Bladder Cancer

A) PUBLIC HEALTH

EPIDEMIOLOGY

- **Incidence**: 16 per 100,000 (males 26 per 100,000, females 7 per 100,000). Accounts for 6.1% of all new male cancer cases and 2.1% of all new female cancer cases in Canada.
- **Mortality**: 5th leading cause of cancer death for males (4%) and 10th leading cause of cancer death for females (1.8%) in Canada. 4.1 deaths per 100,000 (6.8 males, 2.1 females).
- 25% will be MIBC 75% superficial bladder ca.
- Average life expectancy is 14 months

RISK FACTORS

- **Environmental/Chemical/Infections**:  
  - Tobacco use is the number one cause, estimated to account for ~50% of all bladder cancer. Occupational exposures (rubber, textile, metal, electrical and leather workers, painters, hairdressers), exposure to aromatic amines, polyaromatic hydrocarbons (PAHs) and diesel engine exhaust. Analgesics (NSAIDs), cyclophosphamide, pelvic XRT, chronic cystitis.
  - Schistosomiasis in endemic areas (East Africa, middle east) – Squamous cell
- **Genetic**: Most predominately affects Canadians over the age of 70. More prominent in Caucasians than people of African, Hispanic, Asian or First Nations origins. More prevalent in men.

PREVENTION & SCREENING

- **Prevention**: smoking cessation decreases risk but not to level of non-smokers
- **Screening**: Prospective studies confirm a low positive predictive value for screening in older men at average risk. Not currently recommended.

B) PRESENTATION & DIAGNOSIS

SYMPTOMS & SIGNS

- Most common presenting symptom is painless hematuria.
- Frequency, urgency, dysuria, pain in locally advanced or metastatic disease.
- Constitutional symptoms in metastatic disease.

INVESTIGATIONS

- History and Physical including DRE in men and bimanual examination of the vagina and rectum in women
- Laboratory: Urinalysis, Urine cytology, Cr, CBC, ALP, Calcium profile, LFTs
- Cystoscopy and examination under anesthesia
- Assessment of upper tracts with IVP, CT or retrograde pyelograms.
- Metastatic work-up: CXR, CT abd/pelvis, bone scan if symptomatic
PATHOLOGY & MOLECULAR BIOLOGY
- **Common Histology:** urothelial (transitional cell) carcinoma >90%, squamous cell carcinoma, adenocarcinoma, small cell carcinoma, sarcomas, lymphoma, melanoma, schistosoma bladder cancer may make up the rest
- **Common Metastatic Sites:** lymph nodes, liver, bone
- **Relevant Molecular Biology:** A meta-analysis of 168 studies assessing the prognostic value of p53 overexpression showed a significant, although weak association with the overall risk of recurrence and mortality.

STAGING (Bladder cancer TNM staging AJCC UICC 2017)
- **TNM:**
  - Ta: noninvasive papillary carcinoma
  - Tis: carcinoma in situ
  - T1: tumor invades lamina propria (subepithelial connective tissue)
  - T2: tumor invade muscularis propria (T2a – inner half, T2b – outer half)
  - T3: tumor invades perivesical soft tissue fat (T3a: microscopic, T3b: macroscopic (extravesical mass))
  - T4: Extravesical tumor directly invades any of the following: Prostatic stroma, semina vesicles, uterus, vagina (T4a), pelvic wall, abdominal wall (T4b)
  - N1: single lymph node in true pelvis,
  - N2: multiple nodes in true pelvis,
  - N3: nodal involvement of the common iliac lymph nodes
  - M1: distant mets limited to beyond common iliac (M1a), non lymph node mets (M1b)

  - Non-muscle invasive: Ta, Tis, T1 N0M0 (Stage 1 T1N0M0)
  - Muscle invasive: T2-T4a N0M0 (Stage 2/3)
  - Metastatic: T4b, any N, M1

