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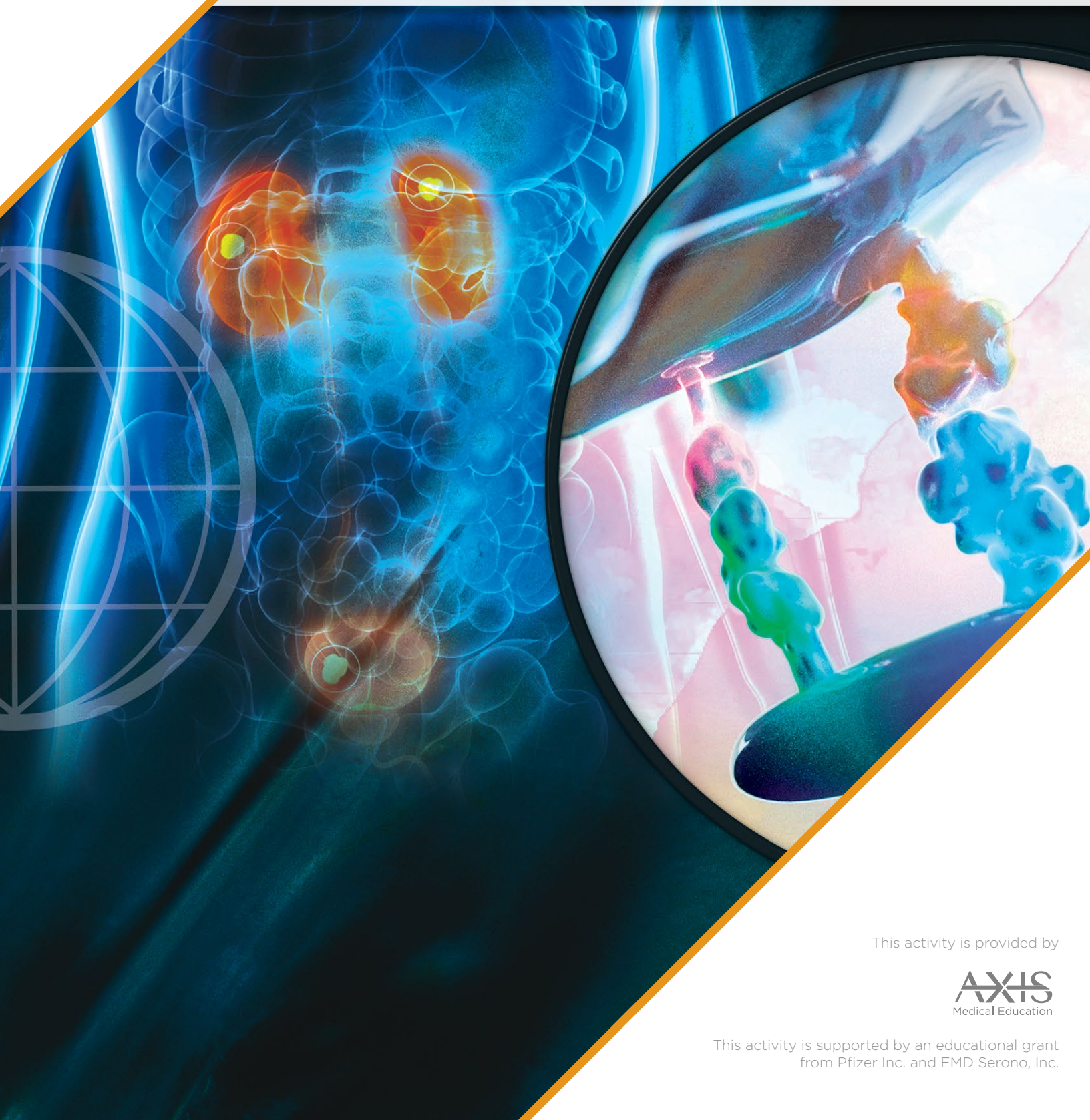
Principles and Practice Strategies for Immunotherapy in Genitourinary Malignancies

This transcript has been edited for style and clarity and includes all slides from the presentation.



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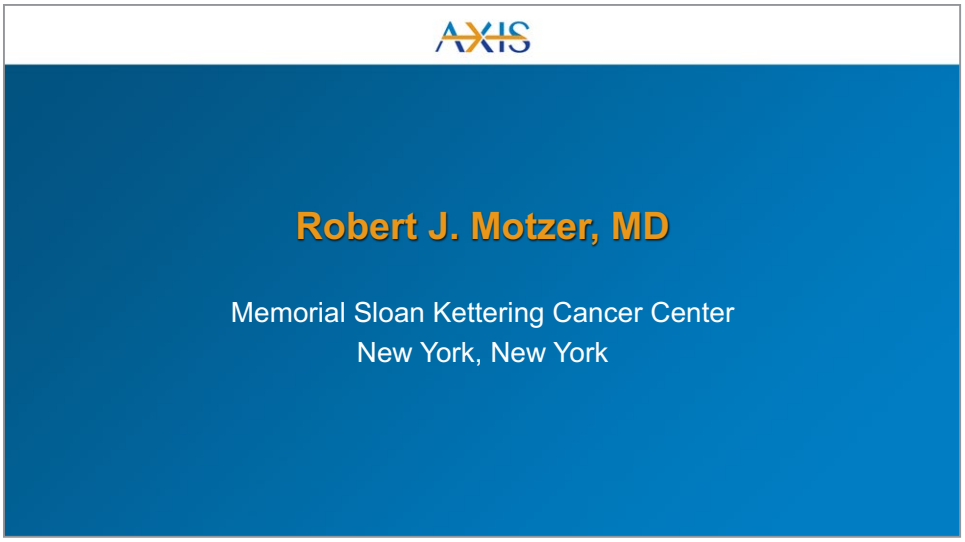
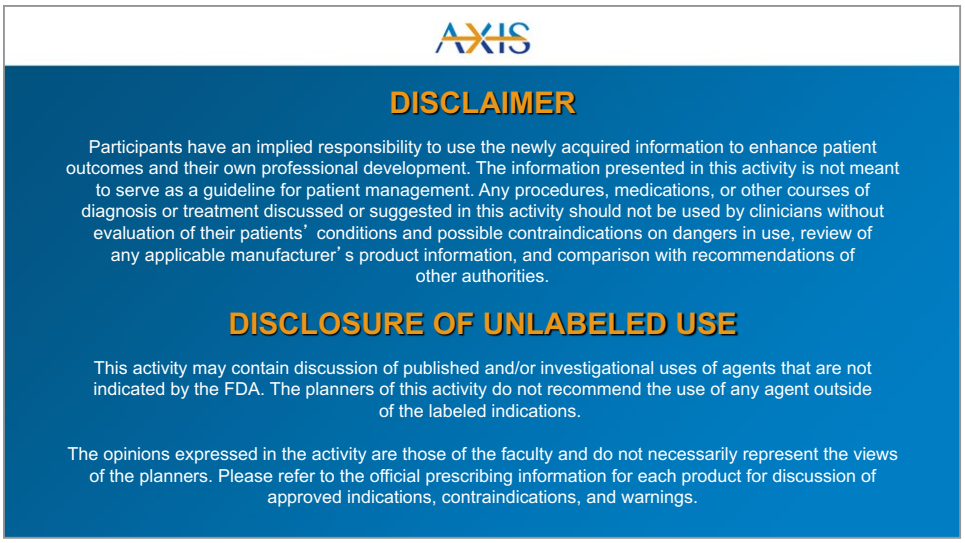
Principles and Practice Strategies for Immunotherapy in Genitourinary Malignancies

Robert J. Motzer, MD and Yohann Loriot, MD, PhD

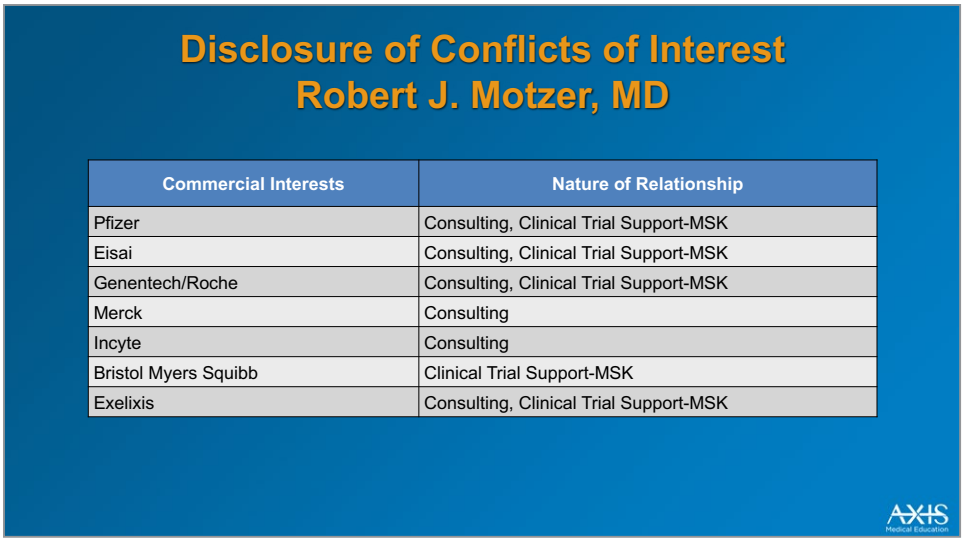
Robert J. Motzer, MD
Hello, and welcome to this educational activity titled *Principles and Practice Strategies for Immunotherapy in Genitourinary Malignancies.*



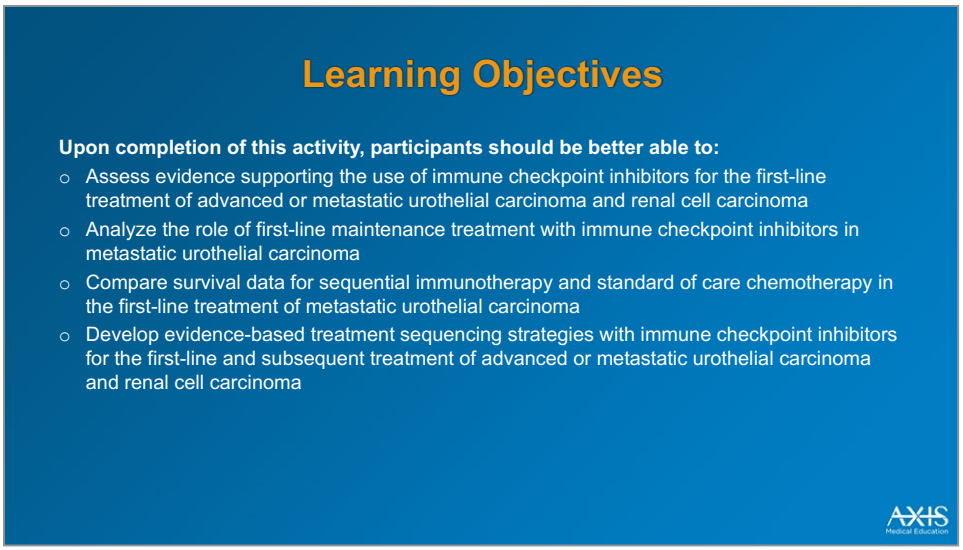
I am Dr. Robert Motzer, Jack and Dorothy Byrne Chair in Clinical Oncology, and Kidney Cancer Section Head in the Department of Medicine at Memorial Sloan Kettering Cancer Center.



- Here is a disclaimer and disclosure indicating that we may be discussing off-label use of approved agents or agents that are in development.

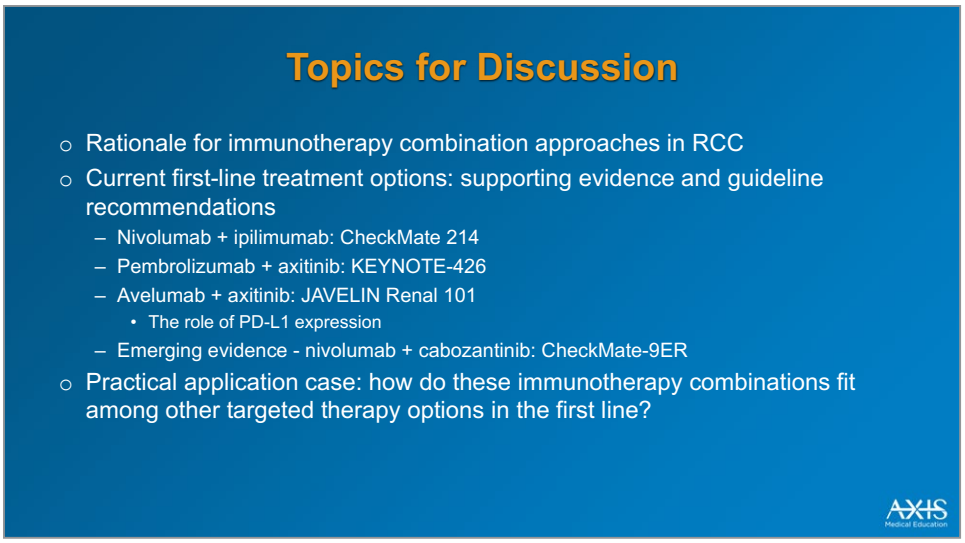


- Here's my financial disclosure information.

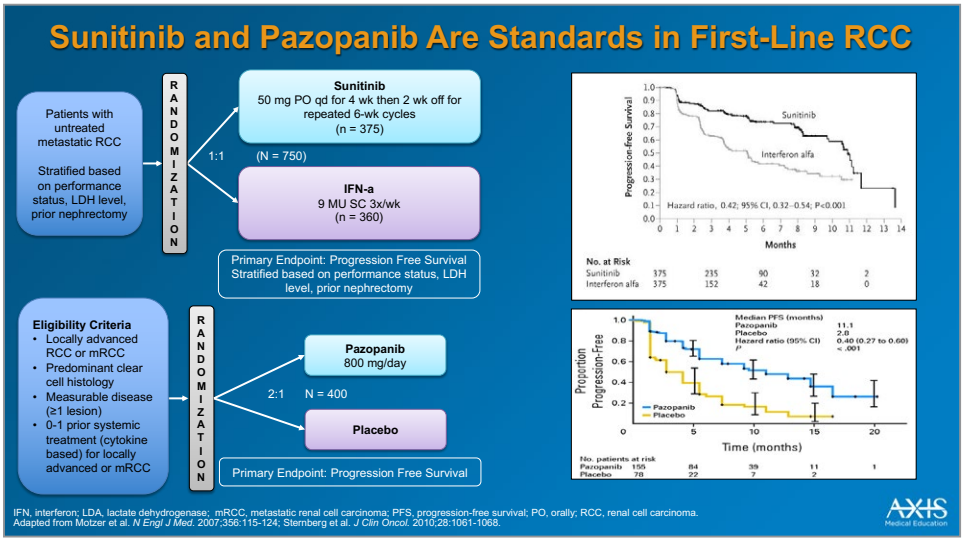


- And these are the learning objectives for this activity.

- This program is going to cover renal cell carcinoma. And the priority is an update on the first line treatment for metastatic RCC as well as some of the new novel targets and strategies.



Topics for discussion include the rationale for immunotherapy combination approaches in RCC; current first-line treatment options; supporting evidence and guideline recommendations including nivolumab plus ipilimumab, pembrolizumab plus axitinib, avelumab plus axitinib; and some of the emerging evidence for nivolumab plus cabozantinib. There will also be a practical application case.



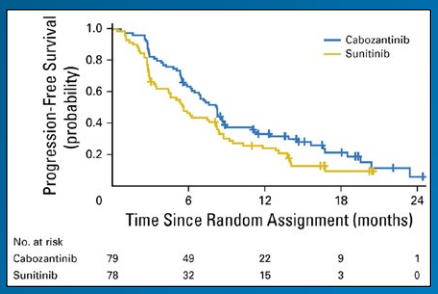
Historically, renal cell carcinoma has been one of the most difficult cancers to treat particularly in the era of chemotherapy. The real breakthrough in this disease came about as a better understanding of the underlying biology with the importance of the *VHL* gene in pathogenesis for a clear cell carcinoma of the kidney. As a result of that, targeted drugs were developed that were VEGF receptor antagonists.

And as a result of these targeted agents, really the treatment was transformed.

We refer to it as the targeted therapy era in RCC. And two of the leaders that dominated first-line treatment were sunitinib and pazopanib. Beginning around 2006 and extending up until just recently, the mainstay for first-line therapy was either one of these two targeted drugs—sunitinib or pazopanib.

There were other targeted agents that were also assessed at first in previously treated patients and then some in first-line therapy. And so, there's a multitude of targeted agents that have been approved for the treatment of kidney cancer. And for the most part, our management strategies have been sequencing these drugs.

CABOSUN: PFS for Cabozantinib vs Sunitinib in First-Line Treatment of Intermediate-/Poor-Risk Patients



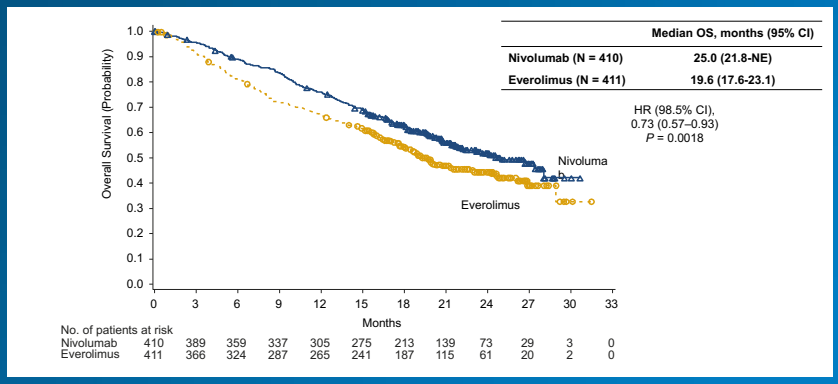
Arm	PFS Events	Median PFS (95% CI), mo	HR (95% CI)*
Cabozantinib	123	8.2 (6.2- 8.8)	0.66 (0.46-0.95) *P* (one-sided) = .012
Sunitinib		5.6 (3.4- 8.1)	

PFS, progression-free survival.
Choueiri et al. *J Clin Oncol*. 2017;35:591-597.

- Several of these were looked at in first-line therapy as well. And cabozantinib is one of those. It was approved based on a large phase 3 trial called the METEOR trial compared to everolimus.

  But the efficacy looked promising, and it was compared to sunitinib in this first-line, randomized phase 2 trial showing superior efficacy and a similar toxicity profile.

Checkmate 025: Nivolumab vs Everolimus as Second- or Third-Line Therapy



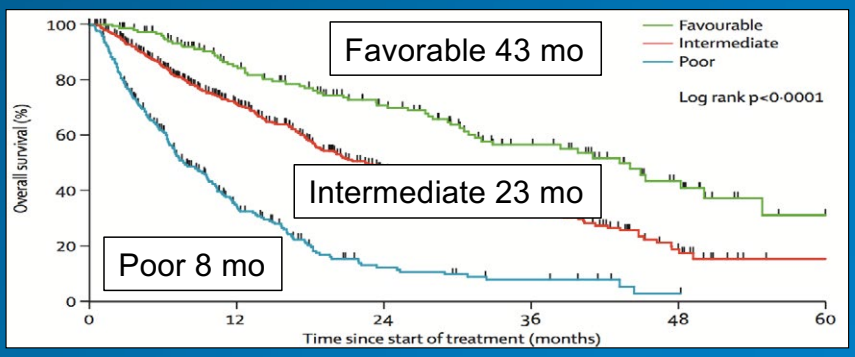
NE, not estimable; OS, overall survival.
Motzer et al. *N Engl J Med*. 2015;373:1803-1813.

- The situation really changed, however, with the advent and study of targeted immunotherapies or PD-1 inhibitors. The first of these agents that was studied and brought into standard of care for renal cell carcinoma was nivolumab.

  In the CheckMate 025 trial, nivolumab was compared to everolimus and showed a higher response rate, improved overall survival as well as better toxicity profile and quality of life. And this really ushered in the era of immunotherapy for the treatment of renal cell carcinoma.

Risk Stratification for First-Line Therapy in mRCC: IMDC Criteria

IMDC Criteria Risk Factors	
KPS	<80%
Time from diagnosis	<12 mo
Hemoglobin	<LLN
Neutrophil count	>ULN
Platelet count	>ULN
Corrected serum calcium	>ULN
Risk Group by No. of Risk Factors	
Favorable	0
Intermediate	1-2
Poor	3 -6



>500 patients with mRCC treated with VEGF-targeted therapy:

- Sunitinib (61%)
- Sorafenib (31%)
- Bevacizumab (8%)

IMDC, International Metastatic RCC Database Consortium; LLN, lower limit of normal; mRCC, metastatic renal cell carcinoma; ULN, upper limit of normal; VEGF, vascular endothelial growth factor.
Heng et al. *J Clin Oncol*. 2009;27:5794-5799; Heng et al. *Lancet Oncol*. 2013;14:141-148.

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In choosing first-line treatments for RCC, it's important to understand the risk stratification groupings that have been developed for this disease. The initial one that was developed was called the MSKCC risk group, and it identified and stratified patients into favorable, intermediate, and poor risk based on five different factors. This was modified after these factors and several others were developed and run on patients who were treated with targeted therapy. And so, the more modern one is the IMDC, which is shown here. There are six different risks factors for short survival. Patients are grouped into these three categories—favorable, intermediate, and poor—based on the number of risk groups.

And you can see on the right, the overall survival really separates with regard to these three different risk groupings. It's important because these groupings have been used in clinical trial stratification and as well are now used in choosing therapies for patients with clear cell carcinoma in first-line treatment.

