Combine and conquer — antiangiogenic immunotherapy

Anti-angiogenesis combined with immunotherapeutics

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I have received education grants, provided consultation, attended advisory boards and/or provided lectures for the following organizations, from whom I have received honoraria:

- **Consultation / Advisory role:** Abbvie, Amgen, AstraZeneca, Bayer, Biocartis, Bioinvent, Blueprint Medicines, Boehringer-Ingelheim, Bristol-Myers Squibb, Clovis, Daiichi Sankyo, Debiopharm, Eli Lilly, F. Hoffmann-La Roche, Foundation Medicine, Illumina, Janssen, Merck Sharp and Dohme, Merck Serono, Merrimack, Novartis, Pharma Mar, Pfizer, Regeneron, Sanofi, Seattle Genetics and Takeda

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AGENDA

- Rational for anti-angiogenesis and IO combinations
- Lung cancer paradigm: from phase 1 to phase 3 trials
- Combinatorial advances in RCC
- Ongoing efforts in early clinical trials across diseases
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Cellular constituents of immune escape within the tumour microenvironment

- Tumor masses contain regulatory lymphocytes, myeloid derived suppressor cells, alternatively activated macrophages, and dendritic cells
- Immune cells in tumors are dysregulated and functionally impaired
- Ablation or reprogramming of this aberrant microenvironment might dramatically augment cancer therapies
VEGF expression is driven by the tumour and is also an HIF-dependent pro-angiogenic factor, in the context of cancer hypoxic niches.
Mechanisms of action of anti-angiogenic therapies

Failure in the development of biomarkers, including angiogenic biomarkers

Effects on cancer cell

Hypoxia and effects on vasculature

Effects on the stroma
VEGF blockade induces antitumor immune response, increases T cell homing and improves vaccine therapy

- DC101: monoclonal antibody for VEGFR2
- DC101 inhibits tumor growth, decreases angiogenesis, and increases apoptosis within tumors of mice
- Combining DC101 with neu-specific vaccination accelerated tumor regression

Manning et al, Clin Ca Res, 2007
Dramatic inhibition of lymphocyte adhesion on activated endothelial cells following either short or long VEGF pretreatments.
VEGF-A induced FasL expression on endothelial cells, which acquired the ability to kill CD8+ T cells, but not Tregs

-> VEGF and PGE2 blockade reduce endothelial FasL and increase in the influx of tumor-rejecting CD8+ over FoxP3+ T cells.
- Endothelial activation with increased lymphocyte and myeloid/monocyte cell trafficking into tumor deposits
- Peripheral blood circulating memory T cells count was increased resulting from the addition of bevacizumab
In Summary

Angiogenic factors and immune response

- Angiogenic factors impair lymphocyte trafficking across endothelia

- VEGF has profound effects on cancer immunity
  - By inhibiting dendritic cell maturation and antigen presentation
  - By inhibiting T-cell responses (upregulation PD-L1, PD-L2, IDO-1, IL-6, IL-10...)
  - By inducing proliferation of regulatory T cells
  - By favoring accumulation of myeloid-derived suppressor cells
Pharmas’ schemes
Effects of bevacizumab and atezolizumab on key VEGF and immune parameters

10 patients with metastatic RCC

Biopsy at 3 time points

Wallin et al Nat Comm 2016
Pharmas’ schemes (2)

Immune suppressive tumor microenvironment

Monocyte

PD-L1 expressed on tumor cells activate PD-1 and suppressed CTL

Cancer

TAM

VEGF CSF

MHC Antigen

TCR

PD-L1

PD-1

TGF-β

Treg

Immune Inhibitory Cytokine (TGF-β)

Immune Inhibitory Receptor (PD-1, Lag3)

Immune Stimulatory cytokine (IL12)

TAM secretes TGF-β, which activates immune suppressive Treg and inhibits cytotoxic T cells.

