UroSchool ΟΓΚΟΛΟΓΙΑ:

Τα σημαντικότερα νέα από το ESMO 2018 και το ASCO 2019

UroGold II

Παναγιώτης Δημόπουλος MD PhD FEBU

Χειρούργος Ουρολόγος

Σύγκρουση Συμφερόντων

- Κανένα

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Renal Cell Carcinoma

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RCC treatment revolutionized in short period of time

Immunotherapy

IFN-a

IL-2

Vaccines

Immune Checkpoint Inhibitors

- *Nivolumab/Pembrolizumab*
- *Avelumab/Atezolizumab/Durvalumab*
- *Ipilimumab/Tremelimumab*

Targeted Therapy

Bevacizumab

Tyrosine Kinase Inhibitors

- *Sunitinib*
- *Sorafenib*
- *Pazopanib*
- *Axitinib*
- *Lenvatinib*
- *Cabozantinib*
- *Tivozanib*

mTOR Temsirolimus/Everolimus

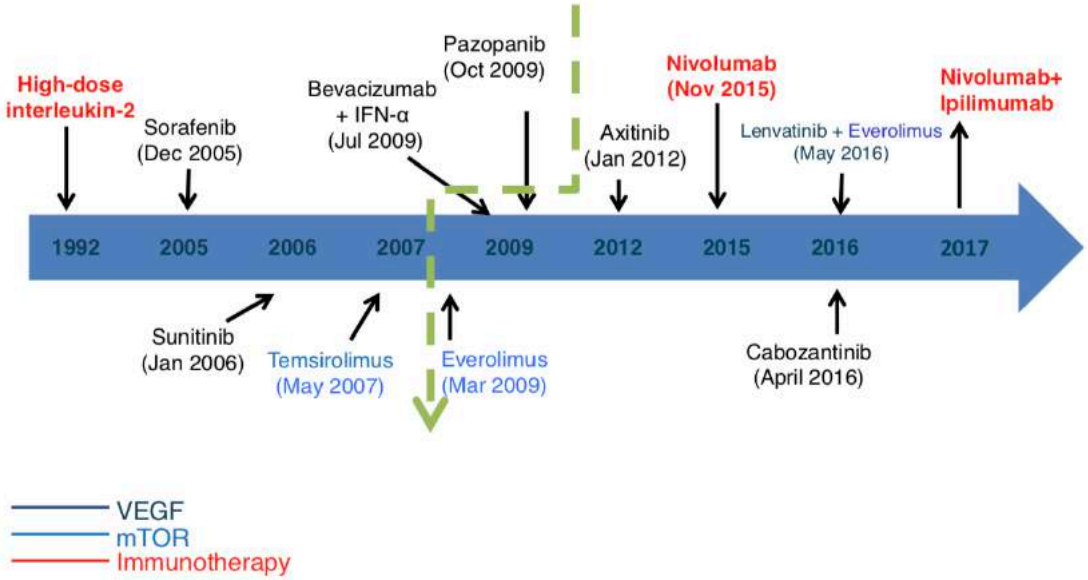

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Table 7.1: The Metastatic Renal Cancer Database Consortium (IMDC) risk model [391]

Risk factors**	Cut-off point used
Karnofsky performance status	< 80%
Time from diagnosis to treatment	< 12 months
Haemoglobin	< Lower limit of laboratory reference range
Corrected serum calcium	> 10.0 mg/dL (2.4 mmol/L)
Absolute neutrophil count (neutrophilia)	> upper limit of normal
Platelets (thrombocytosis)	> upper limit of normal

** The MSKCC (Motzer) criteria are also widely used in this setting [384].*

*** Favourable (low) risk, no risk factors; intermediate risk, one or two risk factors; poor (high) risk, three to six risk factors.*

	First-line therapy	Second-line therapy	Third-line therapy
IMDC favourable risk disease	sunitinib or pazopanib	cabozantinib or nivolumab	cabozantinib or nivolumab
IMDC intermediate and poor risk disease	ipilimumab/ nivolumab	cabozantinib or VEGF-targeted therapy	cabozantinib or an alternative targeted therapy
	cabozantinib, sunitinib or pazopanib*	VEGF targeted therapy or nivolumab	An alternative targeted therapy or nivolumab

Boxed categories represent strong recommendations

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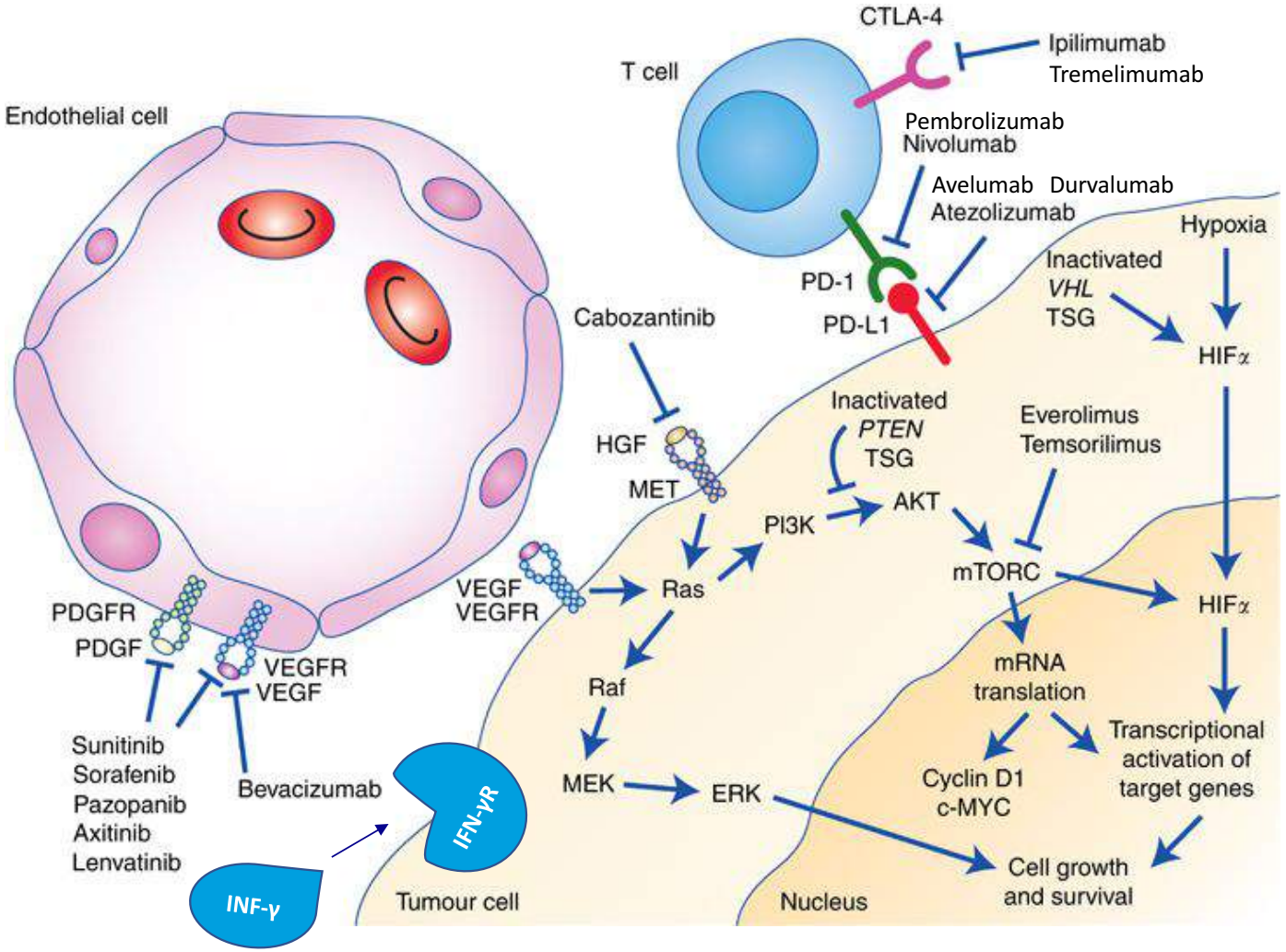
Pathophysiology
Immune Checkpoint Inhibitors