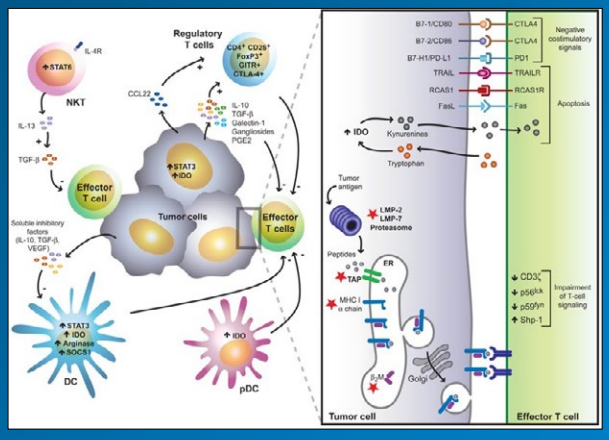
Immunotherapy Combinations For First-Line Clear-Cell RCC

Nivolumab Plus Ipilimumab
Axitinib Plus Pembrolizumab
Axitinib Plus Avelumab

- Over the last couple of years, there have been three different immunotherapy combinations that have been studied in large phase 3 trials in clear cell carcinoma. They've received regulatory approval and now make up our main armamentarium for first-line treatment for clear cell carcinoma.

  Nivolumab plus ipilimumab are two checkpoint inhibitor therapies; so this is usually referred to as combined IO therapy. Axitinib is a tyrosine kinase inhibitor that was developed in second-line therapy and is combined with a PD-1 inhibitor, pembrolizumab. And the third study, axitinib is combined with avelumab, which is a PD-L1 inhibitor.

Immune Recognition



Rabinovich et al. *Annu Rev Immunol*. 2007;25:267-296.

- This diagram emphasizes the different mechanisms of action for these drugs in treatment of kidney cancer. They basically target either PD-1 or PD-L1, and by doing so, they enhance immune surveillance of your own immune system to target the cancer and cause your own immune system to recognize tumor and to be able to fight it.

  Ipilimumab is a related compound. It's called a CTLA-4 inhibitor, which has a similar mechanism of action.

FDA Approval Summary

Drug(s) and Target	FDA Approval Date	Trial	Indication
Nivolumab (PD-1)	November 2015	CheckMate 025	Advanced RCC in patients who have received prior anti-angiogenic therapy
Nivolumab (PD-1) + Ipilimumab (CTLA-4)	April 2018	CheckMate 214	Intermediate or poor risk, previously untreated advanced RCC
Pembrolizumab (PD-1) + Axitinib (VEGFR-TKI)	April 2019	KEYNOTE-426	First-line treatment of patients with advanced RCC
Avelumab (PD-L1) + Axitinib (VEGFR-TKI)	May 2019	JAVELIN Renal 101	First-line treatment of patients with advanced RCC

CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.
FDA News Release, 2015, 2018, 2019.

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- Nivolumab was the first to be approved, and it's approved for patients who have received prior anti-angiogenic therapy as a monotherapy.

  Nivolumab plus ipilimumab was approved in April 2018 based on the CheckMate 214 trial, and its approval has been primarily in intermediate- and poor-risk patients who were previously untreated.

  Pembrolizumab plus axitinib followed this with the KEYNOTE-426 and is approved for first line treatment of patients with advanced RCC as is avelumab plus axitinib per the JAVELIN Renal 101 trial.

First-Line Combination Therapy Trials

Variable	Nivolumab + Ipilimumab CheckMate 214[1] N = 1,096	Pembrolizumab + Axitinib KEYNOTE 426[2] N = 861	Avelumab + Axitinib JAVELIN Renal 101[3] N = 886
IMDC Risk Group			
Favorable	23%	31%	21%
Intermediate	61%	56%	62%
Poor	17%	13%	16%
PD-L1 Expression ≥1%	24% (Dako PD-L1 28-8; Tumor)	60% (Agilent Tech PD-L1 22C3; CPS)	63% (Ventana PD-L1 SP263; Immune)
Primary Endpoint	ORR, PFS, OS in Int/Poor (IRC)	OS, PFS (IRC)	OS, PFS in PD-L1+ (IRC)

CPS, combined positive score; IMDC, International Metastatic RCC Database Consortium; Int, intermediate; IRC, independent review committee; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival.

1. Motzer et al. *N Engl J Med.* 2018;378(14):1277-1290; 2. Rini et al. *N Engl J Med.* 2019;380:1116-1127; 3. Motzer et al. *N Engl J Med.* 2019;380:1103-1115.

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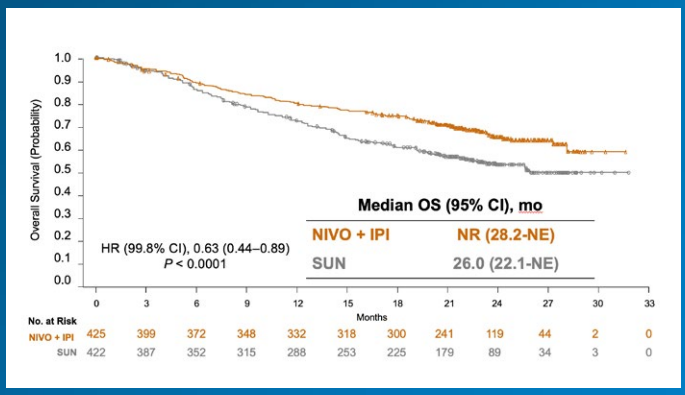
So, let's take a look at these three different phase 3 trials that have changed the way we treat RCC. This slide summarizes some of the details of the trials—the CheckMate 214, KEYNOTE-426, and JAVELIN Renal 101 phase 3 trials.

You can see that these are all large trials—over 800 patients. They included patients from all three different risk groups although the CheckMate 214 had a modest number since the primary endpoint was directed at these patients. They all include some patients with PD-L1 positive tumors although it's clear from this data that the methodology was different for each of these studies in determining PD-L1 positivity.

Primary endpoints for the CheckMate 214 were objective response rate, PFS, and OS in intermediate- and poor-risk patients. In KEYNOTE-426, it was both overall survival and PFS. And in axitinib plus avelumab JAVELIN Renal 101, it was OS and PFS as coprimary endpoints, specifically in the PD-L1 positive population. The three trials met their primary endpoints.

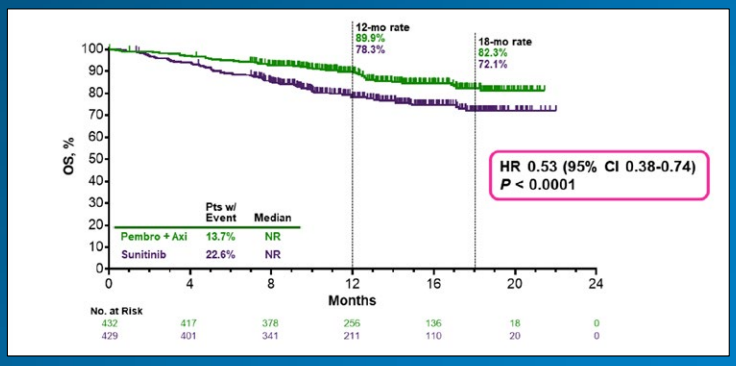
Checkmate-214: Nivolumab/Ipilimumab vs Sunitinib: Overall Survival in Intermediate/Poor Risk



IPI, ipilimumab; OS, overall survival; NE, not estimable; NIVO, nivolumab; SUN, sunitinib.
Escudier et al. *Ann Oncol.* 2017;28(suppl 5):V621-V622.; Motzer et al. *N Engl J Med.* 2018;378(14):1277–1290.

- Here we see the CheckMate 214, which met primary endpoints of objective response rate as well as overall survival. The hazard ratio was 0.63 in favor of nivolumab plus ipilimumab with a strong benefit based in overall survival. The response rate was higher was well.

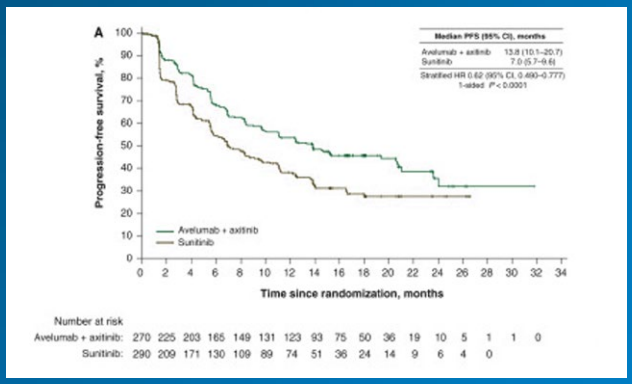
KEYNOTE 426: Axitinib Plus Pembrolizumab vs Sunitinib: Overall Survival



Adapted from Rini et al. *N Engl J Med.* 2019;380:1116-27.

- In KEYNOTE-426, both primary endpoints were reached. The progression-free survival was improved for pembrolizumab plus axitinib and as well as the overall survival shown here. So both KEYNOTE-426 and CheckMate 214 showed benefits in overall survival.

JAVELIN Renal 101: Axitinib + Avelumab vs Sunitinib in the PD-L1+ Group: PFS



PD-L1, programmed cell death protein ligand 1; PFS, progression-free survival.
Adapted from Motzer et al. *N Engl J Med*. 2019; 380:1103-1115; Choueiri et al. *Ann Oncol*. 2020;31:1030-1039.

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- In contrast, JAVELIN Renal 101 met its primary endpoint by showing improvement in progression-free survival in the PD-L1 positive group as well as in the overall group. But there wasn't a benefit shown in overall survival. The overall survival benefit was fairly immature in the report and continues to mature.

First-Line Combination Therapy Trials: ITT

Variable		Nivolumab + Ipilimumab CheckMate 214[1] N = 1,096	Pembrolizumab + Axitinib KEYNOTE 426[2] N = 861	Avelumab + Axitinib JAVELIN Renal 101[3,4] N = 886
Median Follow-Up (mo)		25.2	12.8	13.0
ORR		39%	59%	53%
CR		10.2%	5.8%	3.8%
PFS (mo)	Combination Arm	12.4	15.1	13.3
	Sunitinib	12.3	11.1	8.0
	HR	0.98 (99.1% CI 0.79-1.23)	0.69 (95% CI 0.57-0.84)	0.69 (95% CI 0.57-0.83)
OS	HR	0.68 (99.8% CI 0.49-0.95)	0.53 (95% CI 0.38-0.74)	0.80 (95% CI 0.62-1.03)

CR, complete response rate; ITT, intention to treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
1. Motzer et al. *N Engl J Med*. 2018;378(14):1277-1290.
2. Rini et al. *N Engl J Med*. 2019;380:1116-1127.
3. Motzer et al. *N Engl J Med*. 2019;380:1103-1115.
4. Choueiri et al. *Ann Oncol*. 2020;31:1030-1039.

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- Here's a summary of the high-level results for these different trials, and highlights are the percent of complete responses. With CheckMate 214, it's over 10%, which is quite remarkable and is a metric that is important to many in terms of complete response. For KEYNOTE-426, the response rate is nearly 60%; so that's characterized by a very high response rate. And both of these studies, as shown here, showed benefits in overall survival.

  For progression-free survival, the primary endpoint was not met with CheckMate 214, but it was met with KEYNOTE-426. JAVELIN Renal 101 showed a high response rate as well, a benefit in progression-free survival but has been distinguished somewhat from the others because of a lack of survival benefit.

Patients With Intermediate-/Poor-Risk mRCC

KEYNOTE 426[1]	Intermediate/Poor Risk	
	Pembrolizumab + Axitinib (n = 294)	Sunitinib (n = 298)
ORR*	55.8%	29.5%
P	-	
CR	4.8%	0.7%
Median PFS, mo	12.6	8.2
HR (95% CI)	0.67 (0.53-0.85)	
P	-	
12-month OS	87%	71%
HR (95% CI)	0.52 (0.37-0.74)	
P	-	

CheckMate 214[2]	Intermediate/Poor Risk	
	Nivolumab + Ipilimumab (n = 425)	Sunitinib (n = 422)
ORR*	42%	27%
P	<.001	
CR	9%	1%
Median PFS, mo	11.6	8.4
HR (99.1% CI)	8.2 (0.64-1.05)	
P	.03	
12-month OS	80%	72%
HR (99.8% CI)	0.63 (0.44-0.89)	
P	<.001	

*Per blinded independent radiology review committee by RECIST version 1.1.
CR, complete response; mRCC, metastatic renal cell carcinoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
1. Rini et al. *N Engl J Med.* 2019;380:1116-1127; 2. Motzer et al. *N Engl J Med.* 2018;378(14):1277-1290.

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We can compare these two trials recognizing limitations in cross-study comparisons, and these are shown here for the patients that are intermediate and poor risk. The KEYNOTE 426 is on the left, and the CheckMate 214 is now on the right. You can see the response rates are about the same with pembrolizumab plus axitinib and with nivolumab plus ipilimumab—maybe a little higher with pembrolizumab plus axitinib.

Complete responders seem a little higher with nivolumab plus ipilimumab. Progression-free survival is about the same with both in this population. And both show a really good improvement in overall survival.

So, from the standpoint of efficacy, these two match in the intermediate- and poor-risk patients fairly well.

Patients With Favorable-Risk mRCC

KEYNOTE 426[1]	Favorable Risk		CheckMate 214[2]	Favorable Risk	
	Pembrolizumab + Axitinib (n = 138)	Sunitinib (n = 131)		Nivolumab + Ipilimumab (n = 125)	Sunitinib (n = 124)
ORR*	66.7%	49.6%	ORR*	29%	52%
P	-		*P*	<.001	
CR	-	-	CR	11%	6%
Median PFS, mo	17.7	12.7	Median PFS, mo	15.3	25.1
HR (95% CI)	0.81 (0.53-1.24)		Hazard Ratio (95% CI)	2.18 (1.29-3.68)	
P	-		*P*	<.001	
12-month OS	95%	94%	12-month OS	94%	96%
HR (95% CI)	0.64 (0.24-1.68)		HR (99.8% CI)	1.45 (0.51-4.12)	
P	-		*P*	.27	

*Per blinded independent radiology review committee by RECIST version 1.1.
CR, complete response; mRCC, metastatic renal cell carcinoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
1. Rini et al. *N Engl J Med.* 2019;380:1116-1127; 2. Motzer et al. *N Engl J Med.* 2018;378(14):1277-1290.

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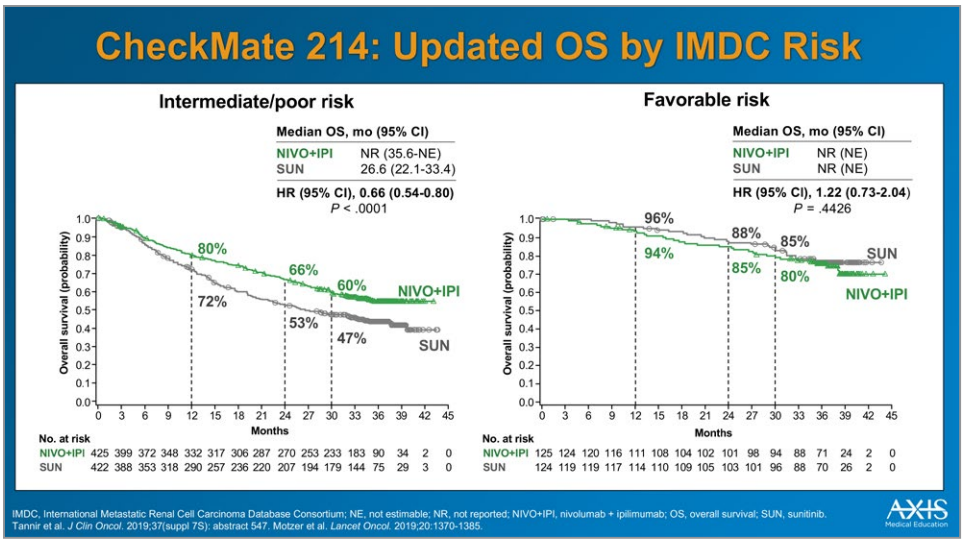
The difference we saw was in the favorable-risk group. In the favorable-risk group, the response rate remains high with pembrolizumab plus axitinib—higher than sunitinib. The progression-free survival is longer, but the survival although it's longer with pembrolizumab plus axitinib, the 95% confidence interval extends well over 1 compared to sunitinib.

With CheckMate 214, we see a different pattern. And that is the response rate was actually higher with sunitinib compared to nivolumab plus ipilimumab. And the progression-free survival was longer. There was also a trend early on towards an improvement in overall survival with sunitinib compared to nivolumab plus ipilimumab. Although again, the 95% confidence intervals are overlapping.

So, for many pembrolizumab plus axitinib is the preferred choice for patients that have favorable-risk tumors compared to nivolumab plus ipilimumab. But let's look at some of the long-term follow-up and toxicity as well.

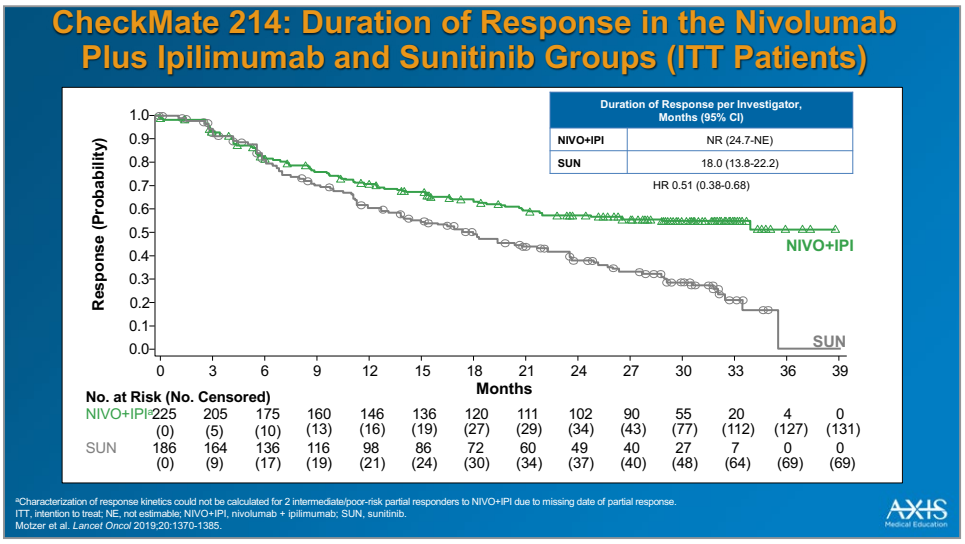
So, let's look at updated results with CheckMate 214 since that study read out early and longer follow-up is available.



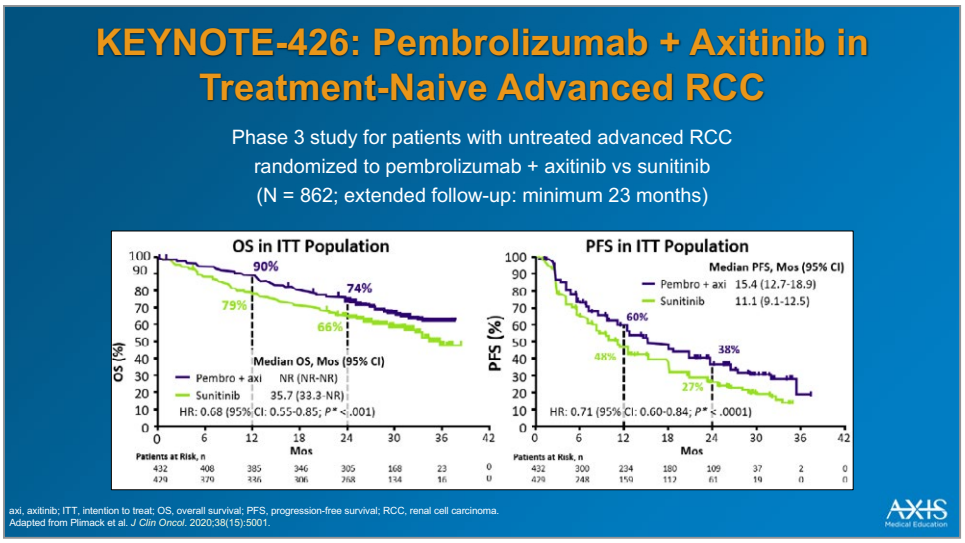
- With updated results, the survival benefit for nivolumab plus ipilimumab in the intermediate- and poor-risk patients is maintained. We see in the favorable risk that the survival is starting to balance out between the two arms and is very similar with longer follow-up.

  What some have highlighted is the fact that favorable-risk patients have a long-term survival regardless of treatment offered and that these patients for the most part can receive multiple regimens sequentially over time. So, if one program works, patients continue with that. If not, then the patient can switch to a different alternative program.

  So, based on this data, there are advocates for ipilimumab/nivolumab in favorable-risk group as well because the feeling is, is that if the patient doesn't respond to ipilimumab/nivolumab they can receive sequential VEGF-targeted therapy.