  - Stage 1 – T1N0 – invades submucosal 5-year OS 88%
  - Stage 2 – T2N0 – invades muscularis layer 5-year OS 63%
  - Stage 3 – T3/T4N0 – invades adjacent near tissues 5-year OS 46%
  - Stage 4 – T4bN1-3/M1 – invades pelvis or abd wall or mets 5-year OS 15%

C) TREATMENT

NON-MUSCLE INVASIVE BLADDER CANCER (NMIBC) (Ta, Tis, T1)

**Bottom Line General Approach:**
- **Surgery:** TURBT – however >50% will recur w/ Sx alone
- **Intravesical Treatment**
  - Low risk disease (Ta disease, < 3 lesions, < 3cm) → TURBT alone +/- MMC
  - High risk (multiple recurrences, T1, >3 lesions, or >3cm)
    - TURBT, intravesical chemo (BCG, MMC) and restaging TURBT
    - **BCG** induction with maintenance therapy is standard of care for high-risk NMIBC (reduces recurrences)
    - All patients should undergo immediate postoperative instillation of chemotherapy (Doxorubicin, Epirubicin or MMC) within 6 hours of TURBT, benefit is less clear if plan for BCG
    - If recurs, can repeat intravesical chemotherapy. After 2 cycles, go to cystectomy
  - Surveillance: cystoscopy & cytology q3m for year 1, then q3-6 months for 4 years, then
Indications for early radical cystectomy: high-grade T1 with any of the following: LVI, variant features, multiple and/or large, concomitant bladder/prostatic CIS, persistent T1 high-grade on re-staging TUR; early high grade recurrence at 3 months; invasive tumours involving bladder diverticula.


MUSCLE-INVASIVE BLADDER CA (T2+)
Bottom Line General Approach:

- Neoadjuvant chemotherapy followed by Radical Cystectomy
  - For T2-T4aN0M0 with cisplatin based chemotherapy
  - If ineligible for cisplatin based chemo, then go directly to cystectomy (unless goal is to downstage surgically unresectable tumors). Cystectomy alone is associated with cure rates of 50-65%, however 5-yr OS for pts with invasion beyond bladder muscle is 40% and lymph node involvement is 35%.
  - Neoadjuvant cisplatin combination chemotherapy (GC/MVAC) is associated with ~5% 5-yr OS benefit (50% vs 45%), HR 0.87, and is the preferred approach (meta-analysis). GC and MVAC have not been compared head-to-head in the neoadjuvant setting.
  - GC is given as Cisplatin 70mg/m2 on Day 1 and Gemcitabine 1250 mg/m2 day 1 and 8 q21 days for 4-6 cycles

- OR Adjuvant Chemotherapy post cystectomy
  - For high risk patients – pT3/T4 or N+ should be offered (detailed discussion of the limited data, risks benefits etc.)
  - OS benefit for patients with high tract urothelial disease who under radical nephroureterectomy

- OR Trimodality Treatment (combined TURBT then chemoradiotherapy)
  - patients not cystectomy candidates or want to preserve their bladder.
  - combined-modality therapy incorporating maximal transurethral resection of bladder tumor (TURBT) followed by radiation therapy (RT) with concurrent chemotherapy is an appropriate alternative, there have been no RCTs comparing cystectomy with a bladder-preservation approach. Salvage cystectomy should be performed in pts with residual disease.
  - Concurrent chemo radiation with Cisplatin 40mg/m2 weekly x 5-7 cycles decreases local recurrence but no statistically significant difference in OS, 5-FU + mitomycin in combination with RT is an alternative (Coppin JCO 1996, James NEJM 2012).

Adjuvant Studies

- No Level 1 Evidence for benefit of adjuvant chemo (small trials with various chemotherapy options), however, various papers (See table below) and three MA have suggested benefit in high risk patients.