Lenvatinib (VEGF blockade)

Decrease

Immune Inhibitory Cytokine (TGF-β)

Down

Immune Inhibitory Receptor (PD-1, Lag3)

Down

Immune Stimulatory cytokine (IL12)

Up

Improved antitumor activity of anti-PD-1 therapy

Monocyte

Cancer

Attack

PD-1 Ab

MHC Antigen

TCR

IFNγ

CTL

Lenvatinib causes Immune stimulating tumor microenvironment

Kato et al., EORTC-NCI-AACR 2015

Kato et al., AACR 2017
AGENDA

- Rational for anti-angiogenesis and IO combinations
- Lung cancer paradigm: from phase 1 to phase 3 trials
- Combinatorial advances in RCC
- Ongoing efforts in early clinical trials across diseases
• Lung cancer is characterized by a strongly immunosuppressive environment

• We have been enrolling thousands of patients in strictly negative vaccine trials

• Lung tumors display ~200 nonsynonymous mutations per tumor. Lung cancers from smokers have 10 times more mutations

• Checkpoint blockade is active in selected NSCLC patients only – and resistance is our ceiling

Vogelstein, Science 2013
Lawrence, Nature 2013
Bevacizumab with platinum-based chemotherapy
Pooled Analysis in NSCLC

**Antiangiogenic Agents in 2\textsuperscript{nd} Line?**

**LUME-LUNG 1 Trial\textsuperscript{1}: Docetaxel +/- nindetanib (VEGFR TKI)**
- PFS (primary endpoint)

- **D+N - Med PFS 3.4 m [95\% CI 2.9-3.9]**
- **D - Med PFS 2.7 m [2.6-2.8]**
- **HR (95\% CI) = 0.79 (0.68-0.92)**
- **P = .0019**

**REVEL Trial\textsuperscript{2}: Docetaxel +/- ramucirumab (VEGFR2 Ab)**
- OS (primary endpoint)

- **OS benefit in SCC and non SCC**
- **OS benefit in adenocarcinoma**

*PFS benefit in first-line refractory patients (HR= 0.67 [0.43-1.04], P = .0725)*

VEGFR, vascular endothelial growth factor receptors
Pembrolizumab + ramucirumab in NSCLC

Lung-MAP ongoing phase 2 trial in IO-resistance
Nintedanib + docetaxel after anti PD(L)-1 in NSCLC

ICI, immune checkpoint inhibitor; ND, not documented; PD, progressive disease; PR, partial response; SD, stable disease.

*Single-agent nintedanib treatment ongoing; § Previous therapies not documented.

<table>
<thead>
<tr>
<th>Best response</th>
<th>n (%)</th>
<th>N=12</th>
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<tbody>
<tr>
<td>Partial response</td>
<td>7 (58)</td>
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<tr>
<td>Stable disease</td>
<td>3 (25)</td>
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<tr>
<td>Disease control rate</td>
<td>10 (83)</td>
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</tbody>
</table>
Nintedanib + docetaxel after anti PD(L)-1 in NSCLC

- Median PFS*: 5.5 months (95% CI 1.9–8.7)

**Conclusion:**
- Consistent evidence of the clinical benefit of nintedanib plus docetaxel, in terms of:
  - PFS
  - Response rate

**Notes:**
- CI, confidence interval; PFS, progression-free survival.
- *n=21: 10 patients had disease progression, four patients had died, and seven patients had been censored.
- Data not yet available for one patient.

Grobé, ELCC 2019
Lenvatinib and pembrolizumab in IO naive (KEYNOTE-146)

Lenvatinib is more effective in immune competent mice in HCC model

Combination antitumor activity in combination with lenvatinib and mice anti-PD-1 Ab in CT26 mice model

Immune deficient mice

Immune competent mice

Relative tumor volume

Days

Tumor volume (mm³)

Days

Immune cell profiling

Kato et al., EORTC-NCI-AACR 2015
Kato et al., AACR 2017
Lenvatinib and pembrolizumab in IO naive (KEYNOTE-146)

Primary end point: ORR_{Week24} 33% (95% CI: 14.6–57.0)
Multi-steps immune simulation
Sitravatinib/nivolumab in IO resistant NSCLC

