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Genitourinary Oncology
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Riverview – Brandon Healthplex -- TGH
• Recognize available therapies for the treatment of kidney cancer
• Discuss important factors needed to make personalized selections of treatments in different clinical contexts
Kinds of kidney cancer
Kinds of medications
A few biomarkers
Initial medical therapy of advanced disease
VEGF medications
PD-1 combinations
mTOR
HIF2
Checkpoint inhibition
Nephrectomy decisions
Adjuvant treatments
Challenges in clinical practice
Summary and what's next?
Kinds of kidney cancer
Different RCC subtypes

Papillary type 1
Papillary type 2
Clear cell, Fuhrman grade 2

Areas of pleomorphic, atypical spindled cells arising from clear cell RCC. (grade 4)
[Daniel Anderson, M.D., M.B.A.]
https://www.pathologyoutlines.com/topic/kidneytumorMalignantRCCsarcoma.html

*courtesy* Jasreman Dhillon
Many other recognized subtypes:

Clear cell type is about 75% of renal cancers

100% of the pivotal trials for RCC medications were 100% clear cell type

Fuhrman grade 1-2-3-4 helps define the histologic pattern

<table>
<thead>
<tr>
<th>Renal cell tumours</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell renal cell carcinoma</td>
<td>8310/3</td>
</tr>
<tr>
<td>Multilocular cystic renal neoplasm of low malignant potential</td>
<td>8316/1*</td>
</tr>
<tr>
<td>Papillary renal cell carcinoma</td>
<td>8260/3</td>
</tr>
<tr>
<td>Hereditary leiomyomatosis and renal cell carcinoma–associated renal cell carcinoma</td>
<td>8311/3*</td>
</tr>
<tr>
<td>Chromophobe renal cell carcinoma</td>
<td>8317/3</td>
</tr>
<tr>
<td>Collecting duct carcinoma</td>
<td>8319/3</td>
</tr>
<tr>
<td>Renal medullary carcinoma</td>
<td>8510/3*</td>
</tr>
<tr>
<td>MiT family translocation renal cell carcinomas</td>
<td>8311/3*</td>
</tr>
<tr>
<td>Succinate dehydrogenase–deficient renal carcinoma</td>
<td>8311/3</td>
</tr>
<tr>
<td>Mucinous tubular and spindle cell carcinoma</td>
<td>8480/3*</td>
</tr>
<tr>
<td>Tubulocystic renal cell carcinoma</td>
<td>8316/3*</td>
</tr>
<tr>
<td>Acquired cystic disease–associated renal cell carcinoma</td>
<td>8316/3</td>
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<tr>
<td>Clear cell papillary renal cell carcinoma</td>
<td>8323/1</td>
</tr>
<tr>
<td>Renal cell carcinoma, unclassified</td>
<td>8312/3</td>
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<tr>
<td>Papillary adenoma</td>
<td>8260/0</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>8290/0</td>
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</table>
Kinds of medications
**Types of medications:**

<table>
<thead>
<tr>
<th>Targets:</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF</td>
</tr>
<tr>
<td>VEGFR1 * VEGFR2 VEGFR3</td>
</tr>
<tr>
<td>PDGFR alpha</td>
</tr>
<tr>
<td>PDGFR beta * C-MET * AXL</td>
</tr>
<tr>
<td>FGFR1 * FGFR2 * FGFR3 FGFR4</td>
</tr>
<tr>
<td>HIF2 alpha mTOR</td>
</tr>
</tbody>
</table>

| VEGF chelation: |
| Bevacizumab |

| Small molecule inhibitors of TKs: |
| **SUFFIX**: “-inib” |
| Axitinib |
| Cabozantinib (+c-met, +axl) |
| Lenvatinib (+ fgfr) |
| Pazopanib |
| Sorafenib (- vegfr1) |
| Sunitinib |
| Tivozanib |

| HIF2 alpha inhibition |
| Belzutifan |

| mTOR inhibition |
| Everolimus |
| Temsirolimus |

| Immunotherapy |
| IL-2 receptor |
| PD-1 |
| CTLA-4 |

| Human antibodies |
| **SUFFIX**: -umab |

| Lymphocyte drugs: |
| **-l- umab** or: **-leuk-** |

| Interleukin-2 |
| Nivolumab (PD-1) |
| Pembrolizumab (PD-1) |
| Avelumab (PD-L1) |

| Ipilimumab (CTLA4) |
Key up-front clear cell RCC treatment combinations
(with positive phase III studies vs monotherapy with sunitinib)

