The Role of Chemotherapy in Bladder Cancer

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Harvard Medical School
Role of Chemotherapy in Bladder Cancer

NMIBC (60%)
- Intravesicular therapy:
  - BCG
  - Mitomycin
  - Gemcitabine
  - Investigational agents
- Established role:
  - BCG
  - Mitomycin
  - Gemcitabine

MIBC (30%)
- Perioperative chemo:
  - Neoadjuvant
  - Adjuvant
  - Bladder-sparing:
    - TURB → chemoradiation

Metastatic disease (10%)
- Established role:
  - Cisplatin
  - Methotrexate
  - Adriamycin
  - Vinblastine
  - Carboplatin
  - Gemcitabine
  - Taxanes
  - Pemetrexed
  - Vinflunine
Neoadjuvant Chemotherapy Trials

- >17 trials with heterogeneous cisplatin regimens, small sizes
- Meta-analysis (n=3000): 14% increase in OS
- Two phase 3 prospective trials (MVAC, CMV)
- Intergroup trial: MVAC x3 + cystectomy vs. cystectomy alone
  - Median followup 8.7 years: 5 yr OS: 57% vs. 43%

![Graph showing survival rates]

- MVAC: methotrexate, vinblastine, adriamycin, cisplatin
- OS: overall survival; DSS: disease-specific survival

Grossman NEJM 2003
ABC Collaboration Eur Urol 2005

Clinically significant vs. Statistically significant
T2 Disease Benefits Too

- Median OS benefits were not limited to higher stage
- T2: 105 vs. 75 months
- T3 or T4a: 65 vs. 24 months
Achieving pT0 disease matters

- pT0: 38% MVAC arm vs. 15% cystectomy (p<0.001)
- pT0 is a surrogate for improved survival
- Cisplatin-based chemotherapy can increase the pT0 rate
**DFCI Dose Dense Neoadjuvant MVAC Trial**

- **Goal:** increase pathologic response which would hopefully translate to increase in overall survival
- **Reduced toxicity with growth factor support**
- **Shorter administration time:** 8 wks vs. 12 weeks

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***Table 1. Treatment Administration Schedule: Dose-Dense MVAC (every 14 days for four cycles)***

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Route</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
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<tbody>
<tr>
<td>Methotrexate</td>
<td>30 mg/m²</td>
<td>IV</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Doxorubicin</td>
<td>30 mg/m²</td>
<td>IV</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Vinblastine</td>
<td>3 mg/m²</td>
<td>IV</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Cisplatin</td>
<td>70 mg/m²</td>
<td>IV</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Pegfilgrastim</td>
<td>6 mg</td>
<td>SC</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

**Abbreviations:** IV, intravenous; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; SC, subcutaneous.

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Choueiri J Clin Oncol 2014
DFCI Dose Dense Neoadjuvant MVAC trial (n=39)

- 49% achieved pT0 (26%) or pT1 pathologic downstaging
- 82% of clinical N1 disease were pN0 at surgery
- Pathologic response was associated with increase in DFS and OS
- No febrile neutropenia or treatment-related deaths
**Can we predict response to neoadjuvant chemoTx?**

<table>
<thead>
<tr>
<th>Gene</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>ATM</td>
<td>0.001542</td>
</tr>
<tr>
<td>RB1</td>
<td>0.001542</td>
</tr>
<tr>
<td>FANCC</td>
<td>0.050980</td>
</tr>
</tbody>
</table>

**Plimack et al. Abstr 4538**

- pCR to DDMVAC
- Sensitivity 93%, specificity 100%
- ≥ 97% accuracy; \( p \leq 0.0001 \)

**Rosenberg et al. Abstr 4510**

- Response to cisplatin-based combination chemoTx
- ERCC2 mutations only found in chemoTx responders

- Common feature: DNA repair genes may affect cisplatin-induced DNA damage
- Validation in independent datasets necessary for both studies

- **3 criteria for biomarkers use:**
  - **analytical validity** (assay accurately and reproducibly measures the analyte?)
  - **clinical validity** (assay actually identifies a biologic difference?)
  - **clinical utility** (assay results lead to clinical decision that improves outcomes?)
miRNA profiling of bladder cancer and treatment response

- MicroRNAs are short non-coding RNAs that bind to mRNA
  - cause inhibition of protein translation
  - Cancer patients have abnormal microRNA profiles, indicating the potential of microRNAs as biomarkers

- Docetaxel resistance
  - miRNA expression in serum
- Platinum response
  - miRNA expression in pre-treatment tissue
SWOG TRIAL: COXEN-directed neoadjuvant chemotherapy
Prospective validation of the COXEN biomarker to predict pT0 /pT1

Muscle-Invasive Bladder Cancer
SWOG 8710 criteria - T2-T4a N0M0, cisplatin eligible

COXEN Model Predicting response to chemotherapy
Cisplatin, Gemcitabine, Methotrexate, Doxorubicin, Vinblastine

NCI-60 Cell Line Panel (IC50)
Human Bladder Cancer Cell Lines
Bladder Cancer patient samples

Gene Expression Model

Cystectomy to assess pT0 or pT1 Pathology
Correlate with COXEN prediction pT0 /pT1

MVAC (N=16)
P = 0.0469

GC (N=14)
P = 0.0303
Advanced Bladder Cancer (ABC) Consortium Meta-analysis

- 6 of 11 small heterogeneous trials (~491 pts)
- Individual patient data collected and re-analyzed
- Adjuvant cisplatin-based therapy:
  - 25% reduction risk of death (RR 0.75, p=0.001)
  - 32% reduction risk of recurrence (RR 0.68, p <0.001)
  - Absolute increases at 3 years: 9% OS and 12% DFS

9% absolute benefit
25% relative reduction
HR 0.75, p=0.019

Eur Urol 2005
Italian Multicenter Randomized Phase III Trial: Adjuvant Gem-Cis vs. Chemotherapy at Relapse