Table and Commentary:

From Booth & Tannock JAMA Oncology 2015

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>ACT Treated</th>
<th>LDI*</th>
<th>OS</th>
<th>DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC Collaboration</td>
<td>Individual patient data meta-analysis from 6 RCTs</td>
<td>491</td>
<td>2a</td>
<td>NA</td>
<td>HR, 0.68 (0.53-0.89)</td>
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<tr>
<td>Auger et al</td>
<td>Literature-based meta-analysis from 3 RCTs</td>
<td>396</td>
<td>2a</td>
<td>RR, 0.74 (0.62-0.88)</td>
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<tr>
<td>Sutliff et al</td>
<td>Retrospective cohort study from 11 high volume centers</td>
<td>3947</td>
<td>3c</td>
<td>NA</td>
<td>HR, 0.65 (0.54-0.76)</td>
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<tr>
<td>Leev et al</td>
<td>Literature-based meta-analysis from 9 RCTs*</td>
<td>945</td>
<td>2a</td>
<td>NA</td>
<td>HR, 0.77 (0.63-0.93)</td>
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<tr>
<td>Booth et al</td>
<td>Population-based prospective cohort</td>
<td>2809</td>
<td>2c</td>
<td>NA</td>
<td>HR, 0.71 (0.62-0.81)</td>
<td></td>
</tr>
</tbody>
</table>

Meta-Analisis Data (most recent):

Eur Urology 2014 - MA of 9 adjuvant trials using cisplatin based chemotherapy in Adjuvant setting

- Results:
  - Improvement in OS HR 0.77 and DFS HR 0.66

Observational Data (most recent):

- Galasky Effectiveness of Adjuvant Chemotherapy for Locally Advanced Bladder Cancer, JCO March 2016
  -observation data on 5639 patients with T3/T4, node positive from National Cancer database who received adjuvant chemotherapy or observation.
  - Results = improvement in OS - HR 0.70
  - Similar HR to Chris Booth’s paper on Ontario patients; HR 0.71 (Booth et al Cancer 2014)

= Therefore, high risk patients pT3/T4 or node positive, use platinum based ACT.

Adjuvant Treatment for Upper Tract Disease

JCO March 2017 Effectiveness of Adjuvant Chemotherapy After Radical Nephroureterectomy for Locally Advanced and/or Positive Regional Lymph Node Upper Tract Urothelial Carcinoma

- Retrospective review of 3000 patients who received AC or observation after radical nephroureterectomy (RNU) for T3/4 N+ upper tract disease
- Results
  - Improved OS – 47 vs 36 months - 5 year OS 44% vs 36% HR 0.77
Bladder Cancer

NEOADJUVANT CHEMOTHERAPY

- Patients are more fit
- Patients sometimes refuse adjuvant therapy
- No delay in treatment of micrometastatic disease
- May result in downstaging
- In vivo chemo-sensitivity trial
- Give systemic chemotherapy while blood supply is intact
- pT1 may correlate with better outcomes
- 30-50% pCR rate in primary tumor with MVAC
- What I tell patients - “Without treatment, 50% of recurrence, with NACT chemo 40% recurrence”

Two Trials for NACT

(1) [JCO 2011 BA06 30894 Trial](http://example.com) - International trial of 967 pts randomized to CIS. MTX and Vinblastine (CMV) or no chemo prior to definitive local treatment (cystectomy or radiotherapy). Follow up was 8 years
  - Results – 10 year OS 36% vs 30% (sig) (HR = 0.84)

(2) NEJM 2003 INT-0080 (below)
  - Results mOS 77 mo vs 46 mo

MVAC : First Approved Regimen

- Methotrexate, vinblastine, Adriamycin, cisplatin
- Improved PFS and OS vs single agent CIS
  - response rate 39% (vs 12%), median time to progression 10 months (vs 4.3 months) and median overall survival 12.5 months (vs 8.2 months, p=.0002). However, toxicity was substantial and greater than the single agent.
- Toxic regimen

