Real World Practice: Adjuvant Therapy Ready for Prime Time? (Con)

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April 21, 2017
Why we are not ready for adjuvant therapy (in 10 minutes or less)

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Conflicting Data from ASSURE and S-TRAC

- **DFS from ASSURE**
  - 1 death on sorafenib
    - Infectious colitis
  - 4 deaths on sunitinib
    - Neurologic sequelae
    - Pulmonary embolism
    - Gastric perforation
    - Disease progression

Conflicting Data from ASSURE and S-TRAC

- DFS from S-TRAC
- No deaths attributed to treatment (5 deaths on each arm)

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- OS from S-TRAC
- No deaths attributed to treatment (5 deaths on each arm)

Conflicting Data from ASSURE and S-TRAC

<table>
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<tr>
<th>Analysis (DFS)</th>
<th>Sunitinib</th>
<th>Placebo</th>
<th>Difference</th>
</tr>
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<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Central)</td>
<td>6.8</td>
<td>5.6</td>
<td>1.2</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Investigator)</td>
<td>6.5</td>
<td>4.5</td>
<td>2.0</td>
</tr>
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</table>

- Could central review explain the discordances?
- Would central review in ASSURE widen or narrow the difference in DFS?

Conflicting Data from ASSURE and S-TRAC

- Could central review explain the discordances?
- Could patient characteristics (esp. risk) explain the discordances?

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Conflicting Data from ASSURE and S-TRAC

• Could central review explain the discordances?

• Could patient characteristics (esp. risk) explain the discordances?

• Could dose intensity affect outcome?

recommendations that dual bronchodilation should be the foundation treatment for the majority of symptomatic COPD patients.

- New data from two head-to-head studies showed **Ultibron Neohaler** provided clinically meaningful and comparable bronchodilation to Anoro® Ellipta® in US patients with COPD. However, the primary endpoint in terms of 24-hour lung function improvement (FEV₁, AUC₀₋₂₄h) was not met statistically. A full evaluation of this new data is ongoing and will be communicated in due course. The primary objective of the two head-to-head studies was to demonstrate that **Ultibron Neohaler** was non-inferior to Anoro® Ellipta® in improving lung function over a 24-hour period (FEV₁, AUC₀₋₂₄h) after 12 weeks of treatment. In December, Novartis announced that it out-licensed US commercial rights for three chronic obstructive pulmonary disease drugs including **Ultibron Neohaler** to Sunovion Pharmaceuticals.

- The pivotal Phase III CANTOS study with **ACZ885** (canakinumab) has achieved the required cardiovascular events (1400) and study close-out procedures have commenced. This large outcomes trial (>10,000 patients randomized with median treatment duration of >4 years) is investigating whether ACZ885 can reduce the risk of recurrent cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) in patients with a history of myocardial infarction and elevated inflammatory burden versus placebo when administered quarterly in addition to standard of care. The study is on track for a readout of results in mid-2017.

- The Phase III PROTECT trial of **Votrient** (pazopanib) in adjuvant renal cell carcinoma did not meet its primary endpoint and we will not file for the indication. Data from the trial will be submitted to an upcoming medical meeting.

- Novartis completed in January 2017 the acquisition of **Ziarco Group Limited**, adding a once-daily oral H₄ receptor antagonist in development for atopic dermatitis (AD), commonly known

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EAU Guidelines on Adjuvant Therapy for RCC

<table>
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<tr>
<th>Study or subgroup</th>
<th>log[hazard ratio]</th>
<th>SE</th>
<th>Total</th>
<th>Total</th>
<th>Weight</th>
<th>Hazard ratio IV, Random, 95% CI</th>
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<tr>
<td>ASSURE</td>
<td>0.0198</td>
<td>0.0824</td>
<td>647</td>
<td>647</td>
<td>55.4%</td>
<td>1.02 [0.87, 1.20]</td>
<td></td>
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<tr>
<td>S-TRAC</td>
<td>-0.2731</td>
<td>0.1264</td>
<td>309</td>
<td>306</td>
<td>44.6%</td>
<td>0.76 [0.59, 0.97]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>956</td>
<td>953</td>
<td>100.0%</td>
<td>0.89 [0.67, 1.19]</td>
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Heterogeneity: Tau² = 0.03; Chi² = 3.77, df = 1 (p = 0.05); I² = 73%
Test for overall effect: Z = 0.76 (p = 0.45)

Table 1 – Recommendation of the European Association of Urology Renal Cell Cancer Guidelines Panel

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<th>Recommendation</th>
<th>Strength</th>
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<td>Adjuvant sunitinib following surgically resected high-risk clear-cell renal cell carcinoma is not recommended</td>
<td>Weak ↓</td>
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EAU Guidelines on Adjuvant Therapy for RCC

IKCC Network Poll (N=22)

“After surgery for kidney cancer, if your doctor told you that you are at high risk for recurrence (spread), would you consider taking sunitinib for 1 year in the hope that you could delay the onset of recurrence even if your overall survival was not improved?”