Sitravatinib (MGCD516) TKI

• TAM family (AXL and MER)
  - Target cellular IC50: 1nM.
• Split family RTKs (VEGFR2, PDGFRα and KIT)
  - Target cellular IC50: 5-10 nM.
• RET, MET, DDR2, TrkA
  - Target cellular IC50: 10-25 nM.
MRTX-500 Clinical Activity
Preliminary Maximum Response in NSCLC Patients Who Failed Prior Checkpoint Therapy by Best Response
(CIT-Experienced Cohorts – Clinical Activity Evaluable Patients, N=56)

Study cycles of 28 days, with disease assessment scans every 2 cycles
Data as of 27-Aug-2018

45/56 Tumor Regression
18/56 Tumor Regression >30%
16/56 CR/PR
9 confirmed
2 yet to be confirmed and on study
5 will not be confirmed
Diversity of inhibitors in multiple tyrosine kinase pathways researched in I-O–experienced NSCLC

<table>
<thead>
<tr>
<th>Ligands</th>
<th>Receptors</th>
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<tr>
<td>Bevacizumab</td>
<td>VEGF-A, VEGF-R2</td>
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<tr>
<td>Ramucirumab</td>
<td>VEGF/PIGF, VEGFR</td>
</tr>
<tr>
<td>Sitravatinib*</td>
<td>FGF, FGFR</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>PDGF, PDGFR</td>
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<tr>
<td>Nintedanib†</td>
<td>SCF, KIT</td>
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<td>GDNF, RET</td>
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<td>Gas6/Pros1, TAM</td>
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</table>

* Additional targets of sitravatinib include DDR2, Ephs, MET, and TRK; †Additional targets of nintedanib include Src, Lck, Lyn, and FLT-3

X = binding leading to inhibition of signal transduction

Borghaei, ELCC 2019
Impower 150 trial design

Stage IV or recurrent metastatic nonsquamous NSCLC
Chemotherapy-naive
Tumor tissue available for biomarker testing
Any PD-L1 IHC status

Stratification factors:
- Sex
- PD-L1 IHC expression
- Liver metastases

N = 1202

Arm A
Atezolizumab$^b$ + Carboplatin$^c$ + Paclitaxel$^d$
4 or 6 cycles

Maintenance therapy (no crossover permitted)

Arm B
Atezolizumab$^b$ + Carboplatin$^c$ + Paclitaxel$^d$
+ Bevacizumab$^g$
4 or 6 cycles

Atezolizumab$^b$

Arm C (control)
Carboplatin$^c$ + Paclitaxel$^d$
+ Bevacizumab$^g$
4 or 6 cycles

Bevacizumab$^g$

Treated with atezolizumab until PD per RECIST v1.1 or loss of clinical benefit

AND/OR

Treated with bevacizumab until PD per RECIST v1.1

Survival follow-up
Carboplatin/paclitaxel/atezolizumab/bevacizumab is superior to carbo/pacli/bev irrespective of PD-L1 (IMpower150)

**Arm A**
- Atezolizumab\(^b\) + Carbo\(^e\) + Paclitaxel\(^d\)
- 4 or 6 cycles

**Arm B**
- Atezolizumab\(^b\) + Carbo\(^e\) + Paclitaxel\(^d\) + Bevacizumab\(^a\)
- 4 or 6 cycles

**Arm C (control)**
- Carbo\(^e\) + Paclitaxel\(^d\) + Bevacizumab\(^a\)
- 4 or 6 cycles

<table>
<thead>
<tr>
<th>Landmark OS, %</th>
<th>Arm B: atezo + bev + CP</th>
<th>Arm C: bev + CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-month</td>
<td>67%</td>
<td>61%</td>
</tr>
<tr>
<td>18-month</td>
<td>53%</td>
<td>41%</td>
</tr>
<tr>
<td>24-month</td>
<td>43%</td>
<td>34%</td>
</tr>
</tbody>
</table>

**Overall Survival (%)**

**Median, 14.7 mo**
- (95% CI: 13.3, 16.9)

**Median, 19.2 mo**
- (95% CI: 17.0, 23.8)

**HR, 0.78**
- (95% CI: 0.64, 0.96)
- \(P = 0.0164\)

Median follow-up: ~20 mo
OS in EGFR-mt patients (Arm B vs Arm C)