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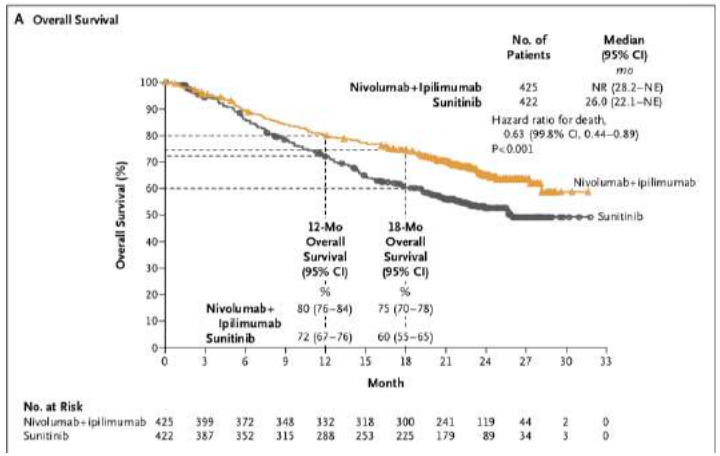
CHECKMATE-214

The NEW ENGLAND JOURNAL of MEDICINE

Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

Robert J. Motzer, M.D., Nizar M. Tannir, M.D., David F. McDermott, M.D., Osvaldo Arén Frontera, M.D., Bohuslav Melichar, M.D., Ph.D., Toni K. Choueiri, M.D., Elizabeth R. Plimack, M.D., Philippe Barthélémy, M.D., Ph.D., Camillo Porta, M.D., Saby George, M.D., Thomas Powles, M.D., Frede Donskov, M.D., Ph.D., et al., for the CheckMate 214 Investigators*



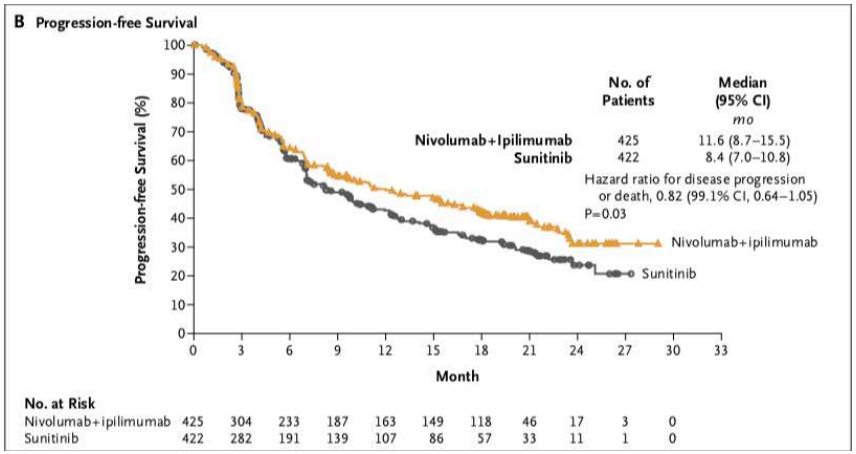


Figure 1. Overall Survival and Progression-free Survival among IMDC Intermediate- and Poor-Risk Patients.

Progression was defined according to the Response Evaluation Criteria in Solid Tumors, version 1.1. For progression-free survival, the between-group difference did not meet the prespecified threshold (P=0.009) for statistical significance. IMDC denotes International Metastatic Renal Cell Carcinoma Database Consortium, NE not estimable, and NR not reached.

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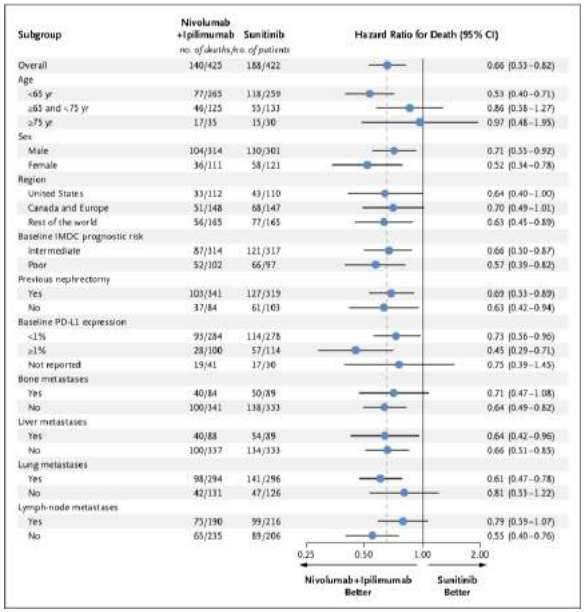

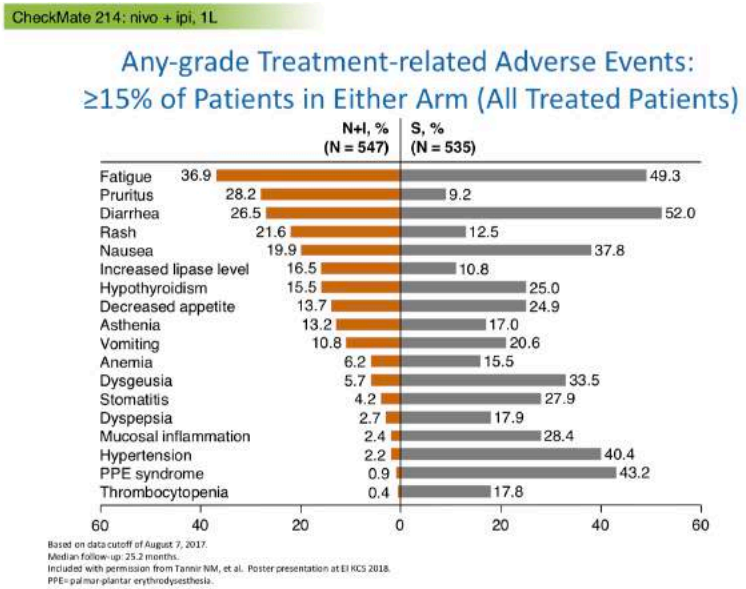

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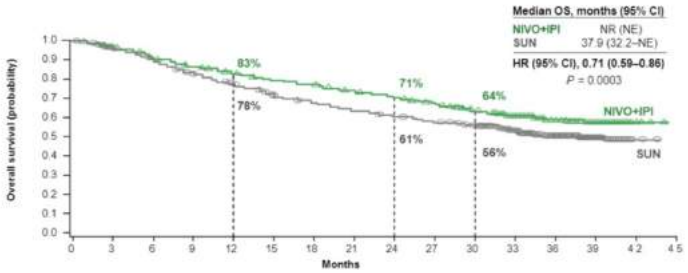
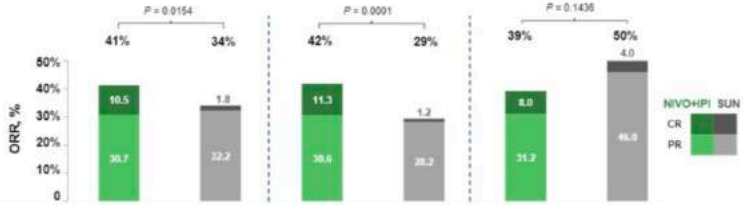
Overall Survival: ITT Patients



Investigator-Assessed Response per RECIST v1.1



	ITT population		Intermediate/poor risk[1]		Favorable risk	
	NIVO+IPI N = 550	SUN N = 546	NIVO+IPI N = 425	SUN N = 422	NIVO+IPI N = 125	SUN N = 124
DOR ≥18 months, %	53	39	52	28	57	60
Ongoing CR, n/N (%)	51/58 (88)	6/10	42/48 (88)	4/5	9/10	2/5

Conclusions

- Improved OS, PFS, and ORR per investigator were maintained with NIVO+IPI versus SUN with extended follow-up in both the ITT and the intermediate/poor-risk populations
- In the small favorable-risk subgroup, no statistical difference was observed between arms in OS, PFS, or ORR
- Regardless of risk category,
  - Impressive CR rates were observed with NIVO+IPI
  - Responses with NIVO+IPI were deeper and more durable
- No new safety signals emerged with longer follow-up

