Practical Management Pearls for Immunotherapy for the Treatment of Renal Cell Carcinoma

December 17, 2021

11:00 a.m. – 12:00 p.m. ET

sitc Society for Immunotherapy of Cancer

Cancer Immunotherapy GUIDELINES

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The Practical Management Pearls and Case Studies Webinars are part of the Cancer Immunotherapy Clinical Practice Guidelines Advanced Webinar Series supported, in part, by grants from Amgen and Merck & Co., Inc. (as of 9/15/2021)

Webinar faculty

Brian Rini, MD –
Vanderbilt University Medical Center

Expert Panel Chair

Hans Hammers, MD, PhD
– UT Southwestern

Tom Hutson, DO, PharmD
– Charles A. Sammons Cancer Center, Baylor

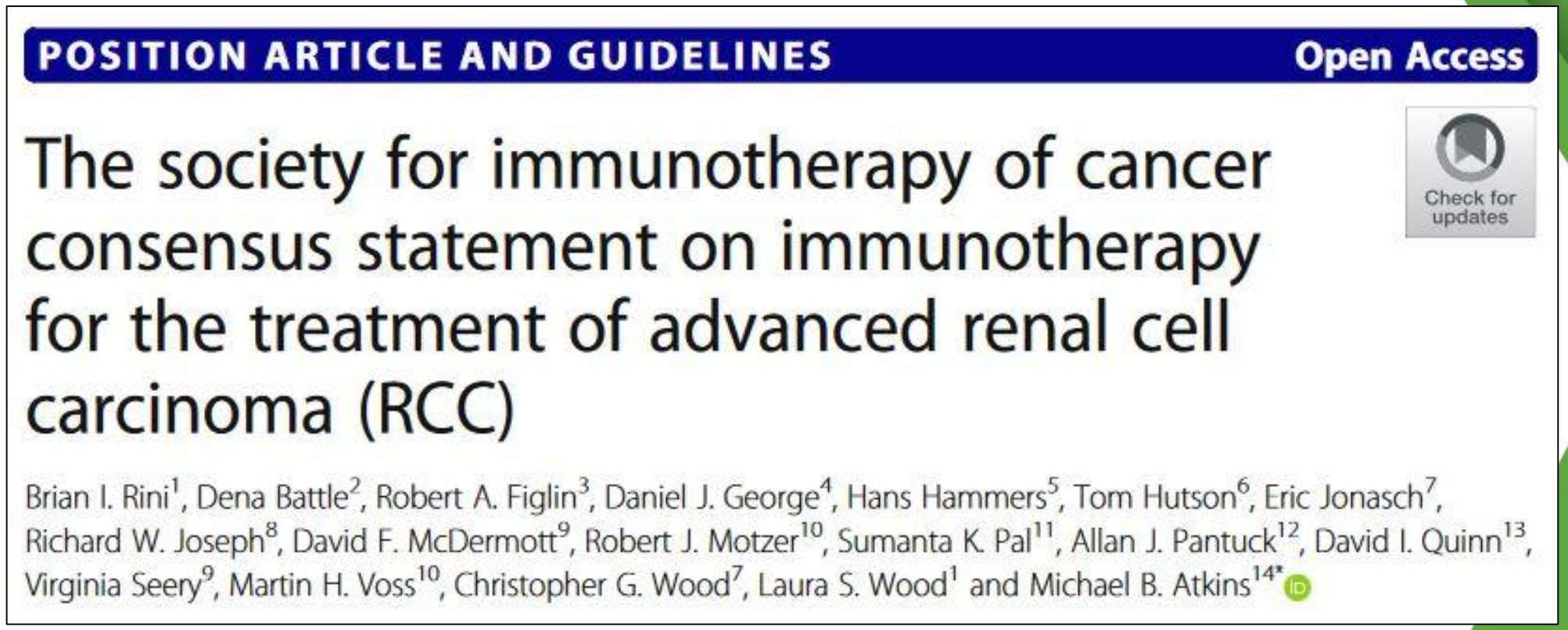
Learning objectives

- Appraise and classify kidney-specific considerations for immunotherapy agents and combinations and associated toxicities/irAEs
- Appropriately manage toxicities/irAEs associated with immunotherapy and combinations in RCC
- Determine optimal sequencing of immunotherapies and combinations for advanced RCC
- Consider the integration of immunotherapies into treatment plans for early-stage RCC

Webinar outline

- Development of the guideline
- Treatment selection – all
- Adjuvant immunotherapy – Dr. Hammers
- Patient selection – Dr. Hutson
- Toxicity – Dr. Hammers
- Emerging data – Dr. Hutson
- Key takeaways

Development of the guideline



POSITION ARTICLE AND GUIDELINES Open Access

The society for immunotherapy of cancer consensus statement on immunotherapy for the treatment of advanced renal cell carcinoma (RCC)

Brian I. Rini[1], Dena Battle[2], Robert A. Figlin[3], Daniel J. George[4], Hans Hammers[5], Tom Hutson[6], Eric Jonasch[7], Richard W. Joseph[8], David F. McDermott[9], Robert J. Motzer[10], Sumanta K. Pal[11], Allan J. Pantuck[12], David I. Quinn[13], Virginia Seery[9], Martin H. Voss[10], Christopher G. Wood[7], Laura S. Wood[1] and Michael B. Atkins[14*]