(Arm A vs Arm C)

HR 0.61 (0.29–1.28)

HR 0.93 (0.51–1.68)

Median, 18.7 mo (95% CI: 13.4, NE)

Median, 21.4 mo (95% CI: 13.8, NE)

Reck, ELCC 2019
IMPower 130: Investigator-assessed PFS and OS in EGFR/ALK+

**PFS (%)**
- Median: 7.0 mo
- Median: 6.0 mo
- HR: 0.75 (95% CI: 0.36, 1.54)

**OS (%)**
- Median: 14.4 mo
- Median: 10.0 mo
- HR: 0.98 (95% CI: 0.41, 2.31)
Is bevacizumab the game changer?

Combined VEGFR/EGFR pathway blockade may be beneficial in the presence EGFR mutation

Immune modulation in poorly immunogenic tumour?

Naumov et al, CCR 2009 (Heymach Group)
Anti-VEGF antibody inhibits IL-6/IL-6R regulation of VEGF.
Neither inhibition of PI3K or MAPK inhibits IL-6 mediated transcriptional up-regulation of VEGF.

Wei et al. Oncogene 2003
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# Anti-angiogenesis and IO in RCC: early trials

<table>
<thead>
<tr>
<th>Combination</th>
<th>Line of therapy</th>
<th># patients</th>
<th>ORR (% CR/% PR)</th>
<th>DCR (CR/PR/SD)</th>
<th>mPFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib</td>
<td>1st line</td>
<td>55</td>
<td>58% (6/52)</td>
<td>78%</td>
<td>N/A</td>
</tr>
<tr>
<td>Axitinib + Avelumab</td>
<td>1st line</td>
<td>52</td>
<td>67% (4/63)</td>
<td>88%</td>
<td>N/A</td>
</tr>
<tr>
<td>Pazopanib + Pembrolizumab</td>
<td>1st line</td>
<td>10</td>
<td>60% (20/40)</td>
<td>100%</td>
<td>N/A</td>
</tr>
<tr>
<td>Lenvatinib + Pembrolizumab</td>
<td>Post-VEGF</td>
<td>30</td>
<td>63% (0/63)</td>
<td>96%</td>
<td>N/A</td>
</tr>
<tr>
<td>Lenvatinib + Pembrolizumab</td>
<td>1st line</td>
<td>12</td>
<td>83% (0/83)</td>
<td>100%</td>
<td>N/A</td>
</tr>
<tr>
<td>Bevacizumab + Atezolizumab</td>
<td>1st line</td>
<td>101</td>
<td>32% (7/25)</td>
<td>N/A</td>
<td>11.7 mo</td>
</tr>
<tr>
<td>Cabozantinib + Ipilimumab</td>
<td>Post-SOC (GU: UC, RCC, others)</td>
<td>42</td>
<td>33% (8/25)</td>
<td>83%</td>
<td>5.8 mo</td>
</tr>
</tbody>
</table>

N/A: Not available
SOC: Standard of Care

Atkins M et al, ESMO 2016
McDermott D et al, GU ASCO 2017
Choueiri TK et al, ASCO 2017
Chowdhury S et al, ASCO 2017
Lee C et al, ESMO 2017
Nadal R et al, ESMO 2017
Axitinib in combination with pembrolizumab in patients with advanced renal cell cancer: a non-randomised, open-label, dose-finding, and dose-expansion phase 1b trial

Michael B Atkins, Elizabeth B Plimack, Igor Puzanov, Mayer N Fishman, David F McDermott, Daniel C Chu, Lilka Vainshaugans, Saby George, Thomas E Olesick, Jamali C Tanaj, Brad Rossbrook, Katherine C Fernandez, Marijose Lechaga, Toni K Choueiri

Preliminary results for avelumab plus axitinib as first-line therapy in patients with advanced clear-cell renal-cell carcinoma (JAVELIN Renal 100): an open-label, dose-finding and dose-expansion, phase 1b trial