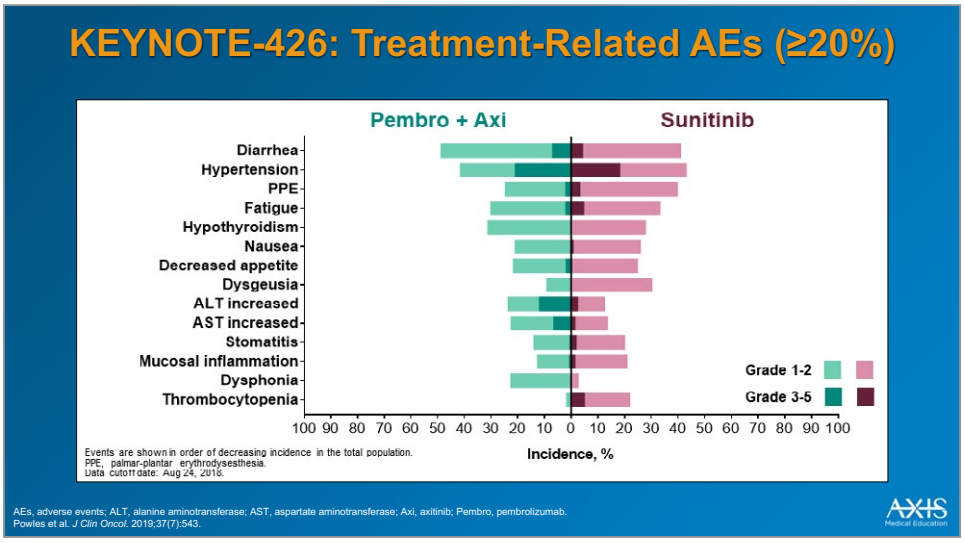


- One of the highlights of nivolumab plus ipilimumab as well that's become apparent with long-term follow-up is that the responses to this can be durable. And so, long-term benefit is a hallmark of nivolumab plus ipilimumab treatment. Shown here is the duration of response. And the fact that the curve at the right begins to flatten up meaning patients remain in durable response with this program.



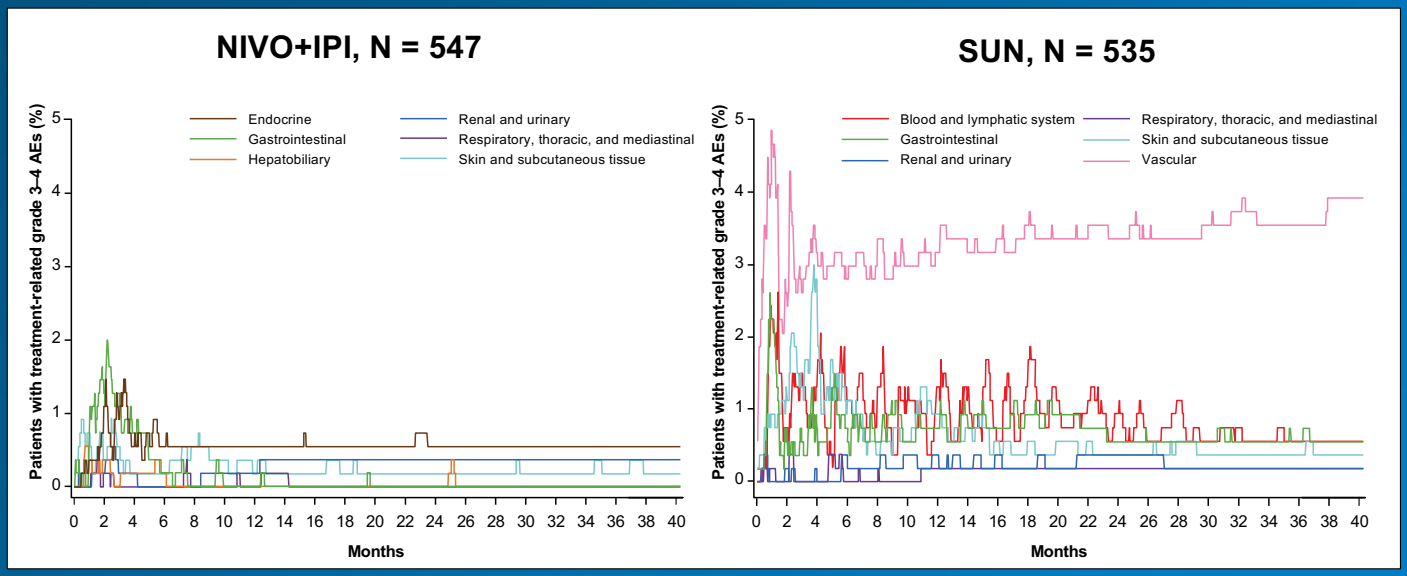
- For the pembrolizumab plus axitinib or the TKI plus IO combinations, the trials were done later on, and so, we don't have much follow-up, but we're beginning to get longer follow-up on some of these programs. And shown here is an update from the KEYNOTE-426 study. It shows that the survival benefit is maintained as shown on the left for pembrolizumab plus axitinib over sunitinib. And on the right, we see progression-free survival.

  There is a benefit overall, but what we have not seen yet is this leveling off of this tail of the curve showing a maintenance of response and maintenance of progression-free survival. And so, that's what we have seen over time with nivolumab plus ipilimumab. And further evaluation, longer follow-up needs to be seen with the IO/TKI treatments to see if we can get the same sort of long-term benefit.



- Comparing the two regimens, the toxicity profiles are quite different. This is a tornado plot that shows toxicity profile for pembrolizumab plus axitinib compared to sunitinib. And for the most part, the toxicities for this IO/TKI combination are driven by the TKI. The toxicities are quite manageable. We've been very used to managing toxicities from TKI.

Checkmate 214: Treatment-Related AEs Over Time



- In the NIVO+IPI arm, 35% of patients received high-dose glucocorticoids (≥40 mg prednisone/day or equivalent) for select treatment-related AE management
- No additional treatment-related deaths occurred

AEs, adverse events; IPI, ipilimumab; NIVO, nivolumab; SUN, sunitinib.
Tannir et al. *J Clin Oncol.* 2019;37(suppl 7S): abstract 547. Motzer et al. *Lancet Oncol.* 2019;20:1370-1385.

AXIS Medical Education

With nivolumab plus ipilimumab, the toxicity profile is quite different. It's essentially all these immune-related side effects which we see with IO therapies that mimic autoimmune disorders. For the most part, most of these immune-related side effects happen early on during the induction phase when the patient is receiving both ipilimumab plus nivolumab. And then, once that is passed, we do see these even after therapy can be discontinued. But for the most part, they are very uncommon.

They can be difficult to diagnose, however, and difficult to manage with high-dose steroids. Sometimes some of these like colitis require hospitalization. So, you can see the toxicity profile is really quite different between these IO/IO combinations shown here with nivolumab plus ipilimumab and TKI/IO combinations.

For the most part, the burden of toxicity is upfront with IO/IO, and with IO/TKI, it occurs later with chronic toxicities like diarrhea.

JAVELIN Renal 101: Treatment-Related AEs

Preferred Term	All Treated Patients (N = 873)			
	Avelumab Plus Axitinib (N = 434)		Sunitinib (N = 439)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	no. (%)			
Patients with events	414 (95.4)	246 (56.7)	423 (96.4)	243 (55.4)
Diarrhea	235 (54.1)	22 (5.1)	196 (44.6)	11 (2.5)
Hypertension	208 (47.9)	106 (24.4)	142 (32.3)	67 (15.3)
Fatigue	156 (35.9)	13 (3.0)	159 (36.2)	16 (3.6)
Palmer-plantar erythrodysesthesia syndrome	144 (33.2)	25 (5.8)	148 (33.7)	19 (4.3)
Dysphonia	116 (26.7)	2 (0.5)	12 (2.7)	0
Nausea	107 (24.7)	3 (0.7)	148 (33.7)	5 (1.1)
Hypothyroidism	105 (24.2)	1 (0.2)	59 (13.4)	1 (0.2)
Stomatitis	96 (22.1)	8 (1.8)	100 (22.8)	4 (0.9)
Decreased appetite	86 (19.8)	7 (1.6)	115 (26.2)	4 (0.9)
Chills	62 (14.3)	1 (0.2)	16 (3.6)	0
Mucosal inflammation	58 (13.4)	5 (1.2)	60 (13.7)	4 (0.9)
Alanine aminotransferase increased	57 (13.1)	21 (4.8)	43 (9.8)	9 (2.1)
Dysgeusia	56 (12.9)	0	141 (32.1)	0
Rash	54 (12.4)	2 (0.5)	42 (9.6)	2 (0.5)
Dyspnea	53 (12.2)	6 (1.4)	24 (5.5)	1 (0.2)
Pruritus	53 (12.2)	0	19 (4.3)	0
Arthralgia	52 (12.0)	1 (0.2)	24 (5.5)	0
Infusion-related reaction	52 (12.0)	7 (1.6)	0	0
Aspartate aminotransferase increased	49 (11.3)	12 (2.8)	48 (10.9)	6 (1.4)
Weight decreased	49 (11.3)	7 (1.6)	17 (3.9)	1 (0.2)
Vomiting	42 (9.7)	1 (0.2)	68 (15.5)	7 (1.6)
Asthenia	41 (9.4)	5 (1.2)	54 (12.3)	8 (1.8)
Dyspepsia	24 (5.5)	0	74 (16.9)	0
Thrombocytopenia	12 (2.8)	1 (0.2)	78 (17.8)	24 (5.5)
Anemia	9 (2.1)	1 (0.2)	73 (16.6)	22 (5.0)
Neutropenia	6 (1.4)	1 (0.2)	79 (18.0)	34 (7.7)

Adapted from Motzer et al. *N Engl J Med.* 2019;380:1103-1115.

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- JAVELIN Renal 101 also highlighted the toxicities for avelumab plus axitinib compared to sunitinib. And you can see here as well, similar to axitinib plus pembrolizumab, the common toxicities are diarrhea, hypertension, skin toxicity, dysphonia, and stomatitis. And these are all primarily related to the axitinib TKI.

  There does seem to be some enhancement as well for the TKI-related toxicities when they're combined with an IO therapy. Nonetheless, these combinations are overall generally well tolerated in management and are outweighed greatly by the therapeutic benefit for these programs.

NCCN® Guidelines for Systemic First-Line Therapy for Relapsed or Stage IV Clear Cell RCC

Risk	Preferred Regimens	Other Recommended Regimens	Useful Under Certain Circumstances
Favorable	**Axitinib + pembrolizumab**	**Ipilimumab + nivolumab**	Active surveillance
	Pazopanib	**Axitinib + avelumab**	Axitinib (category 2B)
	Sunitinib	Cabozantinib (category 2B)	High-dose IL-2
Poor/ Intermediate	**Ipilimumab + nivolumab (category 1)**	Pazopanib	Axitinib (category 2B)
	Axitinib + pembrolizumab (category 1)	Sunitinib	High-dose IL-2
	Cabozantinib	**Axitinib + avelumab**	Temsirolimus

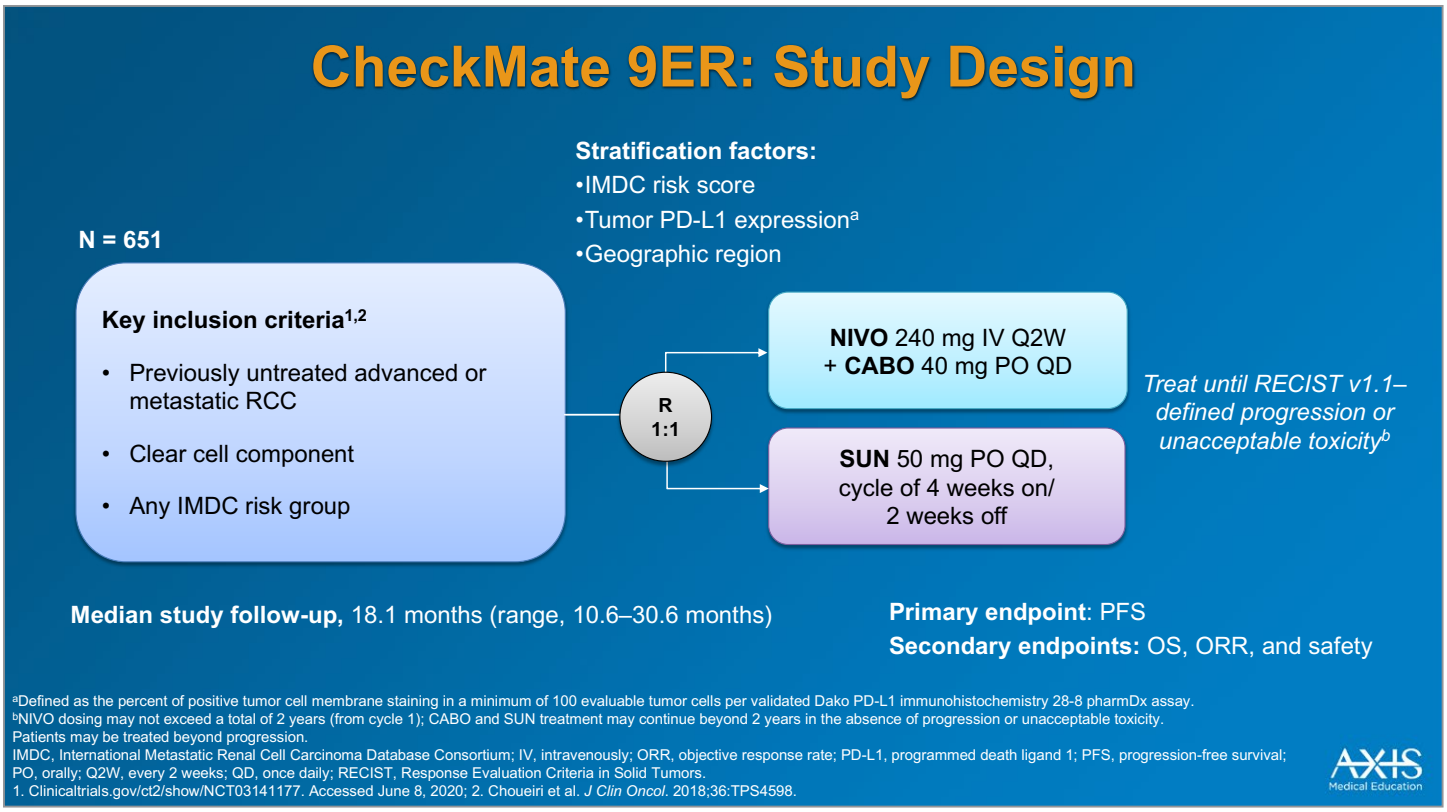
NCCN Guidelines®.Kidney Cancer, Version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf.

AXIS Medical Education

- NCCN sets guidelines for treatment of kidney cancer. And these are some of the more recent ones for first-line therapy. They are separated by risk. So, for favorable risk, preferred regimens are axitinib plus pembrolizumab. Pazopanib and sunitinib are still listed as preferred regimens based on the level of evidence by which these drugs were approved, but for the most part for patients with intermediate- and poor-risk tumors in particular and many with favorable risk as shown here, we recommend an IO therapy in combination with a TKI.

  Other options, however, are ipilimumab plus nivolumab based on the quality of life benefit with this regimen, based on the long-term benefit, based on the fact that favorable risk patients can generally receive multiple regimens.

  In the poor and intermediate, you can see there are two main contenders for preferred regimens, and these are ipilimumab plus nivolumab and axitinib plus pembrolizumab. And both have their relative benefits and their relative disadvantages compared to each other.



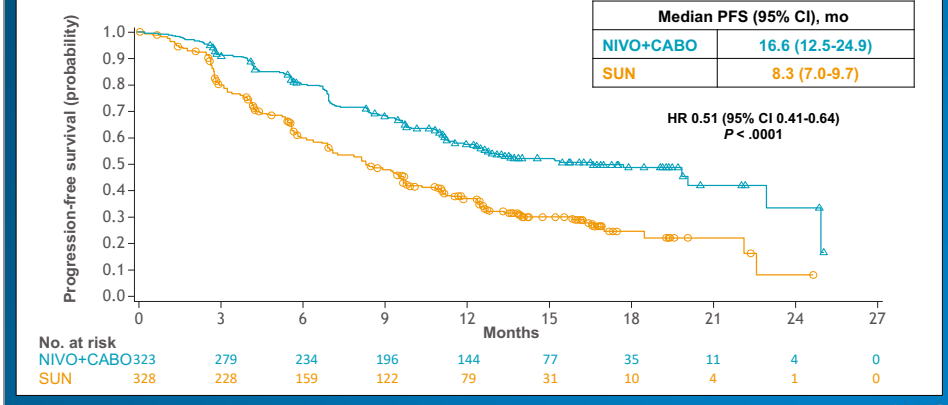
With regard to more recent data, CheckMate 9ER was a randomized phase 3 trial that recently read out. It was presented at the annual ESMO meeting in 2020. This was a large phase 3 trial that also looked at clear cell tumors that were previously untreated and compared the IO/TKI combination of nivolumab plus cabozantinib compared to sunitinib.

So, in certain respects, this mirrors both the JAVELIN 101 and the KEYNOTE-426 trials by comparing an IO/TKI combination to sunitinib.

Primary endpoints were progression-free survival, and overall response and safety were key secondary endpoints.

You'll note here in the regimen that cabozantinib is given at a lower dose than that approved in monotherapy. In monotherapy, cabozantinib is given at 60 mg where here a lower dose of 40 mg was given.

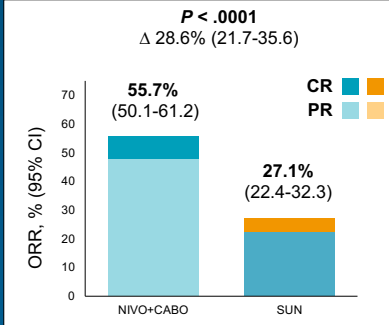
CheckMate 9ER: Progression-free Survival per BICR



Minimum study follow-up, 10.6 months.
BICR, blinded independent central review; CABO, cabozantinib; NIVO, nivolumab; SUN, sunitinib.
Choueiri et al. *J Clin Oncol*. 2018;36:TPS4598.

- This trial met its primary endpoint showing improvement in progression-free survival compared to sunitinib. The median is really quite remarkable at 16.6 months for nivolumab plus cabozantinib. And the hazard ratio was very strong in favor for this combination and statistically significant.

CheckMate 9ER: Objective Response and Best Overall Response per BICR

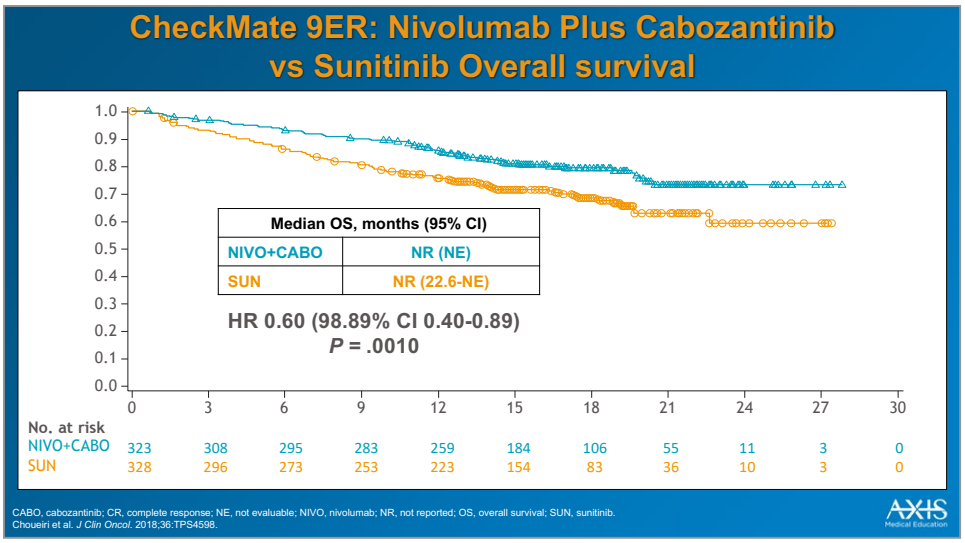


Outcome, %	NIVO+CABO (n = 323)	SUN (n = 328)
Complete response	8.0	4.6
Partial response	47.7	22.6
Stable disease	32.2	42.1
Progressive disease	5.6	13.7
Not evaluable/not assessed[a]	6.5	17.1
Median time to response (range), mo[b]	2.8 (1.0-19.4)	4.2 (1.7-12.3)
Median duration of response (95% CI), mo[b]	20.2 (17.3-NE)	11.5 (8.3-18.4)

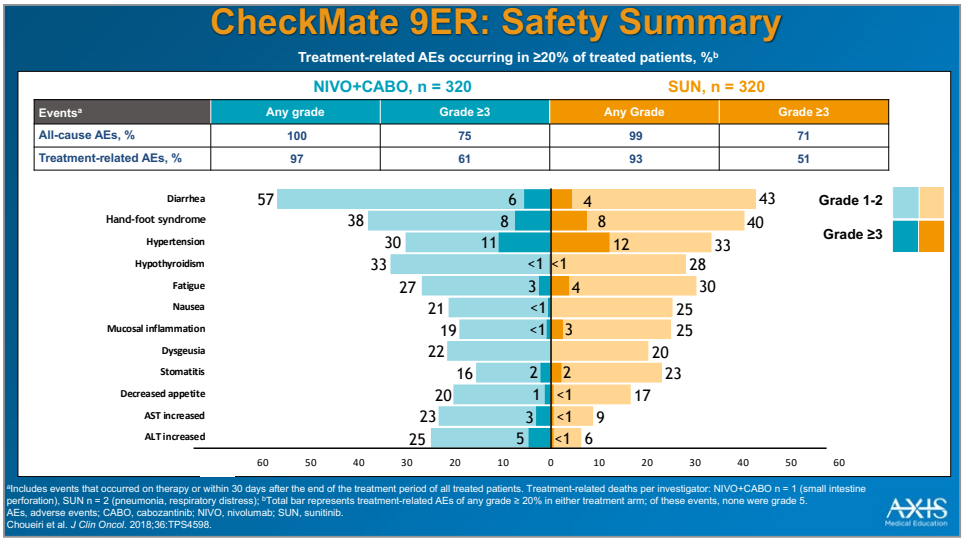
- ORR favored NIVO+CABO over SUN across subgroups including by IMDC risk status, tumor PD-L1 expression (≥1% vs <1%), and bone metastases

BICR-assessed ORR and BOR by RECIST v1.1.
[a]Includes patients who were never treated, those who discontinued/died before disease assessment, those without measurable disease at baseline per BICR, or other reason not reported/specified; [b]Median time to and duration of response were calculated for patients who had a complete or partial response (n = 180 with NIVO+CABO, n = 89 patients with SUN).
BICR, blinded independent central review; CABO, cabozantinib; CR, complete response; NE, not evaluable; NIVO, nivolumab; ORR, objective response rate; PR, partial response; SUN, sunitinib.
Choueiri et al. *J Clin Oncol*. 2018;36:TPS4598.

