External validation of the association of progression-free survival at 6 months (PFS6) with overall survival at 12 months (OS12) in second-line therapy for advanced urothelial carcinoma (UC)

Sonpavde G[1], Maughan B[2], Boucher KM[2], Fougeray R[3], Choueiri TK[4], Niegisch G[5], Wong YN[6], Sridhar SS[7], Sternberg CN[8], Bellmunt J[9]

[1]University of Alabama at Birmingham (UAB) Comprehensive Cancer Center, Birmingham, AL, USA; [2]Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah, USA; [3]Institut de Recherche Pierre Fabre, Boulogne, France; [4]Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA; [5]Heinrich Heine University, Dusseldorf, Germany; [6]Fox Chase Cancer Center, Philadelphia, PA, USA; [7]Princess Margaret Hospital, Toronto, ON, Canada; [8]San Camillo and Forlanini Hospitals, Rome, Italy; [9]University Hospital del Mar-IMIM, Barcelona, Spain

Disclosures

- Maughan B, Boucher K, Sternberg CN: None
- Fougeray R: Employee of Pierre-Fabre
- Choueiri TK: Research support to institution from Astrazeneca
- Bellmunt J: Research support to institution from Pierre-Fabre
- Wong YN, Sonpavde G: Research support to institution from BMS
- Sridhar S, Sonpavde G: Research support to institution from Celgene
- Niegisch G: Research support to institution from Eli Lilly and BMS

Background

- Patients in the second-line UC setting have significant unmet needs: responses in 5% to 20%, median PFS of 2 to 4 months and a median OS of 6 to 9 months (vinflunine is approved in Europe but no agents are approved in USA).

- Response rate (RR) and median PFS are the typical primary endpoints in phase II trials but may not capture activity of cytostatic agents or durable benefits.

- PFS at a fixed time-point slightly beyond the median PFS may partly overcome these drawbacks of measuring RR and median PFS.

- A strong association between PFS at 6 months (PFS6) and OS has been found in other solid tumors (Ballman KV; Foster NR).

- We hypothesized that PFS6 correlates with OS at 12 months (OS12) in second-line therapy for advanced UC.

Objective

- To study the association of PFS6 and Response with OS12 in patients receiving second-line therapy for advanced UC

Methods

- Progression was defined as objective tumor progression or death.
- In the discovery dataset, 10 phase II trials (N=689) evaluating second-line therapy after perioperative chemotherapy only or chemotherapy for metastatic disease were combined with individual patient level data.
- The relationship between PFS6/RR and OS12 was assessed at the trial level using Pearson correlation and weighted linear regression.
- The relationship between PFS6/response and OS12 at the individual level was assessed using Pearson chi-square test with Yates continuity correction.
- External validation was conducted in a second-line phase III trial, N=370 (Bellmunt J et al, JCO 2009).