Development of the guideline

- Developed according to the Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines
- Panel consisted of 18 experts in the field
- Recommendations are based upon published literature evidence, or clinical evidence where appropriate
- Consensus was defined at 75% approval among voting members

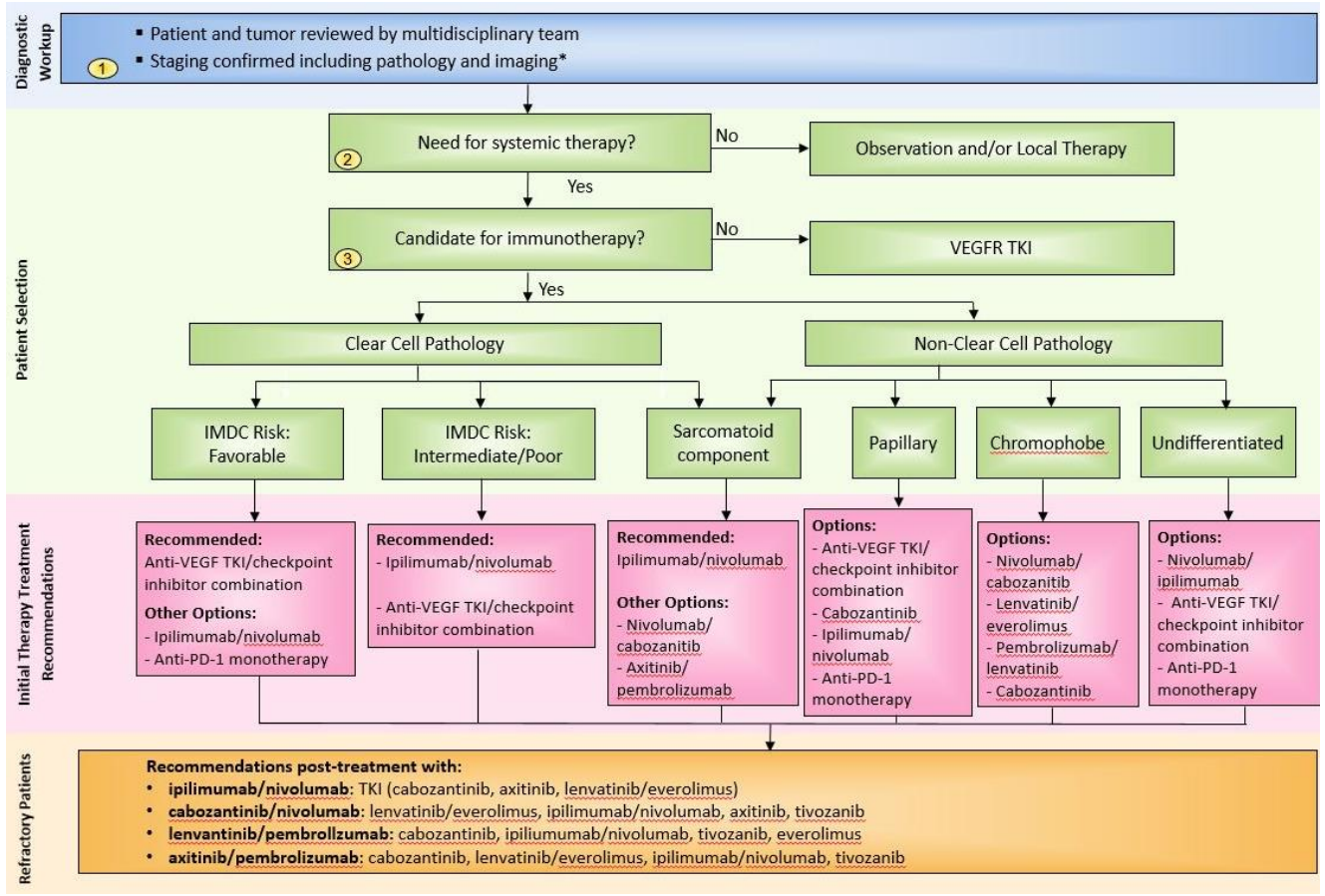
Webinar outline

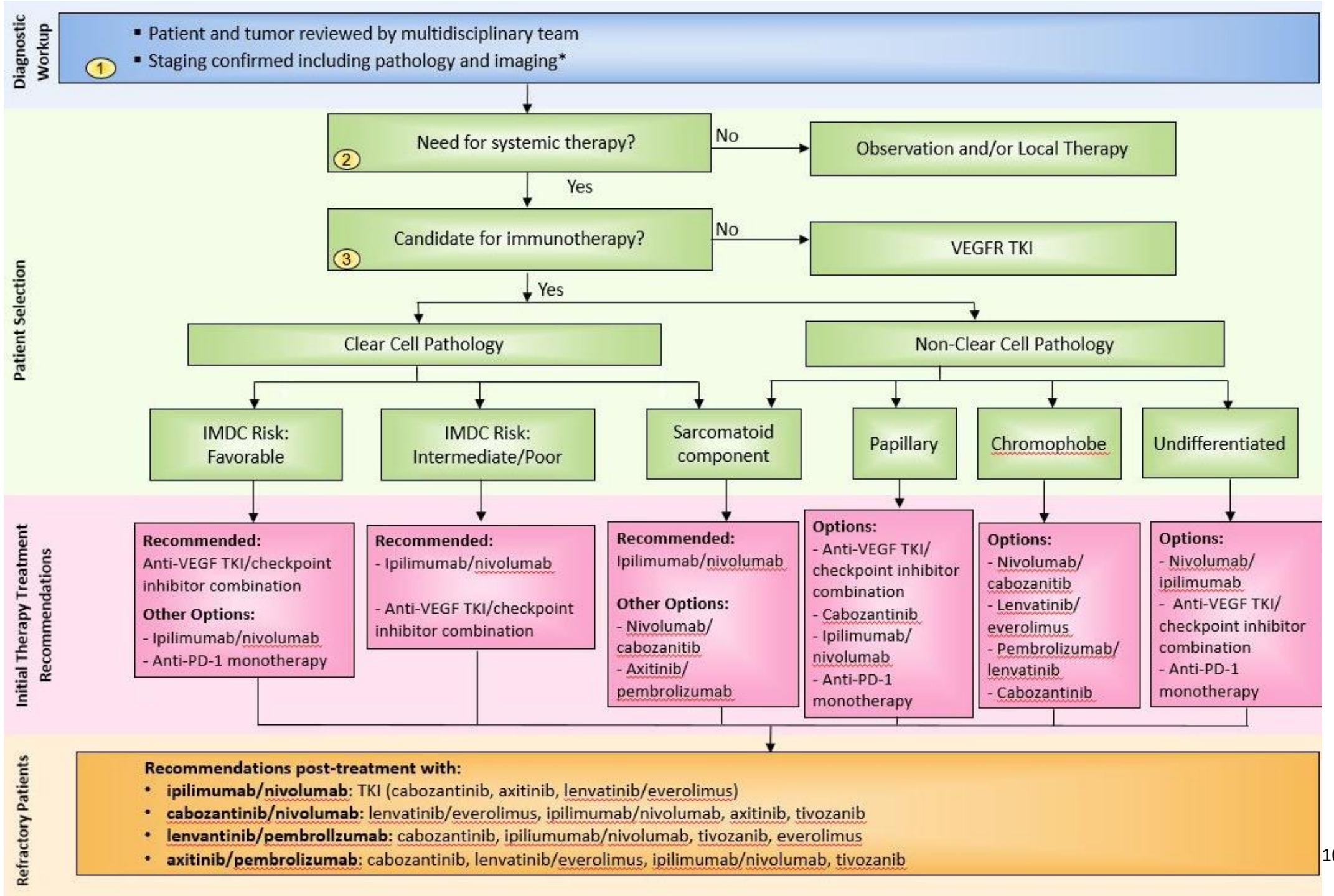
- Development of the guideline
- Treatment selection
- Adjuvant immunotherapy
- Patient selection
- Toxicity
- Emerging data
- Key takeaways

Immunotherapy combinations for first-line treatment of metastatic RCC

	Pembrolizumab + Axitinib	Avelumab + Axitinib	Nivolumab + Ipilimumab	Nivolumab + Cabozantinib	Pembrolizumab + Lenvatinib
Trial	KEYNOTE-426	JAVELIN-01	CheckMate 214	CheckMate 9ER	KEYNOTE-581
Control arm	Sunitinib	Sunitinib	Sunitinib	Sunitinib	Sunitinib
Efficacy population	ITT	ITT	IMDC intermediate/poor-risk	ITT	ITT
PFS (combination vs control arm)	15.4 months vs 11.1 months	13.8 months vs 8.4 months	11.2 months vs 8.3 months	16.6 months vs 8.3 months	23.9 months vs 9.2 months
ORR (combination vs control arm)	60% vs 40%	51.4% vs 25.7%	41.9% vs 26.8%	55.7% vs 27.1%	71% vs 36.1%
OS (combination vs control arm)	Median OS: NR vs 35.7 months; HR = 0.68 24-month OS rates: 74.4% vs 65.5%	Median OS: NE in either arm; HR = 0.8	Median OS: 48.1 months vs 26.6 months; HR = 0.65 4-year OS rates: 50% vs 35.8%	Median OS: NR in either arm; HR = 0.6 12-month OS rates: 85.7% vs 75.6%	Median OS: NR in either arm; HR = 0.66 24-month OS rates: 79.2% vs 70.4%

