Evaluation of concordance between PD-L1 immunohistochemistry 28-8 and 22C3 pharmDx assays in metastatic urothelial carcinoma (mUC) in PIVOT-10

83P

A. Siefker-Radtke[1], U. Hoch[2], Y. Loriot[3], A. Balar[4], M. Bilen[5], N. Tannir[1], D. Cho[4], A. Choudhury[6], D. Chien[7], D. Yu[8], S. Currie[8], J. Novotny[9], L. Santiago[2], M. Tagliaferri[7], J. Zalevsky[10], R. Huddart[11]

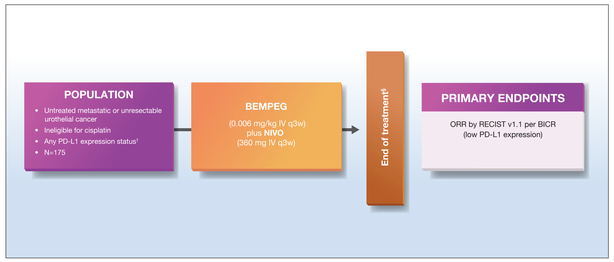
[1]Genitourinary Medical Oncology Department, The University of Texas M.D. Anderson Center, Houston, TX, USA, [2]Clinical Pharmacology, Nektar Therapeutics, San Francisco, CA, USA, [3]Cancer Medicine Department, Institut Gustave Roussy, Villejuif, Cedex, France, [4]Perlmutter Cancer Center, NYU Langone Medical Center and School of Medicine, New York, NY, USA, [5]Oncology Department, Winship Cancer Institute of Emory University, Atlanta, GA, USA, [6]Biostatistics, Nektar Therapeutics, San Francisco, CA, USA, [7]Clinical Development, Nektar Therapeutics, San Francisco, CA, USA, [8]Medical Affairs, Nektar Therapeutics, San Francisco, CA, USA, [9]Pharmacodiagnostics Center of Excellence, Bristol Myers Squibb, Lawrence Township, NJ, USA, [10]Research and Development, Nektar Therapeutics, San Francisco, CA, USA, [11]Radiotherapy and Imaging Department, Royal Marsden Hospital Institute of Cancer Research, Sutton, UK

BACKGROUND

PD-L1 testing in patients with metastatic urothelial carcinoma

- For patients with metastatic urothelial carcinoma (mUC), level of programmed death-ligand 1 (PD-L1) expression by immunohistochemistry (IHC) is used to guide first-line treatment decisions with immune checkpoint inhibitors (ICI)[1]
- There are different assays approved for evaluation of PD-L1 expression by IHC, including the 22C3 (combined positive score [CPS]; pembrolizumab companion diagnostic) 28-8 (tumor proportion score [TPS]; nivolumab complementary diagnostic) PharmDx assays
  - The CPS method evaluates PD-L1 on tumor and immune cells, whereas the TPS evaluates PD-L1 on tumor cells.[1] Both use different scoring cut-offs
  - Concordance between the assays in mUC when using the same scoring method is unknown
- PIVOT-10 (NCT03785925) is a phase 2 study of bempegaldesleukin (BEMPEG; NKTR-214) plus nivolumab (NIVO) in cisplatin-ineligible patients with locally advanced or mUC (**Figure 1**)
  - Patients were enrolled regardless of baseline PD-L1 expression. However, the primary objective was to evaluate the antitumor activity of BEMPEG plus NIVO in patients with low PD-L1 (CPS <10) expression
  - Both assays (22C3 and 28-8) were tested contemporaneously by a single laboratory, providing the unique opportunity to evaluate concordance, with the view of simplifying future clinical practice by using assays interchangeably
- **The purpose of this study is to investigate concordance of the 22C3 and 28-8 pharmDx assays in the PIVOT-10 study using a CPS cut-off of 10**

Figure 1. PIVOT-10: A Phase 2, single-arm study of BEMPEG in combination with NIVO in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer



[1]PD-L1 status (enrollment) was based on PD-L1 IHC 22C3 pharmDx assay: low: CPS <10; high: CPS ≥10. Enrollment will stop once ≥110 patients with low tumor PD-L1 expression are enrolled and have received at least one dose of BEMPEG or NIVO.
[2]Treat for up to 2 years until progressive disease per RECIST v1.1, loss of clinical benefit, death, unacceptable toxicity, symptomatic deterioration, investigator or patient decision to discontinue treatment, patient withdrawal of consent, loss to follow-up, or study termination.
BEMPEG, bempegaldesleukin; BICR, blinded independent central review; CPS, combined positive score; IHC, immunohistochemistry; IV, intravenous; NIVO, nivolumab; ORR, objective response rate; PD-L1, programmed death-ligand 1; q3w, every 3 weeks; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1.