- Among ITT patients, 185 (34%) versus 114 (21%) achieved ≥50% best tumor burden reduction with NIVO+IPI versus SUN

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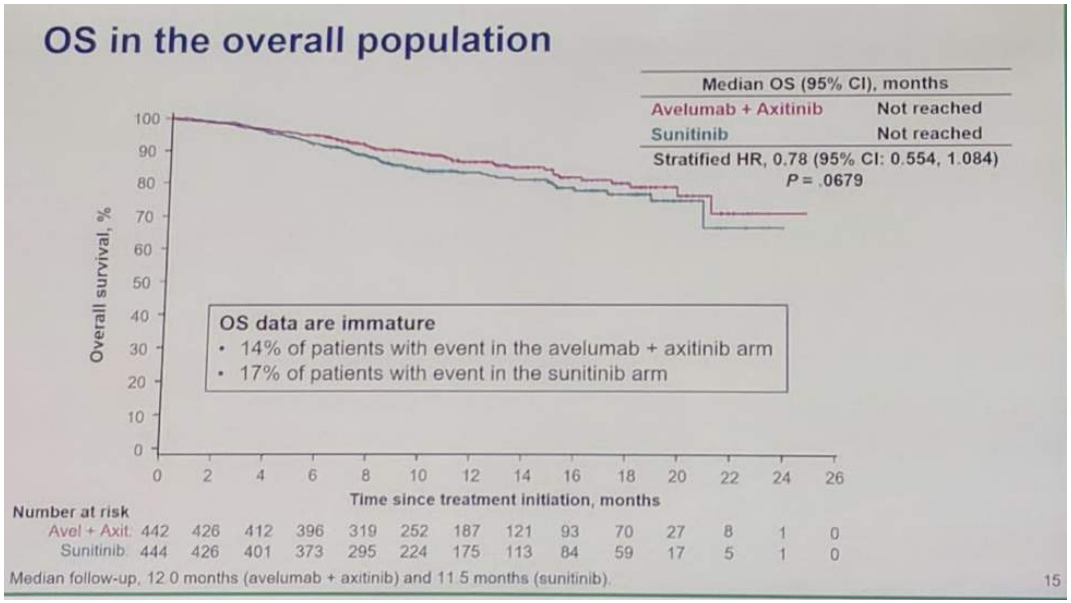
JAVELIN-101

The NEW ENGLAND JOURNAL of MEDICINE

Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

Robert J. Motzer, M.D., Konstantin Penkov, M.D., Ph.D., John Haanen, Ph.D., Brian Rini, M.D., Laurence Albiges, M.D., Ph.D., Matthew T. Campbell, M.D., Balaji Venugopal, M.D., Christian Kollmannsberger, M.D., Sylvie Negrier, M.D., Ph.D., Motohide Uemura, M.D., Ph.D., Jae L. Lee, M.D., Ph.D., Aleksandr Vasiliev, M.D., et al.



March 21, 2019

Patients were randomized 1:1 to receive **Avelumab** (10 mg/kg) IV every 2 weeks + **Axitinib** (5 mg) PO twice daily or
Sunitinib (50 mg) PO once daily for 4 wk (6-wk cycle)

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JAVELIN-101

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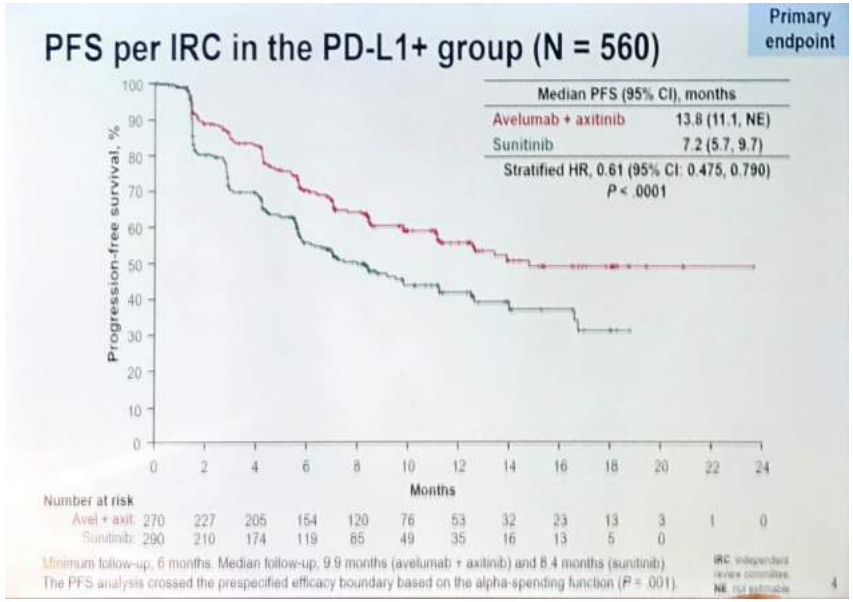

March 21, 2019

	A + Ax (n=442)			S (n=444)		
	n (%)	Median PFS (95% CI), mo	ORR (95% CI), %	n (%)	Median PFS (95% CI), mo	ORR (95% CI), %
MSKCC risk						
F	96 (22)	NE (12.6-NE)	66 (55.2-75.0)	100 (23)	16.7 (11.1-18.6)	38 (28.5-48.3)
I	283 (64)	13.3 (8.5-NE)	50 (43.5-55.5)	293 (66)	7.9 (6.7-9.8)	24 (19.4-29.6)
P	51 (12)	5.6 (2.6-11.2)	31 (19.1-45.9)	45 (10)	2.8 (1.5-2.9)	9 (2.5-21.2)
IMDC risk						
F	94 (21)	NE (16.1-NE)	68 (57.7-77.3)	96 (22)	13.8 (11.1-18.6)	38 (27.8-48.0)
I	271 (61)	13.8 (9.7-NE)	51 (45.2-57.4)	276 (62)	8.4 (7.0-11.2)	25 (20.3-30.9)
P	72 (16)	6.0 (3.6, 8.7)	31 (20.2-42.5)	71 (16)	2.9 (2.7-5.5)	11 (5.0-21.0)
PD-L1 status						
+	270 (61)	13.8 (11.1-NE)	55 (49.0-61.2)	290 (65)	7.2 (5.7-9.7)	26 (20.6-30.9)
–	132 (30)	16.1 (9.7-NE)	47 (38.2-55.8)	120 (27)	11.1 (6.9-17.3)	28 (20.5-37.3)
Unknown	40 (9)	9.9 (7.1-NE)	40 (24.9-56.7)	34 (8)	8.4 (4.3-NE)	18 (6.8-34.5)