RCC Immunotherapy Treatment Algorithm




Diagnostic Workup
1
Patient and tumor reviewed by multidisciplinary team
Staging confirmed including pathology and imaging*
Patient Selection
2
Need for systemic therapy?
No
Observation and/or Local Therapy
Yes
3
Candidate for immunotherapy?
No
VEGFR TKI
Yes
Clear Cell Pathology
Non-Clear Cell Pathology
IMDC Risk: Favorable
IMDC Risk: Intermediate/Poor
Sarcomatoid component
Papillary
Chromophobe
Undifferentiated
Initial Therapy Treatment Recommendations
Recommended:
Anti-VEGF TKI/checkpoint inhibitor combination
Other Options:
- Ipilimumab/nivolumab
- Anti-PD-1 monotherapy
Recommended:
- Ipilimumab/nivolumab
- Anti-VEGF TKI/checkpoint inhibitor combination
Recommended:
Ipilimumab/nivolumab
Other Options:
- Nivolumab/ cabozanitib
- Axitinib/ pembrolizumab
Options:
- Anti-VEGF TKI/ checkpoint inhibitor combination
- Cabozantinib
- Ipilimumab/ nivolumab
- Anti-PD-1 monotherapy
Options:
- Nivolumab/ cabozanitib
- Lenvatinib/ everolimus
- Pembrolizumab/ lenvatinib
- Cabozantinib
Options:
- Nivolumab/ ipilimumab
- Anti-VEGF TKI/ checkpoint inhibitor combination
- Anti-PD-1 monotherapy
Refractory Patients
Recommendations post-treatment with:
ipilimumab/nivolumab: TKI (cabozantinib, axitinib, lenvatinib/everolimus)
cabozantinib/nivolumab: lenvatinib/everolimus, ipilimumab/nivolumab, axitinib, tivozanib
lenvantinib/pembrollzumab: cabozantinib, ipiliumumab/nivolumab, tivozanib, everolimus
axitinib/pembrolizumab: cabozantinib, lenvatinib/everolimus, ipilimumab/nivolumab, tivozanib