- Response rate was double with cabozantinib plus nivolumab compared to sunitinib. There were some complete responses seen as well with nivolumab plus cabozantinib with an about 8% CR rate. This data is new and warrants longer follow-up to better assess duration of response and progression free survival, but certainly, the median duration of response of 20 months here is really quite encouraging.



- Most notably, this trial also met the secondary endpoint of overall survival as shown here with a benefit to nivolumab plus cabozantinib over sunitinib and a hazard ratio of 0.60.



- The safety summary is shown here by this tornado plot. Overall, this combination appears relatively well tolerated with a similar toxicity profile that we've seen with the other TKI/IO combinations. Note in this study that cabozantinib was given at a slightly lower dose than that of the full dose in monotherapy.

Comparison of Phase 3 First-Line Trials

Variable	KEYNOTE-426[1]	CheckMate-9ER[2]	CheckMate-214[3]	JAVELIN Renal 101[4,5]
	Pembrolizumab + Axitinib vs Sunitinib (n = 432 vs 429)	Cabozantinib + Nivolumab vs Sunitinib (n = 323 vs 328)	Nivolumab + Ipilimumab vs Sunitinib (n = 550 vs 546)	Avelumab + Axitinib vs Sunitinib (n = 442 vs 444)
Primary endpoint(s)	OS and PFS in the ITT population	PFS	Hierarchical: first OS, then ORR, then PFS	PFS and OS in PD-L1–positive tumors
Age, median, y	62 vs 61	62 vs 61	62 vs 62	62 vs 61
IMDC risk category, % Favorable Intermediate Poor	 32 vs 31 55 vs 57 13 vs 12	 22.9 vs 22.3 58.5 vs 56.7 18.6 vs 20.7	 23 vs 23 61 vs 61 17 vs 16	 19 vs 20 64 vs 66 16 vs 13
PD-L1 ≥1, %	60 vs 62	25.1 vs 24.7	23 vs 25	63
Most common sites of mets, % Lung Lymph node Bone	 72 vs 72 46 vs 46 24 vs 24	 73.7 vs 75.9 40.2 vs 39.9 16.7 vs 15.2	 69 vs 68 45 vs 49 20 vs 22	 -
Previous nephrectomy, %	83 vs 84	68.7 vs 71.0	82 vs 80	86 vs 87

1. Rini et al. *N Engl J Med* 2019;380:1116-1127; 2. Choueiri et al. *Ann Oncol.* 2020;31(suppl 4):S1142-S1215; 3. Motzer et al. *N Engl J Med* 2018;378:1277-1290.
4. Motzer et al. *N Engl J Med.* 2019;380:1103-1115; 5. Choueiri et al. *Ann Oncol.* 2020;31:1030-1039.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; ITT, intention to treat; mets, metastases; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death protein ligand 1; PFS, progression-free survival.

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This is a comparison of these four phase 3 trials. Three of the four have resulted in regulatory approval for their combinations—pembrolizumab plus axitinib, nivolumab plus ipilimumab, and avelumab plus axitinib. Cabozantinib plus nivolumab remains investigational. But we anticipate that's it's going to receive regulatory approval within 2021 based on the strength of the data for benefit and progression free survival and overall survival over sunitinib.

Comparison of Phase 3 First-Line Trials

Variable	CheckMate-9ER[1]		KEYNOTE-426[2]		CheckMate-214[3]		JAVELIN Renal 101[4,5]	
	Cabozantinib + Nivolumab (n = 323)	Sunitinib (n = 328)	Pembrolizumab + Axitinib (n = 432)	Sunitinib (n = 429)	Ipilimumab + Nivolumab (n = 550)	Sunitinib (n = 546)	Avelumab + Axitinib (n = 442)	Sunitinib (n = 444)
Median PFS, mo								
ITT	16.6	8.3	15.1	11.1	12.4	12.3	13.3	8.0
	HR 0.51 (0.41-0.64) *P* = .0001		HR 0.69 (0.57-0.83) *P* = .00005		HR 0.98 (0.79-1.23) *P* = .85		HR 0.69 (0.574–0.825) *P* < 0.0001	
Median OS, mo								
ITT	NR	NR	NR	NR	NR	32.9	NE	NE
	HR 0.60 (0.40-0.89) *P* = .001		HR 0.59 (0.45-0.78) *P* = .00010		HR 0.68 (0.49-0.95) *P* < .001		HR 0.80 (0.616–1.027) *P* = 0.0392	
Follow-up, mo								
Minimum	10.6		11		17.5		13	
Median	18.1		16.6		25.2		-	

1. Choueiri et al. *Ann Oncol.* 2020;31(suppl 4):S1142-S1215; 2. Powles et al. *J Clin Oncol.* 2019;37: abstract 543. 3. Motzer et al. *N Engl J Med* .2018;378:1277-1290.
4. Motzer et al. *N Engl J Med.* 2019;380:1103-1115; 5. Choueiri et al. *Ann Oncol.* 2020;31:1030-1039.
ITT, intention to treat; OS, overall survival; PFS, progression-free survival.

AXIS Medical Education

The results of these are summarized and shown here between all these four phase 3 trials, which have really changed how we treat kidney cancer in first-line therapy and continue to make changes. These combinations have shown improvement in progression-free survival, in overall survival, and in the response rates as seen previously.

CheckMate 9ER showed a benefit in progression-free survival and overall survival. KEYNOTE-426 benefits in progression-free survival and overall survival for pembrolizumab plus axitinib. CheckMate 214 did not show a clear benefit in progression-free survival early on, but as time goes on, there does seem to be a benefit for ipilimumab plus nivolumab in progression-free survival as well with updated data not shown here but a clear benefit in overall survival. And JAVELIN Renal 101, improvement in progression-free survival but not yet seen in overall survival.

Comparison of Phase 3 Trials

Event	Ipilimumab + Nivolumab[1]	Pembrolizumab + Axitinib[2]	Nivolumab + Cabozantinib[3]	Avelumab + Axitinib[4]
Treatment-related AEs grade 3 or greater	46%	62.9%	60.6%	56.7%
Any cause grade 3 or greater AE	65%	75.8%	75.3%	71.2%
Treatment-related deaths	1.4%	0.9%	0.3%	0.7%
Any event leading to discontinuation of any of the 2 agents	22%	25.9%	15.3%	7.6%
Any event leading to (at least 1) dose reduction of the VEGFR-TKI	NA	20%	56.3%	42.2%

1. Motzer et al. *N Engl J Med* 2018;378:1277-1290; 2. Rini et al. *N Engl J Med* 2019:380:1116-1127;
3. Choueiri et al. *Ann Oncol.* 2020;31(suppl 4):S1142-S1215; 4. Motzer et al. *N Engl J Med*. 2019;380:1103-1115.
AE, adverse event; VEGFR-TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor.

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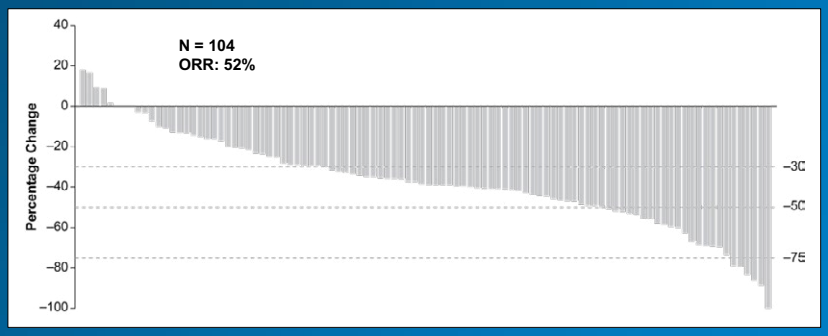
- With regard to safety, for the most part, the safety profiles of pembrolizumab plus axitinib, cabozantinib plus nivolumab, and axitinib plus avelumab are similar since they all contain an IO/TKI combination. They are all pretty much driven by the TKI toxicity with its effects including diarrhea, hypertension, skin toxicity. Ipilimumab plus nivolumab is clearly distinct since there is not a TKI in that combination. With that program, toxicity profile quite different and is centered around a relatively high rate of patients having immune-related side effects and requiring high-dose steroids for management.

Phase 2 Trial of Lenvatinib + Pembrolizumab After PD-1/PD-L1 Inhibitors



Note: Each bar represents 1 patient.
[a]By irRECIST per investigator assessment.
ORR, objective response rate; PD-1, programmed cell death protein 1, PD-L1, programmed cell death protein ligand 1.
Lee et al. *J Clin Oncol.* 2020;38(15):5008.

AXIS Medical Education

- For patients who progress on IO combinations, there's really an unmet need to define the best therapy. And this is because the landscape has changed so dramatically in the last couple of years. There's really a paucity of studies. For the most part, patients are treated with TKIs with cabozantinib being a popular choice.

  There is some question, and one of the issues is around is there a role for continued IO therapy in patients who have progressed on IO combinations in first-line? Perhaps the most intriguing and exciting data comes from this single-arm trial that was conducted in over 100 patients who had progressed on prior IO therapy. Now, this could have been a combination in first-line, or some of these patients may have gotten a TKI followed by nivolumab monotherapy in second-line.

  This data has been presented in abstract form as well at the most recent ESMO meetings and shows a response rate of over 50% with a combination of lenvatinib plus pembrolizumab. Now, lenvatinib is approved in second-line therapy following TKI in combination with everolimus, but it's a very effective promising TKI. And it's been combined here with pembrolizumab.

  So, these results are really quite striking and quite provocative.

The Role of Nivolumab → Ipilimumab (salvage/rescue)

Parameter	HCRN GU16-260 ASCO 2020	TITAN RCC ESMO 2019	OMNIVORE ASCO 2020
N	123	207	83
Prior TKI	No	Yes	Yes
Timing	Nivo→Ipi	Nivo→Ipi	Nivo→Ipi
Ipilimumab Doses	4	4	2
ORR	13%	12%	4%
CR	0%	2.7%	0%

Nivolumab + ipilimumab combination untreated clear-cell RCC ORR 42%, CR 11% (Checkmate 214)[1]

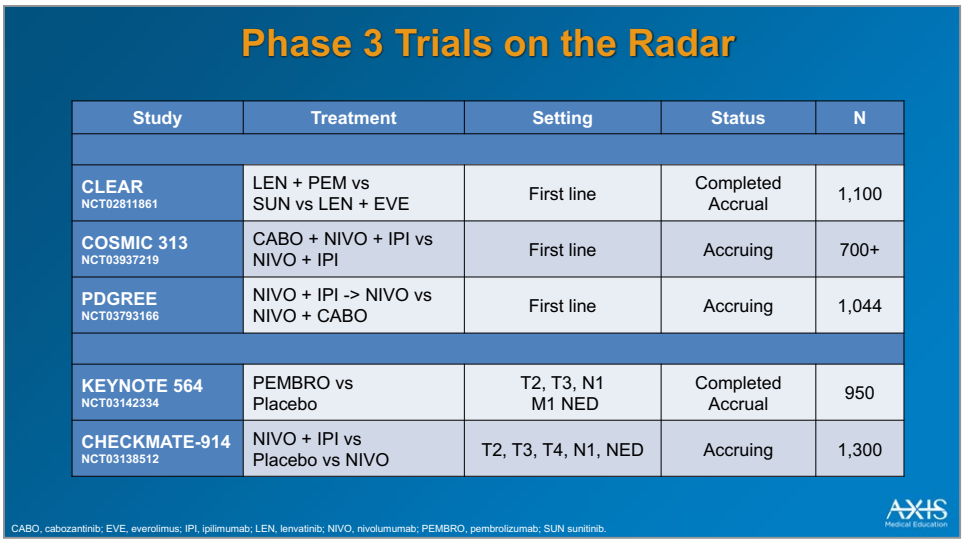
CR, complete response; ORR, objective response rate; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor.
Motzer et al. *N Engl J Med* 2018;378:1277-1290.

AXIS Medical Education

- One of the other questions has been for patients who are on, say, nivolumab monotherapy per its indication—is there an advantage to adding ipilimumab to those patients who have progressed on nivolumab monotherapy? And so, there's been a number of different trials that have looked at that.

For the most part, the data have been somewhat disappointing for ipilimumab given subsequently to patients progressing on nivolumab. There is a marginal response rate in the rate of 10% to 15% for some of the studies, but we don't see complete responses replicated throughout the trials.

And there's a fair amount of toxicity for adding ipilimumab to nivolumab in monotherapy for patients progressing. So, this is not a recommended approach by any means.

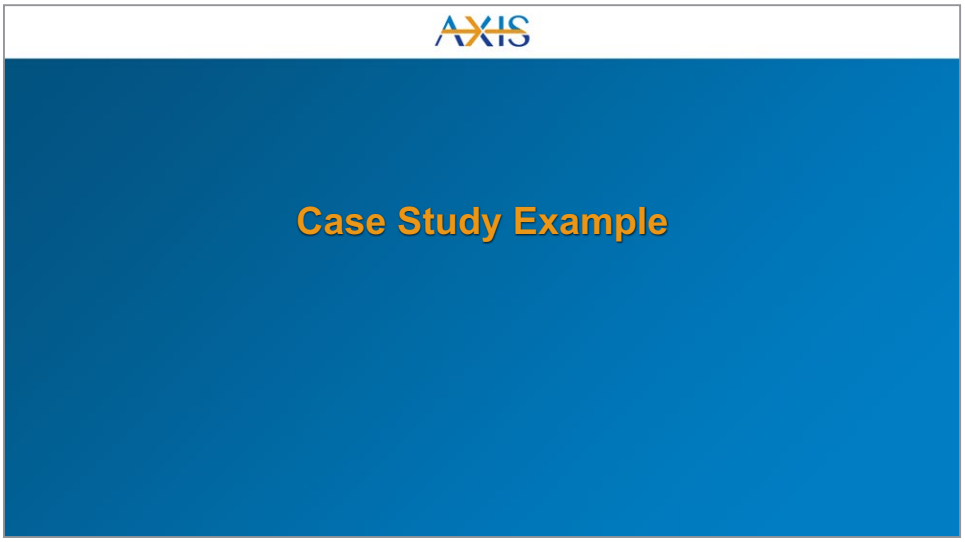


- These are very exciting times for the treatment of renal cell carcinoma, and there are other trials which should be on the radar screen for IO therapy both in first-line and in other settings. And so, these are some trials that I think are particularly promising and may as well add or change the landscape.

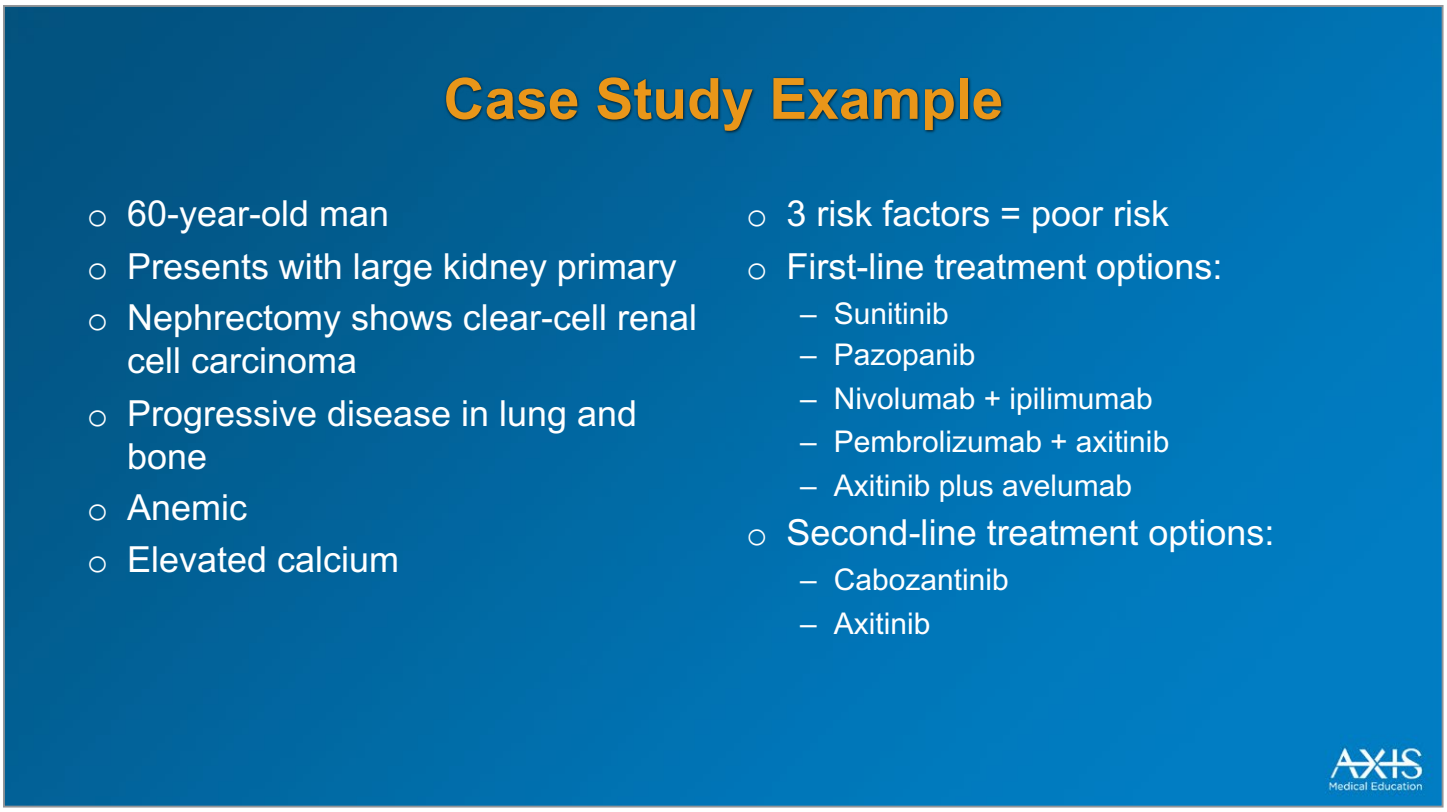
  I'd like to highlight the CLEAR trial, which is lenvatinib plus pembrolizumab versus sunitinib versus lenvatinib plus everolimus in first-line therapy. This trial has completed accrual. And it hasn't been reported out yet. But there has been a press release that the data are very promising, and it met its primary endpoints.

  The COSMIC-313 trial is investigating the triplets—cabozantinib plus nivolumab plus ipilimumab versus nivolumab plus ipilimumab. And so, I think that's really the first trial to look at a triplet to see if we can improve efficacy.

  The other setting that's very important that IOs are being studied in is in the adjuvant setting. And there's two trials to highlight—one is the KEYNOTE-464, which compares pembrolizumab to placebo in patients with high-risk RCC following nephrectomy and the CheckMate 914 trial, which compares the combination of nivolumab plus ipilimumab versus placebo versus nivolumab. A large trial and that's the one that's currently accruing.



- I will review with you a case in terms of treatment choices.



And this is a 60-year-old male who had a diagnosis of renal cell carcinoma. He presented with a large kidney primary. He had a nephrectomy showing clear cell carcinoma. And shortly, thereafter, a metastatic disease workup showed that he had progressive disease in his lung and in his bone area.

His blood work showed that he was anemic and that he had elevated calcium. And so, this patient was deemed to have three risk factors and actually be a poor-risk patient.

So, the treatment options for this patient previously would have been sunitinib or pazopanib, but this has changed now with these drugs. And so, for the most part, the two treatment options for a patient with three risk factors—having relapsed within a short time after nephrectomy, being anemic, having high calcium—is either nivolumab plus ipilimumab or axitinib plus pembrolizumab.

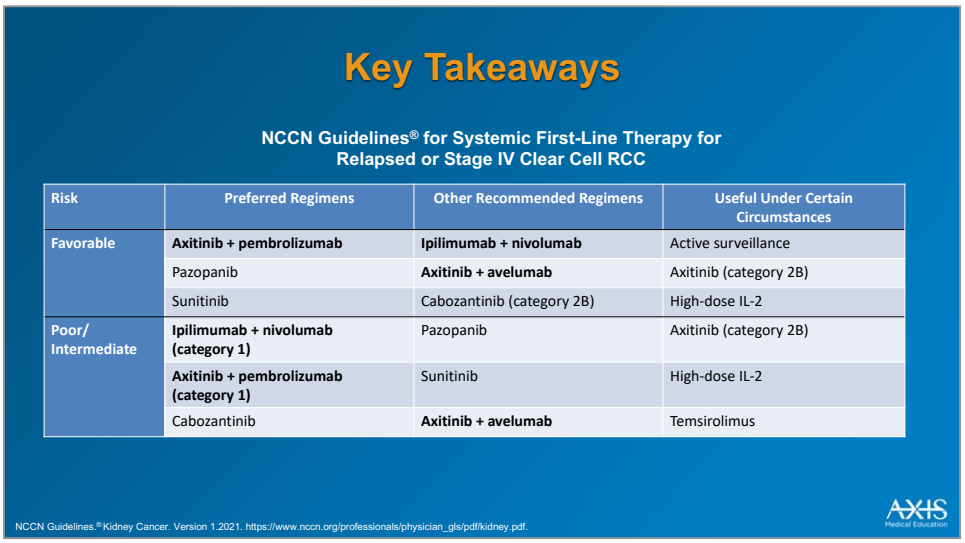
So, those would be the two treatment options, and there are advocates for each. My own recommendation would be to favor nivolumab plus ipilimumab based on the fact that we have more mature data showing durability of response and a flattening or a tail of the curve over time with progression-free survival. So, there seems to be a long-term benefit. But axitinib plus pembrolizumab would also be a good choice.