<table>
<thead>
<tr>
<th>Neoadjuvant Chemotherapy Plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer</th>
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</thead>
<tbody>
<tr>
<td><strong>Regimen</strong></td>
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<tr>
<td></td>
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<tr>
<td><strong>Mechanism of Action of Experimental Drug</strong></td>
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<td><strong>Primary Endpoint</strong></td>
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<td><strong>Size (N)</strong></td>
</tr>
</tbody>
</table>
Bladder Cancer

<table>
<thead>
<tr>
<th>Results</th>
<th>Survival: mOS 77 months vs 46 months (p=0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survival: 5yr OS 57% vs 43% (p=0.06)</td>
</tr>
<tr>
<td></td>
<td>pCR rate: 38% vs 15%</td>
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<td></td>
<td>85% of patients with pCR alive at 5 years</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Gr 4 neutropenia 33%, Gr 3 GI toxicity 17% (n/v, stomatitis, diarrhea or constipation)</td>
</tr>
<tr>
<td>Conclusion</td>
<td>Compared with cystectomy alone, neoadjuvant MVAC chemotherapy increases the likelihood of eliminating residual cancer in the cystectomy specimen and is associated with improved survival among patients with muscle invasive bladder cancer</td>
</tr>
<tr>
<td>Other Comments</td>
<td>Adverse effects were moderate - with at least 1/3 having severe haematological or GI side effects</td>
</tr>
</tbody>
</table>

NACT Protocol – Gem+CIS (same as adjuvant)

**PREMEDICATIONS:**
- Antiemetic protocol for high moderate emetogenic chemotherapy protocols (see protocol SCNAUSEA).
- May consider adding aprepitant 125 mg PO pre-chemotherapy and 80 mg PO once daily in the morning on Days 2 and 3

**TREATMENT:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BCCA Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>1250 mg/m²/day on days 1 and 8 (total dose per cycle = 2500 mg/m²)</td>
<td>IV in 250 mL NS over 30 min</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>70 mg/m²/day on day 1</td>
<td>Prehydrate with 1000 mL NS over 1 hour, then Cisplatin IV in 500 mL NS with 20 mEq potassium chloride, 1 g magnesium sulfate, 30 g mannitol over 1 hour</td>
</tr>
</tbody>
</table>

Repeat every 21 days for total of two cycles prior to restaging. Plan for 4 cycles maximum prior to surgery, if tolerated and if no disease progression. Can use CARBO AUC 5 d1 if can’t have cisplatin.

**MVAC (Regular)**

**PREMEDICATIONS ON DAY 2:**
- Antiemetic protocol for highly emetogenic chemotherapy protocols (see protocol SCNAUSEA).

**TREATMENT:** OUTPATIENT ADMINISTRATION

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BCCA Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>methotrexate</td>
<td>30 mg/m² on days 1, 15, 22</td>
<td>IV push</td>
</tr>
<tr>
<td>vinBLASline</td>
<td>3 mg/m² on days 2, 15, 22</td>
<td>IV in 50 mL NS over 15 minutes</td>
</tr>
<tr>
<td>DOXorubicin</td>
<td>30 mg/m² on day 2</td>
<td>IV push</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>70 mg/m² on day 2</td>
<td>Prehydrate with 1000 mL NS over 60 minutes, then Cisplatin IV in 500 mL NS with 20 mEq potassium chloride, 1 g magnesium sulfate, 30 g mannitol over 1 hour</td>
</tr>
</tbody>
</table>

Adjuvant: Repeat cycle every 28 days x 3 cycles. Advanced: Repeat cycle every 28 days x 2-4 cycles then reassess. Neoadjuvant dose-dense MVAC regimens have not been evaluated in randomized trials.**
Bladder Cancer

TRIMODALITY TREATMENT

Chemoradiotherapy for Curative Intent

(1) Single agent CIS 40mg/m² qw with RT (most commonly used in Ontario)
(2) 5FU and Mitomycin C (like anal protocol)