NE
, not estimable

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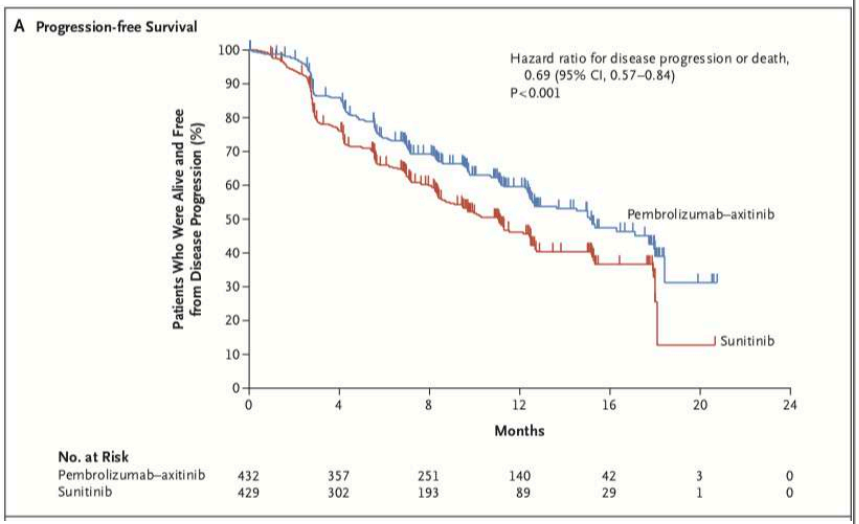
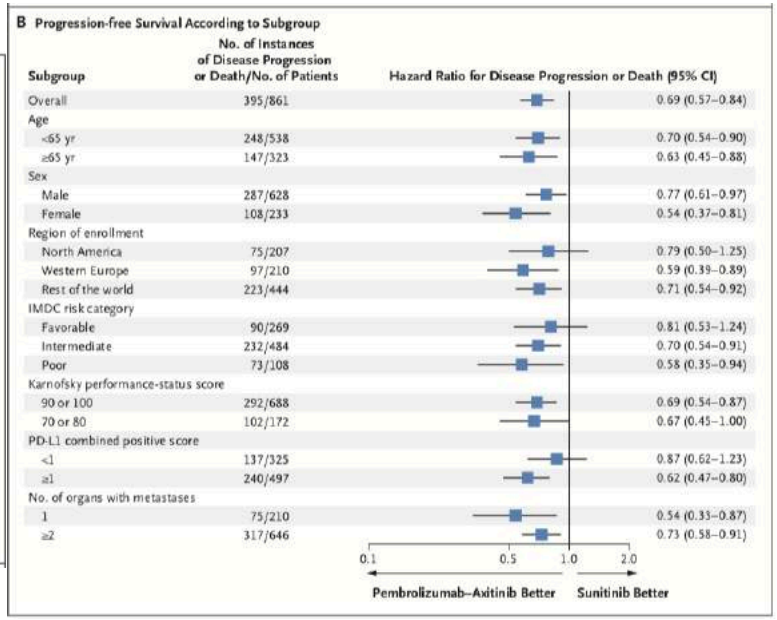
KEYNOTE-426

The NEW ENGLAND JOURNAL of MEDICINE

Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

Brian I. Rini, M.D., Elizabeth R. Plimack, M.D., Viktor Stus, M.D., Ph.D., Rustem Gafanov, M.D., Robert Hawkins, M.B., B.S., Ph.D., Dmitry Nosov, M.D., D.Sci., Frédéric Pouliot, M.D., Ph.D., Boris Alekseev, M.D., Denis Soulières, M.D., Bohuslav Melichar, M.D., Ph.D., Ihor Vynnychenko, M.D., Ph.D., Anna Kryzhanivska, M.D., et al., for the KEYNOTE-426 Investigators*





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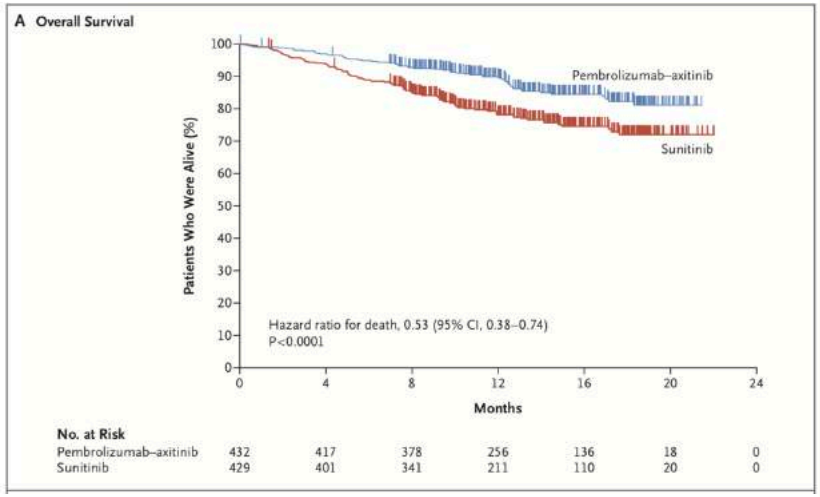

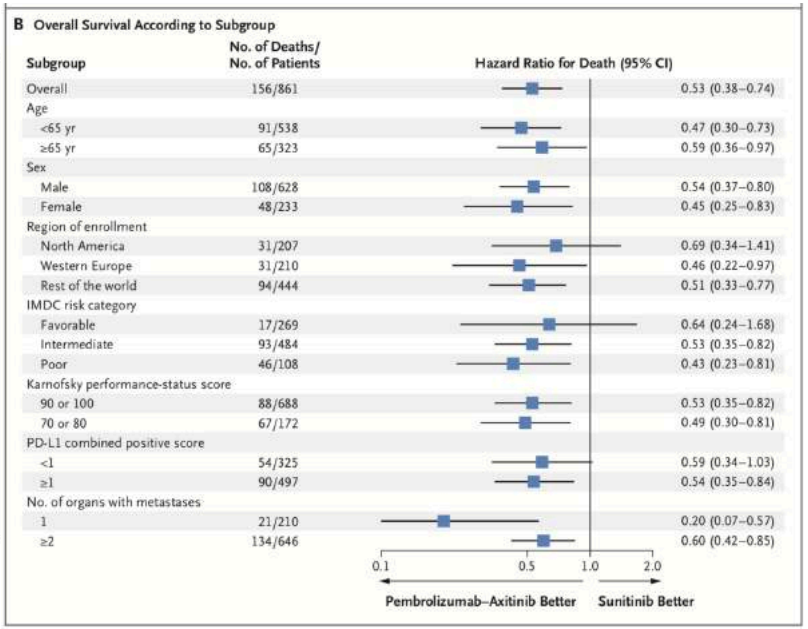

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IMOTION-151

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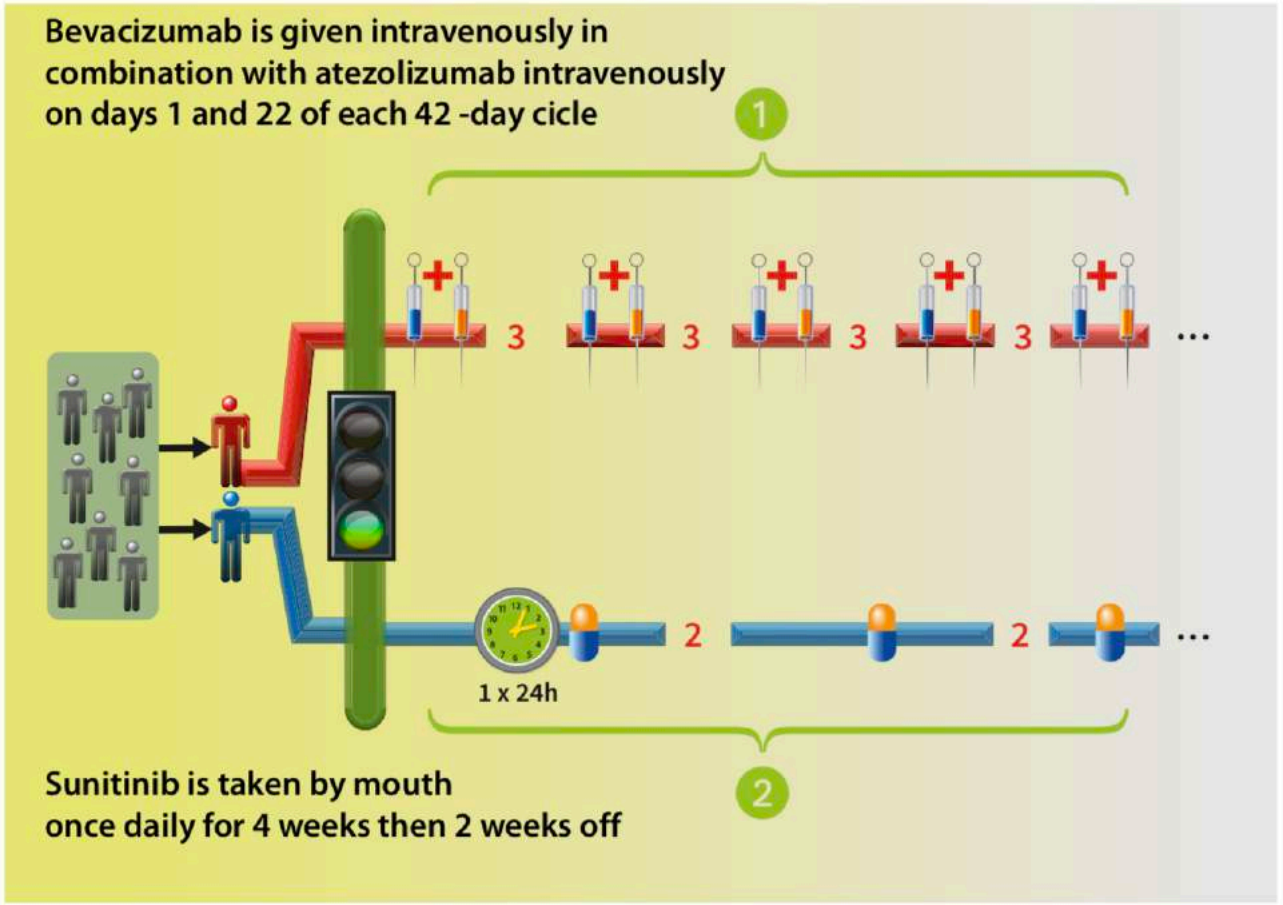
Trial Design