Toni K Choueiri, James Larkin, Mototsugu Oya, Fiona Thirdehwaiza, Marcella Martinoni, Paul Nathan, Thomas Powles, David McDermott, Paul R Robbins, David D Chou, Daniel Chu, Michael B Atkins, Michael J Gordon, Suresh Gopila, Hirotsugu Uemura, Yoshihiko Tomita, Anna Compagnoni, Camilla Fould, Alessandra di Pietro, Brian I Rini
Lenvatinib and pembrolizumab in RCC

KEYNOTE-146
LENVIMA + KEYTRUDA FOR TREATMENT OF PATIENTS WITH aRCC

RR 70%

ALMOST ALL PATIENTS (N=29) EXPERIENCED TUMOR REDUCTION FROM BASELINE

Makker, ASCO 2018
Key eligibility criteria:
- Treatment-naive aRCC with a clear cell component
- ≥ 1 measurable lesion as defined by RECIST v1.1
- Tumor tissue available for PD-L1 staining
- ECOG PS 0 or 1

Stratification:
- ECOG PS (0 vs 1)
- Geographic region (USA vs Canada/Western Europe vs ROW)

Avelumab 10 mg/kg IV Q2W + Axitinib 5 mg PO BID (6-week cycle)

Sunitinib 50 mg PO QD (4 weeks on, 2 weeks off)

N = 886

R 1:1

BID, twice per day; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; PO, orally; Q2W, every 2 weeks; QD, once per day; ROW, rest of the world.
PFS PER IRC IN THE PD-L1+ GROUP

<table>
<thead>
<tr>
<th></th>
<th>Median PFS (95% CI), months</th>
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<tbody>
<tr>
<td>Avelumab + Axitinib</td>
<td>13.8 (11.1, NE)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>7.2 (5.7, 9.7)</td>
</tr>
</tbody>
</table>

Stratified HR, 0.61 (95% CI: 0.475, 0.790)  
\( P < .0001 \)

Minimum follow-up, 6 months. Median follow-up, 9.9 months (avelumab + axitinib) and 8.4 months (sunitinib).  
The PFS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (\( P = .001 \)).  

NE, not estimable.
PFS PER IRC IN THE OVERALL POPULATION

Minimum follow-up, 6 months. Median follow-up, 10.8 months (avelumab + axitinib) and 8.6 months (sunitinib).

The PFS analysis crossed the prespecified efficacy boundary based on the alpha-spending function ($P = .001$).

<table>
<thead>
<tr>
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<th>Median PFS (95% CI), months</th>
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<tr>
<td>Avelumab + Axitinib</td>
<td>13.8 (11.1, NE)</td>
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<tr>
<td>Sunitinib</td>
<td>8.4 (6.9, 11.1)</td>
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<tr>
<td>Stratified HR</td>
<td>0.69 (95% CI: 0.563, 0.840)</td>
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<td>$P = .0001$</td>
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Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Avel + Axit</th>
<th>Sunitinib</th>
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Minimum follow-up, 6 months. Median follow-up, 10.8 months (avelumab + axitinib) and 8.6 months (sunitinib).

The PFS analysis crossed the prespecified efficacy boundary based on the alpha-spending function ($P = .001$).
Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma

- Treatment naive, locally advanced or metastatic RCC
  - N = 305

  Stratification:
  - Prior nephrectomy
  - PD-L1 IHC expression (≥ 5% IC level)
  - MSKCC risk category

  **R**: 1:1:1

  First-line treatment
  - Atezolizumab 1200 mg IV + bevacizumab 15 mg/kg q3w
  - Atezolizumab 1200 mg IV q3w
  - Sunitinib 50 mg (4 wk on, 2 wk off)

  **PD**
  - Atezolizumab + bevacizumab
  - Atezolizumab + bevacizumab

  - Crossover treatment permitted

**The coprimary endpoints are PFS (RECIST v1.1 by IRF) in ITT and PD-L1+ patients**
IMmotion150: IRF-Assessed PFS

Atezolizumab + bevacizumab
Atezolizumab
Sunitinib

**Atezo:** 6.1 mo (5.4, 13.6)
**Sunitinib:** 8.4 mo (7.0, 14.0)
**Atezo + bev:** 11.7 mo (8.4, 17.3)

<table>
<thead>
<tr>
<th></th>
<th>Stratified HR (95% CI)</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezo + bev vs sunitinib</td>
<td>1.00 (0.69, 1.45)</td>
<td>0.982</td>
</tr>
<tr>
<td>Atezo vs sunitinib</td>
<td>1.19 (0.82, 1.71)</td>
<td>0.358</td>
</tr>
</tbody>
</table>

