IMMUNOTHERAPY IN BLADDER CANCER

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Objectives

- Review of clinical trials that led to approval of immunotherapy in bladder cancer
- Review of predictors of immunotherapy efficacy in bladder cancer
- Role of immunotherapy in neoadjuvant and adjuvant muscle invasive bladder cancer management
- Role of immunotherapy in non muscle invasive bladder cancer
- Immune related adverse events

- Stratified according to PD L1 expression on tumor cells.
- Objective response rates
  - PD L1 > 5% - 29%
  - PD L1 > 1% - 23%
  - PD L1 < 1% - 16%
- Median OS 11.3 months in PD L1 > 1% compared to 5.95 months in PD L1 < 1%
Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. Bellmunt et al NEJM 2017

- Urothelial carcinoma that showed predominantly transitional-cell features on histologic testing.
- Progression after platinum-based chemotherapy for advanced disease or recurrence within 12 months after the receipt of platinum-based adjuvant or neoadjuvant therapy.
- Stratified according to programmed death ligand 1 (PD-L1) combined positive score: Percentage of tumor and infiltrating immune cells with PD-L1 expression out of the total number of tumor cells
- Median OS is 10.3 months compared to 7.4 months with chemotherapy
- Median OS in PD-L1 >10%, 8 months compared to 5 with chemotherapy
Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Powles et al Lancet 2018

- Patients stratified by PD-L1 expression (expression on <1% [IC0] or 1% to <5% [IC1] of tumor-infiltrating immune cells vs ≥5% of tumor-infiltrating immune cells [IC2/3])

- The primary endpoint of overall survival improvement with atezolizumab was not met in patients with metastatic urothelial carcinoma with at least 5% PD-L1 expression on tumor-infiltrating immune cells. (11.1 vs 10.6 months)
Efficacy and Safety of Durvalumab in Locally Advanced or Metastatic Urothelial Carcinoma: Updated Results From a Phase 1/2 Open-label Study. Powles et al. JAMA 2017

Unique combined assessment of PD-L1 staining of TCs and immune cells (PD-L1 “high,” ≥25% of either TCs or immune cells staining for PD-L1, and PD-L1 “low or negative,” <25% of both TCs and immune cells staining for PD-L1)
Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial.

PD-L1 status was based on numbers of tumor cells with plasma membrane PD-L1 expression at any intensity using a staining cutoff of 5% or higher.
First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicenter, single-arm, phase 2 study. Lancet 2017

Staining was scored using a combined positive score, defined as the percentage of cells (tumor cells, macrophages, or lymphocytes) expressing PD-L1 in a tumor biopsy.

40% ORR in PD-L1 > 10%
28% ORR in PD-L1 > 1%
11% ORR in PD-L1 < 1%
Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicenter, phase 2 trial. Lancet 2017

Patients were required to be cisplatin ineligible per one or more of the following:
- GFR > 30 mL/min and less than 60 mL/min (Cockcroft-Gault formula)
- Grade 2 or higher hearing loss
- Peripheral neuropathy
- ECOG PS of 2
- PD-L1 expression on tumor-infiltrating immune cells (IC)
FDA approvals

- Nivolumab- February 2017
- Atezolizumab- April 2017
- Pembrolizumab- May 2017
- Durvalumab- May 2017
- Avelumab- May 2017
How do I treat a advanced bladder cancer patient?

- Performance status
- Cisplatin eligibility
- PD L1 vs CPS vs IC score (Companion diagnostic test)
- Urothelial vs Non Urothelial variants
- Liver metastasis
- Mutations in DNA repair enzymes
- Patient preference (Treatment schedule, Toxicity profile)
Immunotherapy in Neoadjuvant setting

Not FDA approved (Yet!)
A phase 3 randomized study of neoadjuvant chemotherapy (NAC) alone or in combination with nivolumab (NIVO) ± BMS-986205 in cisplatin-eligible muscle invasive bladder cancer (MIBC) (Available at NYOH)

- Previously untreated MIBC (clinical stage T2-T4a, N0, M0), creatinine clearance ≥ 50 mL/min, and predominant UC histology who are eligible for cisplatin-based NAC and RC will be enrolled.
- Pts with evidence of positive lymph node; metastatic BC; or prior systemic therapy, radiotherapy, or surgery for BC other than TURBT are not eligible.
- Pts will be randomized to receive NAC (gemcitabine/cisplatin; arm A), NAC + NIVO + oral placebo (arm B), or NAC + NIVO + BMS-986205 (arm C) followed by RC (all arms); arms B and C will receive continued IO tx.
- Primary endpoints include pCR after neoadjuvant tx and event-free survival (arms C vs A; arms B vs A).
- Secondary endpoints are overall survival and safety.
- This global study in 28 countries began accrual in Nov 2018 and has a target enrollment of 1200 pts.
A phase III, randomized, open label, multicenter, global study of efficacy and safety of durvalumab in combination with gemcitabine+cisplatin (G+C) for neoadjuvant treatment followed by durvalumab alone for adjuvant treatment in muscle-invasive bladder cancer (MIBC) (NIAGARA).