- pT2G3, T3-4, N+; closed due to poor accrual: 194/610 (2001-2007)
- Suggestion of benefit to treating at relapse over immediate therapy
- Adds to the meta-analysis data
- Insufficient evidence to reliably base tx recommendations

**mDFS**: 42.3 vs. 37.2%
**p=0.70, HR 1.08**

**mOS**
5yr OS ~48.5%
**p= 0.24**

Cognetti Annal Onc 2012
SOGUG Trial Early vs Delayed Chemotherapy after Cystectomy: (pT3-pT4 or N+, M0)

- Primary endpoint: Overall survival--15% increase in 2 yr OS: 50→65%
- Closed July 2007 to poor accrual: 146/340 pts
- Median f/u: 30 months → Significant increases with PCG:
  - 5yr OS: 60% vs. 30% (p<0.0009), med OS: NR vs. 26 months
  - Statistically significant benefits in DFS, TTP, and DSS
Adjuvant Chemotherapy for Invasive Bladder Cancer: A 2013 Updated Systematic Review and Meta-Analysis of Randomized Trials

Jeffrey J. Leow\textsuperscript{a,b,c}, William Martin-Doyle\textsuperscript{a}, Padma S. Rajagopal\textsuperscript{a}, Chirayu G. Patel\textsuperscript{a}, Erin M. Anderson\textsuperscript{a}, Andrew T. Rothman\textsuperscript{a}, Richard J. Cote\textsuperscript{d}, Yuksel Urun\textsuperscript{e}, Steven L. Chang\textsuperscript{b,c}, Toni K. Choueiri\textsuperscript{e}, Joaquim Bellmunt\textsuperscript{e,f,*}

- 9 randomized controlled trials
- n=945
- OS: pooled HR: 0.77 (95% CI: 0.59-0.99, p=0.049)
- DFS: pooled HR: 0.66 (95% CI: 0.45-0.91, p=0.014)
  - Even greater benefit in Node+
Immediate vs. Delayed Chemo: Phase 3 EORTC Trial: pT3-4 or Node + UC

Eligibility
pT3-pT4, and/or any pN+M0
Within 90 days after cystectomy:

Primary EP: overall survival
- 80% power to detect increase in OS from 35% on deferred chemo to 42% with immediate chemo

Secondary EP: Progression-free survival

Deferred therapy at relapse
6 cycles

Immediate therapy
Gem-Cis or M-VAC or HD-M-VAC
4 cycles

1:1

*Stratified by: center, T stage, Node stage and number nodes negative

1344 patients; closed early for poor accrual at 284 patients

Sternberg ASCO 2014
Immediate vs. Delayed Chemo: 
Phase 3 EORTC Trial: pT3-4 or Node + UC

**PFS**

5 yr PFS: 46.8% vs. 39.5%
HR 0.52, p<0.0001
Median: 2.9 vs. 0.9 yrs

**Overall Survival**

5 yr OS: 53.6% vs. 47.7%
HR 0.78, p =0.13
Median: 6.8 vs. 4.6 yrs

- Largest randomized adjuvant study to date but closed early
- Immediate cisplatin-based chemo improves PFS and non-significant 22.2% reduction in risk of death (underpowered)

Sternberg ASCO 2014
Review – Urothelial Cancer

A Systematic Review and Meta-analysis of Adjuvant and Neoadjuvant Chemotherapy for Upper Tract Urothelial Carcinoma

Jeffrey J. Leow\textsuperscript{a,b}, William Martin-Doyle\textsuperscript{c}, André P. Fay\textsuperscript{a}, Toni K. Choueiri\textsuperscript{a}, Steven L. Chang\textsuperscript{a,b}, Joaquim Bellmunt\textsuperscript{a,*}

\textsuperscript{a} Bladder Cancer Center, Dana-Farber/Brigham and Women’s Cancer Center, Harvard Medical School, Boston, MA, USA; \textsuperscript{b} Division of Urology and Center for Surgery and Public Health, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA; \textsuperscript{c} University of Massachusetts Medical School, Worcester, MA, USA
Conclusions: There appears to be an OS and DFS benefit for cisplatin-based AC in UTUC. This evidence is limited by the retrospective nature of studies and their relatively small sample size. NC appears to be promising, but more trials are needed to confirm its utility.
Recommendations: Muscle Invasive UC

- Neoadjuvant cisplatin-based chemotherapy followed by RC
  - Gold standard if T2 or greater by clinical staging

- Consider adjuvant cisplatin-based chemotherapy after RC if:
  - >T2
  - Presence of nodal disease
  - Presence of lymphovascular invasion

- Cisplatin ineligible: upfront cystectomy

- Chemoradiation with extensive TURBT (“bladder-sparing”)
  - Non-surgical candidate or patient preference to keep bladder
  - Ideal candidate: clinical T2, no hydro or CIS; maximal TURBT possible
  - 25-30% will require salvage cystectomy