Expert Panel recommendations for first-line treatment of advanced clear cell RCC*

- In addressing preliminary issues surrounding frontline management of RCC, the Expert Panel recommends initiating systemic therapy first rather than cytoreductive nephrectomy in patients presenting with mRCC with:
  - IMDC poor risk categorization (80%)
  - Brain metastases (67%)
  - Large tumor burden outside primary kidney lesion (60%)

    Note: Cytoreductive nephrectomy is still considered a preferable option for patients with the majority of their tumor burden confined to their primary and no other IMDC risk factors besides presenting with stage IV disease.
- Given the current data, the Expert Panel felt that all patients without a contraindication to immunotherapy should receive an IO-based regimen in the first line.

**Guideline published December 20, 2019. Recommendations updated April 19, 2021.*

Expert Panel recommendations for first-line treatment of advanced clear cell RCC*

- For first-line VEGF TKI + checkpoint inhibitor combination therapy for RCC, the Expert Panel recommends:
  - Lenvatinib + Pembrolizumab (47%)
  - Cabozantinib + Nivolumab (29%)
  - Axitinib + Pembrolizumab (24%)
- For a treatment naïve, ECOG 0 ccRCC patient with "favorable" risk per IMDC, who is determined to need systemic therapy and has no contraindication to receiving either an IO or an anti-VEGF therapy, the Expert Panel recommends:
  - VEGF TKI + checkpoint inhibitor combination (60%):
    - Pembrolizumab + axitinib (18%)
    - Nivolumab + cabozantinib (18%)
    - Pembrolizumab + lenvatinib (24%)
  - Nivolumab + ipilimumab (29%)
  - Pazopanib (6%)
  - Pembrolizumab or nivolumab monotherapy (6%)

**Guideline published December 20, 2019. Recommendations updated April 19, 2021.*

Expert Panel recommendations for first-line treatment of advanced clear cell RCC*

- For a treatment naïve, ECOG 0 ccRCC patient with “intermediate/poor” risk per IMDC, who is determined to need systemic therapy and has no contraindication to receiving either an IO or an anti-VEGF therapy, the Expert Panel recommends:
  - Nivolumab + ipilimumab (77%)
  - VEGF TKI + checkpoint inhibitor combination (23%):
    - Pembrolizumab + lenvatinib (11%)
    - Pembrolizumab + axitinib (6%)
    - Nivolumab + cabozantinib (6%)
- For a treatment naïve, ECOG ≥ 1 ccRCC patient with “poor” risk per IMDC, who is determined to need systemic therapy and has no contraindication to receiving either an IO or an anti-VEGF therapy, the Expert Panel recommends:
  - Nivolumab + ipilimumab (47%)
  - VEGF TKI + checkpoint inhibitor combination (23%):
    - Pembrolizumab + lenvatinib (17%)
    - Pembrolizumab + axitinib (11%)
    - Nivolumab + cabozantinib (11%)
  - Pembrolizumab or nivolumab monotherapy (6%)

