 86 | 60 | 35 | 24 | 17 | 14 | 9 | 6 | 1 | 1 | 1 | 1 | | |

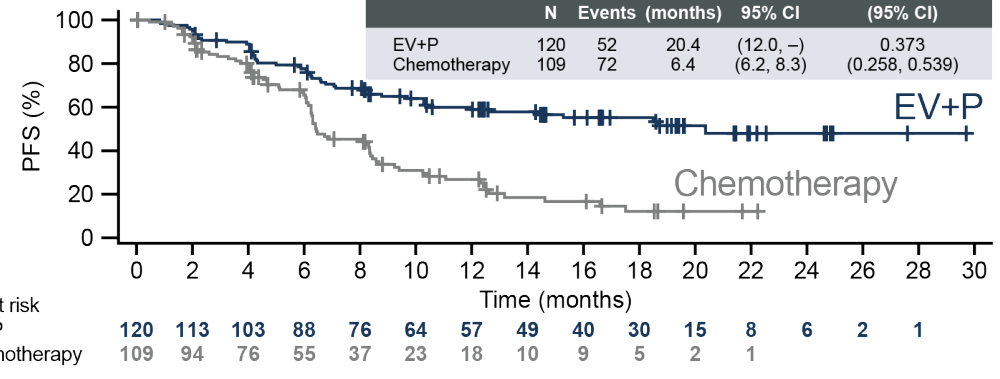
Nectin-4 **H-score ≥275**[a] / PD-L1 **Low**[b]




| | N | Events | Median (months) | 95% CI | Stratified HR (95% CI) |
|---|---|---|---|---|---|
| EV+P | 97 | 54 | 11.6 | (8.2, 22.3) | 0.463 |
| Chemotherapy | 84 | 57 | 6.5 | (6.0, 8.1) | (0.311, 0.688) |

| No. at risk | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EV+P | 97 | 89 | 83 | 71 | 56 | 47 | 40 | 31 | 26 | 17 | 14 | 13 | 4 | 2 | 1 |
| Chemotherapy | 84 | 71 | 52 | 40 | 26 | 17 | 11 | 10 | 6 | 3 | 2 | 1 | 1 | 1 | 1 | 1 | 1 |

Nectin-4 **H-score ≥275**[a] / PD-L1 **High**[c]




| | N | Events | Median (months) | 95% CI | Stratified HR (95% CI) |
|---|---|---|---|---|---|
| EV+P | 120 | 52 | 20.4 | (12.0, –) | 0.373 |
| Chemotherapy | 109 | 72 | 6.4 | (6.2, 8.3) | (0.258, 0.539) |

| No. at risk | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EV+P | 120 | 113 | 103 | 88 | 76 | 64 | 57 | 49 | 40 | 30 | 15 | 8 | 6 | 2 | 1 |
| Chemotherapy | 109 | 94 | 76 | 55 | 37 | 23 | 18 | 10 | 9 | 5 | 2 | 1 | | | |

**Data cutoff: 8 August 2023.**

CPS, combined positive score; EV, enfortumab vedotin; P, pembrolizumab; PD-L1, programmed death ligand 1; PFS, progression-free survival.
[a]The median Nectin-4 H-score was 275 across patients in both arms. [b]CPS <10. [c]CPS ≥10.

Powles TB, et al. Presented at: ESMO Annual Meeting; September 13-17, 2024; Barcelona, Spain. 1966MO.

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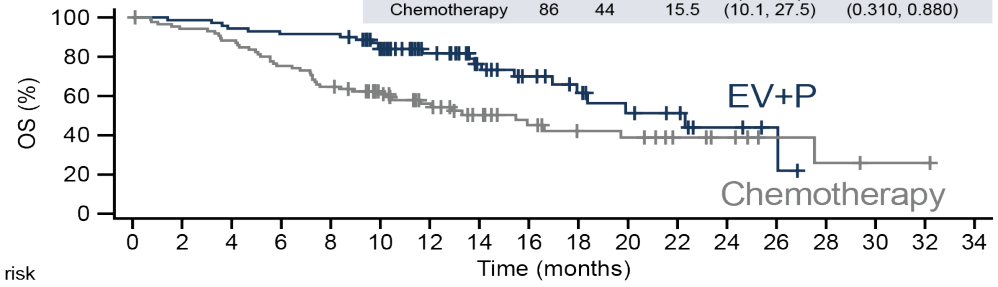
# Consistent OS Benefit with EV+P Across Nectin-4 and PD-L1 Subgroups