RC: radical cystectomy
Natural History of Bladder Cancer

Superficial disease (60%)
Intravesicular therapy

Localized Muscle invasive disease (30%)
Periop chemo + Surgery

Metastatic disease (10%)
Chemotherapy

Prognostic factors for high-grade T1 bladder cancer: a meta-analysis based on 7,663 patients: median f/u 49 months, 43% recurred, 21% progressed, 14% died
Limited Advances Achieved in the Last 20 years of Systemic Chemotherapy
Randomized trials in advanced bladder cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>N</th>
<th>RR (%)</th>
<th>MDS (mo)</th>
<th>Best arm</th>
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<tbody>
<tr>
<td>Loehrer (1)</td>
<td>M-VAC</td>
<td>126</td>
<td>39</td>
<td>12.5</td>
<td>MVAC</td>
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<tr>
<td></td>
<td>CDDP</td>
<td>120</td>
<td>12</td>
<td>8.2</td>
<td></td>
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<td>Logothetis (24)</td>
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<td>65</td>
<td>65</td>
<td>12.6</td>
<td>M-VAC</td>
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<td></td>
<td>CISCA</td>
<td>55</td>
<td>46</td>
<td>10.0</td>
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<td>Von der Maase (27)</td>
<td>M-VAC</td>
<td>202</td>
<td>46</td>
<td>14.8</td>
<td>M-VAC ~ GC</td>
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<td></td>
<td>GC</td>
<td>203</td>
<td>49</td>
<td>13.8</td>
<td></td>
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<td>Sternberg (31)</td>
<td>HS-MVAC</td>
<td>134</td>
<td>62</td>
<td>14.5</td>
<td>HD-M-VAC ~ M-VAC</td>
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<tr>
<td></td>
<td>M-VAC</td>
<td>129</td>
<td>50</td>
<td>14.1</td>
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<td>Bamias (44)</td>
<td>M-VAC</td>
<td>109</td>
<td>54</td>
<td>14.2</td>
<td>M-VAC</td>
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<td>DC</td>
<td>111</td>
<td>37</td>
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<td>Dreicer (48)</td>
<td>M-VAC</td>
<td>44</td>
<td>36</td>
<td>15.4</td>
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<td></td>
<td>CT</td>
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<td>28</td>
<td>13.8</td>
<td></td>
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<td>Bellmunt (72)</td>
<td>PCG</td>
<td>312</td>
<td>57.1</td>
<td>15.7</td>
<td>PCG ~ GC</td>
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<td></td>
<td>GC</td>
<td>315</td>
<td>46.4</td>
<td>12.8</td>
<td>P .03 non eligible</td>
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<td>Bamias</td>
<td>DD MVAC</td>
<td>66+62</td>
<td>60</td>
<td>19</td>
<td>Premature closure</td>
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<tr>
<td></td>
<td>DD CG</td>
<td>64</td>
<td>65.3</td>
<td>18</td>
<td>NS</td>
</tr>
</tbody>
</table>


J.Bellmunt et al, Semin Oncol 2012
Is adding a Taxane the Answer to Increasing OS?

Ph III Trial: GC vs. GCT

- 3 month non-statistically significant survival benefit: 15.8 vs. 12.7 mo.
- No significant increase in PFS: 8.3 vs. 7.6 mo.
- Statistically signific. increased objective responses: 56% vs. 44% (p=0.0031)
- More grade 4 neutropenia and neutropenic fever with PCG

Bellmunt J Clin Oncol 2012
Overall Duration of Survival
Bladder Primary Tumor

Overall Logrank test: p=0.034

<table>
<thead>
<tr>
<th></th>
<th>Gem/Cis Deaths/Patients</th>
<th>Gem/Cis/Pac Deaths/Patients</th>
<th>HR (95% CI)</th>
<th>P Value</th>
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<tr>
<td><strong>Bladder Primary</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Yes</td>
<td>208/258</td>
<td>193/253</td>
<td>0.81 (0.66-0.98)</td>
<td>0.03</td>
</tr>
<tr>
<td>No</td>
<td>39/52</td>
<td>46/57</td>
<td>1.15 (0.75–1.77)</td>
<td>0.51</td>
</tr>
</tbody>
</table>
Randomization and treatment

Inclusion criteria
- T4b, N2/3, M+, Recurrent urothelial cancer
- Transitional histology
- PS ≤ 2*
- CrCl > 50

Stratification
- Visceral metastases
- Center

*PS 2 was accepted in the extension phase

Bamias et al, ASCO 2011
Annals of Oncol, 2013
There was no difference in OS. Although the trial was closed prematurely, PFS appeared worse with larotaxel/cisplatin, suggesting that larotaxel/cisplatin does not improve outcomes versus cisplatin/gemcitabine.
First-line treatment for "fit" patients:

- Gemcitabine / Cisplatin (GC)
- MVAC (+ GCSF)
- Paclitaxel / Cisplatin / Gemcitabine (PGC)

Level 1 evidence

Grade of recommendation: A

#EAU Guidelines 2012

*ESMO CPG 2012, *upToDate 2012
Chemotherapy for Metastatic Urothelial Cancer

• Several clinically relevant issues remain regarding front line chemotherapy
• Without level 1 evidence, there is broad clinical acceptance that cisplatin is superior to carboplatin
• A high percentage of patients with advanced urothelial cancer have a degree of renal insufficiency that makes routine CDDP-based chemotherapy problematic
  ◦ Age related dysfunction
  ◦ Disease related dysfunction
Treatment of Patients With Metastatic Urothelial Cancer “Unfit” for Cisplatin-Based Chemotherapy

Matthew D. Galsky, Noah M. Hahn, Jonathan Rosenberg, Guru Sonpavde, Thomas Hutson, William K. Oh, Robert Dreicer, Nicholas Vogelzang, Cora N. Stemberg, Dean F. Bajorin, and Joaquim Bellmunt

Table 1. Randomized Trials Comparing Cisplatin- and Carboplatin-Based Combinations in Metastatic Urothelial Carcinoma

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Patients</th>
<th>Phase</th>
<th>Treatment Arm</th>
<th>OR (%)</th>
<th>P</th>
<th>CR (%)</th>
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<tbody>
<tr>
<td>Bellmunt et al15</td>
<td>47</td>
<td>II</td>
<td>MVAC</td>
<td>52</td>
<td>.3</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M-CAVI</td>
<td>39</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Petrioli et al17</td>
<td>57</td>
<td>II</td>
<td>MVE-cisplatin</td>
<td>71</td>
<td>.04</td>
<td>25</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>MVE-carboplatin</td>
<td>41</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Dogliotti et al16</td>
<td>110</td>
<td>II</td>
<td>Gemcitabine + cisplatin</td>
<td>49</td>
<td>N/P</td>
<td>15</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Gemcitabine + carboplatin</td>
<td>40</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Dreicer et al2</td>
<td>85*</td>
<td>III</td>
<td>MVAC</td>
<td>36</td>
<td>.6</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Paclitaxel + carboplatin</td>
<td>28</td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; M-CAVI, methotrexate, carboplatin, vinblastine; MVAC, methotrexate, vinblastine, doxorubicin, cisplatin; MVE, methotrexate, vinblastine, epirubicin; N/P, not provided; OR, overall response.