* Axitinib + pembrolizumab (OS and PFS)
* Lenvatinib + pembrolizumab (OS and PFS)
* Cabozantinib + nivolumab (OS and PFS)
* Ipilimumab + nivolumab (OS and PFS, but only intermediate/high risk category)

Lenvatinib and everolimus. (Better than sunitinib; not better than lenvatinib + pembrolizumab)

Other phase III trials:
Axitinib + avelumab (PFS only)
Atezolizumab (PD-L1) + bevacizumab (VEGF)

* Key contemporary options—More on these later
A few biomarkers
RCC biomarkers

**PD-L1:**
Adverse marker for VEGF response (!)

Not much higher overall response rate with PD-1 axis medications.

Not used to select for PD-1 therapy
RCC biomarkers

**PD-L1:**
Adverse marker for VEGF response (!)

Not much higher overall response rate with PD-1 axis medications.

Not used to select for PD-1 therapy
RCC biomarkers

Von Hippel-Lindau protein: pVHL

Always present as defect in clear cell RCC

Typically, one mutation and one deletion

Familial VHL syndrome: Inborn first knock-out mutation.

Edeline, Julien & Vauléon, Dr & Rioux-Leclercq, Pr & Perrin, Dr & Vigneau, Pr & Bensalah, Karim & Laguerre, Dr & Edeline,. (2012). Safety and Efficacy of Sorafenib in Renal Cell Carcinoma. Cancer Growth and Metastasis. 5. 35. 10.4137/CGM.S7526.
RCC biomarkers

Blocked pVHL

No degradation of HIF2alpha

More expression of VEGF
TGF-alpha
PDGF-beta
Erythropoietin
GLUT-1 (glucose transporter-1)

Edeline, Julien & Vauléon, Dr & Rioux-Leclercq, Pr & Perrin, Dr & Vigneau, Pr & Bensalah, Karim & Laguerre, Dr & Edeline, . (2012). Safety and Efficacy of Sorafenib in Renal Cell Carcinoma. Cancer Growth and Metastasis. 5. 35. 10.4137/CGM.S7526.
RCC biomarkers

Adverse:
clear cell
P53
BAP-1

papillary
P53
PBRM-1

chromophobe
PTEN

The Cancer Genome Atlas Comprehensive Molecular Characterization of Renal Cell Carcinoma
CJ Ricketts et al. Cell Reports 23, 313–326, April 3, 2018
RCC biomarkers

Clear-code34 ccA vs ccB type signature
Blocked pVHL

**No** degradation of HIF2alpha

TKI drugs:
- VEGF-R (r1-r2-r3)
- PDGF-R (-α and -β)
- C-MET
- AXL
- FGFR (-1-2-3-4)

Edeline, Julien & Vauléon, Dr & Rioux-Leclercq, Pr & Perrin, Dr & Vigneau, Pr & Bensalah, Karim & Laguerre, Dr & Edeline,. (2012). Safety and Efficacy of Sorafenib in Renal Cell Carcinoma. Cancer Growth and Metastasis. 5. 35. 10.4137/CGM.S7526.
Angiogenic TKI targets – as the tumor grows, the blood supply is stimulated and integrated.
Angiogenic TKI targets – after VEGF is blocked:
Initial medical therapy of advanced disease