METHODS

Patient population

All first-line mUC patients screened for the PIVOT-10 study were eligible for this concordance analysis:

- Archival baseline tumor (≤12 months prior to enrollment) or fresh samples were required
- PD-L1 IHC 22C3 and 28-8 pharmDx assays were run on all eligible samples at a single laboratory, contemporaneously
- Assays were scored using CPS (number of PD-L1-stained cells [tumor cells, lymphocytes, macrophages]/ total number of viable tumor cells x 100)

Statistics

Concordance was assessed on samples that had PD-L1 results on both assays:

- Specificity and sensitivity analysis was implemented with positive percentage agreement (PPA) and negative percentage agreement (NPA). PPA was calculated as the percentage for both comparative and reference assay positive results/reference assay positive results. NPA was calculated as the percentage for both comparative and reference assay negative results/reference assay negative results
- Concordance analysis for PD-L1 expression (positive and negative) as a measure of agreement between two assays was represented by:
  - Overall percentage agreement (OPA; percentage positive or negative results between comparative and reference assays)
  - Inter-assay agreement was evaluated with Cohen's kappa
- Concordance analysis for PD-L1 CPS as a continuous measures was assessed by:
  - Lin's concordance correlation coefficient for two measures of the same variable[2]
  - Rank-based correlations Spearman's rho and Kendall's tau for binary variables
- The 95% confidence interval for each percentage was calculated using the Clopper-Pearson method

RESULTS

Table 1. Number of patients with availability of samples for PD-L1 concordance analysis

Number of patients screened:	389		
PharmDx assay	**22C3 only**	**28-8 only**	**22C3 and 28-8**
Number of patients with PD-L1 results available for concordance analysis	279	260	259

PD-L1, programmed death-ligand 1.

- There was agreement between the assays (**Table 2** and **Figure 2**) (absolute mean difference=0.96 [Lin's Concordance Correlation Coefficient]). OPA, PPA, and NPA were the same regardless of the reference assay used (22C3 or 28-8) with a CPS cut-off of ≥10:
  - OPA was 95%
  - PPA was 93%
  - NPA was 97%
- A similar percentage of PD-L1 negativity (CPS cut-off of <10) between assays was observed (**Figure 3**)
  - Binary results showed good quality of agreement (Cohen's kappa 0.89)
- A Spearman's correlation score of rho=0.925, and Kendall's tau=0.841, between the assays shows a high level of correlation at a CPS cut-off of <10 vs ≥10 (**Figure 4**)

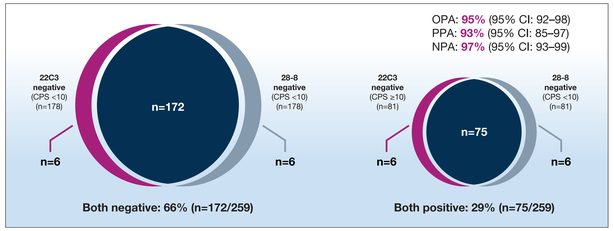
Table 2. High level of agreement between the 22C3 and 28-8 assays observed (CPS 10 cut-off; N=259)

Concordance between assays		22C3	
		Positive (CPS ≥10)	**Negative** (CPS <10)
28-8	**Positive** (CPS ≥10)	75	6
	Negative (CPS <10)	6	172

	22C3 Reference		28-8 Reference		OPA
	PPA	NPA	PPA	NPA	
n/N	75/81	172/178	75/81	172/178	247/259
Agreement, % (95% CI)	93 (85–97)	97 (93–99)	93 (85–97)	97 (93–99)	95 (92–98)

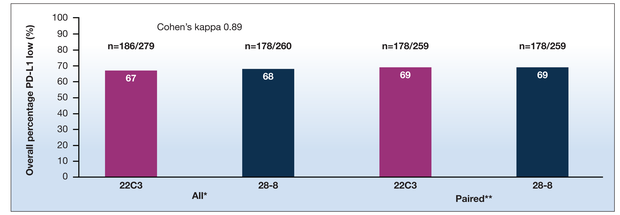
CI, confidence interval; CPS, combined positive score; NPA, negative percentage agreement; OPA, overall percentage agreement; PPA, positive percentage agreement.