*Trial closed early because of poor accrual.

Table 4. Proposed Working Group Eligibility Criteria for Clinical Trials Enrolling Patients With Metastatic Urothelial Carcinoma “Unfit” for Cisplatin-Based Chemotherapy

<table>
<thead>
<tr>
<th>Eligibility Criteria (at least one of the following)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO or ECOG PS of 2 or Karnofsky PS of 60%-70%</td>
</tr>
<tr>
<td>Creatinine clearance (calculated or measured) &lt; 60 mL/min</td>
</tr>
<tr>
<td>CTCAE v4 grade ≥ 2 audiometric hearing loss</td>
</tr>
<tr>
<td>CTCAE v4 grade ≥ 2 peripheral neuropathy</td>
</tr>
<tr>
<td>NYHA Class III heart failure</td>
</tr>
</tbody>
</table>

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; NYHA, New York Heart Association; PS, performance status.
Which Carbo Regimen?: Ph III GCa vs M-CaVI

EORTC 30986

- Chemotherapy-naïve
- Measurable disease
- Impaired renal function (GFR >30 but <60 mL/min)
  OR
  Performance status 2

Randomise

N = 178

GC
- Gemcitabine 1000 mg/m² on days 1 and 8
- Carboplatin area under the serum concentration–time curve [AUC] 4.5 for 21 days

M-CAVI
- Methotrexate 30mg/m² on days 1, 15, and 22
- Carboplatin AUC 4.5 on day 1
- Vinblastine 3 mg/m² on days 1, 15, and 22 for 28 days

- Primary endpoint: overall survival
- Secondary endpoints: PFS, response, severe acute toxicity
- Stratified by treatment group, renal function, PS, and Bajorin risk groups
Cisplatin-Unfit Patients

- Up to 50% of patients are unfit for cisplatin
- No standard therapy in this setting: carbo, gemcitabine, taxanes

- **Phase III GCa vs. M-CaVi**
  - Equivalent/non-inferior efficacy
    - mOS: 9.3 v. 8.1 mo
    - mPFS: 5.8 v.4.2 mo
    - ORR: 41% vs. 30%
  - Increase severe acute toxicity with M-CaVi: 9% vs. 21%
    - Death, renal, NF, mucositis, plts

- Gem/Carbo preferred over M-CaVi for better toxicity profile

DeSantis J Clin Oncol 2009
1st-line patients with urothelial ca. unfit for cisplatin.

Open label 2-arms, multicentre, international, randomised (1:1) phase II trial

1 Cycle = 3 weeks (21days)  Response assessment every 6 weeks (2 cycles)

Treatment D1

Arm A (VG)  N= 31 evaluable
- Vinflunine*  280 or 250 mg/m²
- Gemcitabine*  1000 or 750 mg/m²

Arm B (VC)  N= 31 evaluable
- Vinflunine*  280 or 250 mg/m²
- Carboplatin*  AUC 4.5

Treatment D8

Arm A (VG)  N= 31 evaluable
- Gemcitabine*  1000 or 750 mg/m²

Arm B (VC)  N= 31 evaluable
- Not applicable

End point: DC (CR+ PR +SD)

Treatment until progression or unacceptable toxicities

Special case of CR**

Post treatment follow-up

Every:
- 6 weeks up to PD
- 3 months after PD

4 stratification parameters:
Centre; prior chemo vs none; PS0 vs PS1; CrCl (≥ 60 vs [40-60] vs [30-40])

*Starting dose of drugs depends on baseline creatinine clearance (≥ 30 mL/min and < 60 mL/min)

** In case a patient present a confirmed complete response, he will receive at least two additional cycles of treatment after the complete response confirmation and then further prolongation of the treatment will be under physician decision.
Treatment scheme

Starting dose of drugs depending on CrCl (randomisation value)

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>[30 – 40]</th>
<th>[40 – 60]</th>
<th>≥ 60</th>
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<tbody>
<tr>
<td><strong>Vinflunine (mg/m²)</strong></td>
<td>250</td>
<td>280</td>
<td></td>
</tr>
<tr>
<td><strong>Gemcitabine (mg/m²)</strong></td>
<td>750</td>
<td>750</td>
<td>1000</td>
</tr>
<tr>
<td><strong>Carboplatin</strong></td>
<td>AUC 4.5</td>
<td>AUC 4.5</td>
<td></td>
</tr>
</tbody>
</table>

Starting dose ARM A

Starting dose ARM B

Arm A (VG)

Gemcitabine dose-escalation in cycle 2:
- From 750 up to 1000 mg/m²
- If no toxicity of grade > 2 in cycle 1

D8 Gemcitabine dose-adjustment:
- If neutropenia ≥G2 or thrombopenia ≥G2
- Either reduction to 750 g/m² or dose-cancellation

Arm B (VC)

No dose escalation

Dose-reductions during study course:
only on VFL doses (both arms, maximum 1 level: decrease to 250 or 225 mg/m²)

De Santis et al. ASCO 2014 #4534
### Safety (1)

#### Haematological AEs

<table>
<thead>
<tr>
<th>(NCTC V2) N (%) pt</th>
<th>VFL + GEM (N= 34)</th>
<th>VFL + CBDCA (N= 34)</th>
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<tbody>
<tr>
<td></td>
<td>All G</td>
<td>G3/4</td>
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<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td><strong>Neutropenia</strong></td>
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</tr>
<tr>
<td></td>
<td>28</td>
<td>82</td>
</tr>
<tr>
<td>Anaemia</td>
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<td>97</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>71</td>
</tr>
<tr>
<td>Febrile neutropenia*</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Bleeding or platelet transfusion with thrombocytopenia G3-4</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*ANC < 1.0 x 10^9/L and fever ≥ 38.5°C