Coppin and I Tannock 1996 JCO

- Patients with T2-T4b TCC underwent definitive radiotherapy and were randomized to CIS 100mg/m² q2w for 3 cycles or radiation alone.
- Results
  - Pelvic relapse lower – 50% vs 25% (HR 0.50)
  - But no OS benefit

Contraindications

- Large tumor volume >5cm
- Hydronephrosis
- Contraindication for cisplatin
- Small cell pathology
- ECOG 3 or more
- Metastatic disease
- Creatinine >140

PREHYDRATION:
1000 mL NS with potassium chloride 20 mEq and magnesium sulfate 2 g over 2 hours, prior to CIPlatin

ANTIEMETICS:
As per highly emetogenic protocol

TREATMENT:

Note: Since CIPlatin is used in this protocol as a radio-sensitizing agent, it is to be administered weekly on day 1 or 2 of each week of radiation therapy. Radiation should start after CIPlatin infusion is completed (no specific timeframe after CIPlatin infusion). If radiation therapy is cancelled on the CIPlatin day, do not give CIPlatin that day; postpone until radiation therapy resumes.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BCCA Administration Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIPlatin</td>
<td>40 mg/m²</td>
<td>IV in 500 mL NS with mannitol 30 g and magnesium sulfate 2 g, over 1 hour</td>
</tr>
</tbody>
</table>

Repeat weekly x 5 to 7 cycles (also see under RADIATION THERAPY).
No post-hydration.

ANTIEMETICS POST-CIPlatin:
- dexamethasone 4 mg PO 12 hours after CIPlatin, then 4 mg PO q12h x 2 days (3 days if necessary)
- dimenhydrinate 50 to 100 mg PO q4h pm
- lorazepam 1 mg SL q3-4h pm
- promethazine 10 mg PO q3h pm

BC2001 trial NEJM 2012 - Radiotherapy with or without Chemotherapy in Muscle-Invasive Bladder Cancer

- Pts with MIBC randomized to RT +/- chemo (fluorouracil (500 mg per square meter of body-surface area per day) during fractions 1 to 5 and 16 to 20 of radiotherapy and mitomycin C (12 mg per square meter) on day 1.
- Results
  - 2 year Locoregional disease free survival – 67% vs 54% (HR 0.68)
  - OS the same

METASTATIC

- Bottom Line General Approach:
  - 1st line = Cisplatin-based combination chemotherapy (GC, MVAC or ddMVAC)
    - Gem-Cis (GC) = MVAC with less toxicity.
    - GC+Paclitaxel is not better than GC alone.
    - Response rates are 46-49% but not durable and 5-yr survival rates are ~15%
    - Karnovsky PS < 80 and visceral metastases are prognostic with shortened survival in clinical trials
Who is Cisplatin Unfit?

- Meets at least one of the following:
  - ECOG 2
  - Creatinine Clearance < 60
  - Grade > 2 hearing loss
  - Grade > 2 neuropathy
  - NYHA Class III heart failure
- Use Carboplatin or reduced or split-dose of Cisplatin or clinical trial.
- **EORTC 30986 JCO 2012** – Phase 2/3 randomized to first line patients with impaired renal function or ECOG 2 to Gem/Carbo or M-CAV1 (MTX,carbo,vinblastine)
  - Results – no difference in mOS (9.3 vs 8.1 mo) nor PFS.
- Therefore, in accordance with JCO 2016 Guidelines, use carboplatin combination or single agent if unfit for cisplatin.