VEGF medicines
Antiangiogenesis drugs: &gt;&gt;8&lt;&lt; on-label, for RCC

**Antibodies binding VEGF-A**
- bevacizumab

**Block VEGFR1/2/3 and other targets**
- cabozantinib (& C-MET, AXL)
- lenvatinib (& FGFR [more])
- pazopanib ( & FGFR)

**Block VEGFR1/2/3**
- axitinib
- sorafenib
- sunitinib
- tivozanib

And HIF-2 alpha:
- belzutifan
**Antiangiogenesis drugs: Dose comparisons**

**Antibodies binding VEGF-A**
- bevacizumab 10 mg/kg/dose, q 2 weeks

**Block VEGFR1/2/3**
- axitinib 5 mg po BID
- sorafenib 200 mg x2 = 400 mg po BID
- sunitinib 50 mg po, x 28 d/14 off; or 14/7 (also available in 12.5, 25, 37.5)
- tivozanib 1.34 mg po x 21 d/ 7 off (also available 0.89)

**Block VEGFR1/2/3 and others**
- cabozantinib
  - 60 mg/d (monotherapy)
  - 40 mg/d (combination)
  - 20 mg also available.
- lenvatinib
  - 20 mg (or 18, or 14) po qD (comes in 10 & 4 mg sizes)
- pazopanib
  - 200 mg x4 = 800 mg po qD
Antiangiogenesis drugs: Typical side effects

- Diarrhea
- Hypertension
- Hypothyroidism
- Appetite less
- Fatigue
- Nausea
- Stomatitis

- Dysphonia/hoarseness
- Weight loss
- Hand/foot syndrome
- Joint pain
- Rash
- Dysgeusia

**Management**
- Interrupt
- Wait for resolution
  - Axitinib half life: 2-6 h
  - Lenvatinib 28h
  - Pazopanib 30h
  - Sorafenib 25-40 h
  - Sunitinib 40-60h & N-desethyl sunitinib: 80-100.
  - Cabozantinib 120h
  - Tivozanib 4.5-5.1 days
  - Bevacizumab ~ 20 days
- Re-challenge:
  - Lower doses (on label)
  - Planned breaks (e.g. weekends)
PD-1 combinations
Two trials with combination that didn’t meet OS improvement.

4 trials with combination superior to sunitinib.

VEGF:
- cabozantinib
- lenvatinib
- pazopanib
- sorafenib
- sunitinib
- axitinib
- tivozanib
- bevacizumab

PD-1 & PD-L1:
- nivolumab
- pembrolizumab
- avelumab
- atezolizumab
- ipilimumab

CTLA-4
4 trials with combination superior to sunitinib.

- **CLEAR trial.** Lenvatinib plus pembrolizumab or everolimus [vs sunitinib]
  - Motzer et al. NEJM 2021 384:1289-1300

- **Checkmate 9ER.** Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma
  - Choueiri et al. NEJM 2021 Mar 4;384(9):829-841
4 trials with combination superior to sunitinib.

Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma [only intermediate and high risk] Motzer et al. NEJM 2018; 378:1277-1290

- **Favorable risk:** none
- **Intermediate:** 1 – 2
- **High (poor):** 3 - 5:

Karnofsky PS below 80
< 12 months since diagnosis
Hgb under LLN
LDH > 1.5 ULN
Corrected calcium > 10 mg/dL

ULN == upper limit of normal

PFS: difference less than OS. First 6 months: no difference
4 trials with combination superior to sunitinib.


Favorable risk:

“not significantly worse”

Smaller group of patients

Only counting responders

DURATION OF RESPONSE

Overall survival

Intermediate-high

Only counting responders
4 trials with combination superior to sunitinib.

Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma
Motzer et al. NEJM 2019 Mar 21;380(12):1103-111

OS : not positive yet.

PFS results positive:

Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma
Rini et al. NEJM 2019 Mar 21;380(12):1116-1127

Overall Population

Stratified hazard ratio for disease progression or death, 0.69 (95% CI, 0.56–0.84) P<0.001
Progression-free Survival (95% CI)

- Avelumab+Axitinib: 13.8 (11.1–NE) mo
- Sunitinib: 8.4 (6.9–11.1)

Alive (%)

Hazard ratio for death, 0.53 (95% CI, 0.38–0.74) P<0.0001

Alive and Free from Disease Progression (%)

Hazard ratio for disease progression or death, 0.69 (95% CI, 0.57–0.84) P<0.001
mTOR
TOR: Yeast TOR target of rapamycin

Rapamycin was discovered from *streptococcus hydroscopicus* in soil of Rapa Nui, aka Easter Island, 1964 METEI (Medical Expedition to Easter Island).