De Santis et al. ASCO 2014 #4534
De Santis et al. ASCO 2014 #4534

<table>
<thead>
<tr>
<th>(NCTC V2) N (%)/pt</th>
<th>VFL + GEM (N= 34)</th>
<th>VFL + CBDCA (N= 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All G</td>
<td>G3/4</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Asthenia - Fatigue</td>
<td>20</td>
<td>58.8</td>
</tr>
<tr>
<td>Infection</td>
<td>4</td>
<td>11.8</td>
</tr>
<tr>
<td>Constipation / Ileus</td>
<td>10</td>
<td>29.4</td>
</tr>
<tr>
<td>Flatulence / Abdominal pain</td>
<td>3</td>
<td>8.8</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2</td>
<td>5.9</td>
</tr>
<tr>
<td>Dysphagia / Stomatitis</td>
<td>3</td>
<td>8.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>35.3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7</td>
<td>20.6</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>9</td>
<td>26.5</td>
</tr>
<tr>
<td>Decrease appetite</td>
<td>10</td>
<td>29.4</td>
</tr>
<tr>
<td>Musculoskeletal disorders, pain</td>
<td>3</td>
<td>8.8</td>
</tr>
<tr>
<td>Phlebitis (deep &amp; superficial)</td>
<td>4</td>
<td>11.8</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>5</td>
<td>14.7</td>
</tr>
<tr>
<td>Alopecia</td>
<td>9</td>
<td>26.5</td>
</tr>
</tbody>
</table>

No motor neuropathy, 1 G1 peripheral sensory neuropathy (VG) and 1 G1 paresthesia (VC)

Death ≤ 30 days after the last study drugs administration: 2 pts (VC), relationship suspected for 1.
**Efficacy (ITT)**

Median follow-up: 20.4 months

<table>
<thead>
<tr>
<th></th>
<th>Non evaluable N, (%)</th>
<th>ORR (%) [Confirmed]</th>
<th>Median duration of ORR [mo]</th>
<th>DCR (%)</th>
<th>Median PFS (mo)</th>
<th>Median OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VFL-GEM (34)</strong></td>
<td>2 (6%)</td>
<td>53 [44]</td>
<td>8.2</td>
<td>77</td>
<td>5.9</td>
<td>13.9</td>
</tr>
<tr>
<td><strong>VFL-CBDCA (35)</strong></td>
<td>3 (9%)</td>
<td>43 [29]</td>
<td>7.7</td>
<td>77</td>
<td>6.1</td>
<td>12.8</td>
</tr>
</tbody>
</table>

De Santis et al. ASCO 2014 #4534
SECOND LINE THERAPY
### Single Agent 2nd Line Trials in UC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>Phase</th>
<th>N</th>
<th>Response Rate</th>
<th>TTP Months</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorusso 1998</td>
<td>Gemcitabine</td>
<td>II</td>
<td>35</td>
<td>23</td>
<td>3.8</td>
<td>5</td>
</tr>
<tr>
<td>Albers 2002</td>
<td>Gemcitabine</td>
<td>II</td>
<td>30</td>
<td>11</td>
<td>4.9</td>
<td>8.7</td>
</tr>
<tr>
<td>Vaughn 2002</td>
<td>Paclitaxel</td>
<td>II</td>
<td>31</td>
<td>10</td>
<td>2.2</td>
<td>7.2</td>
</tr>
<tr>
<td>Pronzato 1997</td>
<td>Ifosfamide</td>
<td>II</td>
<td>20</td>
<td>5</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Witte 1997</td>
<td>Ifosfamide</td>
<td>II</td>
<td>56</td>
<td>20</td>
<td>2.5</td>
<td>5.5</td>
</tr>
<tr>
<td>McCaffrey 1997</td>
<td>Docetaxel</td>
<td>II</td>
<td>20</td>
<td>13</td>
<td>NR</td>
<td>9</td>
</tr>
<tr>
<td>Sweeney 2006</td>
<td>Pemetrexed</td>
<td>II</td>
<td>47</td>
<td>28</td>
<td>2.9</td>
<td>9.6</td>
</tr>
<tr>
<td>Dreicer 2007</td>
<td>Epothilone B</td>
<td>II</td>
<td>45</td>
<td>12</td>
<td>2.7*</td>
<td>8</td>
</tr>
<tr>
<td>Bellmunt 2009</td>
<td>Vinflunine</td>
<td>III</td>
<td>370</td>
<td>9</td>
<td>3.0*</td>
<td>6.9</td>
</tr>
</tbody>
</table>

- TTP/PFS: 3-5 months
- OS: 5-9 months

* PFS
## Combination 2\textsuperscript{nd} Line Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>N</th>
<th>RR</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krege 2001</td>
<td>Docetaxel/Ifosfamide</td>
<td>22</td>
<td>25%</td>
<td>4</td>
</tr>
<tr>
<td>Lin 2007</td>
<td>Gem/Ifosfamide</td>
<td>23</td>
<td>22%</td>
<td>4.8</td>
</tr>
<tr>
<td>Bellmunt 2002</td>
<td>MTX/Paclitaxel</td>
<td>20</td>
<td>32%</td>
<td>5</td>
</tr>
<tr>
<td>Sternberg 2001</td>
<td>Gem/Paclitaxel</td>
<td>41</td>
<td>60%</td>
<td>14.4</td>
</tr>
<tr>
<td>Fechner 2006</td>
<td>Gem/Paclitaxel</td>
<td>27</td>
<td>44%</td>
<td>13</td>
</tr>
<tr>
<td>Vaishampayan 2005</td>
<td>Paclitaxel/Carboplatin</td>
<td>44</td>
<td>16%</td>
<td>6</td>
</tr>
<tr>
<td>Pagliaro 2002</td>
<td>Ifos/Gem/Cisplatin</td>
<td>49</td>
<td>41%</td>
<td>NR</td>
</tr>
<tr>
<td>Chen 2004</td>
<td>Gem/Doc/Carboplatin</td>
<td>20</td>
<td>45%</td>
<td>NR</td>
</tr>
<tr>
<td>Tu 1995</td>
<td>Paclitaxel/Cis/MTX</td>
<td>25</td>
<td>40%</td>
<td>NR</td>
</tr>
</tbody>
</table>
Second Line Chemotherapy for Advanced Urothelial Cancer