Now, that patient was treated with ipilimumab plus nivolumab, and he had a response. And the response existed for 11 months. And then he developed progressive disease. So, this happened while he was on treatment with the nivolumab maintenance. And so, in terms of this patient, one could consider adding ipilimumab, which we would not do. Studies have shown there's not really a benefit to adding ipilimumab particularly in a patient whose had the ipilimumab up front. It could be to change to a TKI therapy, and in that setting, there are retrospective data supporting cabozantinib, axitinib or lenvatinib/everolimus. It could be to go on a clinical trial, which is what we would certainly recommend.

One other option or thought would be to provide that patient with lenvatinib/pembrolizumab. Now, lenvatinib/pembrolizumab might be a choice in the future. Right now, that combination is not approved in that setting. So, the standard of care for this patient would be to choose a TKI therapy either cabozantinib, axitinib, or lenvatinib plus everolimus.

- So, in terms of lessons from this around the globe, the treatment for RCC has changed dramatically based on phase 3 trials with the different options.

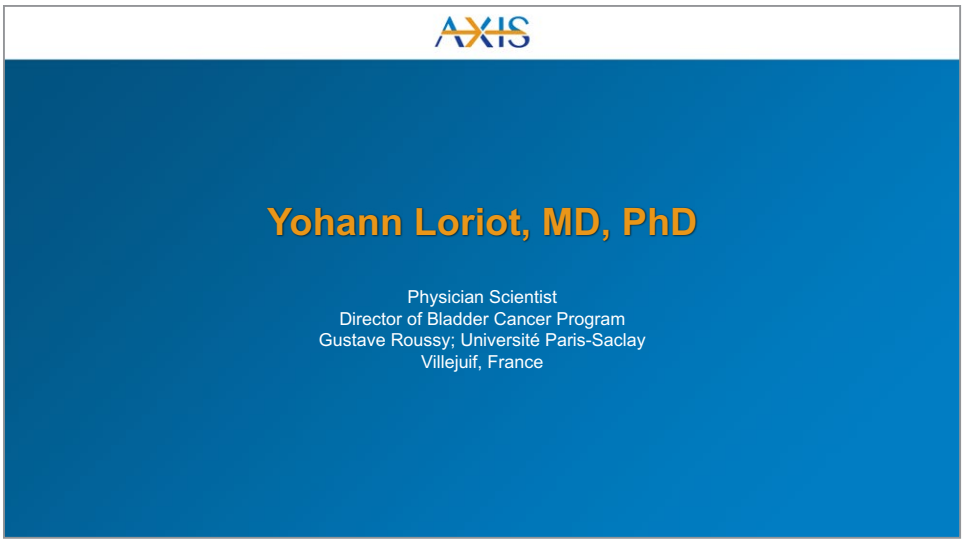
  So, not all options are available in all countries, but certainly, many patients have access to one or more options in various parts of the globe.



- Key takeaways—we made tremendous progress in the treatment of advanced RCC with the study and regulatory approval of sunitinib and pazopanib about 15 years ago followed by multiple other TKIs including cabozantinib or lenvatinib plus everolimus. The next leap was the approval of nivolumab in monotherapy and then more recently these IO/TKI combinations in first-line treatment for RCC.

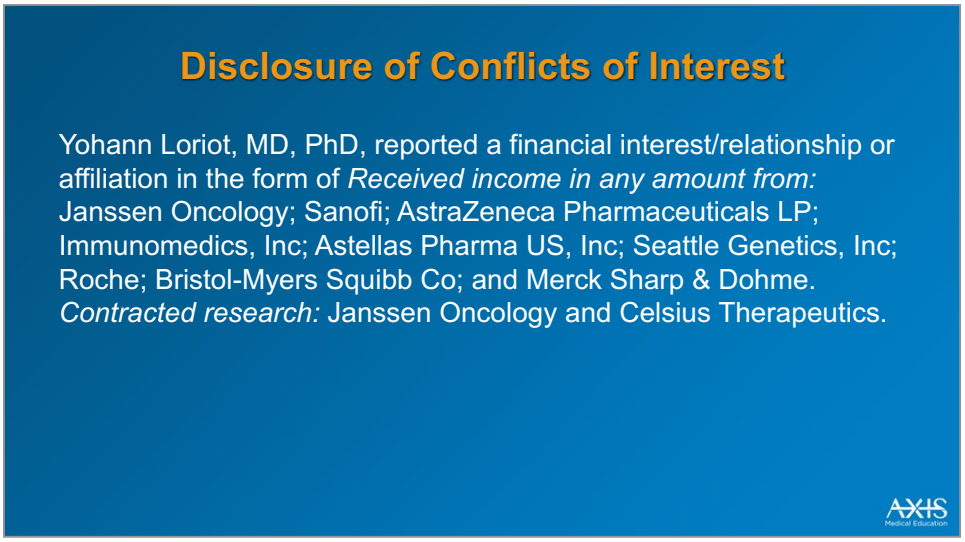
With regard to choice of these agents, for the most part, presently for patients that have intermediate or poor risk, nivolumab plus ipilimumab or axitinib plus pembrolizumab are the primary choices based on the strength of the data with improvement in overall survival. Axitinib plus avelumab is also approved in this scenario but lacks the overall survival benefit.

For patients with favorable-risk tumors, preferred treatment by the NCCN includes pembrolizumab plus axitinib. Some patients who aren't good candidates for IO therapy could be treated with TKIs alone including sunitinib or pazopanib. And there is a role, as well, for ipilimumab plus nivolumab in that population based on the long-term gain.



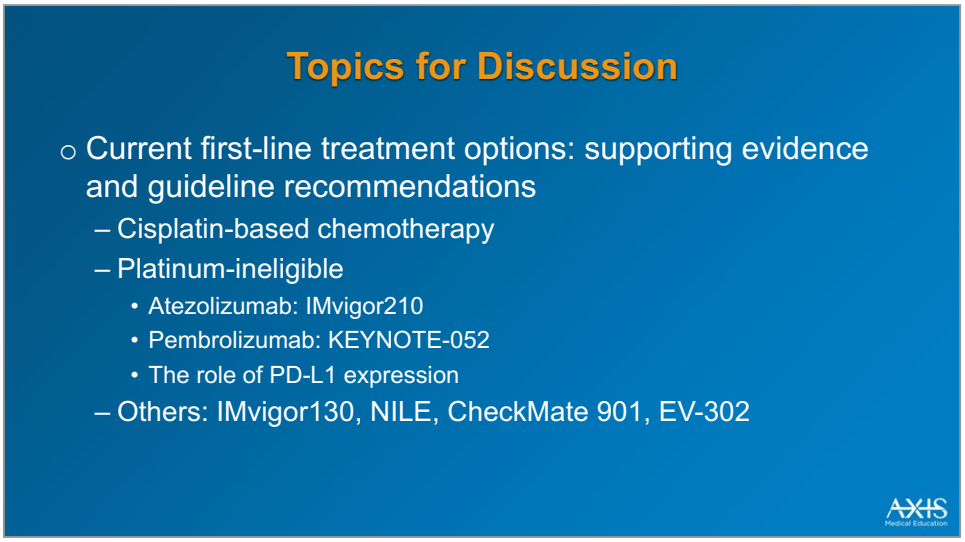
- **Yohann Loriot, MD, PhD**: I'm very pleased to be with you to discuss the strategy for immunotherapy in genitourinary oncology and especially in bladder cancer.

  I'm Yohann Loriot, I'm a Medical Oncologist at Gustave Roussy in Paris. I'm leading the bladder cancer program here in our group. And I will try to go through the recent advances in the field of immunotherapy in both advanced and localized disease in urothelial carcinoma. As you know, we have experienced very significant change in the way we are treating our patient in metastasis setting and so in earlier stage.



- And here, my financial disclosure information.

- So first of all, first-line setting.



- What are the topics I will discuss? So I will review briefly the data regarding first-line chemotherapy and then the role of immunotherapy in platinum-ineligible patients. So I will remind the ongoing phase 3 trial in this setting.

Urothelial Carcinoma Immunotherapy Approval Summary

Drug	Trial	Indication
Atezolizumab (PD-L1)	IMvigor210	Adult patients with locally advanced or metastatic UC who: • are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (≥5%) • are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status
	IMvigor211	Adult patients with locally advanced or metastatic UC who: • have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy
Avelumab (PD-L1)	JAVELIN Bladder 100	Maintenance treatment of patients with locally advanced or metastatic UC that has not progressed with first-line platinum-containing chemotherapy
	JAVELIN Solid Tumor	Patients with locally advanced or metastatic UC who: • have disease progression during or following platinum-containing chemotherapy • have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
Durvalumab (PD-L1)	Study 1108	Adult patients with locally advanced or metastatic UC who: • have disease progression during or following platinum-containing chemotherapy • have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
Nivolumab (PD-1)	CheckMate 275	Patients with locally advanced or metastatic UC who: • have disease progression during or following platinum-containing chemotherapy • have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
Pembrolizumab (PD-1)	KEYNOTE-052	Patients with locally advanced or metastatic UC who: • are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (≥10) • are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status
	KEYNOTE-045	Patients with locally advanced or metastatic UC who: • have disease progression during or following platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; UC, urothelial carcinoma.
Tecentriq (atezolizumab) prescribing information,2020; Keytruda (pembrolizumab) prescribing information, 2020; Opdivo (nivolumab) prescribing information, 2020; Imfinzi (durvalumab) prescribing information, 2020; Bavencio (avelumab) prescribing information, 2020.

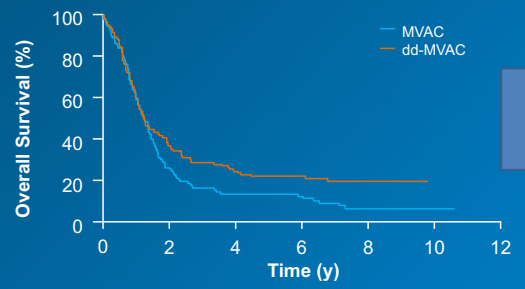
AXIS Medical Education

So 5 different PD-1 and PD-L1 inhibitors have been approved over the last 3, 4 years in metastasis setting in US and 3 in Europe for patients who had disease progression after platinum-based chemotherapy. These include 2 PD-1 inhibitors, pembrolizumab and nivolumab, and 3 PD-L1 inhibitors, atezolizumab, avelumab, and durvalumab. The level of agents is different. Pembrolizumab has been approved based on data from positive phase 3 trial, the KEYNOTE-045. For 2 agents, we have soon approval in the first-line setting—atezolizumab and pembrolizumab—have been approved following the data from 2 phase 2 trials, IMvigor210 and KEYNOTE-052, respectively.

For this indication, only patients who are not eligible to cisplatin-based chemotherapy can receive this adjunct in this case and a high PD-L1 expression is required using CPS score or IC score. So patients who are not eligible to any platinum-based agent can be treated with either atezolizumab or pembrolizumab regardless of PD-L1 expression. More recently—and we will discuss this later in a few minutes—avelumab has been approved in US as maintenance treatment of patient with metastatic urothelial carcinoma that has not progressed with first-line platinum-containing chemotherapy.

dd-MVAC Efficacy in Metastatic Disease

Trial/Analysis	N	ORR (%)	Median PFS (mo)	Median OS (mo)
Phase 3 study of classic MVAC versus dd-MVAC + G-CSF	263	Classic MVAC: 58 **dd-MVAC: 72** *P* = .016	Classic MVAC: 8.1 **dd-MVAC: 9.5** HR 0.73 (95% CI 0.56-0.95) *P* = .017	Classic MVAC: 14.9 **dd-MVAC: 15.1** HR 0.76 (95% CI 0.58-0.99) *P* = .042



5-year survival rate patients treated with dd-MVAC: 21.8% vs classic M-VAC: 13.5%

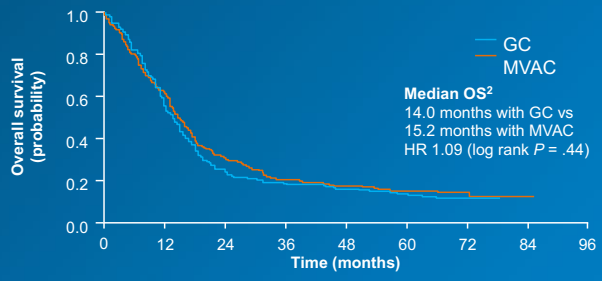
dd-MVAC, dose-dense M-VAC; G-CSF, granulocyte colony-stimulating factor; MVAC, methotrexate, vinblastine, doxorubicin, cisplatin; ORR, overall response rate OS, overall survival; PFS, progression-free survival.
Sternberg et al. *Eur J Cancer* 2006;42:50-54.

AXIS Medical Education

- So at this point, maybe I should remind the standard of care in first line dose-dense MVAC was compared to the classic MVAC in a phase 3 trial 15 years ago, and 263 patients were randomized. As you can see here, those on MVAC seems to better than historical MVAC. Median overall survival was more or less 15 months. As you can see here, the 5-year survival rate for patients treated with dose-dense MVAC was 22% versus only 14% for classical MVAC.

Cisplatin/Gemcitabine Efficacy in Metastatic Disease

Trial/Analysis	N	ORR (%)	Median PFS (mo)	Median OS (mo)
Phase 3 study of classic MVAC vs cisplatin/gemcitabine[1,2]	405	Classic MVAC: 46 **Cisplatin/gemcitabine: 49** HR 0.97 (95% CI: 0.62-1.52) *P* = .51	Classic MVAC: 8.3 **Cisplatin/gemcitabine: 7.7** HR 1.09 (95% CI 0.89-1.34) *P* = .63	Classic MVAC: 15.2 **Cisplatin/gemcitabine: 14.0** HR 1.09 (95% CI 0.88-1.34) *P* = .66



GC, gemcitabine/cisplatin; MVAC, methotrexate, vinblastine, doxorubicin, cisplatin; ORR, overall response rate OS, overall survival; PFS, progression-free survival.
1. von der Maase et al. *J Clin Oncol.* 2000;18:3068-3077.
2. von der Maase et al. *J Clin Oncol.* 2005;23:4602-4608.

AXIS Medical Education

- Another combination was compared to the classical MVAC, the cisplatin/gemcitabine combinations. Again, the median overall survival was close to 15 months with no difference between the 2 regimens. Given the better safety profile of cisplatin/gemcitabine combinations, this regimen was also seen as a new standard, and it widely and rapidly used in first-line setting.

Consensus Definition of Patients With Metastatic Urothelial Carcinoma Who Are Unfit for Cisplatin-based Chemotherapy

Patients meeting at least one of the following are considered 'unfit'

- WHO or ECOG performance status of 2, or Karnofsky performance status of 60%-70%
- Creatinine clearance (calculated or measured) less than 1 mL/s
- CTCAE version 4, grade 2 or above audiometric hearing loss
- CTCAE version 4, grade 2 or above peripheral neuropathy
- NYHA class III heart failure

30%-50% of patients with metastatic disease are ineligible ('unfit') for cisplatin

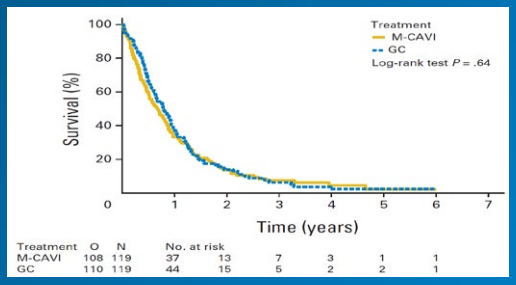
CTCAE, common terminology criteria for adverse events; ECOG, Eastern Cooperative Oncology Group; NYHA, New York Heart Association; WHO, World Health Organization.
Galsky et al. *Lancet Oncol.* 2011;12:211-214.

AXIS Medical Education

- The issue is that around 14% to 15% of patients cannot receive cisplatin-based combinations due to comorbidities. There is not a strong consensus on this criteria; however, the most frequent criteria, at least for clinical trial, are those described on this slide. Poor performance status, renal dysfunction, hearing loss, neuropathy, and heart failure. When these conditions are met in a patient, we try not to involve cisplatin because it is expected to induce serious toxicity. Carboplatin is the preferred option in these patients.

EORTC 30986: Gemcitabine/Carboplatin vs M-CAVI in Cisplatin-ineligible (unfit) Urothelial Cancer

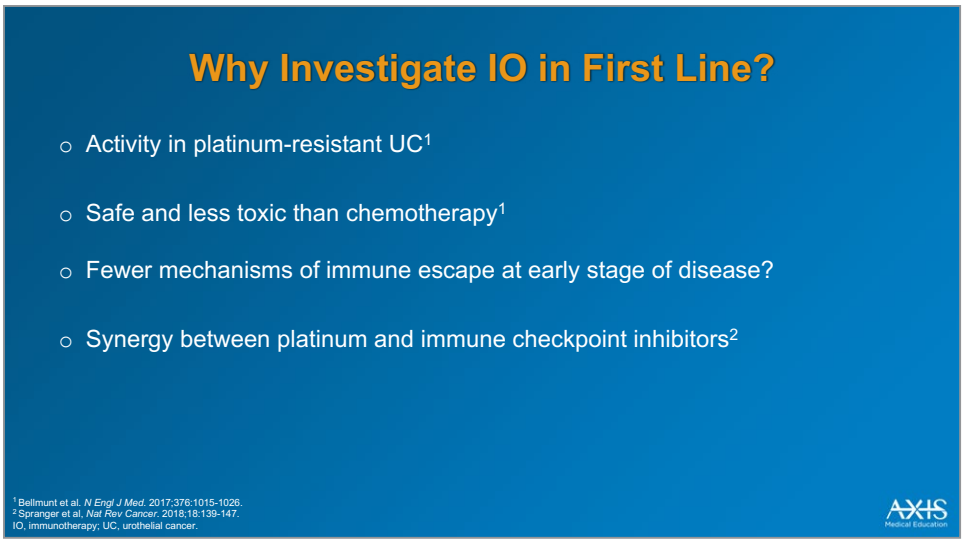
Trial/Analysis	N	ORR (%)	Median PFS (mo)	Median OS (mo)
Phase 3 study of gemcitabine/carboplatin vs M-CAVI	626	Gemcitabine/carboplatin: 41.2 **M-CAVI: 30.3** P = .08	Gemcitabine/carboplatin: 9.3 **M-CAVI: 8.1** HR 0.94 (95% CI 0.72-1.22) P = .64	Gemcitabine/carboplatin: 5.8 **M-CAVI: 4.2** HR 1.04 (95% CI: 0.80-1.35) P = .78



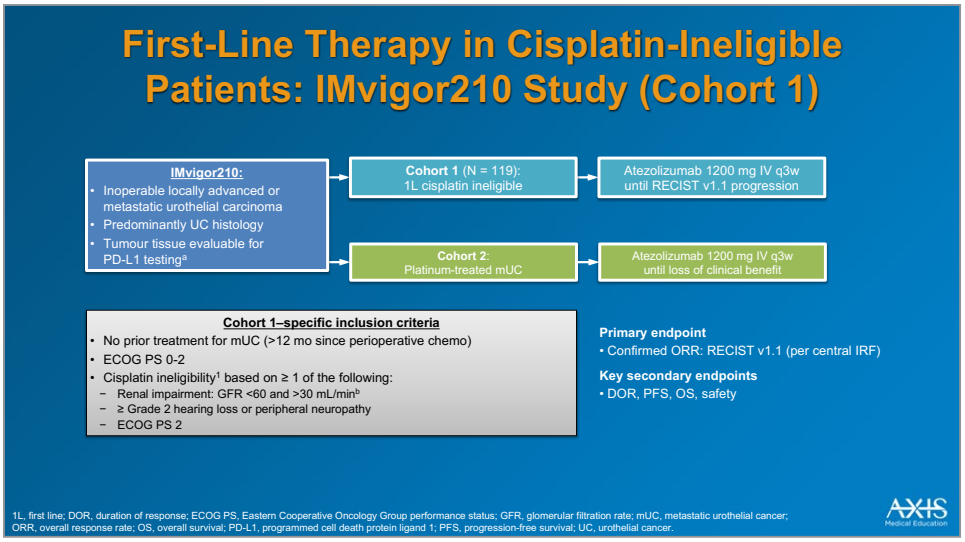
GC, gemcitabine/cisplatin; M-CAVI, methotrexate/carboplatin/vinblastine; ORR, overall response rate OS, overall survival; PFS, progression-free survival.
De Santis et al. *J Clin Oncol.* 2012;30:191-199.

AXIS Medical Education

- And this recommendation stems from a trial conducted by EORTC group 10 years ago. Patients with either a poor performance status or renal dysfunction were randomized to either carboplatin/gemcitabine or MVAC with carboplatin instead of cisplatin and removal of doxorubicin. Again, no difference between the 2 approaches. We can see that the prognosis of this patient is even poorer with a median overall survival of 9 months and median PFS of 6 months. But again, as carboplatin/gemcitabine was much better tolerated, it is a standard of care when we use a chemotherapy in patients unfit for cisplatin-based chemotherapy.