2nd line

- Pembrolizumab (Keynote 45) (new)
- Single agents with modest activity in Phase 2 trials include Gemcitabine (11-22%), Vinflunine (8%), Ifosfamide (5-20%), Paclitaxel (10%), Docetaxel (13%), Pemetrexed (28%), Nab-Paclitaxel (32%).
- Two phase 3 trials are ongoing comparing atezolizumab or pembrolizumab with second-line chemotherapy

- **Prognosis**: median survival 13-15 months with treatment versus 6 months without

**Important Phase III Clinical Trials:**

**MVAC vs GC**
- Metastatic TCC patients randomized to MVAC or GC
- Results
  - mOS 14 (GC) vs 15.2 mo (MVAC), HR 1.09
- Trial was supposed to show GC superior, but not powered for non-inferiority
- We now use GC, but at 3 weekly schedule.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>* GC: Gemcitabine 1000mg/m2 Days 1,8,15 and Cisplatin 70mg/m2 Day 2 q28 days vs.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>* MVAC: methotrexate 30mg/m2 Days 1,15,22; vinblastine 3mg/m2 Days 2,15,22; doxorubicin 30mg/m2 Day 2; cisplatin 70mg/m2 Day 2</td>
</tr>
<tr>
<td></td>
<td>* no GCSF</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mechanism of Action of Experimental Drug</th>
<th>* Gemcitabine: nucleoside analogue that replaces cytidine during DNA replication, thereby inhibiting tumor growth</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>* OS</th>
</tr>
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</table>
Bladder Cancer

| Inclusion/Exclusion Criteria | * Locally advanced (T4b,N2,N3) or metastatic (M1) TCC of urothelium
|                            | * Karnovsky PS ≥ 70
|                            | * no prior systemic therapy, local therapy ok if ≥4 weeks prior
|                            | * CrCl ≥ 60 ml/min
| Size (N)                    | * 405
| Results                     | * Survival: mOS 13.8 vs 14.8 mos, GC vs MVAC (HR 1.04, NS)
|                            | * 6, 12, 18 mos Survival: 82%, 58%, 37% vs 81%, 63%, 38%
|                            | * TTP: 7.4 vs 7.4 mos
|                            | * ORR: 54% vs 55%
|                            | * Quality of Life: similar in both arms
| Toxicity                    | * MVAC had greater Gr 3/4 neutropenia (82% vs 71%), febrile neutropenia (14% vs 2%), neutropenia sepsis (12% vs 1%)
|                            | * MVAC had greater Gr 3/4 mucositis (22% vs 1%)
|                            | * GC had greater Gr 3/4 anemia (27% vs 18%) and Gr 3/4 thrombocytopenia (57% vs 21%), but not higher transfusion rate
|                            | * Deaths from treatment MVAC 3%, GC 1%, NS
| Conclusion                  | * GC and MVAC have similar survival in locally advanced and metastatic bladder cancer, but GC is more tolerable and safer and should be considered standard of care
| Other Comments              | * (e.g. criticisms about the study)

Three main strategies to improve overall survival:
- Dose intensification regimens
- Triplet combinations
- Use in perioperative setting

What about high dose intensity MVAC vs regular MVAC?
- Sternberg et al JCO 2001 – give every 2 weeks with GCSF

GCSF – starting d4 for 7 days. It’s more dose-dense regimen in terms of doxorubicin and cisplatin, less MTX and vinblastine.

Results:
- mOS = 15.1 vs 14.9 months ** significant HR 0.76. 5 year OS 21.8% vs 13.5%
  - NOT CLINICALLY SIGNIFICANT but reduction in toxicity with dose intense
  - Toxicity with MVAC – myelosuppression, sepsis, mucositis, nausea and vomiting. 54% of patients were hospitalized for nausea in the trial. GCSF ameliorates most of them.
- mPFS – 9.5 mo vs 8.0 months
Although the survival curves seem to diverge in favor of the HD-MVAC arm, there are small numbers of patients in the tails of the curves. There is, however, the potential for a cohort of long-term survivors in this study. Survival was the most important end point in this trial, and no statistically significant difference in overall survival was demonstrated.