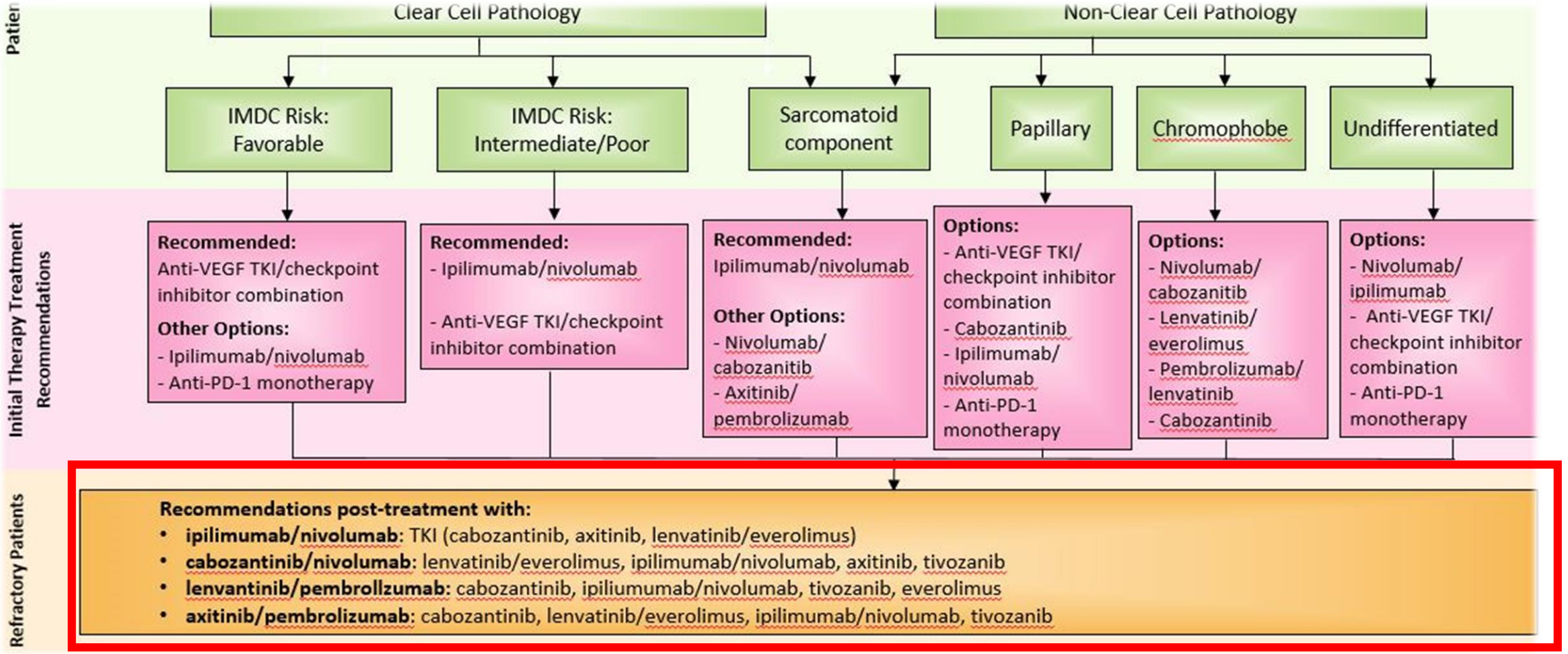
**Guideline published December 20, 2019. Recommendations updated April 19, 2021.*

Expert Panel recommendations for first-line treatment of advanced clear cell RCC*

- In determining when to give a treatment-naïve patient IO monotherapy over an IO-based doublet therapy, the Expert Panel recommends IO monotherapy for:
  - Patients with a history of autoimmune disease that is not potentially life threatening and is not currently on immunosuppressive agents (56%)
  - Elderly patients over 80 years of age (50%)
  - Patients with a history of vascular disease such as stroke, recent ischemic cardiac disease without coronary artery bypass grafting (39%)
  - Patients with poor performance status (28%)
  - Patients with IMDC favorable risk (6%)
  - Patients with liver metastases with mildly increased LFTs (6%)
  - 17% of the Expert Panel would never recommend IO monotherapy over an IO-based doublet therapy.

**Guideline published December 20, 2019. Recommendations updated April 19, 2021.*

Expert Panel recommendations for first-line treatment of advanced clear cell RCC*



**Guideline published December 20, 2019. Recommendations updated April 19, 2021.*

Expert Panel recommendations the treatment of refractory advanced clear cell RCC*

- For patients with accRCC who were previously treated with a VEGFR TKI, the Expert Panel recommends single agent anti-PD-1 immunotherapy based on evidence from CheckMate 025 (Category 1).
- For a previously treated, ECOG 0, clear cell mRCC patient with “favorable” risk whose tumors progressed on front-line therapy with sunitinib, the Expert Panel recommends:
  - Treat with a checkpoint immunotherapy (100%). The Expert Panel was split on the specific treatment recommendations:
    - Ipilimumab plus nivolumab immunotherapy if the patient can tolerate the combination (63%)
    - Nivolumab monotherapy (37%)

  Note: As standard of care shifts to immunotherapy regimens in the first line setting, this situation will be unlikely to occur in the future and the use of VEGFR TKI monotherapy as first-line therapy will be limited to those patients who are perceived to be unable to be receive a checkpoint inhibitor based treatment regimen.
- In treating patients with disease progression after nivolumab/ipilimumab combination therapy, the Expert Panel recommends cabozantinib (72%). Other options are axitinib (22%) or high dose IL-2 (6%).