- So in this context, why we should investigate immunotherapy in first-line setting? Firstly, of course, this PD-1 and PD-L1 inhibitors have activity in more advanced disease. So if we had evidence about the impact of immunotherapy in urothelial carcinoma. Secondly—and importantly enough—this adjunct has the potential to be safe and less toxic than chemotherapy. Can also expect fewer mechanisms of immune escape at early stage. Finally, some preclinical work indicated potential activity of even synergy between platinum and immune checkpoint inhibitors. So obviously, there was a good rationale.



- That was the approach in the IMvigor210 trial. In this phase 2 trial, 2 cohorts were designed.

First-Line Therapy: IMvigor210 Study (Cohort 1)

Timing of Evaluated Analyses[c]

IMvigor210 Cohort 1 N = 119 → Sep 14, 2015 (primary analysis) median follow-up: 8.5 mo → Mar 14, 2016 median follow-up: 14.4 mo → Jul 4, 2016 median follow-up: 17.2 mo → Jul 12, 2017 median follow-up: 29.3 mo

	Sep 14, 2015	Mar 14, 2016	Jul 4, 2016	Jul 12, 2017
ITT (N = 119)				
Responders, n (**ORR, %**)	23 (**19%**)	28 (**24%**)	27 (**23%**)	28 (**24%**)
Ongoing responses, n (%)[c]	22 (96%)	21 (75%)	19 (70%)	19 (68%)
IC2/3[a] (n = 32)				
Responders, n (**ORR, %**)	7 (**22%**)	9 (**28%**)	9 (**28%**)	9 (**28%**)
Ongoing responses, n (%)[c]	7 (100%)	6 (67%)	6 (67%)	6 (67%)
IC0/1[b] (n = 87)				
Responders, n (**ORR, %**)	16 (**18%**)	19 (**22%**)	18 (**21%**)	19 (**22%**)
Ongoing responses, n (%)[c]	15 (94%)	15 (79%)	13 (72%)	13 (68%)

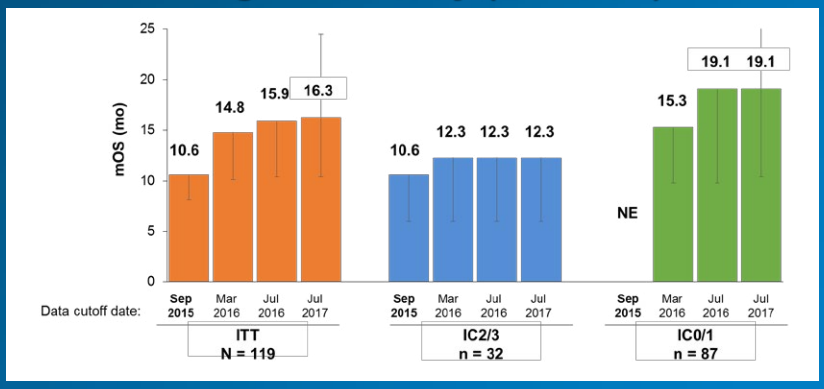
IC2/3, PD-L1 expression ≥5%; IC0/1, PD-L1 expression <5%; ITT, intention to treat; ORR, objective response rate; PD-L1, programmed cell death protein ligand 1.
Duran et al. Poster presentation at the Global Congress on Bladder Cancer 2018.

AXIS Medical Education

- In the cohort 1, our patients ineligible for cisplatin-based chemotherapy and were treated with atezolizumab until progression. The criteria were those shown in my previous slide.

  The primary endpoint was overall response rate. In this study, overall response rate was around 25%, and PD-L1 status did not impact the result.

First-Line Therapy: IMvigor210 Study (Cohort 1)



IC2/3, PD-L1 expression ≥5%; IC0/1, PD-L1 expression <5%; ITT, intention to treat; mOS, median overall survival; ORR, objective response rate; PD-L1, programmed cell death protein ligand 1.
Duran et al. Poster presentation at the Global Congress on Bladder Cancer 2018.

AXIS Medical Education

- Regarding the overall survival, it was a good surprise to see that the median overall survival reached 16 months in this population of patients. Remember that in EORTC study, the median overall survival was 9 months. Again, no impact of PD-L1 expression on the results.

KEYNOTE-052: First-Line Pembrolizumab in Cisplatin-Ineligible mUC

Median F/U: 11.5 mo

Patients (N = 370)
- Advanced UC
- No prior chemo for advanced UC
- ECOG PS 0-2
- Ineligible for cisplatin:
  - CrCl <60 ml/min
  - ECOG PS 2
  - Neuropathy or hearing loss grade ≥2
  - NYHA class III heart failure

→ **Pembrolizumab 200 mg IV/3 wk Up to 2 y** →

Primary endpoint
- ORR

Secondary endpoints
- ORR in PD-L1+
- DOR, PFS, OS, safety

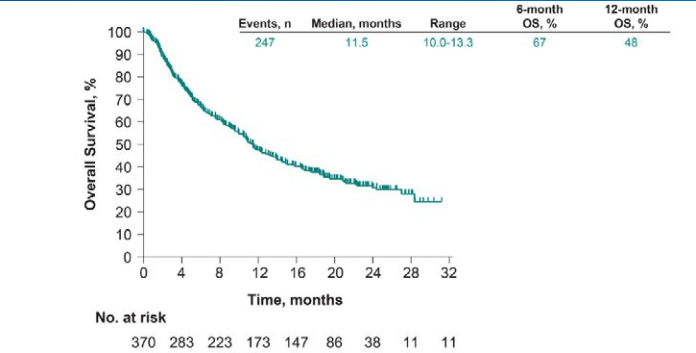
- ORR = 29%, CR = 8%
- ORR = 51% for PD-L1–positive patients (CPS >10%) vs 23% for PD-L1–negative patients (CPS <10%)
- 18 T-cell–associated gene signature correlated with response

:PS, combined positive score; CR, complete response; CrCl, creatine clearance; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; F/U, follow-up; UC, metastatic urothelial cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death protein ligand 1; PFS, progression-free survival; UC, urothelial cancer.
Vuky et al. *J Clin Oncol*. 2018;36:4524.

AXIS Medical Education

Another trial conducted in parallel assessed pembrolizumab in exactly the same population of patients. The study enrolled more patients—270 patients. In this study, overall response rate was 29%; 8% of patients achieved complete response. CPS score was associated with the efficacy since overall response rate was 51% for PD-L1–positive patients versus 23% for PD-L1–negative patients.

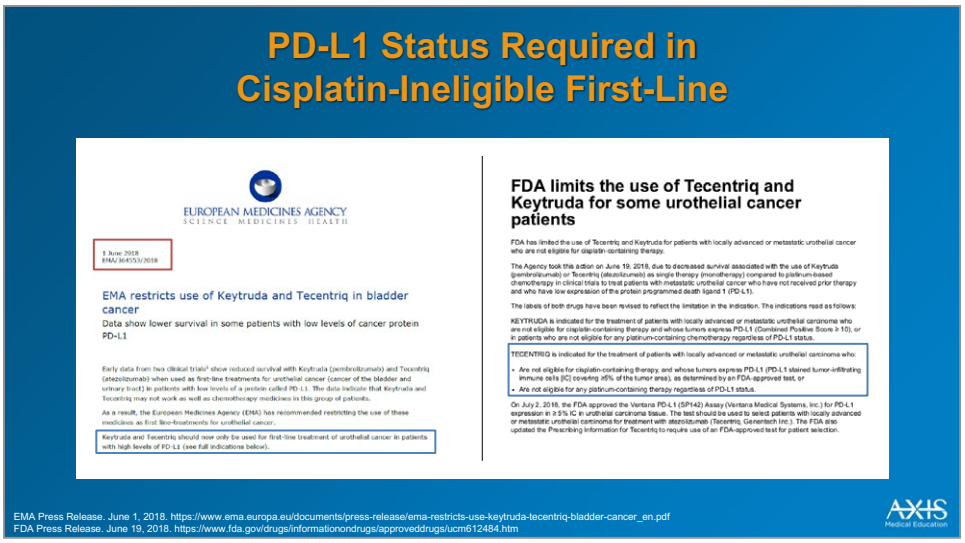
KEYNOTE-052: Overall Survival



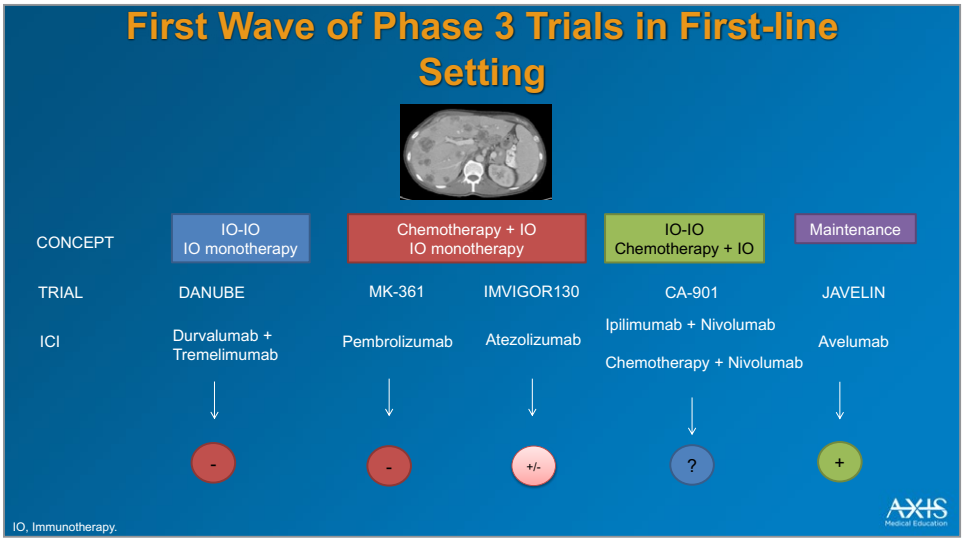
OS, overall survival.
Vuky et al. *J Clin Oncol*. 2018;36:4524.

AXIS Medical Education

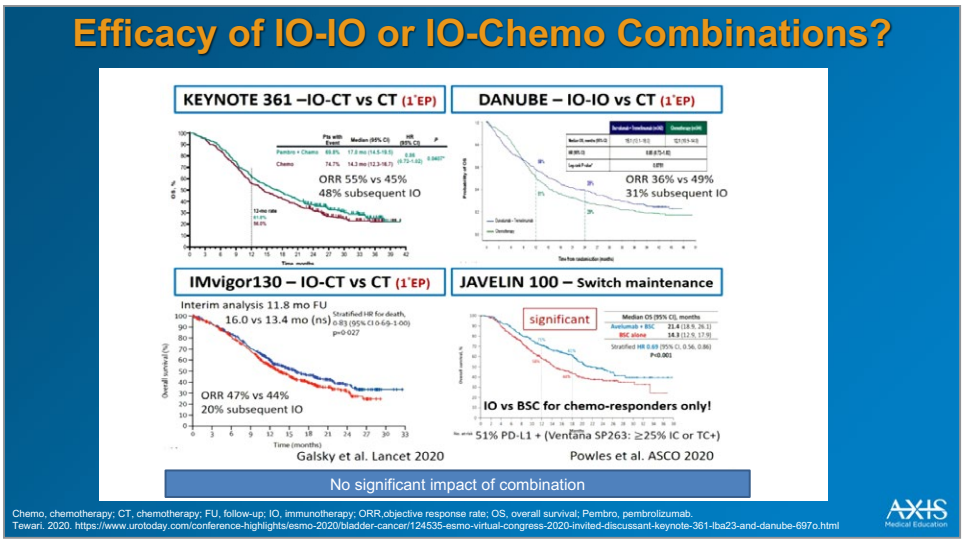
Here is the median overall survival. Median overall survival was only 12 months, but still better with historical data reported with the use of chemotherapy. So based on this result, both atezolizumab and pembrolizumab were approved in first-line setting in patients ineligible for cisplatin-based chemotherapy regardless of PD-L1 expression.



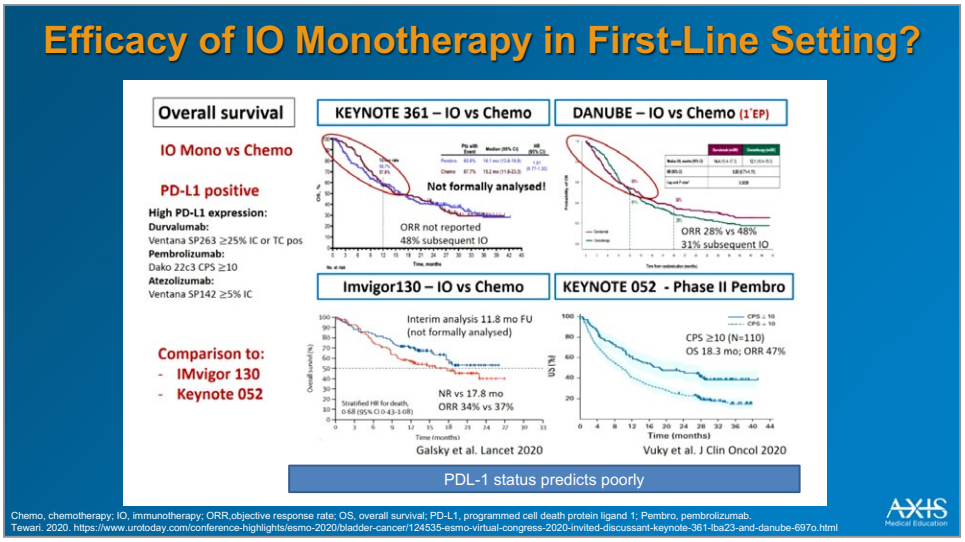
- Surprisingly, during the summer 2018, FDA and EMA indicated that both pembrolizumab and atezolizumab should be used for first-line of urothelial carcinoma in patient with high level of PD-L1 expressions. So FDA allowed the use of this agent for patients who were not eligible for any platinum-containing therapy regardless of PD-L1 status. At this stage, nobody knew on what data these statement were based on. Several phase 3 trials were ongoing. An interim analysis drove the decision of these authorities.



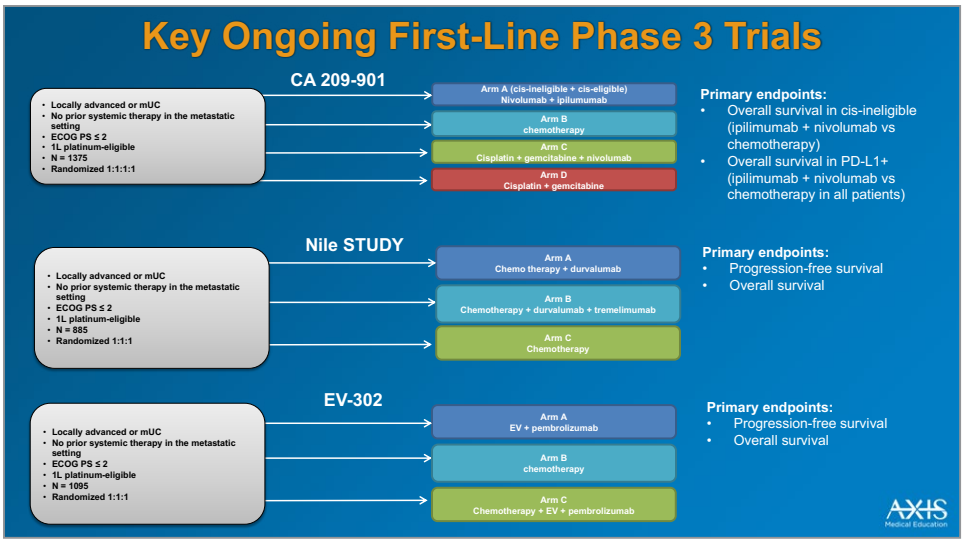
- So based on this data and the result of trials conducted in second-line setting, a couple of phase 3 trials have been designed. Each of them investigated a new combination – either a combination of immunotherapy or a combination of chemotherapy plus immunotherapy in first-line setting in both cisplatin-eligible and cisplatin-ineligible patient. The second experimental arm was added with the immunotherapy as single agent. Usually, the control arm were the chemotherapy only. One trial was a bit different. The JAVELIN trial investigated the impact of avelumab, given as maintenance, for only 4 to 6 cycles of chemotherapy. Now we have data for a lot of them, DANUBE, KEYNOTE-361, IMvigor130 failed to show a significant overall survival benefit. CheckMate 901 is still enrolling patients. And finally, JAVELIN trial is the only that improve overall survival.



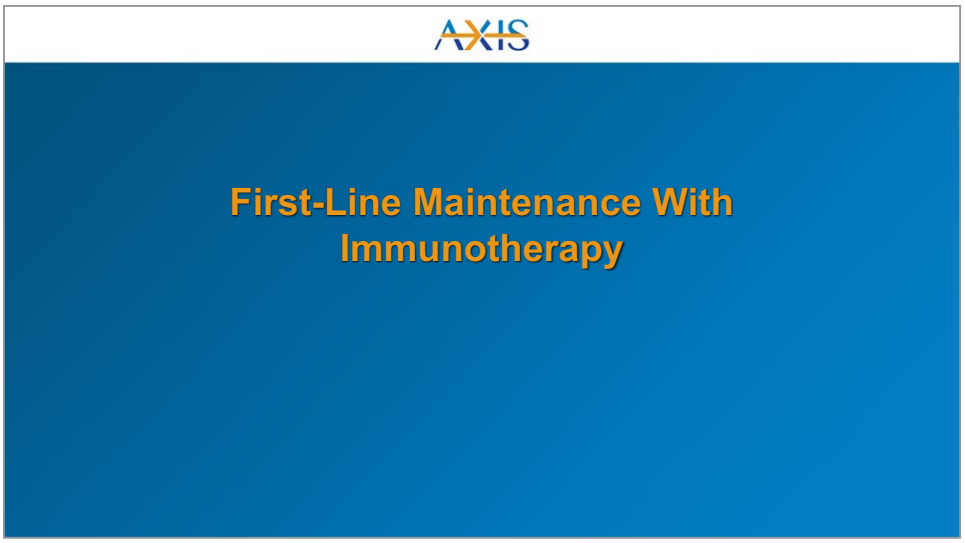
- So here are the data of combination arm in this trial. As you can see, the curves are very similar. The differences are not significant. There is a trend maybe in the IMvigor130, the difference might be significant in the future with longer follow-up. The overall response rates are not different. In DANUBE, again, no significant difference in ITT population. You can see on the bottom right panel, that by contrast, the results in JAVELIN are clearly different. Hazard ratio was 0.69, and median overall survival was 14 months in the control arm versus 21 months in the avelumab arm.



- So now, we look at the single immunotherapy arm. This arm were enriched in PD-L1–positive patients following the FDA and EMA release that I described earlier. The curves cross over and more deaths in the immunotherapy arm within the first 3 months were observed. Anyway, there's no difference between single agent and chemotherapy. In IMvigor130, hazard ratio was 0.69, but the difference was not formally analyzed given the statistical design of the trial. And so, only 20% of the patient enrolled in the control arm received subsequent immunotherapy in this trial versus around 50% in KEYNOTE-361 and DANUBE trial.



So we have still phase 3 trial investigating immunotherapy in first line. CheckMate 901, as I said earlier, but also the NILE study. These assessing the concept of chemotherapy combined with immunotherapy. The last one, EV-302, compare enfortumab vedotin, an antibody-drug conjugate targeting nectin-4 combined with pembrolizumab chemotherapy. It is approved in US given the data of EV-201 study in past platinum plus immune checkpoint setting. Recently, where there's press release indicating that the phase 3 EV-301, comparing EV to chemotherapy in third line, was positive. So, 2 years ago, EV-103 study reported impressive interim results with the combination in first-line setting with a 70% overall response rate in cisplatin-ineligible patients. So building on this encouraging data, EV-302 was designed and launched.



So let's move in the details now of the JAVELIN study.

The role of the maintenance therapy was investigated recently in 3 important studies. The rationale that platinum-based chemotherapy mean just more mutation, more neoantigens that prime immune system to be active with subsequent PD-1 or PD-L1 inhibitors. As so, by including patients that benefit from chemotherapy, we select patients who are more likely to respond to immune checkpoint inhibitors. Lastly, chemotherapy can induce detrimental effect of immune system when given concomitantly to immunotherapy. So sequential strategy may be relevant than concomitant strategy.

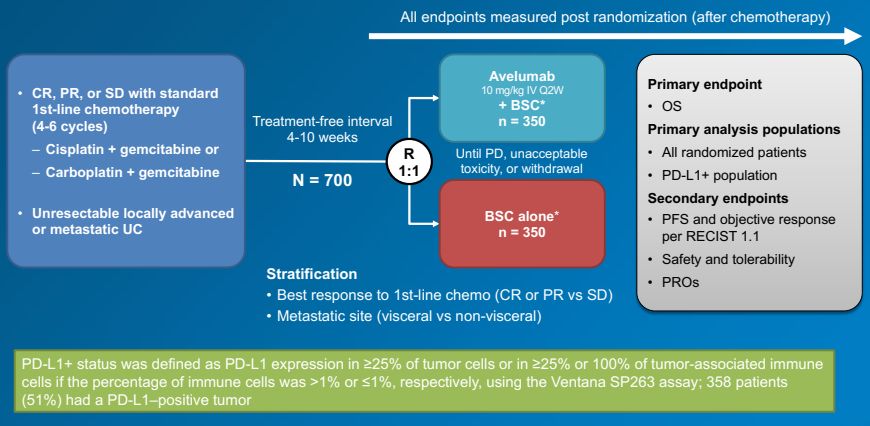
Topics for Discussion

- First-line maintenance with immunotherapy
  - Role and rationale for maintenance therapy in metastatic urothelial cancer
  - Avelumab: JAVELIN Bladder 100
    - Examining the overall survival benefit
  - Pembrolizumab: Phase 2 HCRN GU14-182 trial
  - Others
- Practical application case: maintenance therapy for a patient with response to first-line chemotherapy

AXIS Medical Education

- So we have a phase 3 trial, JAVELIN, with avelumab, and a phase 2 trial with pembrolizumab.

