Summary of 2nd line trials and beyond

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“2\textsuperscript{nd} line and beyond” Regimens in RCC – Historical Perspective

2006:
- Sorafenib
- Sunitinib

2015:
- Sunitinib
- Sorafenib
- Pazopanib
- Axitinib
- Everolimus
- Cabozantinib
- Lenvatinib + Everolimus
- Nivolumab

Until 2018:
- 1L: Temsirolimus
- 1L: Sunitinib
- 2L: Axitinib
- 2L: Everolimus + Lenvatinib
- 2/3L: Nivolumab
- 1L: Cabozantinib
- 2L+: Cabozantinib
RCC Treatment Landscape – Recent Emphasis on 1st line / Adjuvant Space

1L: Sorafenib
1L: Temsirolimus
1L: Pazopanib
1L: Bevacizumab + Inf-α
2/3L: Everolimus
2L+: Cabozantinib
1L: Ipi+Nivo
2L: Axitinib
2L: Nivolumab
3+L: Tivozanib
1L: Lenvatinib
1L: VHL: Belzutifan
1L: Lenvatinib + Pembrolizumab
2L: Cabozantinib
2L: Everolimus
2L: Avelumab + Axitinib
1L: Pembrolizumab
1L: Cabozantinib + Nivolumab
Adjuvant: Pembrolizumab
HD IL-2
VHL: Belzutifan
2022 Kidney Cancer Research Summit

Targeted therapy
IO therapy
Targeted + IO therapy
Phase 3 TIVO-3: Tivozanib & ‘Prior IO’ Subgroup

Primary endpoint: PFS (BICR)
Secondary endpoints: OS, ORR, DOR, and safety

TKI Monotherapy Post IO - **Cabozantinib** on CANTANA

**PFS (IRC): Subgroup of Patients With Prior ICI**

![Graph showing PFS (Progression-Free Survival) probability over time for patients treated with Telaglenastat + Cabozantinib and Placebo + Cabozantinib. The graph includes the number at risk at each time point and the median PFS.](image)

- **Telaglenastat + Cabozantinib**:
  - Median PFS: 11.1 months
- **Placebo + Cabozantinib**:
  - Median PFS: 9.2 months
  - Hazard ratio (95% CI): 0.77 (0.56, 1.06)
  - Log-rank P-value*: 0.1058

**Number at risk**
- Telaglenastat + Cabozantinib: 137
  - 114 at 0 months, 88 at 3 months, 75 at 6 months, 29 at 9 months, 13 at 12 months, 5 at 15 months, 0 at 18 months, 0 at 21 months, 0 at 24 months
- Placebo + Cabozantinib: 139
  - 113 at 0 months, 76 at 3 months, 57 at 6 months, 19 at 9 months, 9 at 12 months, 3 at 15 months, 1 at 18 months, 0 at 21 months, 0 at 24 months

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*Nominal P-value
IO+IO post IO – FRACTION, Track 2 Ipilimumab plus Nivolumab

N = 46

ORR (95% CI), % 15.2 (6.3-28.9)

Complete responses 0

Partial responses (%) 7 (15.2)

Stable disease (%) 17 (37.0)

Progressive disease (%) 15 (32.6)

Not evaluable / available (%) 7 (15.2)

Median follow-up = 21.6 months

modified from: Choueiri, T. ASCO 2020, abstract 5007
TKI+IO post IO – Phase 2 data: Lenvatinib plus Pembrolizumab

Lee CH et al., Lancet Oncol 2021
Ongoing efforts
CONTACT-03 – ongoing Phase 3 study

- Histologically confirmed advanced, metastatic ccRCC or non-ccRCC
- Radiographic progression during or following ICI treatment
- ICI in adjuvant setting permitted

Atezolizumab IV 1200 mg q3w + Cabozantinib po 60 mg qd

Treatment until unacceptable toxicity or loss of clinical benefit

Stratification factors
- IMDC risk group (0 vs 1-2 vs ≥ 3)
- Most recent ICI (1L vs 2L)
- Histology (dominant cc without sarcomatoid vs dominant non-cc [papillary or unclassified] without sarcomatoid vs any sarcomatoid component [cc or non-cc])

Primary endpoints
- IRF-assessed PFS and OS

Additional endpoints
- INV-assessed PFS, IRF- and INV-assessed ORR and DOR, per RECIST 1.1
- HRQoL, biomarkers and safety