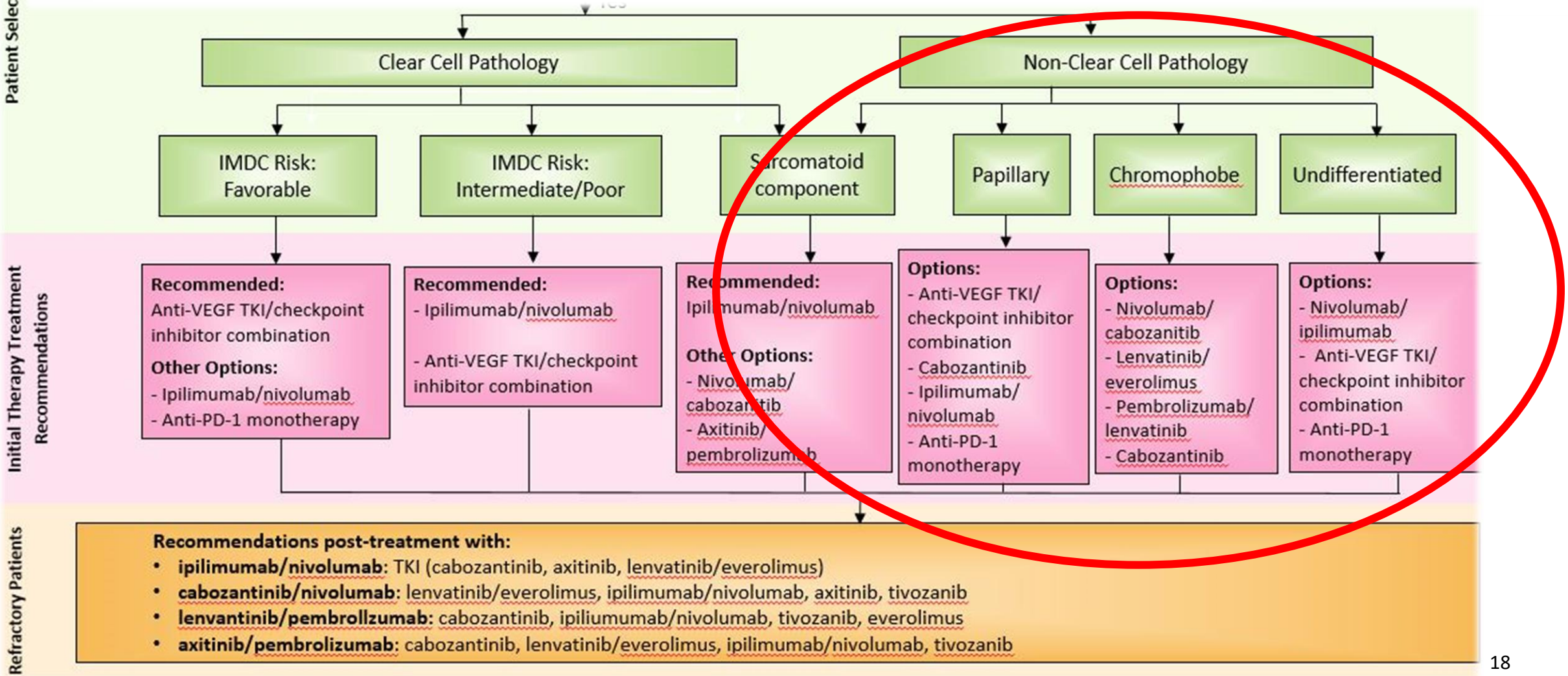
**Guideline published December 20, 2019. Recommendations updated April 19, 2021.*

Expert Panel recommendations the treatment of refractory advanced clear cell RCC*

- For a patient who has progressed after axitinib + pembrolizumab combination therapy, the Expert Panel recommends:
  - Cabozantinib (65%), Lenvatinib + everolimus (23%), Ipilimumab + nivolumab (12%)
- For a patient who has progressed after cabozantinib + nivolumab combination therapy, the Expert Panel recommends:
  - Lenvatinib + everolimus (64%), Ipilimumab + nivolumab (12%), Axitinib (12%), Tivozanib (6%), Clinical trial enrollment (6%)
- For a patient who has progressed after lenvatinib + pembrolizumab combination therapy, the Expert Panel recommends:
  - Cabozantinib (76%), Ipilimumab + nivolumab (12%), Tivozanib (6%), Everolimus (6%)
- The Expert Panel also acknowledged that no data existed for the use of nivolumab/ipilimumab in patients with disease progression on an IO/TKI combination or for the use of an IO/TKI combination in patients with disease progression on front-line nivolumab/ipilimumab, and suggested that clinical trials to obtain such data would be useful.

**Guideline published December 20, 2019. Recommendations updated April 19, 2021.*

Expert Panel recommendations on the treatment of non-clear cell RCC*



**Guideline published December 20, 2019. Recommendations updated April 19, 2021.*

Expert Panel recommendations on the treatment of non-clear cell RCC*

- For first-line treatment for patients with papillary RCC, the Expert Panel recommends:
  - Nivolumab + cabozantinib (35%), Cabozantinib (35%), Nivolumab + ipilimumab (18%), Single agent anti-PD1 (12%)
- For first-line treatment for patients with chromophobe RCC, the Expert Panel recommends:
  - VEGF TKI + checkpoint inhibitor (42%)
    - Nivolumab + cabozantinib (24%), Pembrolizumab + lenvatinib (18%)
  - Lenvatinib + everolimus (41%), Cabozantinib (12%), Sunitinib or pazopanib (6%)

**Guideline published December 20, 2019. Recommendations updated April 19, 2021.*

Expert Panel recommendations on the treatment of non-clear cell RCC*

- For first-line treatment for patients with undifferentiated RCC, the Expert Panel recommends:
  - VEGF TKI + checkpoint inhibitor combination (54%):
    - Nivolumab + Cabozantinib (30%), Pembrolizumab + Lenvatinib (18%), Pembrolizumab + Axitinib (6%)
  - Nivolumab + Ipilimumab (46%)
  - For patients with nccRCC whose disease has progressed on frontline VEGFR TKI, the Expert Panel recommends anti-PD-1 monotherapy with nivolumab (56%) or TKI therapy, specifically cabozantinib (22%).