JAVELIN Bladder 100 Study Design (NCT02603432)

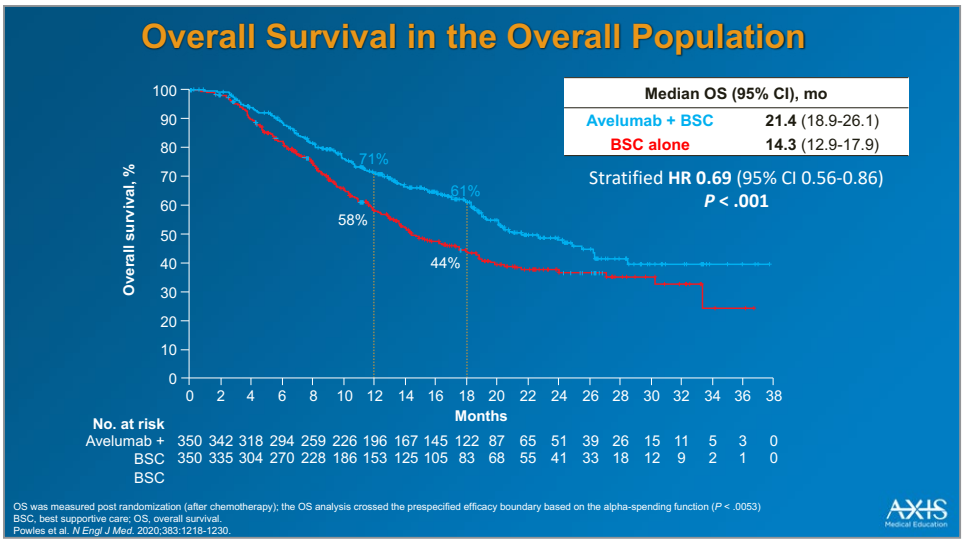


PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumor

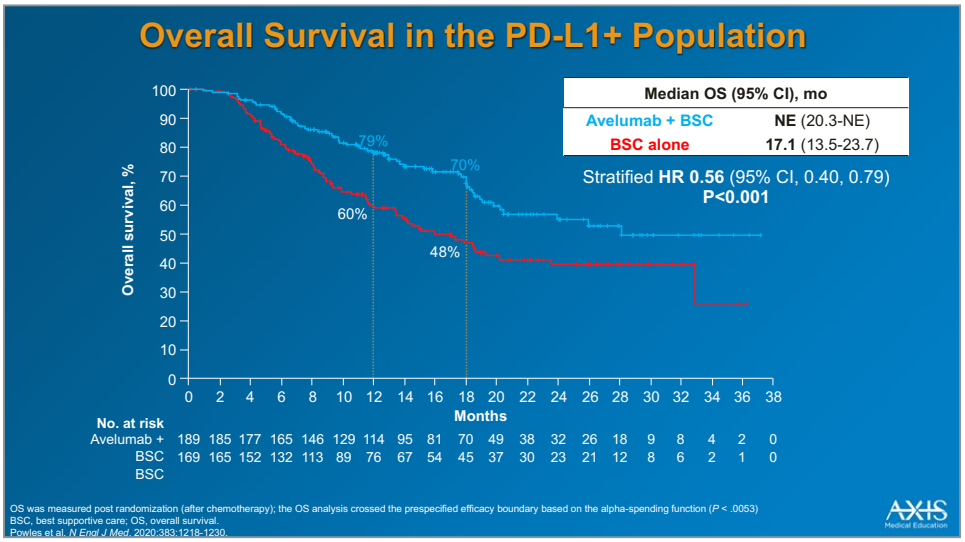
BSC, best supportive care; CR, complete response; OS, overall survival; PD, progressive disease; PD-L1, programmed cell death protein ligand 1; PR, partial response; PROs, patient-reported outcomes; SD, stable disease; UC, urothelial cancer.
Powles et al. *N Engl J Med.* 2020;383:1218-1230.

AXIS Medical Education

- This is a design of JAVELIN. Only patients who achieve at least stable disease were allowed to be included in this study. The JAVELIN enrolled both cisplatin-eligible and cisplatin-ineligible patients. Almost 700 patients were enrolled and received, after randomization, either avelumab every 2 weeks until disease progression or toxicity or managed by surveillance only. The primary endpoint was overall survival in all randomized patients and in PD-L1–positive patients. Secondary endpoint including progression-free survival, safety, and quality of life. The primary endpoint was met. The risk of death was reduced by 31% with the use of maintenance avelumab.

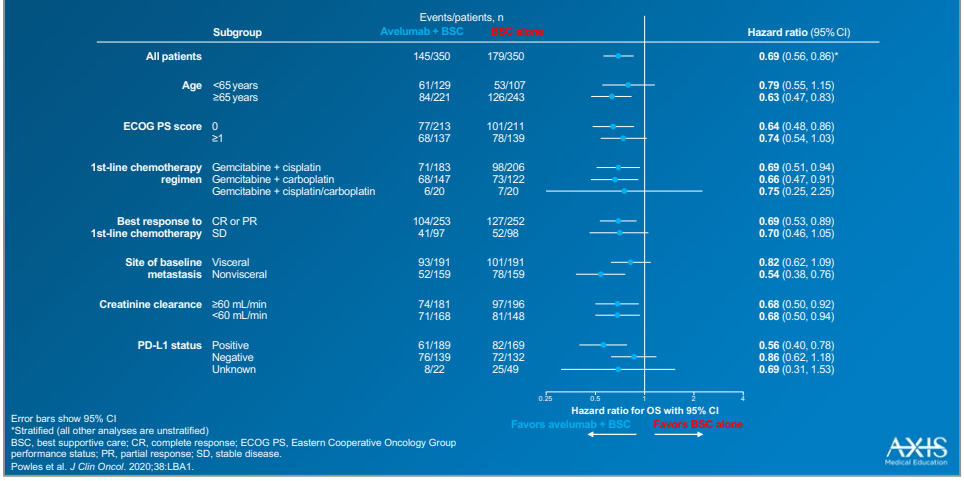


- Median overall survival in avelumab arm was 21 months versus 14 months in the control arm.



- In PD-L1–positive patients, hazard ratio was 0.56 and median overall survival was not met in avelumab arm versus 17 months in the control arm.

Subgroup Analysis of Overall Survival in the Overall Population



Error bars show 95% CI
*Stratified (all other analyses are unstratified)
BSC, best supportive care; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; PR, partial response; SD, stable disease.
Powles et al. *J Clin Oncol.* 2020;38:LBA1.

- Globally, all subgroups benefit from this approach. The benefit was observed regardless of PD-L1 expression, regardless of the type of chemotherapy or clinical response to prior chemotherapy.

Subsequent Anticancer Therapy

	Overall population		Subgroup who discontinued study therapy due to PD	
	Avelumab + BSC (N=350)	BSC alone (N=350)	Avelumab + BSC (N=189)	BSC alone (N=263)
Discontinued and received subsequent drug therapy, %	**42.3**	**61.7**	**70.4**	**75.3**
PD-L1/PD-1 inhibitor	**6.3**	**43.7**	**9.0**	**52.9**
Fibroblast growth factor receptor inhibitor	2.6	2.3	4.8	3.0
Any other drug	40.0	34.0	67.2	41.8
Discontinued with no subsequent drug therapy, %	33.4	30.9	29.6	24.7
Study treatment ongoing, %	24.3	7.4	–	–

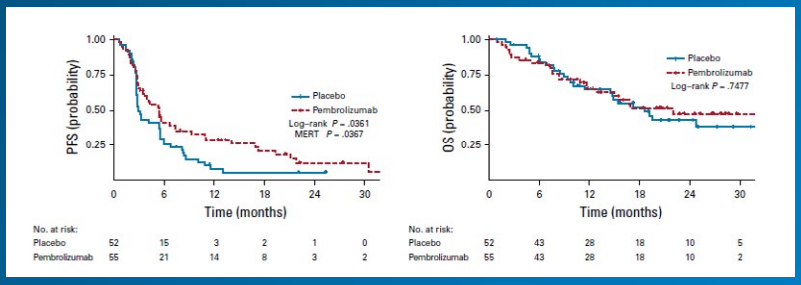
75% of patients with disease progression received a second-line therapy
Among them, Immunotherapy was the 2nd therapy in two thirds of patients

BSC, best supportive care; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1.
Powles et al. *J Clin Oncol.* 2020;38:LBA1.

- Importantly, more than 16% of the patients in the control arm receive a second line, and 44% had PD-L1 or PD-1 inhibitor, which I think reflect the reality of the management of these patients in daily practice.

  If we focus now on patients who went off the study due to disease progression, three-quarter of them receive a second-line therapy, which was immunotherapy in two-third among them.

HCCR Study



Among patients in placebo group:

- 50% received pembrolizumab as subsequent therapy
- 23% died
- 24.5% still on study

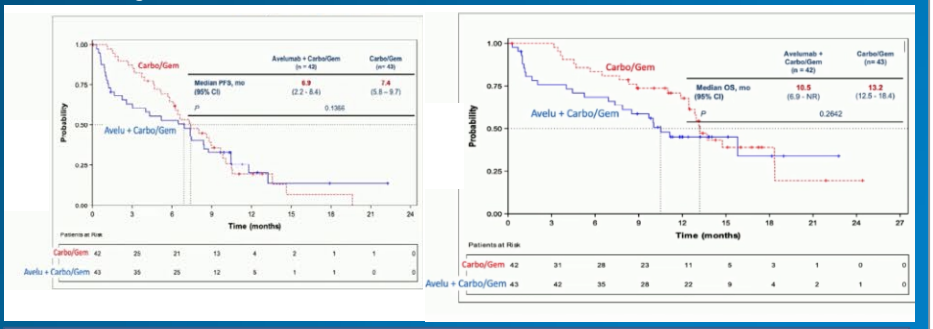
Galsky et al. *J Clin Oncol.* 2020;38:1797-1806.

AXIS Medical Education

- As I said before, another study investigated the concept of maintenance. It was an academic trial conducted in US comparing pembrolizumab versus placebo in patients with at least stable disease after initial chemotherapy. Median PFS was significantly better in the pembrolizumab arm. There was no difference for overall survival between the 2 arm. In this trial, 50% of the patients enrolled in the placebo arm received pembrolizumab as subsequent therapy; 23% of the patients died at time of analysis.

INDUCOMAIN Study

Progression-free Survival | **Overall Survival**



Front-line IO produces inferior results to front-line IO + chemotherapy combination – chemotherapy should be started first

Avelu, avelumab; Carbo, carboplatin; Gem, gemcitibine; IO, immunotherapy; NR, not reached.
Valderrama et al. *Ann Oncol.* 2020;31:S1142-S1215.

AXIS Medical Education

- In this context, another piece of the puzzle stems from this study conducted by the Spanish group. Cisplatin-ineligible patients were randomized to be treated with either first avelumab and then chemotherapy or upfront chemotherapy. There was no different for PFS. But for overall survival, since they're starting chemotherapy first, it's better strategy than treating this patient with immunotherapy first. So chemotherapy should be given first.

Case Study Example

81-year-old man with diagnosis of metastatic urothelial carcinoma

Comorbidities:

- Renal dysfunction (creatinine clearance = 51 mL/min)
- Coronary heart disease
- Pacemaker for atrial fibrillation

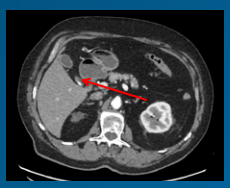
Disease history

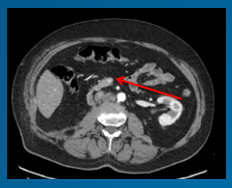
- Hematuria in February 2018 -> mass in the right upper urinary tract
- Nephroureterectomy in June 2018
- No perioperative systemic therapy
- October 2018: no symptoms, excellent health status (PS1)

AXIS Medical Education

So let's try to use this data in a clinical case. This is an 81-year-old man diagnosed with metastatic urothelial carcinoma has several comorbidities with renal dysfunction and coronary artery disease. The disease story started in February 2019 where they observed a gross hematuria which revealed a mass in the right upper urinary tract. A radical surgery was perform in June, and no perioperative systemic therapy was given. In October, he was doing well. But several lymph node was diagnosed in the retroperitoneum along with a local relapse.

Case Study Example





Which additional tests do you ask for ?

a) PD-L1 status
b) FGFR2/3 mutation
c) TMB
d) Other

PD-L1, programmed cell death protein ligand 1; TMB, tumor mutation burden.

AXIS Medical Education

So the question, at this point, is which additional test do you ask for? PD-L1 status, *FGFR2* or *3* mutations, mutational burden, or other.

Case Study Example

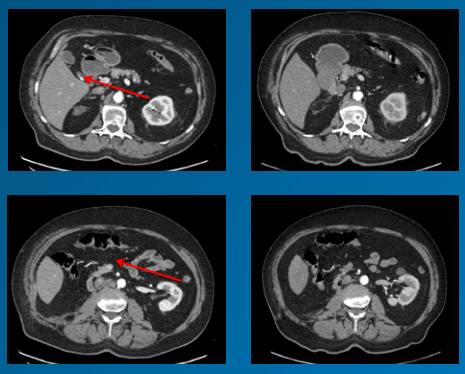
- PD-L1 status : CPS = 10%, *FGFR2/3* WT
- Which strategy sounds optimal for this patient in late 2020?
  a) Chemotherapy first and then avelumab as maintenance
  b) Chemotherapy and then close follow-up
  c) PD-L1 inhibitor in first line
  d) Chemotherapy + PD-L1 inhibitor
  e) Other

CPS, combined positive score; PD-L1, programmed cell death protein ligand 1; TMB, tumor mutation burden.

AXIS Medical Education

- So for this patient, you can request CPS or IC score and *FGFR3* status. CPS score was 10%, and *FGFR2* and *3* were wild-type. So which strategy sound optimal for this patient in late 2020? Chemotherapy first and then avelumab as maintenance; chemotherapy and then close follow-up; PD-L1 inhibitor in first line; chemotherapy plus PD-L1 inhibitor; or other.

Case Study Example



- The patient received 4 cycles of carboplatin + gemcitabine
- Complete response on computed tomography scan

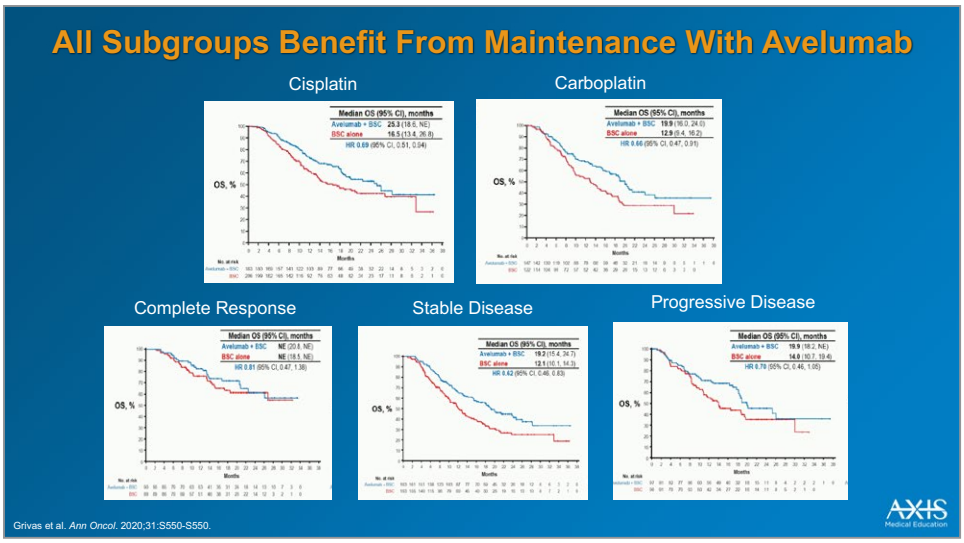
Now, do you consider:

a) Avelumab as maintenance?
b) Chemotherapy and then close follow-up?

AXIS Medical Education

- So the patient received 4 cycles of carboplatin combined with gemcitabine, and a complete response was achieved. So now, do you consider avelumab as maintenance or chemotherapy and then close follow-up?

All Subgroups Benefit From Maintenance With Avelumab



Grivas et al. *Ann Oncol*. 2020;31:S550-S550.

- In JAVELIN trial, as I said before, a lot of subgroups were analyzed, and we observed that the benefit of avelumab, as maintenance, was observed regardless of the type of chemotherapy and regardless of the status of response to the prior chemotherapy. So patients with a complete response benefit from avelumab as maintenance.

ESMO Guidelines

Patient Characteristics[b]	Treatment Recommendation
Cisplatin eligible	Cisplatin-based ChT [I, A] followed by maintenance avelumab for tumours which have not progressed on ChT [I,A][a]
Cisplatin ineligible and PD-L1 unknown or negative	Gemcitabine/carboplatin [II, B] followed by maintenance avelumab for tumours which have not progressed on ChT [I,A][a]
Cisplatin ineligible and PD-L1-positive	Gemcitabine/carboplatin [II, B] followed by maintenance avelumab for tumours which have not progressed on ChT [I, A][a] Or Atezolizumab or pembrolizumab [III, B]

ChT, chemotherapy; PD-L1, programmed death-ligand 1; PS, performance status, UC, urothelial cancer
[a] Not approved by EMA
[b] Creatinine clearance <60 ml/min or PS2 or comorbidity
eUpdate – Bladder Cancer Treatment Recommendations. July 16, 2020. https://www.esmo.org/guidelines/genitourinary-cancers/bladder-cancer/eupdate-bladder-cancer-treatment-recommendations

- So this has been added in the current guideline. Here an example, with the ESMO guidelines to the recommendation for the use of avelumab of level IA.

NCCN® Guidelines for Bladder Cancer: First-line Systemic Therapy for Locally Advanced or Metastatic Disease

	Preferred Regimens	Other Recommended Regimens	Useful Under Certain Circumstances
Cisplatin Eligible	Gemcitabine and cisplatin (category 1) followed by avelumab maintenance therapy	-	-
	DDMVAC with growth factor support (category 1) followed by avelumab maintenance therapy	-	-
Cisplatin Ineligible	Gemcitabine and carboplatin followed by avelumab maintenance therapy	Gemcitabine +/- paclitaxel	Ifosfamide, doxorubicin, and gemcitabine (good kidney function and good PS)
	Atezolizumab (PD-L1+, or not eligible for platinum-containing chemotherapy)		
	Pembrolizumab (PD-L1+, or not eligible for platinum-containing chemotherapy)		

DDMVAC, dose-dense methotrexate, vinblastine, doxorubicin, cisplatin; PD-L1, programmed cell death protein ligand 1; PS, performance status.
NCCN Clinical Practice Guidelines in Oncology. Bladder Cancer. V6.2020. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. © 2020 National Comprehensive Cancer Network, Inc.

AXIS Medical Education

- NCCN Guidelines provided us all an update. In cisplatin-eligible patients, avelumab should be given after either cisplatin/gemcitabine or dose-dense MVAC, provided the chemotherapy induced complete response, partial response, or stable disease. For the patient unfit for cisplatin, carboplatin and gemcitabine should be given first and then avelumab. Atezolizumab and pembrolizumab are seen possible and remain an option according to the NCCN Guidelines.

AXIS

Second-Line Treatment Options: Immunotherapy

- So let's move to the second line.

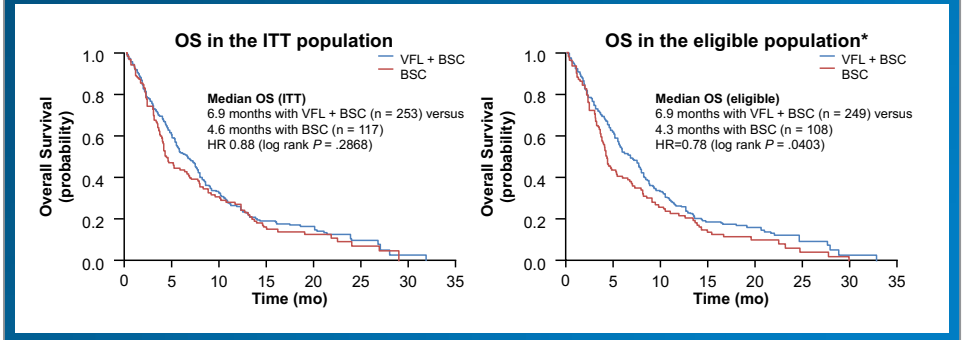
Topics for Discussion

- Current second-line treatment options for cisplatin-refractory patients: supporting evidence and guideline recommendations
  - Atezolizumab: IMvigor211
  - Avelumab: JAVELIN Solid Tumor
  - Durvalumab: Study 1108
  - Nivolumab: CheckMate 275
  - Pembrolizumab: KEYNOTE-045
- Practical application case: considerations for optimal sequencing of therapy with immune checkpoint inhibitors in metastatic UC

AXIS Medical Education

- Five different PD-1 or PD-L1 inhibitors are approved based on data from phase 1, 2, or 3. Of course, with the JAVELIN maintenance study, only patients who progress during chemotherapy will be treated with immune checkpoint inhibitor in second line.