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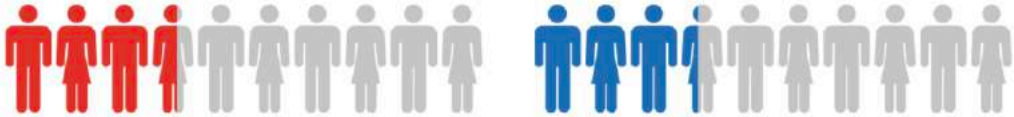
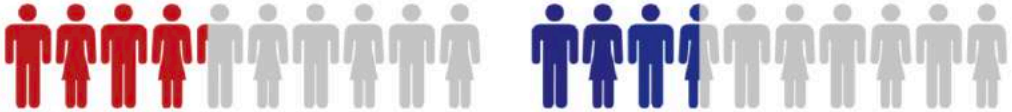
Objective Response Rate (ORR)



37% vs 33%

% of Patients with Partial or Complete Response

Patients with PD-L1+ tumours



43% vs 35%

% of Patients with Partial or Complete Response

Progression Free Survival (PFS)

11.2 Months **8.4 Months**

Patients with PD-L1+ tumours

11.2 Months **7.7 Months**

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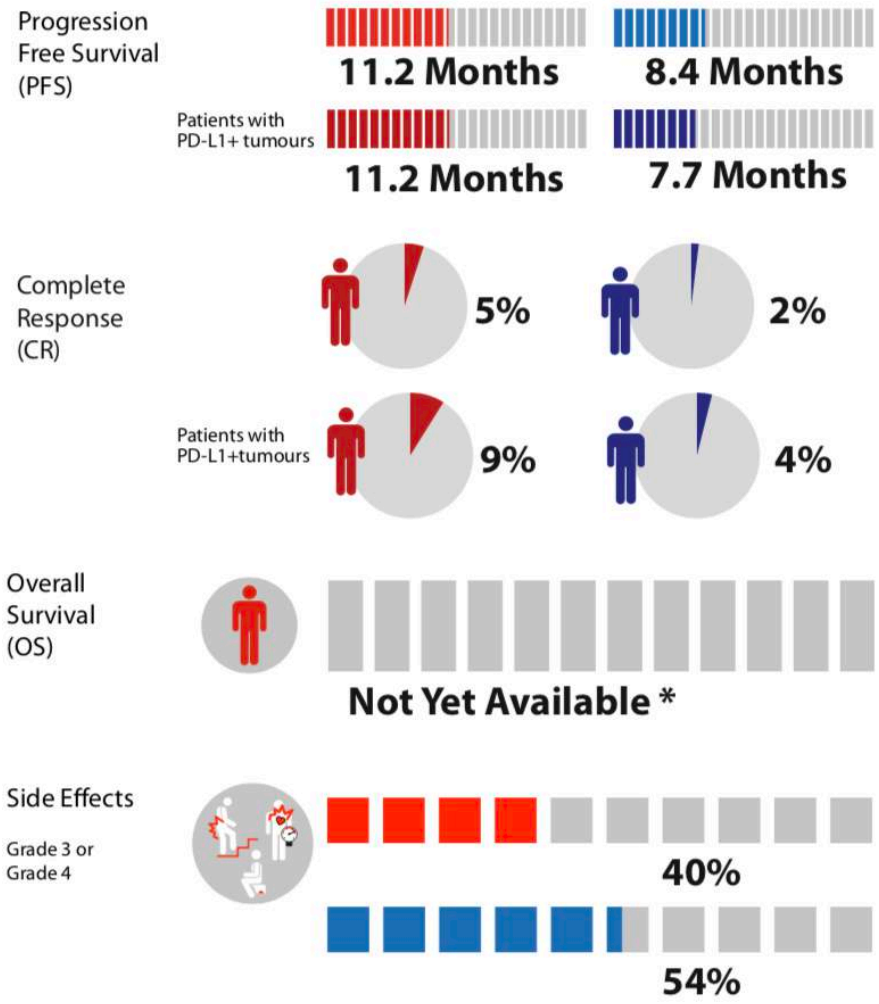

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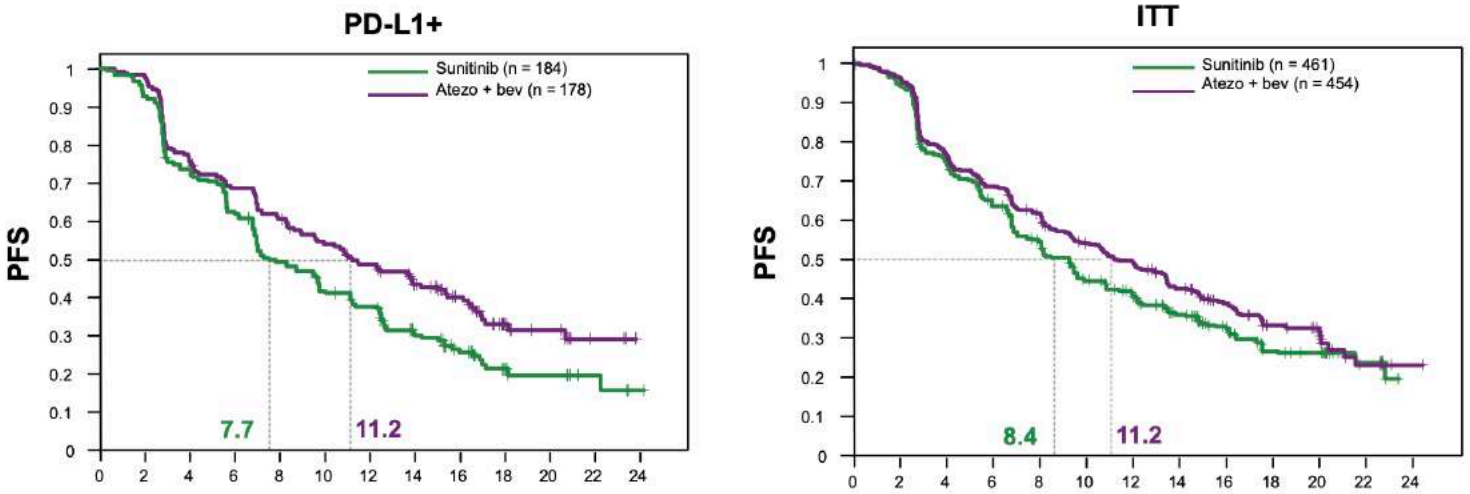

	HR (95% CI)	
	PD-L1+	ITT
Atezo + bev vs sunitinib	0.74 (0.57, 0.96); *P* = .02[a]	0.83 (0.70, 0.97)

PFS-assessed by investigators. Minimum follow-up, 12 months. Median follow-up, 16 months (PD-L1+) and 15 months (ITT).
[a]The PFS analysis passed the pre-specified *P* value boundary of α = 0.04.

Motzer RJ, et al. Journal of Clinical Oncology. 2018;36:(suppl): Abstract 578.
Rini BI, et al. Ann Oncol. 2018;29(Suppl 8): Abstract LBA31.