Discovery phase II trials dataset: Trial and patient characteristics

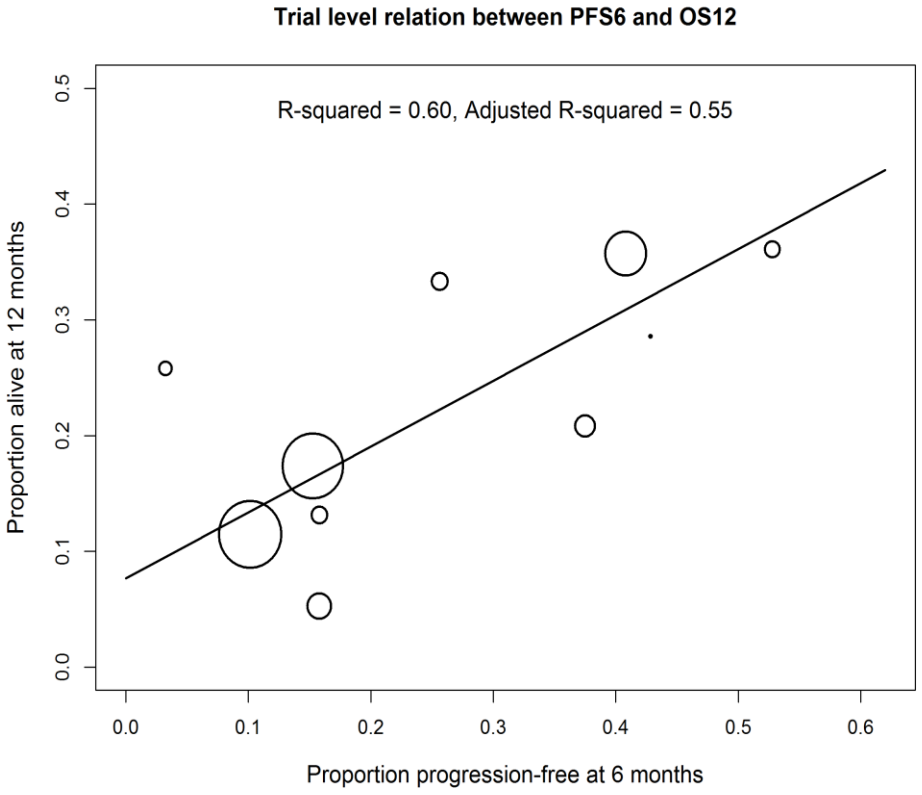
Therapy	**Total number of enrolled subjects**	**Number of evaluable Subjects**	**Median Age**	**Male gender (%)**	**ECOG PS 0-1 (%)**	**Visceral metastasis (%)**
Gemcitabine Paclitaxel	102	98	65	74	70	40%
Irinotecan	45	38	63	74	85	87%
Docetaxel + Vandetanib/Placebo†	152	144	66	69	100	70%
Vinflunine	57	57	63	81	97	49%
Nab-paclitaxel	48	48	68	83	83	58%
Gefitinib	31	31	68	81	87	74%
Gemcitabine Paclitaxel	41	36	64	78	47	53%
Pazopanib	23	7	66	43	100	57%
Vinflunine	151	148	66	80	100	49%
Cetuximab +/- paclitaxel	39	39	69	87	92	87%
All Studies	**689**	**646**	**65**	**77**	89	**59%**

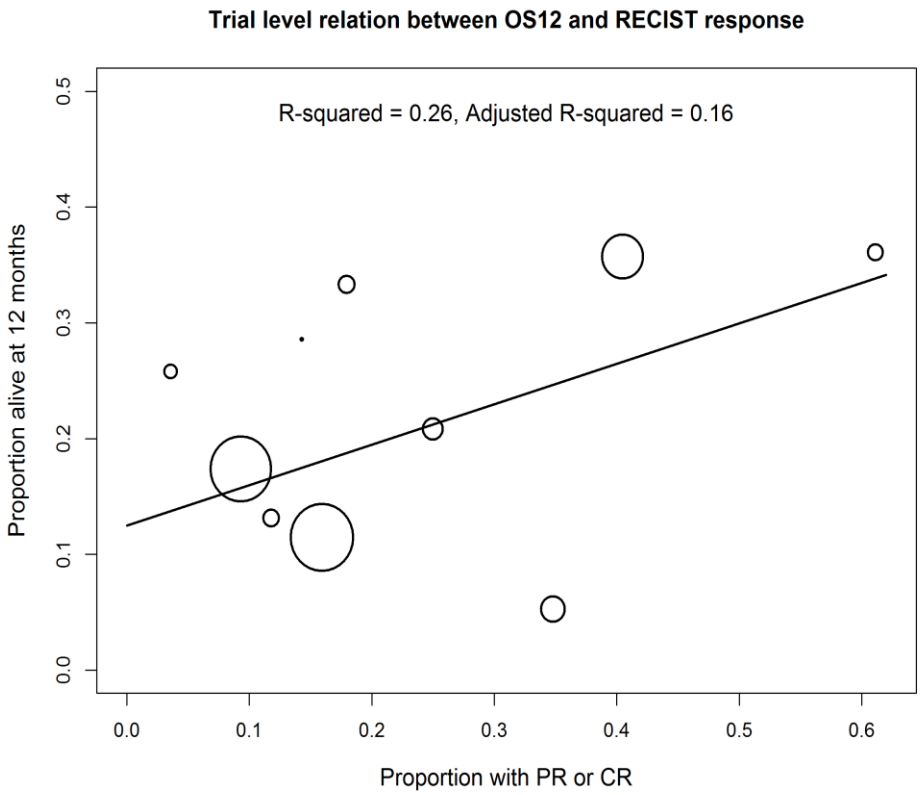
Discovery phase II trials dataset: Outcomes