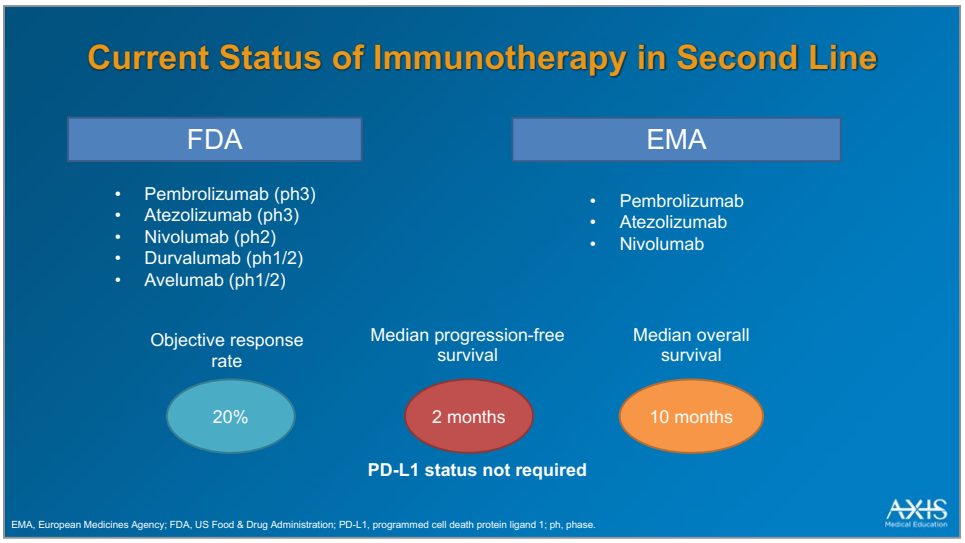
Metastatic Disease: OS Rates for Patients Receiving Second-Line Vinflunine



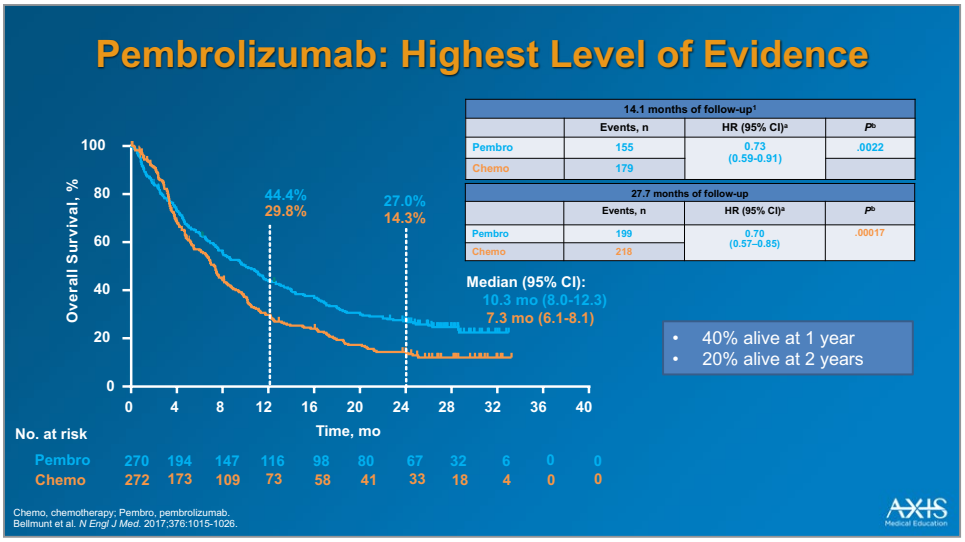
*The eligible population excludes 13 patients who presented at least one major protocol violation at baseline.
BSC, best supportive care; ITT, intention to treat; OS, overall survival; VFL, vinflunine.
Bellmunt et al. *J Clin Oncol*. 2009;27:4454-4461.

AXIS Medical Education

- This slide to remind everyone that the phase 3 trial was conducted 10 years ago, assessing vinflunine versus best supportive care in second line. The trial was negative in ITT analysis. And so the drug is not approved in most countries. However, the per protocol analysis suggested benefit of vinflunine over best supportive care. So this analysis supported the European approval, and currently, only a minority of European countries reimburse the drug.



- In second line, PD-L1 status is not required to select patients. We can expect a 20% response rate. In the trial, median PFS was 2 months, and median overall survival was 10 months.



- The best level of evidence we have was provided by KEYNOTE-045 trial, which compared pembrolizumab to chemotherapy in second or third line. The trial met its primary endpoint, hazard ratio about 0.70 after a median follow-up of 2 years—40% are alive at 1 year, and 20% are alive at 2 years.

PD-L1 Inhibitors Are Quite Similar

	Atezolizumab	Atezolizumab	Pembrolizumab	Nivolumab	Durvalumab	Avelumab
Trial	IMvigor210 Cohort 2	IMvigor211	KEYNOTE-045	CheckMate 275	Study 1108	JAVELIN solid tumour
Phase	2	3	3	2	1/2	1b
Number of patients	310	467	270	270	191	249
Dosing	1,200 mg q3w	1,200 mg q3w	200 mg q3w or 400 mg q6w	3 mg/kg q2w	10 mg/kg q2w for 1 year	10 mg/kg q2w
Median follow-up, mo	32.9	17.3	27.7	33.7†	5.8	19.6
ORR, %	16	13.4	21.1	20.7	17.8	16.1
Median DoR, mo	24.8	21.7	NR	20.3	NR	Not reported
Median OS, mo	7.9	8.6*	10.1	8.6	18.2	7.7
Median PFS, mo	Not reported	2.1	2.1	1.9	1.5	1.5
Grade 3-4 TRAEs, %	All grade: 71%	19.8	16.5	24.8	6.8	10.4

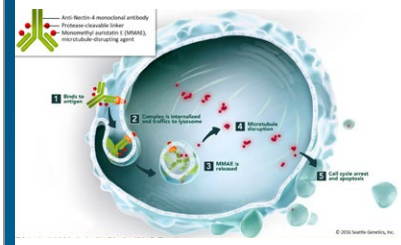
DoR, duration of response; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death protein ligand 1; PFS, progression-free survival; TRAEs, treatment-related adverse events.
Rosenberg et al. *Lancet* 2016;387:1909-1920.; Powles et al, *Lancet* 2018;391:748-757; Bellmunt et al, *N Engl J Med*. 2017;376:1015-1026.; Sharma et al, *Lancet Oncol*. 2017;18:312-322; Massard et al. *J Clin Oncol*. 2016;34:3119-3125; Patel et al. *Lancet Oncol*. 2018;19:51-64.

AXIS Medical Education

- So this table show you that there's no big difference between PD-1 and PD-L1 inhibitors in terms of efficacy or safety. These drugs are well tolerated with very few patients developing serious toxicities.

The Landscape in Second Line Is Moving Very Fast

Enfortumab vedotin targets nectin 4–expressing UC

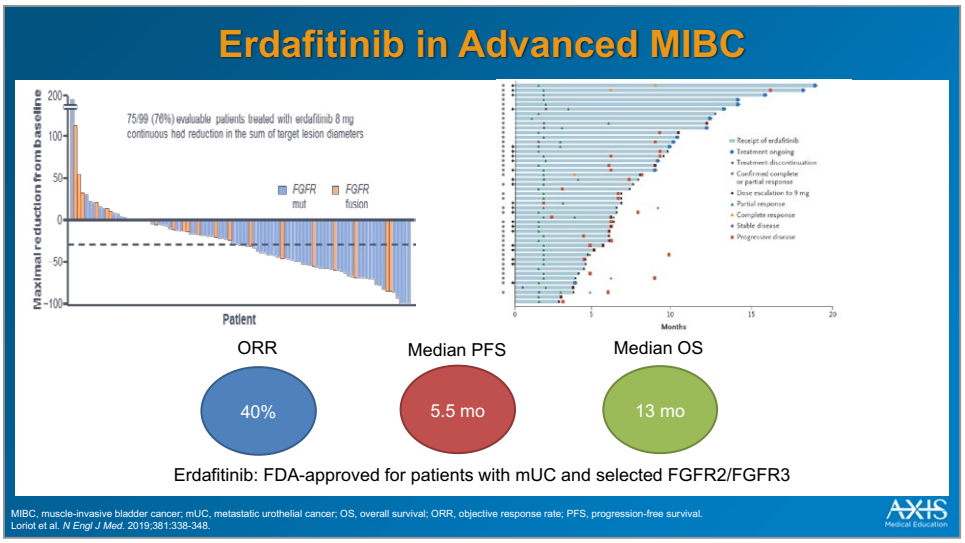


ORR	Median PFS	Median OS
41%	5 months	13 months

ORR, objective response rate; OS, overall survival; PFS, progression-free survival; UC, urothelial cancer.
Rosenberg et al. *J Clin Oncol*. 2019;37:2592-2600.

AXIS Medical Education

- So now the landscape is changing very fast with the development of antibody-drug conjugate. I discussed enfortumab vedotin earlier. In third line, EV-201 study reported an overall response rate of 41%, median PFS around 6 months, and median overall survival of around 1 year. Based on this data, the drug has been approved by FDA.



- Another class of drug, FGFR inhibitors, 20% exhibit *FGFR3* mutation or *FGFR2* and *3* fusions. In a phase 2 trial, BCL2001 study erdafitinib, a pan-FGFR inhibitor, was given to around 100 patients with metastatic urothelial carcinoma—90% had been treated with other therapy. Overall response rate was 40%, median PFS close to 6 months, and median overall survival of 13 months. Based on this data, erdafitinib is approved in US for patients with selected *FGFR2* and *3* gene alterations.

ESMO Guidelines

	Standard therapy	When standard therapy is not possible
Unselected platinum-refractory	ICI [I, A]	ChT [II, B] Enfortumab vedotin [III, B]* [5]
Platinum-refractory with FGFR DNA alterations [4]	ICI [I, A] Erdafitinib [III, B]*	ChT [II, B]
>1 year from first-line ChT treatment (with or without subsequent immune therapy)	ICI [I, A]	Cisplatin-based ChT rechallenge [IV, B]
ICI-refractory, ChT-naive	Platinum based-ChT [IV, B] [3]	
Platinum-based ChT and ICI-refractory	Enfortumab vedotin [III, B]* Erdafitinib [III, B]* (with selected FGFR DNA alterations) ChT [IV, B]	

*Not EMA approved.
ICI, immune checkpoint inhibitor; ChT, chemotherapy.
eUpdate – Bladder Cancer Treatment Recommendations. July 16, 2020. https://www.esmo.org/guidelines/genitourinary-cancers/bladder-cancer/eupdate-bladder-cancer-treatment-recommendations4

- Again, this new data have been integrated in the guidelines, and both drug are options in second-line therapy, especially for patients previously treated with PD-L1 or PD-1 inhibitor. Here an example with the ESMO guidelines.

NCCN® Guidelines for Bladder Cancer: Second-Line Systemic Therapy for Locally Advanced or Metastatic Disease

	Preferred Regimens	Alternative Preferred Regimens	Other Recommended Regimens	Useful Under Certain Circumstances
Post-Platinum	Pembrolizumab (category 1)	Immune checkpoint inhibitor: • Atezolizumab • Nivolumab • Durvalumab • Avelumab	Paclitaxel or docetaxel	Ifosfamide, doxorubicin, and gemcitabine
				Gemcitabine and paclitaxel
			Gemcitabine	Gemcitabine and cisplatin
				DDMVAC with growth factor support
		Erdafitinib		
	Preferred Regimens Cisplatin Ineligible (chemotherapy naïve)	**Preferred Regimens Cisplatin Eligible (chemotherapy naïve)**	**Other Recommended Regimens**	**Useful Under Certain Circumstances (based on prior therapy)**
Post-Checkpoint Inhibitor	Gemcitabine/carboplatin	Gemcitabine and cisplatin	Erdafitinib	Ifosfamide, doxorubicin, and gemcitabine
			Paclitaxel or docetaxel	
		DDMVAC with growth factor support	Gemcitabine	Gemcitabine and paclitaxel

Participation in clinical trials of new agents is recommended

DDMVAC, dose-dense methotrexate, vinblastine, doxorubicin, cisplatin; PD-L1, programmed cell death protein ligand 1; PS, performance status.
NCCN Clinical Practice Guidelines in Oncology. Bladder Cancer. V6.2020. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. © 2020 National Comprehensive Cancer Network, Inc.

AXIS Medical Education

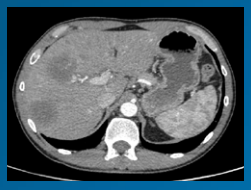
- And here with the NCCN Guidelines, where you can see that pembrolizumab is a preferred regimen in post-platinum setting. If patient has been treated with PD-1 or PD-L1 inhibitor in first line, a lot of options can be discussed. Carbo/Gem is a preferred regimen. Of course, given the low level of evidence, participation in clinical trials of neoadjuvant is recommended.

Clinical Case

50-year-old man with diagnosis of metastatic bladder cancer

Comorbidities:

- Former smoker
- Hypertension



Disease history

- Hematuria in April 2019 -> mass in the right wall of the bladder
- TURB found urothelial carcinoma
- CT scan revealed pelvic and retroperitenum lymph nodes and liver metastases
- PD-L1 not evaluable
- 3 cycles of cisplatin-gemcitabine administered -> CR

CR, complete response; CT, computed tomography; PD-L1, programmed cell death protein ligand 1; TURB, transurethral resection of the bladder.

AXIS Medical Education

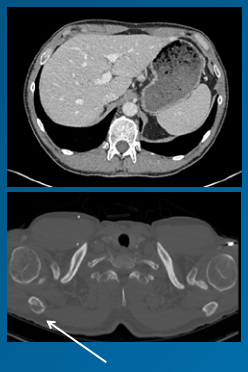
- Now a second clinical case with a 50-year-old man with a diagnosis of metastatic bladder cancer. Again, some comorbidities in this patient with high blood pressure. He was diagnosed in April 2019 with a urothelial carcinoma in the bladder. CT scan revealed liver and lymph node metastasis. Unfortunately, PD-L1 status was not available. So 3 cycles of cisplatin/gemcitabine have been administered to this patient, and a complete response was observed on the first CT scan.

Clinical Case

- **Now, do you consider:**
  a) Three additional cycles of chemotherapy?
  b) Switch to avelumab right now
  c) Stop and follow
  d) Other

So now, do you consider 3 additional cycles of chemotherapy, switch to avelumab right now, stop and follow, or other?

Clinical Case



- After 6 cycles: CT scan revealed CR in the liver and lymph nodes, but bone progression (clavicular, pelvis, and spine)
- FGFR3 S249C mutation, TMB = 5 mut/Mb

Now, do you consider:
a) Multiple bone radiation
b) PD-L1 inhibitor
c) Erdafitinib
d) Chemotherapy

The patient received pembrolizumab

CR, complete response; CT, computed tomography; PD-L1, programmed cell death protein ligand 1; TMB, tumor mutation burden.

The patient received 3 additional cycles of chemotherapy, so 6 in total. After the last one, a complete response was confirm in the liver and lymph node, but the bone progression, as you can see here, was diagnosed. Sequencing for the *FGFR3* S249C mutation and tumor mutational burden were 5 mutation/Mb. So now, do you consider multiple bone radiations, PD-L1 or PD-1 inhibitors, erdafitinib, chemotherapy? Actually, the patient received pembrolizumab but died 2 months later from disease progression.

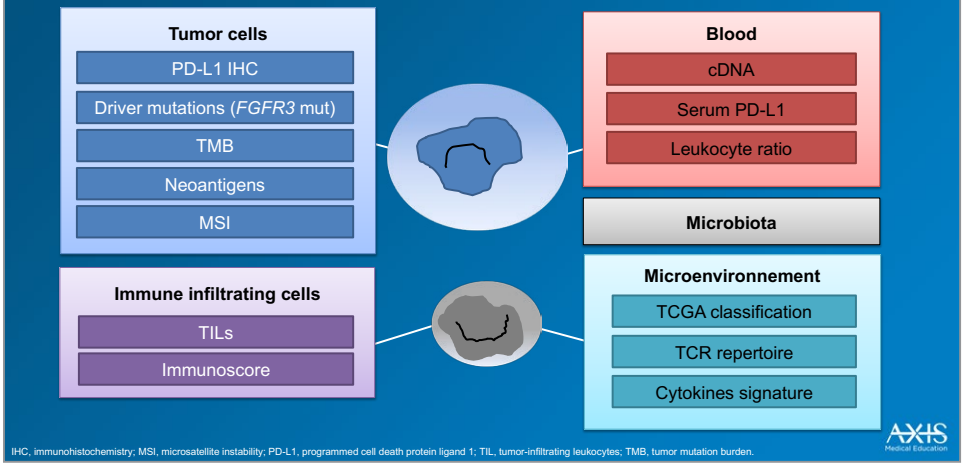
Questions

- Should we start avelumab as maintenance as soon as a complete response is obtained (even after 2 cycles)?
- Should we give pembrolizumab in patients with *FGFR3* mutation?

AXIS Medical Education

- So 2 important questions from this clinical case arise. Should we start avelumab earlier, as soon as the complete response is obtain? Should we give pembrolizumab in patients with *FGFR3* mutation?

The Lack of Biomarkers With Immunotherapy



IHC, immunohistochemistry; MSI, microsatellite instability; PD-L1, programmed cell death protein ligand 1; TIL, tumor-infiltrating leukocytes; TMB, tumor mutation burden.

AXIS Medical Education

- This question is important in the context of the lack of strong biomarker of response with the use of immunotherapy in bladder cancer. A lot of biomarkers are currently investigated on tumor cells, immune cells, blood, and microenvironment.

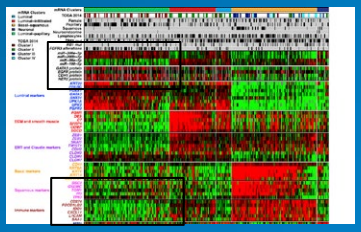
Questions

- TMB not associated with benefit from pembrolizumab[1]

	TMB ≥175 mut/exome	TMB ≥175 mut/exome	TMB <175 mut/exome	TMB <175 mut/exome
	Pembro n = 66	Chemo n = 61	Pembro n = 133	Chemo n = 121
ORR, %	34.5	13.1	15.8	14.0
PFS, HR (95% CI)	0.65 (0.42-1.00)	-	1.19 (0.91-1.55)	-
OS, HR (95% CI)	0.66 (0.42-1.04)	-	0.72 (0.55-0.96)	-

Luminal-papillary UC[2,3]

- Enriched in *FGFR3* alterations
- Low immune infiltration
- Data suggesting low response to ICI



1. Bellmunt et al. *Ann Oncol*. 2020;31:S550.
2. Robertson et al. *Cell* 2017;171:540-556.
3. Siefker-Radtke et al. *J Clin Oncol*. 2018; 36:450.

ICI, immune checkpoint inhibitors; TMB, tumor mutation burden; UC, urothelial cancer.

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- For example, TMB does not fully explain the response to immune checkpoint inhibitors. There is a correlation, right here, in the KEYNOTE-045 and KEYNOTE-052 trial, but not enough to implement in daily practice. Regarding the *FGFR3* mutations, we know that luminal-papillary tumor, which are enriched in *FGFR3* gene alteration, have a low immune infiltration. They're kind of immune desert. And retrospective analysis suggested that this tumor respond poorly to immune checkpoint inhibitors. But this is highly debated, and we need prospective data.

Varying Global Perspectives

Topics for Discussion:

- What nuances exist on how patients with urothelial cancer patients are treated from a global perspective?
- NCCN vs ESMO Guidelines

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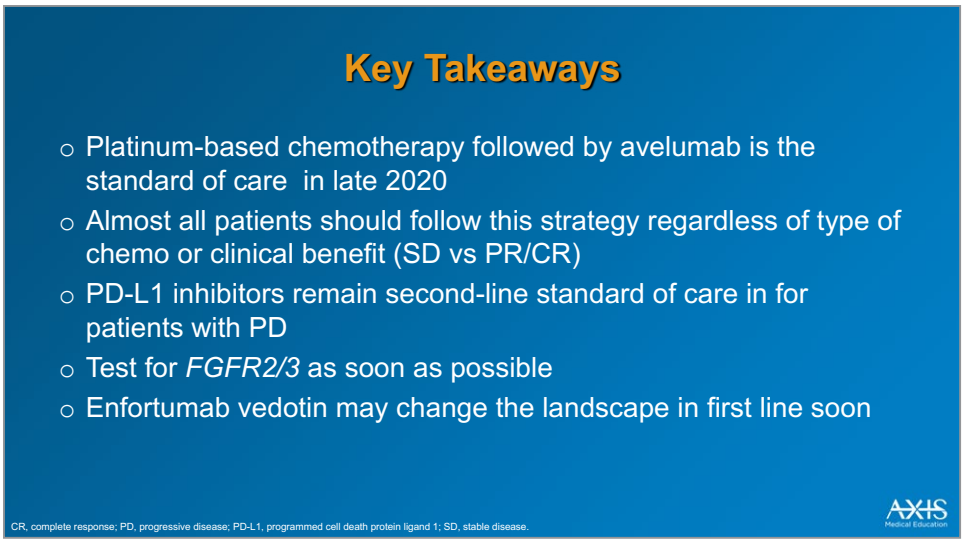
- So the management of patients in metastasis setting is evolving quite fast. But of course, the management could be different across countries and continent. Erdafitinib and EV are approved in US but not in Europe, for example. US has already approved avelumab as maintenance; this is not the case in Europe. Five immune checkpoint inhibitors are approved in second line by FDA, only 3 by EMA. But fortunately, the recommendations are not so different between ESMO guideline and NCCN.



- So to conclude, platinum-based chemotherapy followed by avelumab is the standard of care in late 2020. Almost all patients should follow this strategy regardless of type of chemotherapy or clinical benefit. PD-1 and PD-L1 inhibitors remain second-line standard of care for patients with PD. We should test for *FGFR2* or *3* gene alteration as soon as possible. And enfortumab vedotin may change the landscape in the first line soon.

- Thank you for participating in this activity. Thank you, again.

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