- Phase 3, randomized, open-label, multicenter, global study that will enroll ~1050 patients randomized (1:1) to durvalumab and G+C combination (Arm 1) or G+C (Arm 2) as neoadjuvant chemotherapy prior to radical cystectomy.

- Following radical cystectomy and during adjuvant therapy, patients in Arm 1 will receive durvalumab monotherapy for 8 cycles (8 months); patients in Arm 2 will receive no adjuvant treatment.

- Patients with resectable MIBC (clinical stage T2N0M0-T4aN0M0) with transitional cell histology planning to undergo a radical cystectomy will be included.

- Primary endpoints are pCR rates at time of cystectomy following neoadjuvant treatment and EFS.

- Secondary and exploratory endpoints include proportion of patients who achieve pathologic response <P2 (stages Pa, P1, and carcinoma in situ) at time of cystectomy following neoadjuvant treatment, EFS at 24 months, metastasis-free survival, proportion of patients who undergo cystectomy, and OS at 5 years.
Avelumab as neoadjuvant therapy in subjects with muscle-invasive urothelial carcinoma (AURA trial).

- For the group of cisplatin-eligible, chemotherapy with high dose of Metotrexate-Vinblastin-Adriamycin-Cisplatin or Cisplatin-Gemcitabine will be associated with Avelumab.
- For the group of cisplatin-ineligible, Avelumab as monotherapy or associated with Paclitaxel-Gemcitabine will be used.
- Four cycles of treatment are provided.
- A radiological evaluation will be performed after 2 cycles and if evidence of progressive disease exists the neoadjuvant treatment will be stopped and the surgery will be performed.
- Primary end point is pathological complete response.
PURE-01: A phase 2, open-label study of neoadjuvant pembrolizumab (pembro) before radical cystectomy for muscle-invasive urothelial bladder carcinoma (MIUC)

- The study includes cisplatin eligible- and ineligible pts.
- Pts receive 3 cycles of pembro 200mg 3 weekly before RC (planned < 3 weeks of the last dose).
- Computed tomography (CT) scan, FDG-PET/CT scan, and bladder multiparametric magnetic resonance imaging (mpMRI) are done during screening and before RC.
- Radiologically non responders to pembro are given 3 additional courses of dose-dense MVAC chemotherapy. After RC, pts are managed according to local guidelines (adjuvant chemotherapy vs observation)
- CR rates are 54% in PDL1 high group compared to 13% in PDL1 low group.
A phase II study investigating the safety and efficacy of neoadjuvant atezolizumab in muscle invasive bladder cancer (ABACUS)

- 2 cycles of atezolizumab (1200mg Q3) prior to cystectomy in muscle invasive transitional cell cancer (T2-4N0M0)
- 69 patients with median age of 73 yrs are enrolled
- The pCR rate was 18/62 (29%); 40% in PD-L1 positive patients
- pT0 23%, Tis 6%, T1 10% T2 21% T3 24% T4 16% stage at surgery.
- 39% of patients were down staged to non-muscle invasive disease.
- 3/18 (17%) of the pCR patients had pT3/4 disease at baseline
PECULIAR: An open label, multicenter, single-arm, phase 2 study of neoadjuvant pembrolizumab (PEM) and Epacadostat (EPA), preceding radical cystectomy (Cy), for patients (pts) with muscle-invasive urothelial bladder cancer (MIUBC).

- EPA, an anti-IDO1 agent, combined with PEM, safely improved the response-rate in metastatic UC.
- 3 cycles of PEM 200mg intravenously, q3 weekly and EPA will be orally taken at the dose of 100 mg BID, from Day 1 until 10 days before Cystoscopy.
- Cy should be performed within 3 weeks of the last PEM dose.
- Computed tomography (CT) scan, 18FDG-PET/CT scan, and multiparametric bladder MRI (mpMRI) will be done during screening and before Cy to stage and evaluate response.
- After Cy, pts will be managed according to EAU guidelines.
DUTRENEO Trial: A phase II randomized trial of Durvalumab and Tremelimumab as Neoadjuvant approach in muscle-invasive urothelial bladder cancer (MIBC) patients prospectively selected by immune signature scores.

