New Frontiers in Urologic Oncology:

Updates on Pivotal Trials in Metastatic Renal Cell Carcinoma

Ibex at Ein Gedi, Israel; 5/2017
New Frontiers in Urologic Oncology:

Updates on Pivotal Trials in Metastatic Renal Cell Carcinoma

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What makes a trial pivotal?

- OS
- PFS
- ORR
- Non-inferiority
**Immune-type treatments**

**Cytokines**

IV Interleukin-2 (Proleukin™)
- Inpatient 14 x 2 (6 days x 2)
- Inpatient 5 x 4 (3 days x 4)

Interferon

**Engineered cytokines**

ALKS-4230
NKTR-214
ALT-801

**CHECKPOINT**

Nivolumab IV (Opdivo™) [PD1]

Pembrolizumab IV [PD-1]
Avelumab IV [PD-L1]
Durvalumab IV [PD-L1]
Atezolizumab IV [PD-L1]
Ipilumimab IV (Yervoy™) [CTLA4]

**Targeted type therapies**

VEGF = vascular endothelial growth factor
mTOR = mammalian target of rapamycin

**VEGF-type treatments**

-inib: inhibitor
-umab: human-antibody

Sunitinib 50 mg (Sutent™): 14 on/ 7 off
Pazopanib 200 mg (Votrient™): 800 /d
Sorafenib 200 mg (Nexavar™): 400 + 400 /d
Axitinib 5 or 1 mg (Inlyta™): 5+5 (or 2+2 to 10+10)/d
Bevacizumab (Avastin™) IV every 2 weeks

**VEGF & FGFR & mTOR**

Lenvatinib (Lenvima™) with everolimus
18 mg (10+4+4) and 5 mg

**VEGF & C-MET**

Cabozantinib (Cabometyx ) 60 (or 40)/d

**mTOR**

-olimus or “TOR”

Everolimus 10 (Afinitor) mg/d
Temsurolimus 25 IV (Torisel) once a week.

Investigational for kidney cancer treatment
Marketed drugs’ trials

- **Sorafenib** vs placebo, 2nd line
- **Sunitinib** vs interferon
- **Temsirolimus** vs interferon (high-risk)
- **Pazopanib** vs placebo
- **Everolimus** vs placebo, after prior VEGFR
- **Bevacizumab/interferon** vs interferon (2x)
- **Pazopanib** vs sunitinib
- **Axitinib** vs sorafenib (**post-immuno biggest diff.**)
- **Sunitinib** vs everolimus
- 2nd line **Cabozantinib** vs everolimus
- 2nd line **BOTH** vs either lenvatinib or everolimus *
- 2nd line **nivolumab** vs everolimus

* Rand. phase II
Recent negative trial – endoglin pathway

2\textsuperscript{nd} line Axitinib +/- dalantercept

2\textsuperscript{nd} line Axitinib +/- TRC-105
Adjuvant trials—past/negative

- Interferon alpha vs none (x4)
- Interferon gamma vs none
- HD-IL2 vs none
- IL-2/IFN vs none
- Reniale vaccine vs none
- Thalidomide vs none
- Renal bed irradiation vs not *

(*renal bed PFS difference, only)
Adjuvant trials—recent/almost

PROTECT pazopanib vs placebo

Journal of Clinical Oncology 9/13/17
Randomized Phase III Trial of Adjuvant Pazopanib Versus Placebo After Nephrectomy in Patients With Localized or Locally Advanced Renal Cell Carcinoma

Adjuvant trials–recent/almost

PROTECT pazopanib vs placebo

JOURNAL OF CLINICAL ONCOLOGY  9/13/17
Randomized Phase III Trial of Adjuvant Pazopanib Versus Placebo After Nephrectomy in Patients With Localized or Locally Advanced Renal Cell Carcinoma


Starting dose lowered for reason of attrition

- Randomly assigned (N = 1,538)
  - Assigned to starting dose of 800 mg once daily (n = 403)
  - Assigned to starting dose of 600 mg once daily (n = 1,135)
Adjuvant trials—recent/almost

PROTECT pazopanib vs placebo

Randomly assigned
(N = 1,538)

ITT-ALL

HR, 0.802; 95% CI, 0.676 to 0.954
Log-rank P = .0126

Secondary

ITT-800

HR, 0.693; 95% CI, 0.510 to 0.943
Log-rank P = .0201

Secondary

ITT-600

HR, 0.862; 95% CI, 0.699 to 1.063
Log-rank P = .1649
Adjuvant trials–recent/almost

PROTECT pazopanib vs placebo

“A correlation was observed between higher trough plasma concentration and longer DFS.”

“Final OS cut-off will be 4/15/19"
Adjuvant trials—recent/almost

ASSURE: sorafenib vs sunitinib vs placebo
Adjuvant trials–recent/almost

ASSURE: sorafenib vs sunitinib vs placebo

Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial

Lancet 2016; 387: 2008–16

N=1943
- Placebo/placebo
- Sunitinib/placebo
- Sorafenib/placebo
Adjuvant trials—recent/almost

ASSURE: sorafenib vs sunitinib vs placebo

Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial

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3/8/16

N= 1943
• Placebo/placebo
• Sunitinib/placebo
• Sorafenib/placebo
Adjuvant trials–recent/almost

S-TRAC: sunitinib vs placebo

OS: Not mature
Not different(yet)
N=64 (20.7%) vs N = 64 (20.9%)
HR = 1.01, ns
Data for overall survival, a

So... What do you think about PFS but not OS, for 1 year of adjuvant treatment with sunitinib?