No. at Risk
- Atezo + Bev: 101 73 62 55 48 40 34 21 13 6 1 1
- Atezo: 103 59 43 35 31 29 24 14 10 4 2 1
- Sunitinib: 101 69 53 37 30 26 22 11 7 4 2
IMmotion150: IRF-Assessed PFS: PD-L1 positive (IC)

Atezolizumab + bevacizumab

Atezolizumab

Sunitinib

Atezo: 5.5 mo (3.0, 13.9)

Sunitinib: 7.8 mo (3.8, 10.8)

Atezo + bev: 14.7 mo (8.2, 25.1)

<table>
<thead>
<tr>
<th></th>
<th>Stratified HR (95% CI)</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezo + bev vs sunitinib</td>
<td>0.64 (0.38, 1.08)</td>
<td>0.095</td>
</tr>
<tr>
<td>Atezo vs sunitinib</td>
<td>1.03 (0.63, 1.67)</td>
<td>0.917</td>
</tr>
</tbody>
</table>

No. at Risk
Atezo + Bev 50 36 31 26 24 22 19 12 7 3 1 1
Atezo 54 29 19 15 14 13 13 7 6 3 1 1
Sunitinib 60 40 29 21 16 13 12 6 3 1 1
Transcriptome Map of Angiogenesis and Immune-Associated Genes
Renal Cell Carcinoma


Atkins, IMMmotion150 Crossover
**IMmotion151: Trial design**

**Key eligibility**
- Treatment-naive advanced or metastatic RCC
- Clear cell and/or sarcomatoid histology
- KPS ≥ 70
- Tumor tissue available for PD-L1 staining

**Stratification**
- MSKCC risk score
- Liver metastases
- PD-L1 IC IHC status (< 1% vs ≥ 1%)<sup>a</sup>

**N = 915**

**Randomization**
1:1

**Treatment arms**
- Atezolizumab 1200 mg IV q3w + Bevacizumab 15 mg/kg IV q3w
- Sunitinib 50 mg PO QD (4 weeks on, 2 weeks off)

**Co-primary endpoints**
- PFS by INV assessment in PD-L1+
- OS in ITT

**Other key endpoints**
- PFS in ITT
- OS in PD-L1+
- ORR

**Patient-reported outcomes**
- Safety

Motzer, ASCO GU 2018
IMmotion151: PFS in PD-L1 positive

Median PFS, mo (95% CI)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median PFS, mo (95% CI)</th>
<th>HR, 95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezo + Bev</td>
<td>11.2 (8.9, 15.0)</td>
<td>0.74 (0.57, 0.96)</td>
<td>0.02</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>7.7 (6.8, 9.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Motzer, ASCO GU 2018
AGENDA

- Rational for anti-angiogenesis and IO combinations
- Lung cancer paradigm: from phase 1 to phase 3 trials
- Combinatorial advances in RCC
- Ongoing efforts in early clinical trials across diseases
# Anti-angiogenesis and IO trials for advanced HCC

<table>
<thead>
<tr>
<th>Earlier Stages HCC</th>
<th>Advanced-Stage HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line</td>
</tr>
<tr>
<td>Treme + TACE/RF</td>
<td>Ph 1</td>
</tr>
<tr>
<td>Nivo vs Sorafenib</td>
<td>Ph 3</td>
</tr>
<tr>
<td>Atezo +Beva</td>
<td>Ph 1</td>
</tr>
<tr>
<td>Atezo +Beva</td>
<td>Ph 3</td>
</tr>
<tr>
<td>Lenva +Pembro</td>
<td>Ph 1</td>
</tr>
<tr>
<td>Pexa Vec + Soraf vs Soraf</td>
<td>Ph 3</td>
</tr>
</tbody>
</table>