**Guideline published December 20, 2019. Recommendations updated April 19, 2021.*

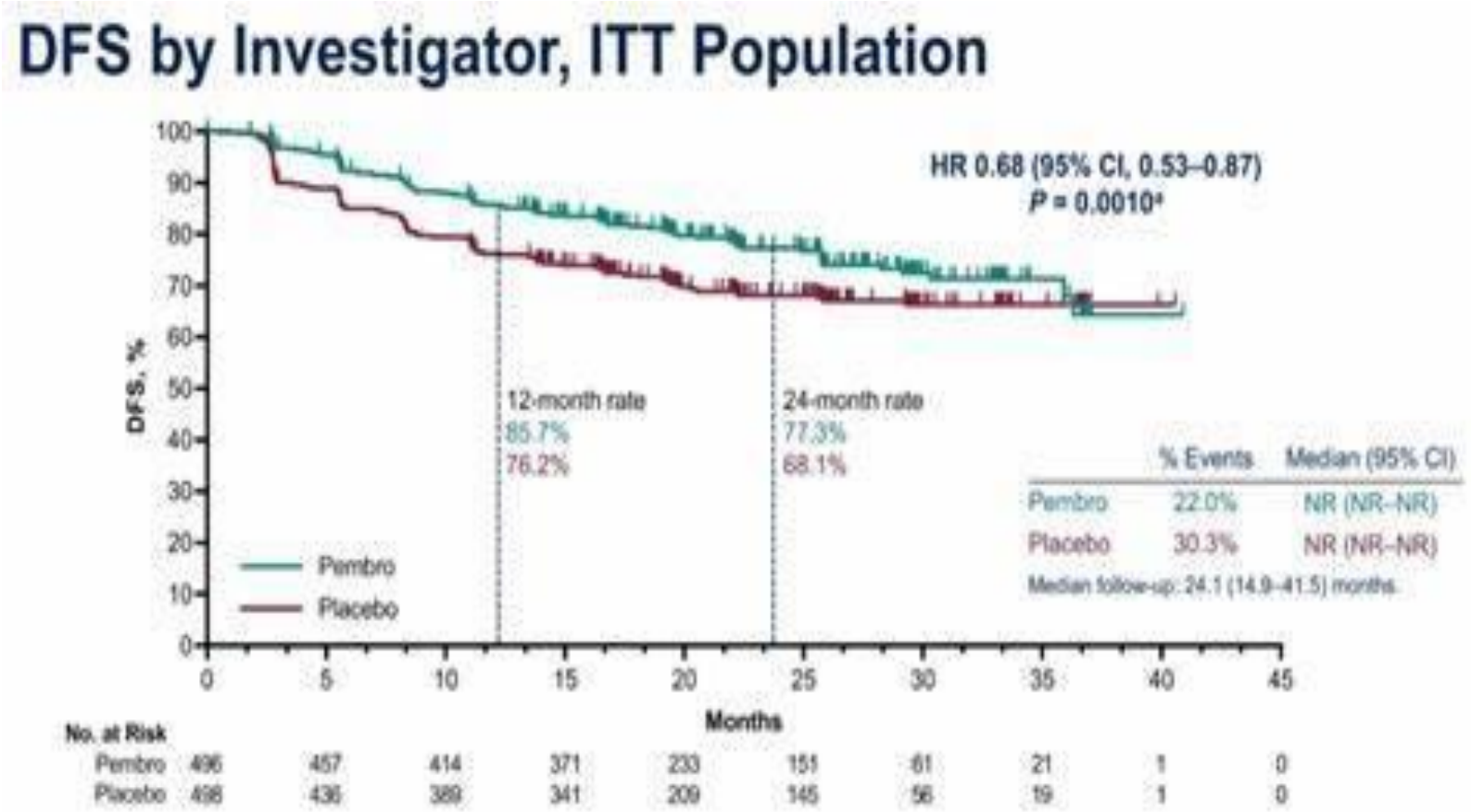
How to selection anti-PD-(L)1 combinations for first-line therapy?

When to add targeted therapy vs immunotherapy?

Webinar outline

- Development of the guideline
- Treatment selection
- Adjuvant immunotherapy
- Patient selection
- Toxicity
- Emerging data
- Key takeaways

KEYNOTE-564 supporting FDA approval of adjuvant pembrolizumab



Webinar outline

- Development of the guideline
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Expert Panel Recommendations on combination therapy in special patient populations

- When determining NOT to give nivolumab/ipilimumab combination therapy in patients with aRCC, the Expert Panel felt that the most influential factors to consider were:
  - History of potentially life threatening autoimmune condition and/or need for immunosuppressive therapy (94%), Poor performance status (50%), Advanced patient age and IMDC risk stratification (39%)
- When determining NOT to give IO/TKI combination therapy in patients with aRCC, the Expert Panel felt that the most influential factors to consider were:
  - History of potentially life threatening autoimmune condition and/or need for immunosuppressive therapy (72%), Recent history of cardiovascular co-morbidities (39%), Advanced patient age (33%), Poor performance status (33%)

Expert Panel Recommendations on combination therapy in special patient populations

- Currently active autoimmune disease requiring medication would be considered a reason not to provide combination immunotherapy to an intermediate/poor risk patient with metastatic RCC (mRCC) (94% Expert Panel agreement). Additionally, the Expert Panel recommends:
  - Do not treat patients receiving steroid dosing (for any reason) > 10 mg per day prednisone or equivalent (75%).
  - Do not recommend excluding patients from treatment due to significant burden/pace of disease requiring rapid tumor burden reduction (56%).
- Specific to VEGFR TKI/checkpoint inhibitor combination therapy, the Expert Panel recommends NOT treating patients with aRCC who:
  - Currently have active autoimmune disease requiring immunosuppressive medication (87%), Require corticosteroid use > 10 mg/d prednisone equivalent (53%), Have poor performance status (20%)

Expert Panel Recommendations on special patient populations

- Specific to checkpoint inhibitor monotherapy, the Expert Panel recommends NOT treating patients with aRCC who:
  - Currently have active autoimmune disease requiring immunosuppressive medication (93%), Require corticosteroid use > 10 mg/d prednisone equivalent (67%)
- For patients with advanced RCC who currently have controlled HIV and/or a history of hepatitis C or B infection, the Expert Panel would NOT recommend AGAINST using checkpoint inhibitor-based therapy (89%).