• Variability in definition
  ◦ Pt receiving CDDP-based chemotherapy for de-novo metastatic disease
  ◦ Pt receiving perioperative therapy for locally advanced disease
# 2\(^{\text{nd}}\) line chemotherapy, single agent phase II trials, Pemetrexed

<table>
<thead>
<tr>
<th>Reference</th>
<th>Scheme</th>
<th>N</th>
<th>ORR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sweeney</strong></td>
<td>Single agent q3w Pem 500 mg/m(^2) + folic acid and vitamin B12</td>
<td>45</td>
<td>28%</td>
<td>2.9 mo</td>
<td>9.6 mo</td>
</tr>
<tr>
<td><strong>J Clin Oncol 2006</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Galsky</strong></td>
<td>Single agent q3w Pem 500 mg/m(^2) + folic acid and vitamin B12</td>
<td>13</td>
<td>8%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Invest New Drug 2007</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Vinflunine Phase II Trial Results in 2\textsuperscript{nd} line TCCU

<table>
<thead>
<tr>
<th></th>
<th>No. of pts treated</th>
<th>Initial dose (mg/m(^2) q3w)</th>
<th>Objective response rate (%)</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Culine et al.</strong></td>
<td>51</td>
<td>320</td>
<td>8 (17.0)</td>
<td>3.0</td>
<td>6.6</td>
</tr>
<tr>
<td>(BJC, 2006)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vaughn et al.</strong></td>
<td>151</td>
<td>320*/280**</td>
<td>21 (15.9)</td>
<td>2.8</td>
<td>7.9</td>
</tr>
<tr>
<td>(ASCO GU 2008)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* PS0 = 320 mg/m\(^2\)/q3w

** PS0 with pelvic irradiation and PS1 = 280 mg/m\(^2\)/q3w
Phase III trial of vinflunine+BSC vs BSC alone – OS: ITT/Eligible population

**Fig 2.** Overall survival (OS) in the intent-to-treat population (n = 370). VFL, vinflunine; BSC, best supportive care.

**Fig 3.** Overall survival (OS) in the eligible population (n = 357; 96.5% of intent-to-treat population). VFL, vinflunine; BSC, best supportive care.
European guidelines recommendations for 2\textsuperscript{nd} line treatment

\section*{EAU 2012:}

12.10 Conclusions and recommendations for metastatic disease

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinflunine reached the highest level of evidence ever reported for second-line use.</td>
<td>1b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Second-line treatment:</strong></td>
<td></td>
</tr>
<tr>
<td>In patients progressing after platinum-based combination chemotherapy for metastatic disease, vinflunine should be offered. Alternatively, treatment within a clinical trial setting may be offered.</td>
<td>A*</td>
</tr>
<tr>
<td>Zoledronic acid or denosumab, are recommended for the treatment of bone metastases.</td>
<td>B</td>
</tr>
</tbody>
</table>

* Grade A recommendation is weakened by a problem of statistical significance. A. Stenzl et al. update February 2012

\section*{ESMO 2013:}

- “The only valid randomized phase III trial in patients progressing after 1st-line treatment with platinum-containing combination CT for metastatic disease tested vinflunine”
- This trial reached the highest level of evidence ever reported for 2nd-line treatment
- In Europe, vinflunine is the only approved drug in this setting [I, B]”
- Implementation of prognosis factors in 2\textsuperscript{nd} line setting
The impact of prior platinum therapy on survival in patients with metastatic urothelial cancer receiving vinflunine

L C Harshman1, R Fougeray2, T K Chouein1, F A Schutzi3, Y Salhi2, J E Rosenberg1 and J Bellmunt*,1,3

1Bladder Cancer Center at Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute/Brigham and Women’s Hospital, Harvard Medical School, 480 Brookline Avenue, 1230 DANA, Boston, MA 02215, USA; 2Institut de Recherche Pierre Fabre, 45, Place Abel Gance 92604, Boulogne, France and 3University Hospital del Mar-MIMF, Paseo Marítimo 25-29 08003, Barcelona, Spain

Interpretation: Differences in prognostic factors between patients who can receive prior cisplatin and those who cannot may explain the survival differences in patients who undergo second line therapy. Prior cisplatin administration did not diminish the subsequent benefit of vinflunine over BSC.
MAINTENANCE THERAPY IN BLADDER (after 1st line)

• No role of maintenance therapy

• Ongoing Studies (vs observation)
  ◦ JASIMA, MAJA: Vinflunine
  ◦ MRC: Lapatinib in her1/2 +
Estudio **MAJA**, Grupo SOGUG: Estudio aleatorizado en fase II de vinflunina en mantenimiento en pacientes con respuesta o estabilización tras 6 ciclos de gemcitabina-cisplatino

- **Estudio JASIMA**: Ensayo en fase II de vinflunina en mantenimiento en pacientes con respuesta o estabilización tras 4 ciclos de gemcitabina-cisplatino

<table>
<thead>
<tr>
<th>Pacientes con respuesta o estabilización tras 4-6 ciclos de gemcitabina-cisplatino</th>
<th><strong>Vinflunina</strong> 320/280 mg/m² día 1 cada 3 semanas hasta progresión</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observación</strong>: mejor tratamiento de soporte</td>
<td></td>
</tr>
</tbody>
</table>