What about mTOR?

- Mammalian Target of Rapamycin (mTOR)

Eukaryotic life on this planet depends on mTOR: Don’t inhibit it too much

mTOR in kidney cancer therapy

mTOR medications
• ORR rate: low
• PFS, OS: improved

Everolimus
• 10 mg/d monotherapy (inferior to nivolumab)
• 5 mg everolimus with 18 mg/d lenvatinib

Temsirolimus
• 25 mg IV weekly, in high risk patients

Rare subtype:
Malignant perivascular epithelioid cell tumors (PEComas)
• rare malignant mesenchymal neoplasms TSC1 or TSC2 mutations (leading to mTOR activation)
• Treated with sirolimus; or nab-sirolimus

HIF2
Hypoxia inducible factor
Targeting HIF-2 alpha: Belzutifan

- On label for inherited VHL syndrome
- Off label for post-VEGF RCC
- Many studies, including adjuvant treatment

Belzutifan
120 mg/d
40 mg tablets

Multiple bilateral tumors
CT reconstruction view.

https://www.ctisus.com/teachingfiles/kidney/339265
(Case 6825)
Targeting HIF-2 alpha: Belzutifan


- Smaller tumors
- Fewer procedures
Targeting HIF-2 alpha: Belzutifan


- Frequent moderate anemia
- Rare high-grade problems

![Graph showing hemoglobin levels over time for Men and Women](image)

**A few B-based RCC trials:**

- B monotherapy
- B + lenvatinib
- B + pablociclib*  
  [* not approved in RCC]

**ALL ARE INVESTIGATIONAL COMBINATIONS**

- Cabozantinib vs B + lenvatinib
- Adjuvant pembrolizumab +/- B
- Lenvatinib/pembrolizumab  
  Alone [on-label] vs +B, vs + Quavonlimab*  
  [* investigational CTLA4 medication]

**Most frequent adverse events**

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Grade</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>55 (90)</td>
<td>24 (39)</td>
<td>26 (43)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>40 (66)</td>
<td>29 (48)</td>
<td>8 (13)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Headache</td>
<td>25 (41)</td>
<td>20 (33)</td>
<td>5 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>24 (39)</td>
<td>20 (33)</td>
<td>4 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>21 (34)</td>
<td>15 (25)</td>
<td>6 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>14 (23)</td>
<td>13 (21)</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12 (20)</td>
<td>10 (16)</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>12 (20)</td>
<td>10 (16)</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>12 (20)</td>
<td>9 (15)</td>
<td>2 (3)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>
Checkpoint inhibitors
IL2 receptor:
  low affinity: T-effector
  high affinity: T-reg; NK

PD-1: on lymphocyte
PD-L1: on target cell

CTLA-4: on lymphocyte
  interacts with dendritic cell

“RCC ipi-nivo 1-3”:
  ipi 1 mg/kg/dose, nivo 3 mg/kg/dose x 4
“melanoma ipi-nivo 3-1”
  ipi 3 mg/kg/dose, nivo 1 mg/kg/dose x 4
... and then nivolumab monotherapy

Immune checkpoint inhibitor side effects.

All PD-1 therapies – across all diagnoses:
Risks, with early or delayed latency:

*Every organ system is at risk*

**Respiratory:**
- Pneumonitis
- Respiratory depression

**GI:**
- Diarrhea, colitis, GI bleeding
- Jaundice, nausea, vomiting
- Constipation
- Abdominal pain
- Pancreatitis

**Endocrine**
- Thyroiditis
- Hypopituitary
- Hypoadrenal
- Testosterone

**Renal**
- Creatinine elevation
- Nephritis

**Skin**
- Dry rash
- Itching
- Blistering rash

**Central nervous system**
- Headache
- RPLS

**Musculoskeletal**
- Myasthenia-like syndrome
- Arthritis
- Myositis

**Cardiac**
- Carditis
- Heart-conduction
- Tachycardia

<table>
<thead>
<tr>
<th>Nivolumab plus Ipilimumab</th>
<th>Any Grade</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number of patients (percent)</td>
<td></td>
</tr>
<tr>
<td>All events</td>
<td>509 (93)</td>
<td>250 (46)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>202 (37)</td>
<td>23 (4)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>154 (28)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>145 (27)</td>
<td>21 (4)</td>
</tr>
<tr>
<td>Rash</td>
<td>118 (22)</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>109 (20)</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Increased lipase level</td>
<td>90 (16)</td>
<td>56 (10)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>85 (16)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>75 (14)</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>72 (13)</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>59 (11)</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>Anemia</td>
<td>34 (6)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>31 (6)</td>
<td>0</td>
</tr>
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</table>
Null hypothesis <45% ORR

**CLINICAL RESULTS: Phase 2 trial result pembrolizumab and IL-2 (not on-label)**

Summary mechanisms

ANGIOGENESIS

GROWTH STIMULATION

TUMOR METABOLISM

IMMUNE ACTIVATION
Building on immunotherapy

Breaking T cell exhaustion:
Nephrectomy decisions
Now
Maybe later
Maybe never
• Papillary type 2
• Liver dominant
T4 (duodenal invasion)

- Bleeding 1-3 units/week
- XRT (kidney too)
- Neoadjuvant sunitinib
- Surgery
- Off treatment
- NED + 19 months
Nephrectomy Now?

- Projected reserve of remaining kidney is good.
  - Creatinine level
  - Differential renal scan
- No general medical contraindication to surgery
  - Recent MI; new stents
  - Pulmonary reserve
- No other identifiable dominant disease
  - COPD
  - Dementia
- No evident other disease: Going for cure
- Possible partial nephrectomy?
**Nephrectomy **maybe later?


Randomize

nephrectomy \(\rightarrow\) sunitinib

sunitinib

nephrectomy sometimes (17%)

**CARMENA trial:**
55% intermediate
45% high-risk

**Survival evaluations**

**Intermediate and high risk**

Conclusion: Not much advantage to up-front nephrectomy.

... and then sunitinib lost about 6 consecutive trials.

(vs lenvatinib/everolimus, vs cabozanitinb, vs ipilumimab-nivolumab, vs cabozantinib-nivolumab, vs axitinib-pembrolizumab, vs lenvatinib/pembrolizumab)
Nephrectomy later?

- Extent of other disease:
  Balance of renal vs extrarenal tumor burden after up-front medical therapy

8 months treatment:
  - cabozantinib
  - nivolumab

& 3 months more, then nephrectomy (and partial colectomy, and lymphadenectomy):
No extrarenal disease on scan or in specimen. No remaining visible disease.
Nephrectomy, maybe never?

- Projected reserve of remaining kidney is good.
  - Creatinine level
  - Differential renal scan

- Low (under 80%) fractional debulking; balance of renal vs extrarenal tumor burden after up-front medical therapy

- Age of patient vs size of mass, natural growth rate.
  - Cardiac, pulmonary reserve
  - Pulmonary reserve

- Downstage to a cryotherapy or partial nephrectomy?
Adjuvant treatments

Successes

Trials with no benefit

Ongoing trials
**Adjuvant treatments**

**Successes**
- Trials with no benefit
- Ongoing trials

**Yes (PFS): (no OS)**
- S-TRAC
- Sunitinib 12mo vs NOT

**Yes (OS, PFS)**
- Keynote 564
- Pembrolizumab x12 mo vs NOT

**NO:**
- Vaccines (several: Reniale; Vitespen)
- Interferon
- Interleukin-2
- Interferon with IL-2
- Cytokines with 5-FU
- Sunitinib (ASSURE)
- Sorafenib (ASSURE)
- Pazopanib (PROTECT)
- Axitinib (ATLAS)
- Ipilimumab-nivolumab
- Atezolizumab
Yes (PFS): (no OS)  
S-TRAC  
Sunitinib 12mo vs NOT

Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy


A. Ravaud, R.J. Motzer, H.S. Pandha, D.J. George, A.J. Pantuck, A. Patel,  
Y.-H. Chang, B. Escudier, F. Donskov, A. Magheli, G. Carteni, B. Laguerre,  
P. Tomczak, J. Breza, P. Gerletti, M. Lechuga, X. Lin, J.-F. Martini, K. Ramaswamy,  
M. Casey, M. Staehler, and J.-J. Patard, for the S-TRAC Investigators*

OS:  
deaths reported:  
64 patients sunitinib group  
64 (20.9%) in placebo group
NO: ASSURE
Sunitinib vs placebo
Sorafenib vs placebo

1 year:
Sorafenib 400 mg po BID (+ placebo)
Sunitinib 50 mg/d (28 on/ 14 off) (+ placebo)
Placebo + placebo

Yes (OS, PFS)
Keynote 564
Pembrolizumab x12 mo vs NOT

Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

Lancet Oncol 2022; 23: 1133–44

<table>
<thead>
<tr>
<th>Type of nephrectomy</th>
<th>Partial</th>
<th>Radical</th>
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<tbody>
<tr>
<td></td>
<td>37 (7%)</td>
<td>459 (93%)</td>
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<tr>
<td></td>
<td>38 (8%)</td>
<td>460 (92%)</td>
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<table>
<thead>
<tr>
<th>Primary tumour stage</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
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<tbody>
<tr>
<td></td>
<td>11 (2%)</td>
<td>27 (5%)</td>
<td>444 (90%)</td>
<td>14 (3%)</td>
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<tr>
<td></td>
<td>15 (3%)</td>
<td>33 (7%)</td>
<td>437 (88%)</td>
<td>13 (3%)</td>
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<table>
<thead>
<tr>
<th>Tumour nuclear grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td></td>
<td>19 (4%)</td>
<td>153 (31%)</td>
<td>219 (44%)</td>
<td>103 (21%)</td>
</tr>
<tr>
<td></td>
<td>16 (3%)</td>
<td>150 (30%)</td>
<td>213 (43%)</td>
<td>119 (24%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metastatic stage</th>
<th>M0</th>
<th>M1 with no evidence of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>467 (94%)</td>
<td>29 (6%)</td>
</tr>
<tr>
<td></td>
<td>469 (94%)</td>
<td>29 (6%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease risk category</th>
<th>M0 intermediate to high</th>
<th>M0 high</th>
<th>M1 with no evidence of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>427 (86%)‡</td>
<td>40 (8%)</td>
<td>29 (6%)</td>
</tr>
<tr>
<td></td>
<td>433 (87%)</td>
<td>36 (7%)</td>
<td>29 (6%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sarcomatoid features</th>
<th>Present</th>
<th>Absent</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>52 (10%)</td>
<td>414 (83%)</td>
<td>30 (6%)</td>
</tr>
<tr>
<td></td>
<td>59 (12%)</td>
<td>415 (83%)</td>
<td>24 (5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PD-L1 combined positive score</th>
<th>&lt;1</th>
<th>≥1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>124 (25%)</td>
<td>365 (74%)</td>
</tr>
<tr>
<td></td>
<td>113 (23%)</td>
<td>383 (77%)</td>
</tr>
</tbody>
</table>

Thomas Powles, Peter Tomczak, Se Hoon Park, Babji Vemugopad, Thomas Ferguson, Stefan N Symeonides, Jaroslav Hajek, Howard Gurney, Yen-Hwa Chang, Jae Lynn Lee, Navroz Sarver, Antoine Thiery-Vigliet, Marine Gross-Goupil, Mauricio Mahase, Naomi B Haz, Peter Sawyck, Joseph E Burgents, Li Xu, Kenzaro Imai, David Quinn, Tore K Chouvet, for the KEYNOTE-564 Investigators.*
Yes (OS, PFS)
Keynote 564
Pembroizumab x12 mo vs NOT

Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

Lancet Oncol 2022; 23: 1133–44

Thomas Powles, Pietro Tomczak, Se Hoan Park, Babaji Venugopal, Thomas Ferguson, Stefan N Symeonides, Jaroslav Hajek, Howard Gimney, Yen-Hwa Chang, Jae Lynn Lee, Naved Sarwar, Antoine Thiery-Vuillermoz, Marine Gross-Goupil, Mauricio Mahade, Naomi B Haz, Pietro Sawyck, Joseph E Burgents, Le Xu, Kentaro Imai, David Quinn, Terri K Chevets, for the KEYNOTE-564 Investigators

[Graph showing disease-free survival and hazard ratio between pembrolizumab and placebo.]
Adjuvant nivolumab and ipilimumab vs placebo (CheckMate 914)

6 months:
nivolumab 240 q2 w + Ipilimumab 1 mg/kg/dose q6w (vs None)

- pT2a (G 3 or 4); or
- pT2b, pT3, pT4; N0M0; or
- pT (any) N1 M0

>>All were M0<<

- Adverse events:
  - G3+: 28.5% vs 2.0%

Motzer et al. Adjuvant nivolumab plus ipilimumab versus placebo for localised renal cell carcinoma after nephrectomy (CheckMate 914): a double-blind, randomised, phase 3 trial. *THE LANCET: VOLUME 401, ISSUE 10379, P821-832, MARCH 11, 2023*

DFS was not met (HR, 0.92; 95% CI, 0.71–1.19; P = 0.5347)
Adjuvant atezolizumab vs placebo (IMmotion 010)

Atezolizumab 1200 mg, q3w x 1 year.

- T2 G4;
- T3a Gr 3/4;
- T3b/c or T4
- TxN+
- M1 resected with no evidence of disease

- Adverse events:
  - G3+: 27% vs 21%

Pal et al.  Adjuvant atezolizumab versus placebo for patients with renal cell carcinoma at increased risk of recurrence following resection (IMmotion010): a multicentre, randomised, double-blind, phase 3 trial

THE LANCET VOLUME 400, ISSUE 10358, P1103-1116, OCTOBER 01, 2022

DFS was not met (0.93, 95% CI 0.75-1.15, p=0.50)
Adjuvant conclusions:

- Trials are long
- Huge amount of resources
- Disease are heterogenous

More studies: Same general format

>>>Use selectively <<<
Challenges in clinical practice
Challenges in practice:
A lot of issues are not covered in clinical trials:

Brain lesions

• At presentation vs at recurrence
• How often to scan
• Surgery or radiation immediately
• Medical treatment and close re-evaluation
Challenges in practice:
A lot of issues are not covered in clinical trials:

Restarting after good response

- Debulking nephrectomy
- Nephrectomy for cure after initial treatment
- Anatomically isolated site of progression—can it be resected, irradiated, embolized and then stay on the same treatments?
Challenges in practice:
A lot of issues are not covered in clinical trials:

Choosing which VEGF drug to take next
• Cabozantinib: Also targets C-MET, AXL
• Lenvatinib: Also targets FGFR
• Axitinib: Very short half life
• Tivozanib: Trial specific to third line treatment
• Bevacizumab: low intensity ascites control
Challenges in practice:
A lot of issues are not covered in clinical trials:

Histology factors
- Sarcomatoid: Better difference with ipilimumab-nivolumab
- Papillary: No specific trials
- Chromophobe: No specific trials; lenvatinib-everolimus appeared good in a part of a single-arm trial
- Rare subtypes – all extrapolations
- Nephrectomy decisions for not-clear-cell cases
Summary and what’s next?
Summary and future directions

- Trials emphasize first-line treatment two-part PD-1 combinations
  - Most people take these
  - No practical ranking among them

- Single agent therapies are active
  - Mulityear responses are a regular occurrence.

- PD-1 and lymphocyte target medications: Benefit for most
- VEGFR medications: Major contribution to RCC
- Belzutifan targeted therapy: Some differences to VEGF treatment; may be something to overlap; trials are in progress.
Summary and future directions

• Treatment decisions should be individualized
• Trials don’t seem to capture patient nuances

• Sequencing these remains largely a heuristic endeavor

• T cell function—many ways to affect it
  • Reversing exhaustion
  • T cell drugs
  • Microbiome factors

Thank you!