**Triplet Chemotherapy**

- Bellmunte et al ASCO 2007 EORTC 30987
- Phase 3 trial of Paclitaxel/CIS/Gem (PGC) in first line met TCC
- Patients randomized to GEM/CIS or PGC to max of 6 cycles
- Results
  - Increase in ORR 56% vs 44%
  - mOS 16 vs 13 months trend HR 0.87 (CI cross 1)

**Second Line Therapy**

- Despite high response rates (40-45%) with cisplatin based treatments cure rates remain low, most patients relapse
- No approved 2nd line treatment option
- Numerous trials of single agents and combination chemotherapy have been reported
- Low response rates – <20% and no OS benefit

**Single Agent 2nd Line Trials**

<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>
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<tbody>
<tr>
<td>Lorusso 1998</td>
<td>Gemcitabine</td>
<td>II</td>
<td>35</td>
<td>22.5</td>
<td>3.8</td>
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<tr>
<td>Albers 2002</td>
<td>Gemcitabine</td>
<td>II</td>
<td>30</td>
<td>11</td>
<td>4.9</td>
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<td>Vaughn 2002</td>
<td>Paclitaxel</td>
<td>II</td>
<td>31</td>
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<td>2.2</td>
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<tr>
<td>Pronzato 1997</td>
<td>Ifosfamide</td>
<td>II</td>
<td>20</td>
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<td>NR</td>
<td>NR</td>
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<td>Witte 1997</td>
<td>Ifosfamide</td>
<td>II</td>
<td>56</td>
<td>20</td>
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<td>5.5</td>
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<td>McCaffrey 1997</td>
<td>Docetaxel</td>
<td>II</td>
<td>20</td>
<td>13</td>
<td>NR</td>
<td>9</td>
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<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>
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<tr>
<td>Dreicer 2007</td>
<td>Epothilone B</td>
<td>II</td>
<td>45</td>
<td>12</td>
<td>2.7*</td>
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<th>32</th>
<th>6.0*</th>
<th>10.8</th>
</tr>
</thead>
</table>

**Abraxane in second line** Ko,Y, Sridhar SS Lancet 2013 - Phase 2 - RR 27%

**Second Line Immunotherapy**

**Pembrolizumab** - [Keynote-045 NEJM March 2017 ****]

- Progressed on platinum, randomized to pembro 200mg q3w for 24 months or investigators choice of chemo (taxol or vinflunine). Enrolled regardless of PD-L1 expression
- Results
  - OS 10.3 vs 7.4 months (HR 0.73)
  - 1 year OS 43.9 vs 30.7%
  - No difference in PFS (2.1 vs 3.3)

**Protocols**

**PREMEDICATIONS:**
- Antiemetic protocol for highly emetogenic chemotherapy protocols (see protocol SCNAUSEA).

**TREATMENT:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BCCA Administration Guideline</th>
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<tbody>
<tr>
<td>gemcitabine</td>
<td>1250 mg/m²/day on days 1 and 8 (total dose per cycle = 2500 mg/m²)</td>
<td>IV in 250 to 500 mL NS over 30 min</td>
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<tr>
<td>CI Splatin</td>
<td>70 mg/m²/day on day 1 OR 35 mg/m²/day on days 1 and 2 (or days 1 and 8)</td>
<td>Prehydrate with 1000 mL NS over 1 hour, then CI Splatin IV in 500 mL NS with 20 mEq potassium chloride, 1 g magnesium sulfate, 30 g mannitol over 1 hour</td>
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</tbody>
</table>

Repeat every 21 days to two cycles beyond best response (maximum 6 cycles)*.

*No Compassionate Access Program (CAP) approval required to retreat a patient with worsening disease. Patient must have had lasting response from initial therapy, continue to have good performance status and adequate renal function.

Note: A growing international consensus is recommending that the 28 day CI Splatin and gemcitabine cycle be replaced with a 21 day cycle that delivers the same dose of CI Splatin on day 1 and gemcitabine 1250 mg/m² on days 1 and 8.