- **Vinflunina** 320/280 mg/m² día 1 cada 3 semanas hasta progresión
Nanoparticle albumin-bound paclitaxel for second-line treatment of metastatic urothelial carcinoma: a single group, multicentre, phase 2 study

Yoo-Joung Ko, Christine M Canil, Som D Mukherjee, Eric Winquist, Christine Elser, Andrea Eisen, M Neil Rezume, Lijing Zhang, Srikala S Srichar

<table>
<thead>
<tr>
<th>All patients (N=47)</th>
<th>Patients with previous chemotherapy for metastatic disease (N=32)</th>
<th>Patients without previous chemotherapy for metastatic disease (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>CR</td>
<td>1 (2%)</td>
<td>...</td>
</tr>
<tr>
<td>PR</td>
<td>12 (26%)</td>
<td>...</td>
</tr>
<tr>
<td>SD ≥ 4 months</td>
<td>10 (21%)</td>
<td>...</td>
</tr>
<tr>
<td>PD</td>
<td>24 (51%)</td>
<td>...</td>
</tr>
<tr>
<td>Objective response (CR plus PR)</td>
<td>13 (28%)</td>
<td>17.3-44.4</td>
</tr>
<tr>
<td>Disease control (CR plus PR plus SD ≥ 4 months)</td>
<td>23 (49%)</td>
<td>36.1-63.9</td>
</tr>
</tbody>
</table>


Table 2: Best response to second-line nab-paclitaxel

- Median 6 cycles
- AEs: fatigue, pain, alopecia, neuropathy, hypertension

Lancet Oncol 2013
Extended Phase II Objectives (currently active – as of January 2011)

• To determine the response rate of patients with advanced urothelial carcinomas to E7389 in the setting of progression after prior platinum-based chemotherapy for advanced or recurrent disease, in two cohorts: tubulin-inhibitor treated or tubulin-inhibitor naïve.

• To determine the 6-month progression-free survival and overall survival of patients with advanced urothelial carcinomas treated with E7389 after platinum-based therapy for recurrent or advanced disease.

• To document the toxicity associated with the administration of E7389 to patients with advanced urothelial carcinoma patients in the second line and later setting.

TREATMENT PLAN

• Stratification by Prior Treatment with a Tubulin Inhibitor
  - Patients will be stratified into tubulin-inhibitor treated and tubulin-inhibitor naïve cohorts, which will be analyzed separately.

• E7389 will be administered on an outpatient basis as an intravenous bolus over 1-2 minutes, once a week for two weeks in a row (on Day 1 and 8) of a 21 day cycle.

• The patient’s starting dose will be 1.4 mg/m²/week.
A Randomized Phase II/III study of Cabazitaxel versus Vinflunine in Metastatic or Locally Advanced Transitional Cell Carcinoma (APRO-SECAVIN-12)

J. Bellmunt & R. de Wit

Eligible pts
Randomize 1:1

- Cabazitaxel 25mg/m2 q3w
- Vinflunine 280-320mg/m2 q3w

Randomization and stratification

After registration is complete, the subject will be randomized. Subjects will be randomized based on the following stratification factors:

- Risk factors: 0 versus 1
- Risk factors: hemoglobin < 10g/l, liver involvement, ECOG PS 1

Phase II: 160 pts
Phase II/III: 396 pts
<table>
<thead>
<tr>
<th>Phase</th>
<th>PS</th>
<th>No. of prior lines allowed</th>
<th>Prior peri-op counted as 1 line</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>0-1</td>
<td>( \leq 2 ) (No prior taxane)</td>
<td>Yes (&lt;1 year)</td>
<td>Docetaxel</td>
<td>Docetaxel-IMC18F1</td>
<td>Docetaxel-Ramucirumab</td>
</tr>
<tr>
<td>II</td>
<td>0-2</td>
<td>1 (No prior taxane)</td>
<td>Yes (&lt;1 year)</td>
<td>Paclitaxel</td>
<td>Nab-paclitaxel</td>
<td>Nab-paclitaxel</td>
</tr>
<tr>
<td>II</td>
<td>0-1</td>
<td>( \leq 2 ) (allows paclitaxel)</td>
<td>Yes (&lt;1 year)</td>
<td>Docetaxel</td>
<td>Docetaxel-OGX427</td>
<td>Paclitaxel-Pazopanib</td>
</tr>
<tr>
<td>III</td>
<td>0-1</td>
<td>1 (No prior taxane)</td>
<td>Yes (&lt;6 mo)</td>
<td>Paclitaxel</td>
<td>Paclitaxel-Pazopanib</td>
<td>Paclitaxel-Pazopanib</td>
</tr>
</tbody>
</table>
Molecular targets on the horizon for kidney and urothelial cancer

Joaquim Bellmunt, Bin T. Teh, Giampaolo Tortora and Jonathan E. Rosenberg

Bellmunt J, Nat Rev Clin Oncol. 2013
Chemotherapy plus a targeted agent in bladder cancer

ONGOING

CG + Bevacizumab
CG + OGX
CG + lapatinib
CG + Ramucirumab

Sorafenib
Cetuximab
Trastuzumab
Targeting EGFR: Gem/cis plus cetuximab

- “Negative” study of EGFR-targeted treatment plus chemo
- EGFR not the right target?
  - EGFR/KRAS mutation rare in bladder cancer
  - Unselected population: not enriched for the mutation
  - Added cetuximab toxicity compromises chemo dose?
- Is gem/cis the right combination—stronger rationale with the taxanes?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Current Study (28d cycles)</th>
<th>Pancreatic/NSCLC (21d cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>1000mg/m² on days 1, 8, 15 dose↓800mg/m²</td>
<td>1000mg/m² on days 1 and 8</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>500mg/m² q 2 week</td>
<td>500mg/m² q 2 weeks</td>
</tr>
</tbody>
</table>

Inoue, Clin Cancer Res 2000
Grivas ASCO 2012
GC +/- Trastuzumab for Her2+ (IHC 3+ or 2+FISH+) advanced UC:
13.3% (75 of 563) Her2+; 61 randomized
Oudard S, ESMO 2012

<table>
<thead>
<tr>
<th>Time to progression (months)</th>
<th>Survival Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>6</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td></td>
</tr>
</tbody>
</table>

Stratified Log-Rank: $p=0.33$

Median PFS (95% CI, months)
- A: 10.5 (4.3-10.4)
- B (+trastuzumab): 8.3 (4.7-10.6)

At risk:
- A: 29, 19, 10, 5, 4, 3, 4, 2, 1
- B (+trastuzumab): 31, 20, 8, 4, 3, 4, 2, 0, 1
The addition of vandetanib did not result in any benefit as compared to placebo.