FDA evaluation *** ongoing ***
Adjuvant trials—recent/almost

ASSURE: sorafenib vs sunitinib vs placebo

** high risk subset **

Adjuvant Treatment for High-Risk Clear Cell Renal Cancer
Updated Results of a High-Risk Subset of the ASSURE Randomized Trial

Naomi B. Haas, MD; Judith Manola, MS; Janice P. Dutcher, MD; Keith T. Flaherty, MD; Robert G. Uzzo, MD; Michael B. Atkins; Robert S. DiPaola, MD; Toni K. Choueiri, MD

JAMA Oncol. 2017;3(9):1249-1252. 3/9/17

DFS: p = NS

N= 1069/1943
- pT3,
- pT4
- node-positive
- clear cell renal cancer
Adjuvant trials—current

• Accrual completed, no data yet
  – Everolimus vs placebo (all histologies)

• Accrual open
  – Atezolizumab vs placebo (most RCC; open at MCC)
  – Ipilimumab/nivolumab vs placebo (ccRCC)
  – Pembrolizumab vs placebo (ccRCC)
The big news from Madrid
Checkpoint inhibitor trials/done
Checkpoint inhibitor trials/new!

CHECKMATE 214 at 
the ESMO 2017, Madrid

Initial therapy of ccRCC

ipilumimab (1 mg/kg/dose, w-1-4-7-10)
nivolumab (3 mg/kg/dose, w 1-4-7-10)
then nivolumab 240 mg/dose q2...

Vs

sunitinib 50mg, 28 on/14 off
**CHECKMATE 214**

Co-primary endpoint: ORR (p < 0.0001)

- **Ipi-nivo**: 41.6%. Median duration: 95% CI: (21.82, Not reached)
- Sunitinib: 26.5%. Median duration 18.7 mo. 95% CI: 14.82, Not reached)

Co-primary endpoint: PFS:

- HR favors **Ipi-nivo** = 0.82; 95% [CI] = 0.64–1.05; 2-sided \( P = .03 \) *NS*

Median PFS: (NS)

- Ipi-nivo: 11.6 months (95% CI = 8.7–15.5)
- Sunitinib: 8.4 months (95% CI = 7.0–10.8)
CHECKMATE 214: More analyses

“PDL1 > 1% subset”: (11-12% of good risk; 26-29% of intermediate risk)

ORR

**Ipi-nivo**: 58% med. dur. 22.8 (95% CI 9.4, NR)
sunitinib 25%, med. dur 5.9 (95% CI 4.4, 7.1)
HR 0.48 (.28-.82), p = 0.0003

Favorable risk subset: ***opposite result***

ORR (p = 0.0002)

**Ipi-nivo** 29% median PFS 15.3 (95% CI 9.7, 20.3) mo.

**Sunitinib 52%** median PFS 25.1 (95% CI 20.9, NR)
HR 2.17 (95% CI 1.46, 3.22; p < 0.0001).

The differentially better immunotherapy outcomes in the PD-L1 positive contrasts with some prior clear cell RCC experiences.
Checkpoint inhibitor trials/new!

CHECKMATE 214: Summary:

ipilimumab-nivolumab
Better in intermediate-high risk
Much better in PDL-1% subset

Sunitinib
Better in good-risk subset

“Stop treating everyone the same”
Checkpoint inhibitor trials/accruing

VEGF $\rightarrow$ (off study other drug, such as nivolumab (PD-1)
VEGF and PDL-1

JAVELIN

sunitinib vs
axitinib/avelumab

Open at MCC
Target completion 1\textsuperscript{st} week of Dec.

\textit{NCT02684006}
Checkpoint inhibitor trials/accruing

VEGF/mTOR → (off study other drug, such as nivolumab (PD-1)
VEGF and PDL-1
VEGF → (off study other drug, such as nivolumab (PD-1)

CLEAR

Compare

• Lenvatinib in Combination with Everolimus or
• Lenvatinib Pembrolizumab or
• Sunitinib Alone

in First-Line Advanced Renal Cell Carcinoma

NCT02811861
Checkpoint inhibitor trials/accruing

VEGF-CMET/PD-1
VEGF-CMET/PD-1, CTLA-4
VEGF → (off study other drug, such as nivolumab (PD-1))

A Phase 3, Randomized, Open-Label
• Cabozantinib + Nivolumab Combined
• Cabozantinib + Nivolumab and Ipilimumab
• Sunitinib

BMS/Exelixis

NCT03141177
RCC trials at Moffitt (p1)

Clear cell RCC, randomized: (closing soon):

JAVELIN axitinib/avelumab vs sunitinib
(* we may open CLEAR).

Adjuvant (not restricted to ccRCC)

Atezolizumab vs placebo

First line, not-clear cell (pRCC, chromophobe)
Lenvatinib and everolimus
RCC trials at Moffitt (p2)

Checkpoint based

Huya HBS-8000 with nivolumab
This is an oral HDAC inhibitor. Trial through Cutaneous Program

Durvalumab +/- IDO inhibitor AMP-514
Trial through phase I Program, Dr Gray

Cytokine based, and engineered cytokines

• Pembrolizumab and high dose IL-2 (See next slide)

• Nektar 214 (pegylated IL-2 prodrug) with nivolumab

• ALKS-4230 (IL-2/IL-2receptor alpha)
Pembrolizumab/IL-2 schema

= outpatient
Pembrolizumab
every 3 weeks.

= inpatient IL-2,
3-day admission,
5 doses
Thank you very much!

* They are both in college.