## Nectin-4 H-score <275[a] / PD-L1 Low[b]

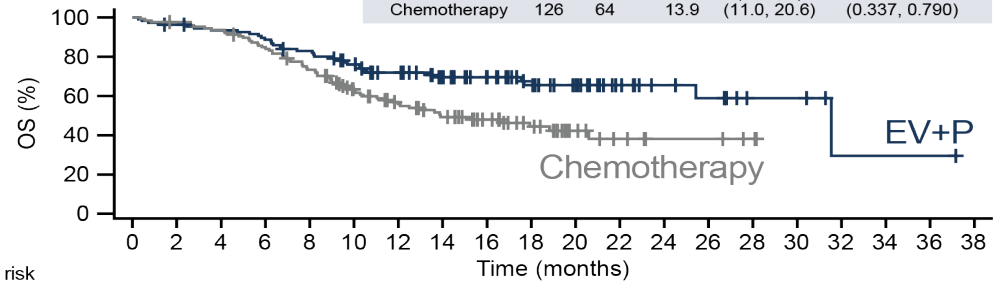
| | N | Events | Median (months) | 95% CI | Stratified HR (95% CI) |
|---|---|---|---|---|---|
| EV+P | 70 | 22 | 22.3 | (17.0, –) | 0.522 |
| Chemotherapy | 86 | 44 | 15.5 | (10.1, 27.5) | (0.310, 0.880) |




| No. at risk | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EV+P | 70 | 69 | 66 | 64 | 64 | 53 | 37 | 26 | 19 | 14 | 10 | 8 | 4 | 2 | | | |
| Chemotherapy | 86 | 80 | 75 | 64 | 55 | 44 | 32 | 23 | 17 | 13 | 12 | 8 | 6 | 3 | 2 | 1 | 1 |

## Nectin-4 H-score <275[a] / PD-L1 High[c]

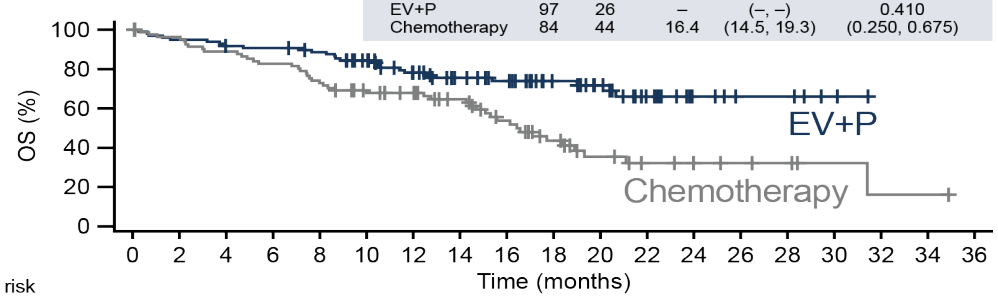
| | N | Events | Median (months) | 95% CI | Stratified HR (95% CI) |
|---|---|---|---|---|---|
| EV+P | 107 | 35 | 31.5 | (25.4, –) | 0.516 |
| Chemotherapy | 126 | 64 | 13.9 | (11.0, 20.6) | (0.337, 0.790) |




| No. at risk | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EV+P | 107 | 102 | 98 | 93 | 86 | 75 | 65 | 55 | 45 | 32 | 26 | 16 | 11 | 9 | 4 | 4 | 1 | 1 | 1 |
| Chemotherapy | 126 | 122 | 117 | 105 | 90 | 70 | 55 | 43 | 33 | 23 | 12 | 7 | 4 | 4 | 2 | | | | |

## Nectin-4 H-score ≥275[a] / PD-L1 Low[b]

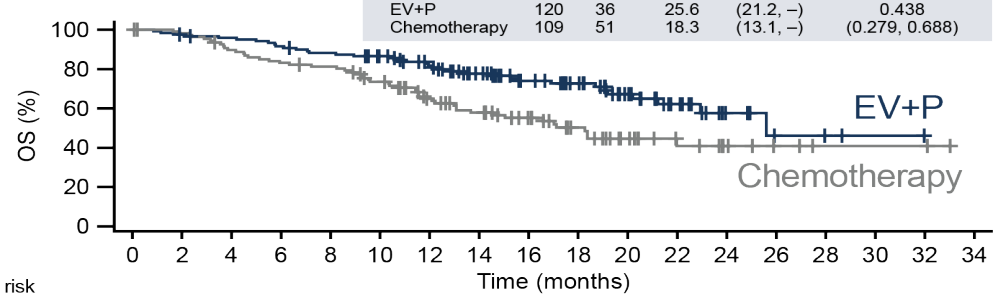
| | N | Events | Median (months) | 95% CI | Stratified HR (95% CI) |
|---|---|---|---|---|---|
| EV+P | 97 | 26 | – | (–, –) | 0.410 |
| Chemotherapy | 84 | 44 | 16.4 | (14.5, 19.3) | (0.250, 0.675) |




| No. at risk | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EV+P | 97 | 92 | 88 | 87 | 83 | 74 | 60 | 51 | 46 | 35 | 28 | 17 | 9 | 5 | 5 | 2 | |
| Chemotherapy | 84 | 78 | 72 | 67 | 59 | 51 | 46 | 38 | 28 | 19 | 12 | 8 | 6 | 5 | 4 | 2 | 1 | 1 |

## Nectin-4 H-score ≥275[a] / PD-L1 High[c]

| | N | Events | Median (months) | 95% CI | Stratified HR (95% CI) |
|---|---|---|---|---|---|
| EV+P | 120 | 36 | 25.6 | (21.2, –) | 0.438 |
| Chemotherapy | 109 | 51 | 18.3 | (13.1, –) | (0.279, 0.688) |




| No. at risk | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EV+P | 120 | 116 | 113 | 108 | 103 | 95 | 84 | 70 | 57 | 46 | 31 | 18 | 8 | 3 | 2 | 1 |
| Chemotherapy | 109 | 105 | 95 | 88 | 85 | 74 | 57 | 48 | 37 | 27 | 18 | 11 | 7 | 4 | 2 | 2 | 2 |

**Data cutoff: 8 August 2023.**

CPS, combined positive score; EV, enfortumab vedotin; OS, overall survival; P, pembrolizumab; PD-L1, programmed death ligand 1.
[a]The median Nectin-4 H-score was 275 across patients in both arms. [b]CPS <10. [c]CPS ≥10.