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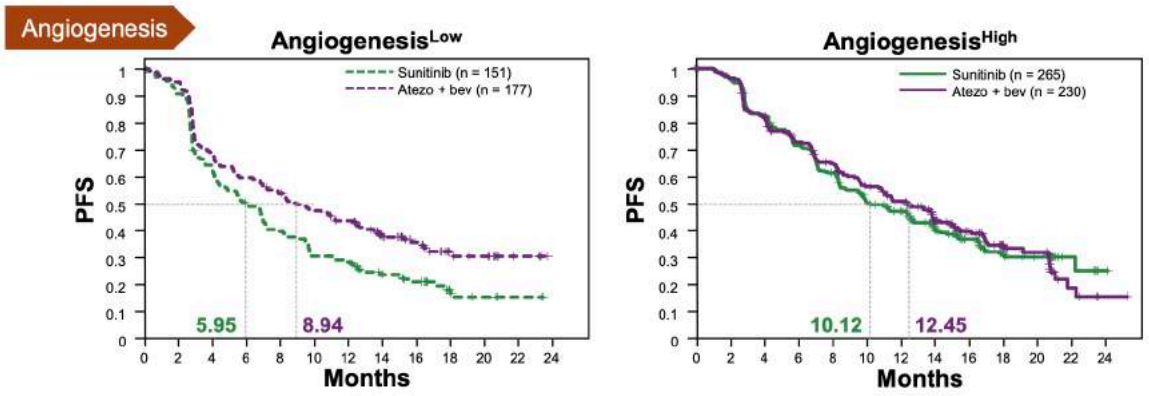
Atezolizumab + Bevacizumab Improved PFS vs Sunitinib in the Angiogenesis^{Low} Subset



	HR (95% CI)	
	Angiogenesis^{Low}	Angiogenesis^{High}
Atezo + bev vs sunitinib	0.68 (0.52, 0.88)	0.95 (0.76, 1.19)

Rini BI, et al. Ann Oncol. 2018;29(Suppl 8): Abstract LBA31.

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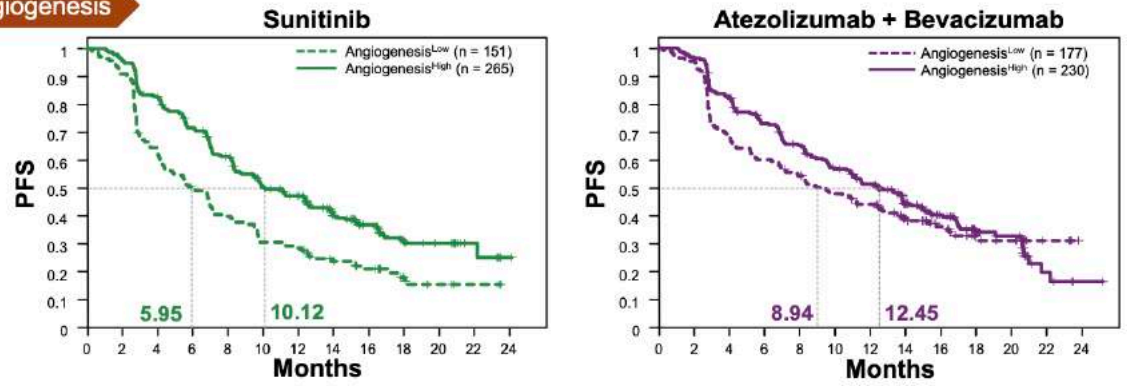
Sunitinib Demonstrated Improved PFS in Angiogenesis^{High} vs Angiogenesis^{Low} Subsets

Angiogenesis



	HR (95% CI)	
	Sunitinib	Atezo + Bev
Angiogenesis (High vs Low)	0.59 (0.47, 0.75)	0.86 (0.67, 1.1)

Rini BI, et al. Ann Oncol. 2018;29(Suppl 8): Abstract LBA31.

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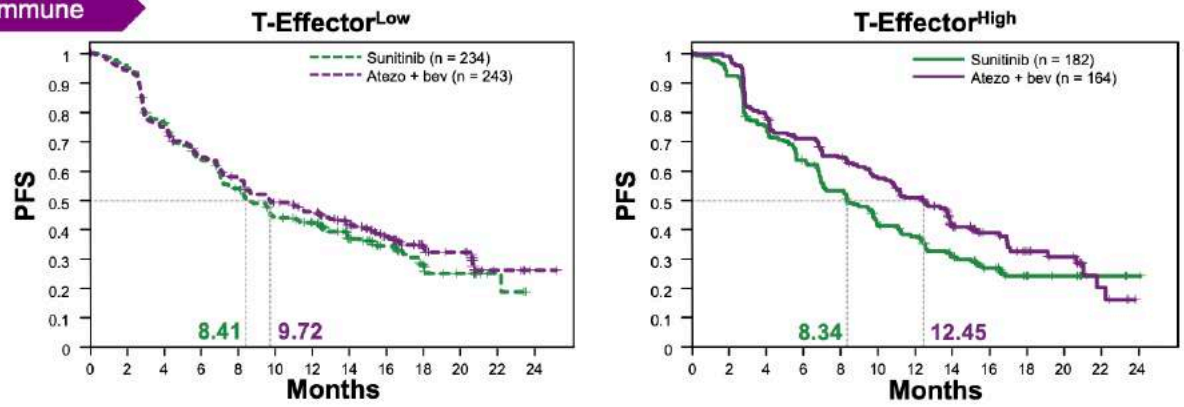
Atezolizumab + Bevacizumab Demonstrated Improved PFS vs Sunitinib in T_{eff}^{High} Subset

Immune



	HR (95% CI)	
	T-effector^{Low}	T-effector^{High}
Atezo + bev vs sunitinib	0.91 (0.73, 1.14)	0.76 (0.59, 0.99)

- **T-effector gene signature did not differentiate PFS within the sunitinib or atezo + bev treatment arms**

Rini BI, et al. Ann Oncol. 2018;29(Suppl 8): Abstract LBA31.

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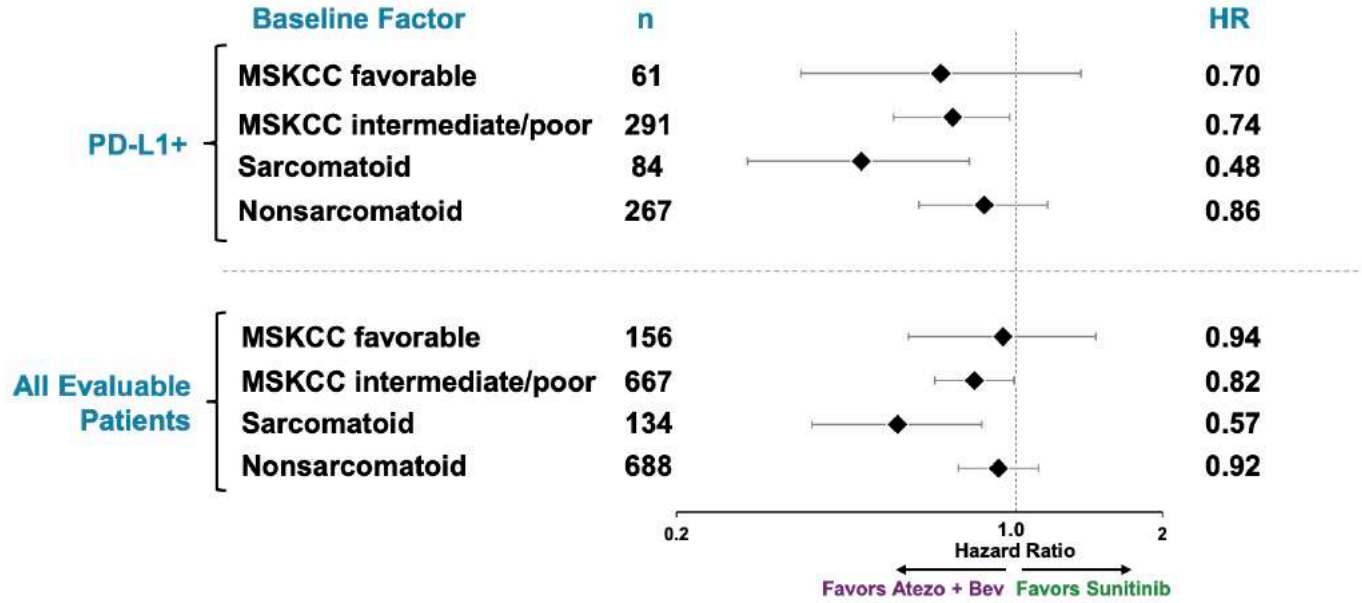
Subgroup PFS Analyses in PD-L1+ and All Evaluable Patients[a]