N ≈ 500

1L, first-line; 2L, second-line; ccRCC, clear cell renal cell carcinoma; DOR, duration of response; HRQoL, Health-related quality of life; IMDC, International Metastatic RCC Database Consortium; INV, investigator; IRF, independent review facility; RECIST, Response evaluation criteria in solid tumors
TiNivo2 – ongoing Phase 3 study

- Recurrent/metastatic ccRCC
- Failed one or two prior regimen
- Prior IO exposure
- No more than 1 prior TKI

**Tivozanib**
0.89mg qd 3wk/1wk
plus **Nivolumab**
480mg FLAT q28d

**Tivozanib 1.34mg**
qd 3wk/1wk

Treatment until unacceptable toxicity or loss of clinical benefit

**Stratification factors**
- IO given immediately prior (y/n)
- IMDC prognostic score

**Primary endpoints**
- PFS

**Additional endpoints**
- OS, ORR, DoR, Safety

TKI, tyrosine kinase inhibitor; ccRCC, clear cell renal cell carcinoma; DOR, duration of response; IO, immune oncology therapy IMDC, International Metastatic RCC Database Consortium; INV, investigator; IRF, independent review facility; RECIST, Response evaluation criteria in solid tumors
HIF2 inhibitor containing approaches in pre-treated patients

- Metastatic ccRCC
- Prior treatment w PD1/L1i
- Prior treatment w VEGFi
- Max 3 prior lines
- NCT04195750

Phase 3

R 1:1

N = 736

Belzutifan 120mg qd

Everolimus 10mg qd

Co-Primary endpoints
- PFS
- OS

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HIF2 inhibitor containing approaches in pre-treated patients

**Phase 3**
- Metastatic ccRCC
- Prior treatment w PD1/L1i
- Prior treatment w VEGFi
- Max 2 prior lines
- NCT04195750

**Co-Primary endpoints**
- PFS
- OS

**N = 708**

- Belzutifan 120mg qd
- Everolimus 10mg qd
- Cabozantinib 60mg qd

**Phase 3**
- Metastatic ccRCC
- Prior treatment w PD1/L1i
- Max 3 prior lines
- NCT04195750

**Co-Primary endpoints**
- PFS
- OS

**N = 736**

- Belzutifan 120mg qd + Lenvatinib 20mg qd
- Everolimus 10mg qd
HIF2 inhibitor containing approaches in pre-treated patients

**Phase 2**
- Metastatic ccRCC
- 2+ prior lines
- Prior TKI, prior IO – combo or sequence
- NCT05468697

**Belzutifan + Palbociclib**

*Dose Exploration*

- Belzutifan 120mg qd
- Belzutifan + Palbociclib

- Primary endpoints
  - Safety
  - ORR

- N ≈ 180

**Phase 3**
- Metastatic ccRCC
- Prior treatment w PD1/L1i
- Prior treatment w VEGFi
- Max 3 prior lines
- NCT04195750

**Belzutifan 120mg qd**

- Everolimus 10mg qd
- Cabozantinib 60mg qd

- Co-Primary endpoints
  - PFS
  - OS

- N ≈ 736

**Phase 3**
- Metastatic ccRCC
- Prior treatment w PD1/L1i
- Max 2 prior line
- NCT04586231

**Belzutifan 120mg qd + Lenvatinib 20mg qd**

- Co-Primary endpoints
  - PFS
  - OS

- N ≈ 708

**Phase 3**
- Metastatic ccRCC
- Prior treatment w PD1/L1i
- NCT04195750

**Belzutifan 120mg qd**

- Everolimus 10mg qd
- Cabozantinib 60mg qd

- Co-Primary endpoints
  - PFS
  - OS

- N ≈ 736
Adaptive Design 1\textsuperscript{st} -> 2\textsuperscript{nd} line: Phase 3 PEDIGREE study
Building Level-1 Evidence for Sequencing:

**PAST**

**PRESENT**

**? FUTURE**
Sequencing Approved Agents in RCC
Expanding our Toolkit

2006:
- Sorafenib
- Sunitinib

2015:
- Sorafenib
- Sunitinib
- Pazopanib
- Axitinib
- Everolimus

2022:
- IO TKI
- HIF
- 2a
- TKI
- TOR
- C
- IO
- IO
- Adj TKI
- TOR
- KI
- Adj TKI
In Summary:

• There currently is no well-defined standard for the treatment of IO-exposed patients, 2\textsuperscript{nd}+ line; common practice is off-label use of approved regimens.

• Ongoing efforts in Ph3 development:
  
  • Theme 1): sequencing TKI/IO combinations

  • Theme 2): integrating novel agents: HIF2i

  • Theme 3): adaptive approaches
Thank you