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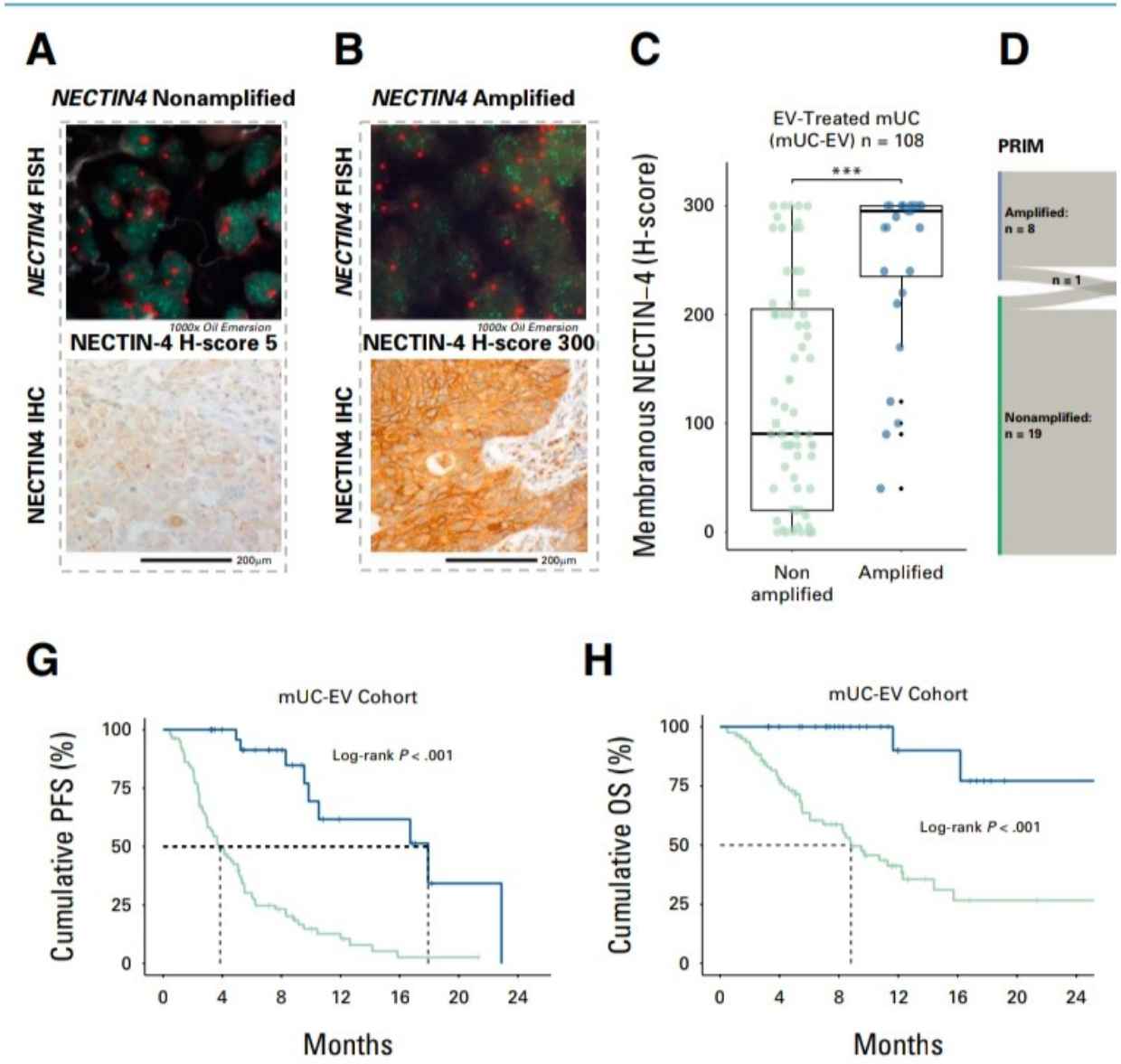
# NECTIN 4 gene amplification

- 25% mUC
- ORR :96 vs 32% (amp vs non amp)



# Authors' Conclusions

- Nectin-4  by IHC >90%
- Nectin-4  and PD-L1 by IHC is not predictive
- NECTIN 4 gene amplification –is predictive

EV, enfortumab vedotin; la/mUC, locally advanced or metastatic urothelial cancer; P, pembrolizumab; PD-L1, programmed death ligand 1; UC, urothelial cancer.

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