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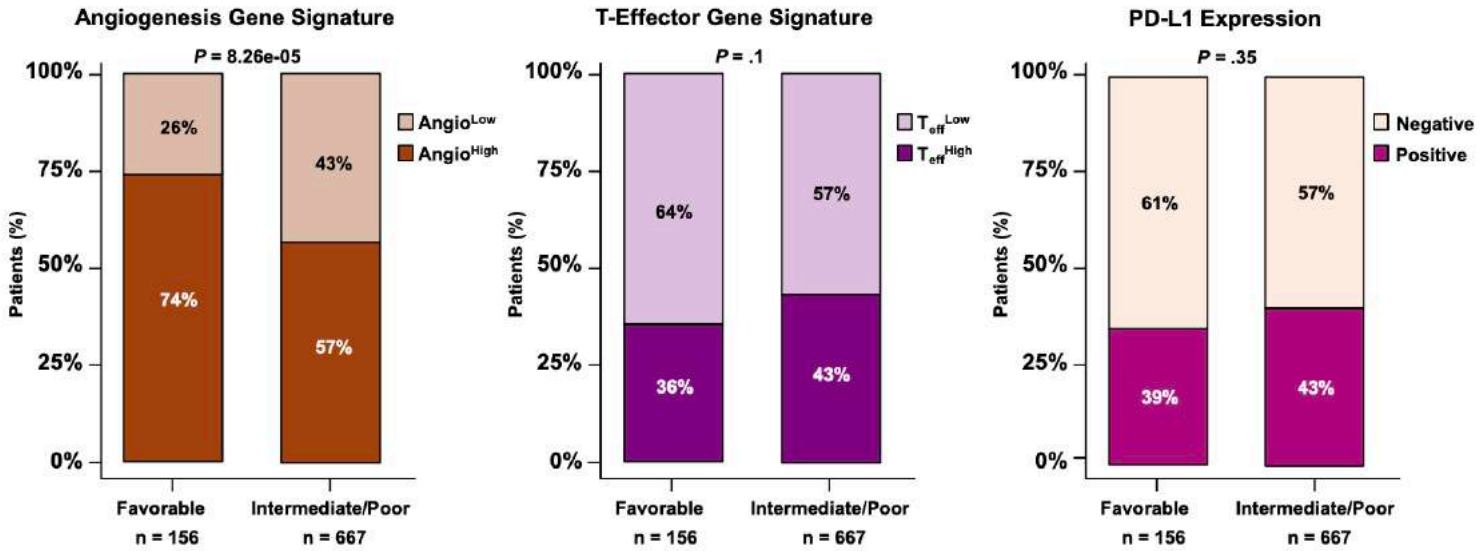
Angiogenesis Gene Expression Is Higher in Favorable MSKCC Risk Group



Rini BI, et al. Ann Oncol. 2018;29(Suppl 8): Abstract LBA31.

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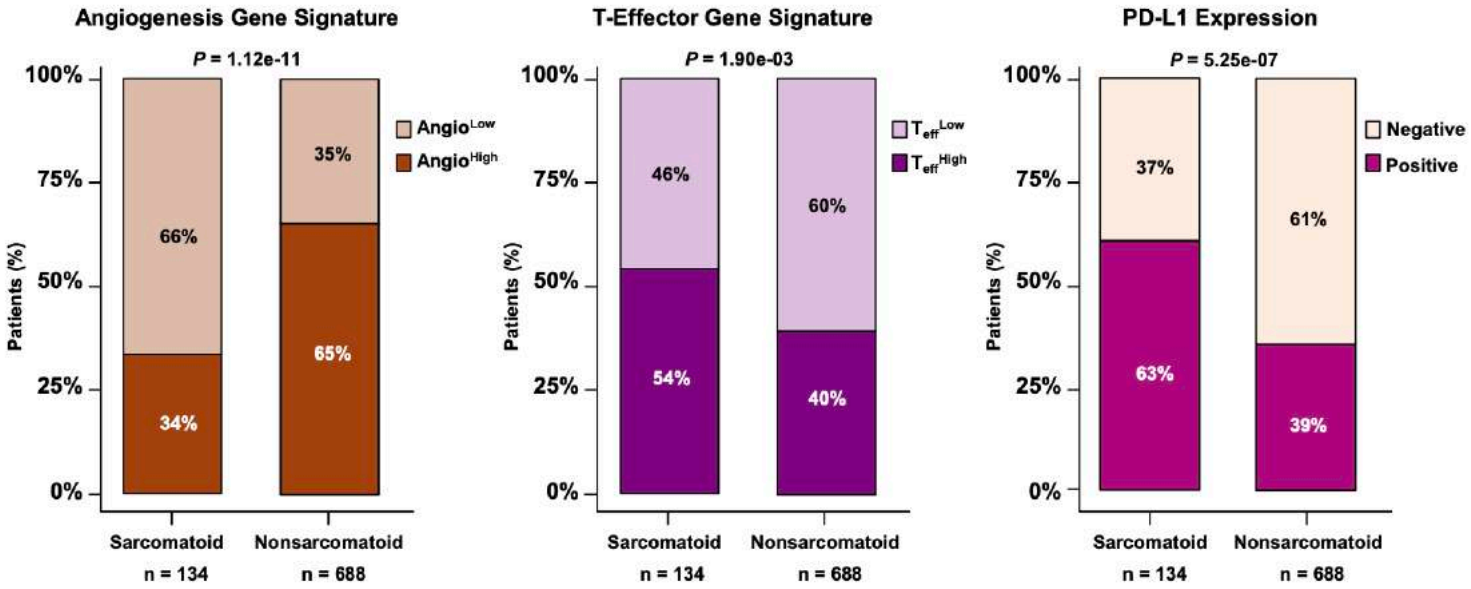
Angiogenesis Gene Expression Is Lower and PD-L1 Expression Is Higher in Sarcomatoid Tumors



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IMOTION-151

- Prespecified analyses in IMmotion151 validated angiogenesis and T-effector gene signatures identified in IMmotion150
  - Atezolizumab + bevacizumab **improved PFS** vs sunitinib in T-effector^{High} and angiogenesis^{Low} tumors
  - Within the sunitinib arm, patients with an angiogenesis^{High} gene signature showed **improved PFS** vs the angiogenesis^{Low} subgroup
- Patients classified as MSKCC favorable–risk are characterized by a dominant angiogenesis^{High} gene signature
- *Sarcomatoid RCC* is characterized by an angiogenesis^{Low} gene signature, a T-effector^{High} gene signature/higher PD-L1 expression, and **enhanced clinical benefit** with atezolizumab + bevacizumab
- Findings from this study further the understanding of RCC biology and inform future strategies to enable personalized therapy

Rini BI, et al. Ann Oncol. 2018;29(Suppl 8): Abstract LBA31.