Figure 2. High level of agreement between the 22C3 and 28-8 assays observed (CPS 10 cut-off; N=259)



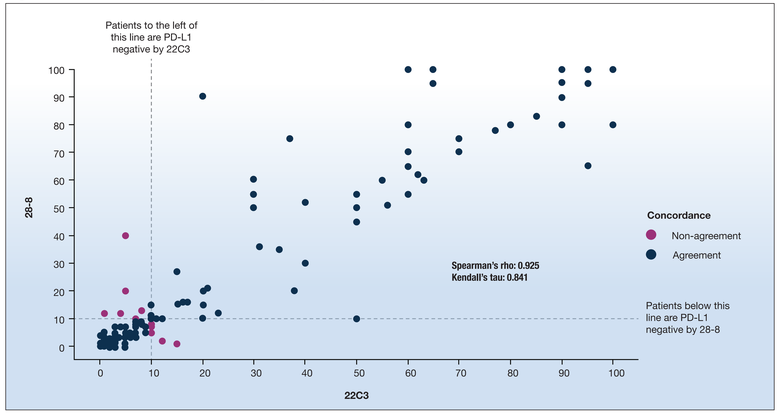
CI, confidence interval; CPS, combined positive score; NPA, negative percentage agreement; OPA, overall percentage agreement; PPA, positive percentage agreement.

Figure 3. Similar rates of PD-L1 negativity (CPS cut-off <10) using the 22C3 and 28-8 assays



*All = analysis conducted on all available samples; **Paired = analysis conducted on samples that had PD-L1 results from both assays.
CPS, combined positive score; PD-L1, programmed death-ligand 1.

Figure 4. Correlation of CPS scoring (N=259)



CPS, combined positive score; PD-L1, programmed death ligand-1.

Table 3. Discordant cases

Anatomical location	22C3 CPS	22C3 Percentage PD-L1 (tumor)	28-8 CPS	28-8 Percentage PD-L1 (tumor)
Bladder	15	0	1	0
Bladder	12	2	2	0
Lung	10	0	7	5
Bladder	10	0	8	0
Bladder	10	10	5	3
Bladder	10	0	7	0
Bladder	8	5	13	10
Kidney/ureter	7	0	10	0
Lymph node	5	3	20	0
Prostate	5	0	40	0
Breast	4	2	12	10
Bladder	1	0	12	10

CPS, combined positive score; PD-L1, programmed death-ligand 1

CONCLUSIONS

PD-L1 is an important cancer biomarker used to help guide treatment decisions in mUC:

- These data demonstrate high concordance between the 22C3 and 28-8 pharmDx assays for evaluating baseline PD-L1 status, based on CPS, for patients with mUC
- Both assays demonstrated a similar proportion of PD-L1 low tumors in patients with mUC, suggesting that either assay is suitable for patient selection. PD-L1 negativity rate was similar to that previously reported[3]
- A high correlation between the assays was observed at a CPS cut-off of <10 vs ≥10
- Taken together, these results suggest the interchangeability of these assays to define PD-L1 status (using a CPS cut-off of 10) in patients with mUC, potentially simplifying treatment decision making in this patient population

ACKNOWLEDGMENTS

This study was sponsored by Nektar Therapeutics, San Francisco, CA. Medical writing assistance was provided by Alison Lovibond PhD of BOLDSCIENCE Inc., and was funded by Nektar Therapeutics.

REFERENCES

1. Huddart R, et al. *Future Oncol* 2020;17:137–149; 2. McBride GB. *NIWA Client Rep* 2005;HAM2005-06:14. Available from: https://www.medcalc.org/download/pdf/McBride2005.pdf Accessed August 5, 2021; 3. Vuky J, et al. *J Clin Oncol* 2020;38:2658–66.

DISCLOSURES

A Siefker-Radtke has served as an advisor to AstraZeneca, Basilea, Bavarian Nordic, Bristol-Myers Squibb, EMD Serono, Genentech, Janssen, Merck, Mirati Therapeutics, NCCN, Nektar and Seattle Genetics and has received research funding from Basilea, BioClin Therapeutics, Bristol-Myers Squibb, Janssen, Merck Sharp & Dohme, Michael and Sherry Sutton Fund for Urothelial Cancer, Nektar, NIH and Takeda. She has also received patents, royalties, and/or other intellectual property pertaining to methods of characterizing and treating molecular subsets of muscle-invasive bladder cancer.

Poster presented at ESMO 2021 | September 16–21, 2021, Virtual. Corresponding author Arlene Siefker-Radtke: asiefker@mdanderson.org