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Top 3 most common adverse events associated with ICI/TKI combos

	Pembrolizumab + Axitinib	Avelumab + Axitinib	Nivolumab + Cabozantinib	Pembrolizumab + Lenvatinib
Trial	KEYNOTE-426	JAVELIN-01	CheckMate 9ER	KEYNOTE-581
Most Common AEs (any grade)	• Diarrhea • Hypertension • Fatigue	• Diarrhea • Hypertension • Fatigue	• Diarrhea • Palmer-plantar erythrodesia • Hypertension	• Diarrhea • Hypertension • Hypothyroidism
Most common AEs (Grade 3 or higher)	• Hypertension • Elevated ALT • Diarrhea	• Hypertension • Diarrhea • Palmer-plantar erythrodesia	• Hypertension • Diarrhea • Palmer-plantar erythrodesia	• Hypertension • Diarrhea • Fatigue

Open access Position article and guidelines

Journal for ImmunoTherapy of Cancer

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events

Julie R Brahmer,[1] Hamzah Abu-Sbeih,[2] Paolo Antonio Ascierto ,[3] Jill Brufsky,[4] Laura C Cappelli,[5] Frank B Cortazar,[6,7] David E Gerber,[8] Lamya Hamad,[9] Eric Hansen,[10] Douglas B Johnson,[11] Mario E Lacouture,[12] Gregory A Masters,[13] Jarushka Naidoo,[1,14] Michele Nanni,[10] Miguel-Angel Perales,[12] Igor Puzanov,[10] Bianca D Santomasso,[15] Satish P Shanbhag,[5,16] Rajeev Sharma,[10] Dimitra Skondra,[17] Jeffrey A Sosman,[18] Michelle Turner,[1] Marc S Ernstoff [19]

Expert Panel recommendations for immune-related adverse events

- Regarding when to hold IO/TKI combination therapy due to grade 3 toxicity (e.g. diarrhea, LFT abnormalities) that could be from either drug, the Expert Panel recommends:
  - Hold axitinib for 2–3 days to see if toxicity improves (56%)
  - Hold both drugs and give steroids (22%)
  - Hold both drugs to see if toxicity improves (17%)
  - Give steroids and hold the IO component, but continue axitinib (6%)
- Regarding when to hold IO/TKI combination therapy due to any grade irAEs, the Exert Panel was split in their recommendations:
  - Hold axitinib treatment for grade 1 or 2 toxicities (diarrhea, arthritis, LFT abnormalities) to see if they worsen before resuming (60%)
  - Do not hold treatment unless the patient is experiencing a grade 3 toxicity (33%)

Practical pearls for managing immunotherapy toxicity

Initial dosing intervals of ICIs

- Pembrolizumab (+ axitinib or lenvatinib) dosing = every 3 or 6 weeks
- Nivolumab (+ ipilimumab or cabozantinib) dosing = every 2 or 4 weeks

Other considerations for immunotherapy regimens

- Lenvatinib + Pembrolizumab – no limiting liver toxicity
- VEGF TKI toxicities are dose-dependent (lenvatinb vs axitinib)
- Ipilimumab + Nivolumab
  - Higher frequency of use of steroids
  - Important to address with patients
  - Ipilimumab can drive specific immune-mediated adverse events (hepatitis, colitis, etc)

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Immunotherapy trials for RCC expected to report outcomes in 2022

Advanced or metastatic RCC

- **COSMIC-313**: Triple combination of cabozantinib + nivolumab + ipilimumab

Adjuvant trials

- **CheckMate 914**: Nivolumab + ipilimumab vs. placebo as adjuvant therapy
- **IMmotion010:** Atezolizumab vs. placebo as adjuvant therapy for 1 year
- **PROSPER RCC:** Perioperative nivolumab vs. nephrectomy alone
- **RAMPART:** Durvalumab monotherapy vs. durvalumab + tremelimumab vs. no intervention (active monitoring) as adjuvant therapy for 1 year

Society for Immunotherapy of Cancer

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https://www.sitcancer.org/CPG-webinars

Case Studies in Immunotherapy for the Treatment of Renal Cell Carcinoma

January 20, 2021, 11 a.m. – 12 p.m. ET

Case Studies in Immunotherapy for the Treatment of Hepatocellular Carcinoma

January 10, 2021, 6:30 – 7:30 p.m. ET

Practical Management Pearls for Immunotherapy for the Treatment of HNSCC

January 13, 2021, 6:30 – 7:30 p.m. ET

The Practical Management Pearls and Case Studies Webinars are part of the Cancer Immunotherapy Clinical Practice Guidelines Advanced Webinar Series supported, in part, by grants from Amgen and Merck & Co., Inc. (as of 9/15/2021)

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Questions or comments: connectED@sitcancer.org

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