Few randomized trials have been conducted in the second-line treatment of advanced bladder cancer. Their results, although clinically disappointing, will help to optimize the design of future trials in this setting.[5]

Stéphane Culine
Saint-Louis Hospital, University Paris 7, Paris, France

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: None **Consultant or Advisory Role:** Stéphane Culine, Pierre Fabre (C) **Stock Ownership:** None **Honoraria:** Stéphane Culine, Pierre Fabre **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

REFERENCES

1. Wong YN, Litwin S, Vaughn D, et al: Phase II trial of cetuximab with or without paclitaxel in patients with advanced urothelial tract carcinoma. J Clin Oncol 30:3545-3551, 2012
2. Sonpavde G, Sternberg CN, Rosenberg JE, et al: Second-line systemic therapy and emerging drugs for metastatic transitional-cell carcinoma of the urothelium. Lancet Oncol 11:861-870, 2010
3. Lièvre A, Bachet JB, Boige V, et al: KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. J Clin Oncol 26:374-379, 2008
4. Juanpere N, Agell L, Lorenzo M, et al: Mutations in FGFR3 and PIK3CA, singly or combined with RAS or AKT1, are associated with AKT but not with MAPK pathway activation in urothelial bladder cancer. Human Pathol 43:1573-1582, 2012
5. Bellmunt J, Choueiri TK, Schutz FA, et al: Randomized phase III trials of second-line chemotherapy in patients with advanced bladder cancer: Progress and pitfalls. Ann Oncol 22:245-247, 2011

DOI: 10.1200/JCO.2012.47.5004; published online ahead of print at www.jco.org on March 11, 2013

Reply to S. Buti and S. Culine

The comments Buti[1] and Culine[2] regarding our article[3] about the role of cetuximab with or without paclitaxel in patients with advanced urothelial cancer. Their comments highlight some of the challenges in conducting clinical trials in this area.

Buti proposes an additional analysis comparing the study's overall survival to the expected survival on the basis of the distribution of patient characteristics using the Bellmunt criteria published in 2010.[4] Using these criteria, seven patients in the combination arm of our study had zero risk factors, 13 patients had one risk factor, seven patients had two risk factors, and one patient had three risk factors. The small size of these subsets precludes a meaningful statistical comparison of survival. We did report the progression-free and overall survival of patients who received chemotherapy for metastatic disease and those who had visceral metastases. However, because of the small sample size, we believe these results should be considered hypothesis generating only, and we discuss this limitation in our article.[3]

We agree with Culine that time from prior chemotherapy may be an important prognostic factor. We have contributed data from this study to a pooled analysis that recently demonstrated that a shorter time from prior chemotherapy is associated with worse response.[5] This information may be used to design additional studies.

KRAS mutation status was not known to be predictive of response to cetuximab in advanced colorectal cancer when this study began enrolling patients in 2006. However, we would not recommend testing for *KRAS* mutational status as an entry criteria for future studies of this combination on the basis of the low probability of finding a *KRAS* mutation in a patient with metastatic urothelial cancer. Juanpere et al[6] found just one *KRAS* mutation among the 33 patients within the cohort of high-grade invasive bladder cancer. A higher but still low frequency of *KRAS* mutations were found in superficial tumor samples, which have a lower probability for metastasis. Other investigators have also found a low frequency of *KRAS* mutations in patients with urothelial carcinoma.[7,8]

This study was designed as a noncomparative phase II study; therefore, each arm was investigated separately. We hope to test this combination in a randomized comparative fashion using paclitaxel as a control arm. Vinflunine, although available in Europe, is not available in the United States and is not a practical comparator arm.

Our study met its prespecified primary end point, which demonstrated that the combination of cetuximab and paclitaxel extended progression-free survival compared with historical controls, providing the rationale for future testing of this combination in a larger randomized trial.

Yu-Ning Wong, Elizabeth R. Plimack, and Samuel Litwin
Fox Chase Cancer Center, Philadelphia, PA

David Vaughn
University of Pennsylvania, Philadelphia, PA

James Lee
Virtua Cancer Center, Mt Holly, NJ

Wei Song
Pottstown Hospital, Pottstown, PA

Gary R. Hudes
Fox Chase Cancer Center, Philadelphia, PA

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: None **Consultant or Advisory Role:** Yu-Ning Wong, Bristol-Myers Squibb (C), Bristol-Myers Squibb (U); Gary R. Hudes, Bristol-Myers Squibb (U) **Stock Ownership:** None **Honoraria:** None **Research Funding:** Yu-Ning Wong, Bristol-Myers

Squibb; Gary R. Hudes, Bristol-Myers Squibb **Expert Testimony:** None **Other Remuneration:** None

REFERENCES

1. Buti S: Does the cetuximab plus paclitaxel combination deserve to be studied in a phase III trial? J Clin Oncol 31:1613-1614, 2013
2. Culine S: Cetuximab in advanced bladder cancer. J Clin Oncol 31:1614-1615, 2013
3. Wong YN, Litwin S, Vaughn D, et al: Phase II trial of cetuximab with or without paclitaxel in patients with advanced urothelial tract carcinoma. J Clin Oncol 30:3545-3551, 2012
4. Bellmunt J, Choueiri TK, Fougeray R, et al: Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. J Clin Oncol 28:1850-1855, 2010
5. Sonpavde G, Pond GR, Fougeray R, et al: Time from prior chemotherapy enhances prognostic risk grouping in the second-line setting of advanced urothelial carcinoma: A retrospective analysis of pooled prospective phase 2 trials. Eur Urol [epub ahead of print on November 26, 2012]
6. Juanpere N, Agell L, Lorenzo M, et al: Mutations in FGFR3 and PIK3CA, singly or combined with RAS and AKT1, are associated with AKT but not with MAPK pathway activation in urothelial bladder cancer. Hum Pathol 43:1573-1582, 2012
7. Gui Y, Guo G, Huang Y, et al: Frequent mutations of chromatin remodeling genes in transitional cell carcinoma of the bladder. Nat Genet 43:875-878, 2011
8. Sjödahl G, Lauss M, Gudjonsson S, et al: A systematic study of gene mutations in urothelial carcinoma; inactivating mutations in TSC2 and PIK3R1. PLoS One 6:e18583, 2011

DOI: 10.1200/JCO.2012.47.8255; published online ahead of print at www.jco.org on March 11, 2013