Efficacy data presented
Reminder KEYNOTE-240

Finn, ASCO 2019

Overall Survival

- Events: Pembrolizumab 183, Placebo 101
- HR (95% CI): Pembrolizumab 0.781 (0.611-0.998), Placebo
- Pre-specified p=0.0174 required for statistical significance

PFS and OS: Not statistically significant
Expanding the atezolizumab-bevacizumab opportunity HCC cohort

- **Overall, n (%)**: 23/73 (32)
  - CR: 1/73 (1)
  - PR: 22/73 (30)
- SD: 33/73 (45)
- PD: 13/73 (18)

- **By region, n/n (%)**
  - Asia excluding Japan: 12/41 (29)
  - Japan/USA: 10/31 (32)

- **By aetiology, n/n (%)**
  - HBV: 11/36 (31)
  - HCV: 10/23 (43)
  - Non-viral: 2/14 (14)

- **By baseline AFP, n/n (%)**
  - < 400 ng/mL: 12/41 (29)
  - ≥ 400 ng/mL: 11/27 (41)

- **By EHS/MVI, n/n (%)**
  - EHS and/or MVI: 18/64 (28)
  - MVI negative: 13/32 (41)
  - EHS negative: 9/22 (41)
  - Neither EHS nor MVI: 5/8 (63)
Basket with pembrolizumab-ramucirumab
Lenvatinib and pembrolizumab in endometrial cancer

- **Key Eligibility Criteria**
  - Aged ≥ 18 years
  - Pathologically confirmed and metastatic endometrial carcinoma
  - ≤ 2 Prior systemic therapies
  - Measurable disease by irRECIST
  - ECOG performance status ≤ 1
  - Life expectancy ≥ 12 weeks

- **Phase 2**
  - Open-label, single-arm
  - **Lenvatinib**
    - 20 mg/day (oral)
  - **Pembrolizumab**
    - 200 mg/3 weeks (IV)

- **Primary End Point**
  - ORR_{week 24}

- **Key Secondary End Points**
  - Overall ORR
  - DOR
  - PFS
  - Safety and tolerability

- **ORR 45%**

- **FDA breakthrough designation August 2018**

- **Ongoing cohorts across diseases (3 randomized phase 2 trials in lung)**

Makker, ASCO 2018
Lenvatinib and pembrolizumab across malignancies

Endometrial carcinoma
- Microsatellite instability (MSI) status
  - MSI-high
  - MSI-stable
  - Unknown
- PD-L1 status
  - POS
  - NEG
  - O Unknown
  - Complete response in 3 patients
- Tumor response was observed regardless of PD-L1 and MSI status
- Breakthrough therapy designation granted in July 2018
- ORR$_{Week24}$ = 39.6%

Renal cell carcinoma
- No prior treatment history: 40%
- With prior treatment history: 60%
- PD-L1+: 40.0%
- PD-L1 -: 46.7%
- Unknown: 13.3%
- Tumor response was observed regardless of PD-L1 status or prior treatment history
- Breakthrough therapy designation granted in December 2017
- ORR$_{Week24}$ = 63.3%

Head and neck carcinoma
- No prior treatment history: 9.1%
- With prior treatment history: 90.9%
- HPV$^+$ infection status
  - POS: 27.3%
  - NEG: 31.8%
  - Unknown: 40.9%
- Tumor response was observed in most patients
- Confirmed tumor shrinkage regardless of HPV infection status
- ORR$_{Week24}$ = 36.4%

Hepatocellular carcinoma
- With prior sorafenib treatment history: 13.3%
- Complete response
- ORR = 42.3%
- Tumor response was observed regardless of cause of carcinogenesis

Makker, ASCO 2018
Conclusions

- Rational for anti-angiogenic combination with immunotherapy is very solid and known since 20 years
- This strategy is extensively being explored in RCC, NSCLC, endometrial cancer and HCC, where it will define new standards of care
- Both anti-angiogenic TKIs and anti-VEGF therapies transversally demonstrate interesting signals of activity
- Integration of PD1, PD-L1 and possibly CTLA-4 inhibition have all shown some synergistic activity with anti-angiogenic drugs
Thank you for your attention