- Randomized phase II, open-label study conducted in urothelial MIBC pts diagnosed of T2-T4 and/or N+ candidates to cystectomy, ECOG 0-1 and adequate organ function.
- Pts will be treated according to the score of a pro-inflammatory signature (PIS) determined with Nanostring technology.
- Pts with a low PIS will receive standard cisplatin-based neoadjuvant therapy (22 pt).
- Pts with a high PIS will be randomized 1:1 to receive cisplatin-based neoadjuvant therapy (22 pt) or DU 1500 mg + TRE 75 mg every 4 weeks x 3 cycles (22 pt).
- If more than 8 responses (pT0) are observed in first 22 pts included in DU+TRE arm, 24 additional pts will be recruited in this arm.
- Primary objective is to assess the antitumor activity of DU+TRE measured as pT0 rate in pts with a positive PIS.
<table>
<thead>
<tr>
<th>Therapy Description</th>
<th>Country</th>
<th>Eligibility</th>
<th>Cisplatin Eligibility</th>
<th>Trial Identifier</th>
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<td>Nivolumab + gemcitabine/cisplatin (BLAST-1)</td>
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<td>Durvalumab + tremelimumab + dose-dense MVAC (NEMIO)</td>
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Selecting a patient for neoadjuvant immunotherapy

- PD-L1
- Tumor mutation burden
- CD8 infiltration
- EMT signature
- Tumor microenvironment signature
- Performance status
- Cisplatin eligibility
# Phase 3 studies in Adjuvant setting

<table>
<thead>
<tr>
<th>IO Therapy/Study</th>
<th>Phase/N</th>
<th>Study Arms</th>
<th>Primary Endpoints</th>
<th>Secondary Endpoints</th>
<th>Estimated Primary Completion Date</th>
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<tr>
<td>Nivolumab¹ CheckMate 274</td>
<td>Phase 3</td>
<td>Nivolumab (adjuvant)</td>
<td>Disease-free survival</td>
<td>Non-urothelial track recurrence-free survival</td>
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<td>OS</td>
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<td>Pembrolizumab² AMBASSADOR</td>
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<td>Disease-free survival and OS in PD-L1⁺ and PD-L1⁻ patients</td>
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<td>Non-urinary tract recurrence-free survival</td>
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Immunotherapy in Non muscle invasive bladder cancer

Not FDA approved (Yet!)
S1605: Phase II trial of atezolizumab in BCG-unresponsive nonmuscle invasive bladder cancer

- Systemic atezolizumab (1200 mg IV) every 3 weeks for one year in 135 patients with BCG-unresponsive high risk NMIBC.
- The study will enroll 70 patients with CIS (with or without concomitant Ta/T1) and 65 with Ta/T1 only.
- The co-primary endpoints are:
  - *complete response (CR) at 6 months in the CIS subgroup*
  - *event-free survival (EFS) at 18 months in the overall population.*
KEYNOTE-057: Pembrolizumab in non muscle invasive bladder cancer.

- Phase 2 study enrolling patient with non muscle invasive bladder cancer unresponsive to BCG who decline to undergo or are ineligible for cystectomy.
- Papillary disease must be fully resected at study entry.
- Cohort A enrolls CIS with or without papillary disease.
- Cohort B enrolls papillary disease (high grade Ta or any T1) without CIS.
- Treatment will continue every 3 weeks for 24 months as long as cystoscopy performed every 12 weeks show no high risk NMIBC.
- So far 102 patients were enrolled and 40% have CR with 0 patients progressing to T2 disease.
Phase 3 trials in Non muscle invasive bladder cancer

- ALBAN: An open label, randomized, phase III trial, evaluating efficacy of atezolizumab in addition to one year BCG (bacillus Calmette-Guerin) bladder instillation in BCG-naive patients with high-risk nonmuscle invasive bladder cancer (AFU-GETUG 37).

- Bacillus Calmette-Guerin (BCG) with or without pembrolizumab (pembro) for high-risk (HR) nonmuscle invasive bladder cancer (NMIBC) that is persistent or recurrent following BCG induction: Phase III KEYNOTE-676 study.
Immune related adverse events
Organs Affected by Immune Checkpoint Blockade

Possible Mechanisms Underlying Immune-Related Adverse Events

Management

- Most of the current guidelines are borrowed from managing autoimmune conditions (by Rheumatology)

- Treatment is based on CTCAE grading of the IrAEs.

- High dose steroids (Prednisone or Methylprednisolone 1 to 2 mg/kg) are first line of treatment for most of the adverse events.

- Infliximab at 5mg/kg is used in steroid refractory cases

- Cytoxan, Cyclosporine, Mycophenolate, IVIG, Plasmapheresis, ATG are used according to indications
Conclusion

- Immunotherapy with check point inhibitors are an effective treatment in Bladder cancer
- Chemo-immunotherapy and combination immunotherapies are likely going to be approved in neoadjuvant setting very soon
- Immune related adverse events are a concern but so far were very manageable with single agent check point inhibitors
- Patient selection is key in translating the clinical trial data into real world success
- Stage 4 bladder cancer is still associated with high mortality.
- Increasing cure rates in early stage bladder cancer patients is possible with immunotherapy.
- Encourage clinical trial participation in bladder cancer patients.