Choueiri TK, J Clin Oncol 2012
GC +/- Sorafenib: No improvement in PFS or OS
Krege S, et al. BJU Int 2014
Pazopanib in advanced and platinum-resistant urothelial cancer: an open-label, single group, phase 2 trial

Andrea Necchi, Luigi Mariani, Nadia Zaffaroni, Lawrence H Schwartz, Patrizia Giannatempo, Flavio Crippa, Carlo Morosi, Rodolfo Lanocita, Teodoro Sava, Cinzia Ortega, Caterina Messina, Cosimo Sacco, Marzia Pennati, Maria G Daidone, Nicola Nicolai, Filippo De Braud, Alessandro M Gianni, Roberto Salvioni

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Number of patients (%, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed partial response</td>
<td>7 (17·1%, 7·2–32·1)</td>
</tr>
<tr>
<td>Confirmed stable disease</td>
<td>14 (34·1%, 20·1–50·6)</td>
</tr>
<tr>
<td>Disease control (partial response + stable disease)</td>
<td>21 (51·2%, 35·1–67·1)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>20 (48·8%, 32·9–64·9)</td>
</tr>
</tbody>
</table>

RECIST = Response Evaluation Criteria in Solid Tumors.

**Table 2:** Response according to RECIST (version 1.1) in 41 patients with urothelial cancer given at least one dose of pazopanib.

CALGB 90601TCC Trial: GC +/- Bevacizumab

- Metastatic TCC and/or
- Unresectable TCC
- Minimum CrCl 60 cc/m
- No Prior Chemotherapy

Randomize

- GC x 6 cycles plus Bevacizumab
- GC x 6 cycles + placebo

N=500 patients for 88% power with a 2-sided alpha level of 0.05 to detect a 35% decrease in the hazard ratio (equivalent to an increase in OS from 13.8 to 18.6 months).

*Open at DFCI

PI - J. Rosenberg
**First line, Ph II Study design in Bladder Ca**

**Arm A**

For every 21 day cycle:
- Gemcitabine IV on Day 1 and 8 Cisplatin IV on Day 1
- Placebo IV on Day 1, 8 and 15

Placebo every week until disease progression, toxicity or 6 months total study treatment

**Arm B**

For every 21 day cycle:
- Gemcitabine IV on Day 1 and 8 Cisplatin IV on Day 1
- 600mg OGX-427 IV on Day 1, 8, 15

600mg OGX-427 every week until disease progression, toxicity or 6 months total study treatment

**Arm C**

For every 21 day cycle:
- Gemcitabine IV on Day 1 and 8 Cisplatin IV on Day 1
- 1000mg OGX-427 IV on Day 1, 8, 15

1000mg OGX-427 every week until disease progression, toxicity or 6 months total study treatment

6 Cycles (~ 4.5 months treatment)

**Primary Objective**

- Effect of OGX-427 with Gem/Cis on the initial PFS rate at 6 months from initiation of study treatment

**Secondary Objectives:**

- Evaluate the safety and tolerability of 600 mg and 1000 mg doses of OGX-427 with Gem/Cis. Optimal dose of OGX-427 (600mg vs 1000 mg)
- Compare disease control rate (CR, PR and stable disease), overall progression-free survival (PFS) and overall survival (OS). Serum OGX-427 levels, PD markers, and efficacy measures
Phase II: OGX427 + Docetaxel

Eligible patients
Stratify for:
1) Time from prior systemic chemo
2) Bellmunt criteria

Randomize

Treatment with docetaxel q 3 wks (maximum of 10 docetaxel cycles*)

Follow for Survival

Treatment with OGX-427 (loading doses then q wk) + docetaxel q 3 wks (maximum of 10 docetaxel cycles), followed by weekly OGX-427 maintenance*

Follow for Survival

*Study treatment until RECIST 1.1 progression or unacceptable toxicity

- **HSP27:**
  - Upregulated on cell surface in times of stress
  - Protects against radiation, chemotherapy damage, other stressors

- **OGX-427:** antisense oligonucleotide

*Open at DFCI*
Precision oncology for bladder cancer

Metastatic advanced bladder cancer patient

Tumor-only variants

Inherited ("germline") variant

BRCA2 K3326* nonsense

PI3K inhibitor
AKT inhibitor
mTOR inhibitor

PARP inhibitor
Platinum chemotherapy

Responds to cisplatin!

Five potential therapies for a patient who exhausted standard-of-care options!
Systemic treatment in UC

Conclusions

- Cisplatin combination chemotherapy is standard in first line
- Consensus definition of „unfit“ for cisplatin
- Carboplatin/gemcitabine preferred chemo for „unfit“ patients. Vinflunine/Gemcitabine under study
- Vinflunine approved in Europe for second line. Unmet need in US
- Prognostic factors for 2nd line identified
- Targets: mTor/PI3K (TSC1m) interesting targets
- Anti VEGF therapy promising, but some toxicity and further trials needed
- FGFr is a clear target for therapeutic intervention
- Immunotherapy is the new emerging target (45% of 35%)
Thanks for your attention !!!