“Which results from S-TRAC would change your standard practice in the context of data available in ASSURE and toxicity profiles consistent with those seen for sunitinib?”

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IO offers the possibility of protracted survival

The Horizon: Adjuvant Immunotherapy


IO offers the possibility of protracted survival

Toxicity profile more tenable in adjuvant setting?

< 10% discontinuation due to AEs

Few latent toxicities?
The Horizon: Adjuvant Immunotherapy

**ECOG Adjuvant Study (PIs: Harshman, Allaf)**

- **Clinical stage:** ≥T2 (7cm renal mass) or T\textsubscript{any}N+
- **Randomize:** N=766

- **Mandatory Biopsy**

- **Stratify by:** cT2 or >cT2, cN0 or cN+, histology

- **Nivolumab**
  - q 2 wks x 2 doses
  - q2 wks x 3 mos then q4 wks x 6 mo

- **Resection**

- **Observation**

Slide courtesy of L. Harshman, MD
The Horizon: Adjuvant Immunotherapy

**Key Eligibility (N=664)**
- High risk OR limited metastasis s/p metastasectomy
- s/p nephrectomy ≤ 12 weeks
- No evidence of residual disease
- Clear cell or sarcomatoid histology

**Stratification Factors**
- Disease stage (T2/T3a vs. T3b/c/T4/N+ vs metastasectomy)
- PD-L1 (IC0 vs IC1/2/3)
- Region (US/Canada vs ROW)

**Primary endpoint:** DFS

**Key secondary endpoint:** OS with interim OS analysis at final DFS, DFS in IC1/2/3, Safety, HrQoL, Other immune biomarkers

**Randomization:**

- Placebo IV q3w x 16 cycles
- Atezolizumab 1200 mg IV q3 wk x 16 cycles

Enrolling now in Europe; needs your support!
The Horizon: Adjuvant Immunotherapy

**Key Inclusion Criteria:**
- Histologically confirmed clear cell RCC or RCC with clear cell component (with or without sarcomatoid features). Diagnosis to be made by the site's central histology review required.
- Have received no prior systemic therapy for advanced RCC.
- ECOG PS 0 or 1.
- Must have undergone nephrectomy (or metastasectomy for M1 NED) ≥ 4 weeks prior to the time of screening and must be randomized ≤ 12 weeks after surgery.
- Must be tumor free, validated by either computed tomography (CT) or magnetic resonance imaging (MRI) scan of head, chest, abdomen, and pelvis and a bone scan ≤ 4 weeks from randomization.

**Patient population:**
Post nephrectomy incl. M1 NED: Intermediate + High Risk + M1 NED
- pT2, Gr. 4 or sarcomatoid, N0
- pT3, Gr. Any, N0
- pT4, Gr. Any, N0
- pT any stage, any Gr., N1
- M1 NED

**Key Exclusion Criteria:**
- Has positive surgical tumor tissue margins in the resected kidney after nephrectomy and/or in the resected metastatic lesion in M1 NED participants.
- Has a diagnosis of immunodeficiency
- Has had a prior solid organ transplant.
- Active pneumonitis, autoimmune disease
- Prior treatment with immune checkpoint inhibitor

Study launching in Q2 2017

Randomize 1:1

Pembrolizumab
200 mg Q3W x17 (12 mo)

Placebo
Q3W x17 (12 mo)

N = 950

1st EP
DFS (%)

OS

2nd Objectives:
- Safety (post-surgical complications)
- Overall Survival (OS)
- Disease recurrence specific survival
- PD-L1+ vs all comers
- QoL

Exp Objectives:
- Other biomarkers

Slide courtesy of T. Choueiri, MD
The Horizon: Adjuvant Immunotherapy

Renal Cell Carcinoma → Surgery → Nivolumab + Ipilimumab

Placebo

Details forthcoming

Toxicity/Cost?

Personal communication: R. Motzer, MD
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  • Siraj Ali, MD, PhD
  • Axel Bex, MD
  • Brian Rini, MD
  • Laurence Albiges, MD
  • Rob Uzzo, MD

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  • Marcin Kortylewski, PhD
  • Jeremy Jones, PhD
  • Xueli Liu, PhD

• Kidney Cancer Association