Regimen	Adjusted PFS6 %	Adjusted RR %	Adjusted OS12 %
Gemcitabine Paclitaxel	40	39	34
Irinotecan	17	14	16
Docetaxel + Vandetanib / placebo	16	10	18
Vinflunine	17	32	10
Nab-paclitaxel	36	24	21
Gefitinib	9	9	24
Gemcitabine Paclitaxel	48	55	32
Pazopanib	32	18	23
Vinflunine	11	16	13
Cetuximab+/-Paclitaxel	25	19	30
All Studies	**23**	**21**	**21**

Of 646 patients evaluable for PFS, 535 had objective tumor progression, and 111 died; 560 were evaluable for response

Discovery dataset: Trial level association of PFS6 and response with OS12





- The fitted line is from a weighted least squares regression model with weights proportional to the study size, i.e. the circles are proportional to the study size. R-square=0.55 (p = 0.0086).
- Pearson correlation treats all trials as equal regardless of size and was 0.66 (p = 0.037)

- R-square=0.16 (p = 0.1359).
- Pearson correlation between trial level response and OS12 was 0.37 (p = 0.30)

Discovery dataset: Individual level association of PFS6 and response with OS12

		OS12	
		N Alive at 12 months Count (Expected count)	**N Dead at 12 months Count (Expected count)**
Response	**No response**	64 (99.1)	374 (338.9)
	Response	62 (26.9)	57 (92.1)
PFS6	**No progression at six months**	78 (29.0)	65 (114.0)
	Progression at six months	53 (102.0)	450 (401.0)

- Individual level agreement for PFS6 and OS12 was 82% (Ķ=0.45, p <0.0001).
- Individual level agreement for response and OS12 was 78% (Ķ=0.36, p <0.0001).

External validation phase III trial (Bellmunt J, JCO 2009): BSC VS. BSC + Vinflunine: Patient characteristics

Variable	BSC (N=117)	BSC+Vinflunine (N=253)
Age <65	51.3%	53.4%
Visceral metastasis	74.9%	73.9%
ECOG PS 0-1	100%	100%
Median OS	4.9 mo	6.9 mo
Median PFS	1.5 mo	3.0 mo
Response rate	0%	8.6%

•Of 357 eligible patients, 17 with PFS censored before 6 months or OS censored before 12 months were excluded, leaving 340 evaluable patients for external validation of PFS6.

Of the progression events, 231 were objective tumor progression and 104 were deaths and 5 patients were alive with PFS > 6 months and OS > 12 months.

270 patients with baseline measurable disease were evaluable for response.

External validation of individual patient level association of PFS6 and Response with OS12

PFS6 and OS12

- Agreement between PFS6 and OS12 = 81%
  (Ķ= 0.44, p<0.0001).

- PFS6 and OS12 were associated when stratified by risk groups based on anemia, PS, liver metastasis (p < 0.0001).

RESPONSE and OS12

- Agreement between response and OS12 in 270 evaluable patients = 76%
  (Ķ= 0.17, p=0.0002).

- Excluding the 108 BSC arm patients (who exhibited no responses) showed a stronger agreement between response and OS12 of 82%
  (Ķ= 0.53, p<0.0001).

Conclusion

- PFS6 is robustly associated with OS12 at the trial and individual patient levels in second-line therapy for advanced UC receiving chemotherapy and/or biologic agents.

- Response was not statistically associated with OS12 at the trial level and displayed a weaker association at the individual level.

- PFS6 may be a more optimal endpoint to capture the durable benefits of agents being screened in phase II trials

- The magnitude of improvement in PFS6 that translates to extension of OS is unclear: improvement in PFS6 from 13.25% with BSC to 26.48% with vinflunine plus BSC translated to 23% reduction in hazard of death.