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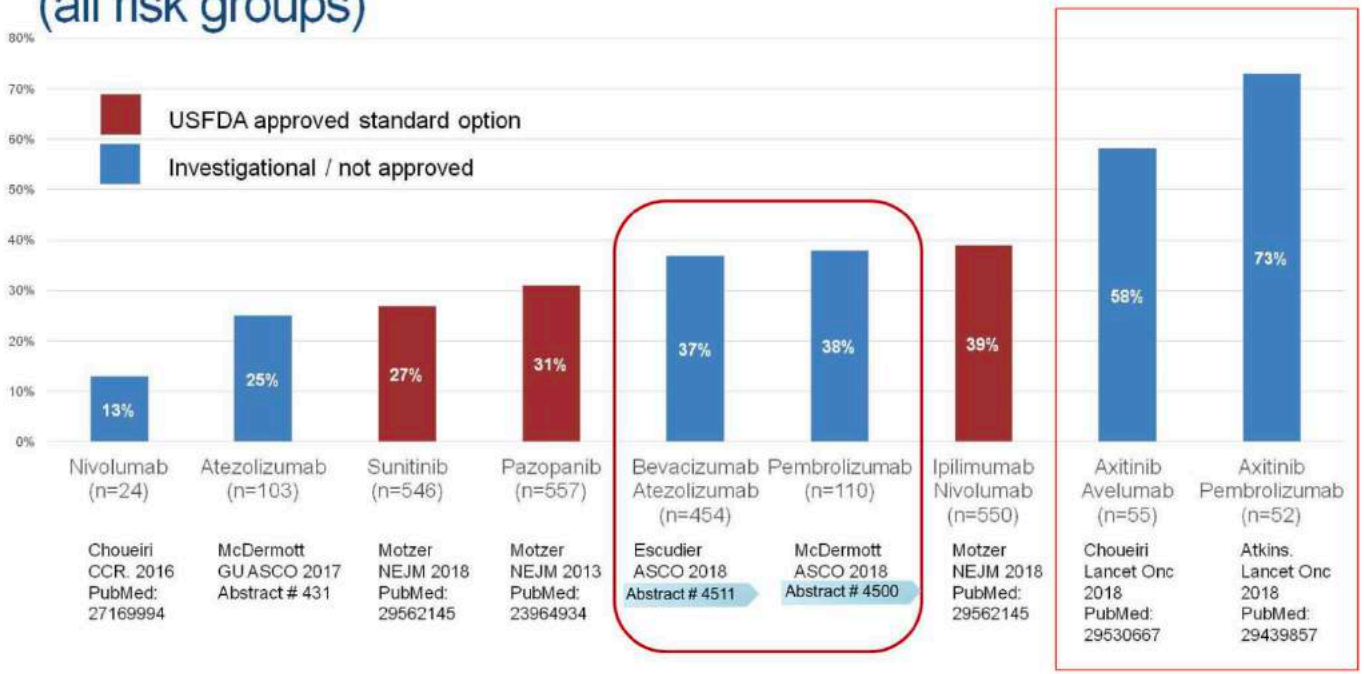
Response Rates in Front Line metastatic ccRCC (all risk groups)



Presented By Elizabeth Plimack at 2018 ASCO Annual Meeting

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Bladder Cancer

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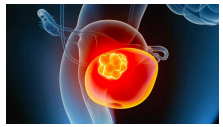
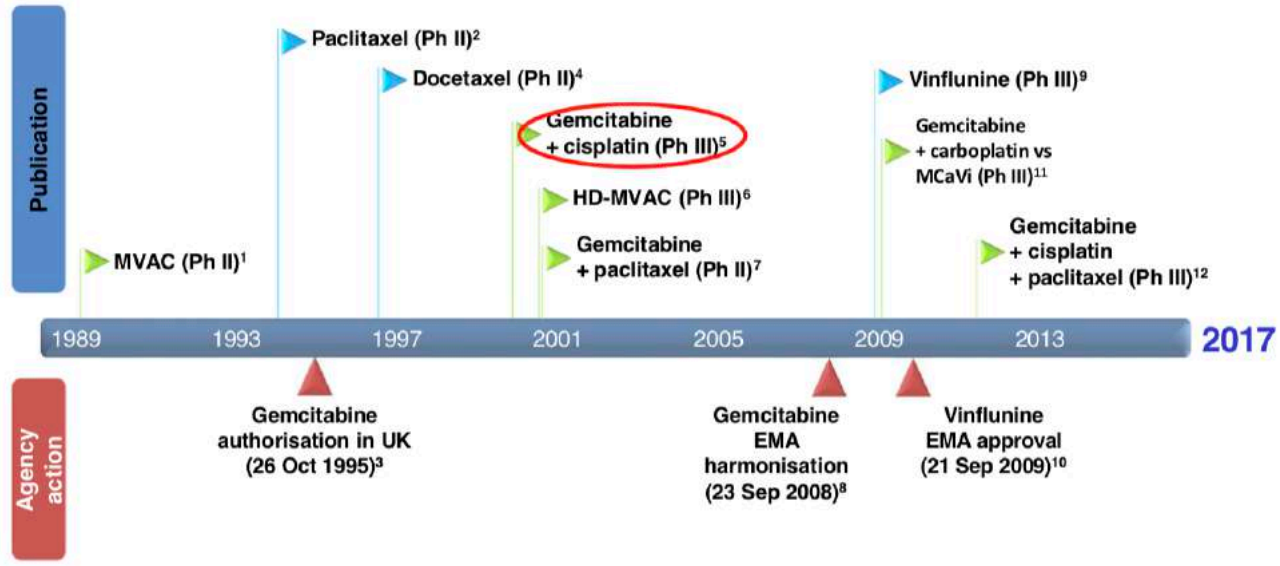


Bladder Cancer



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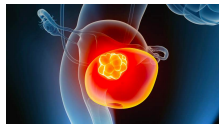
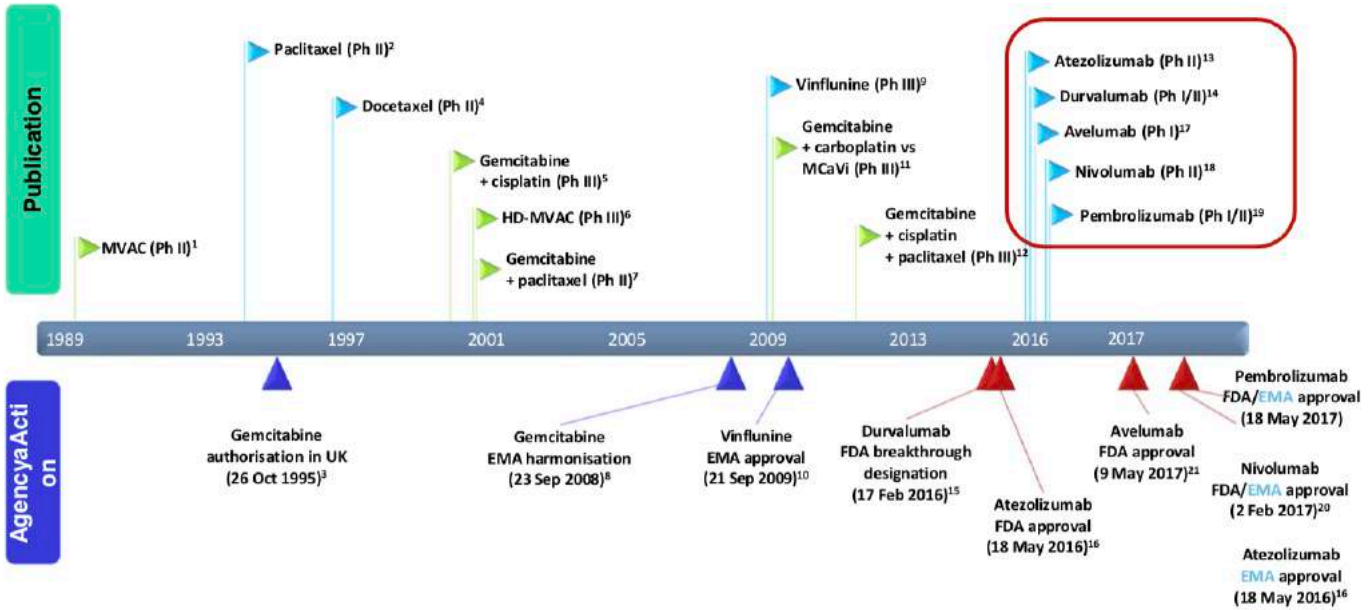


Bladder Cancer



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Bladder Cancer

Figure 7.2: Flow chart for the management of metastatic urothelial cancer

Patient characteristics
PS 0-1/ 2/ >2
GFR ≥/< 60 mL/min
Comorbidities

CISPLATIN?

YES

PS 0-1 and
GFR ≥ 60 mL/min

STANDARD GC
MVAC
HD MVAC
PCG

NO

PS 2 or
GFR < 60 mL/min
1. carboplatin and gemcitabine
2. pembrolizumab
3. atezolizumab
4. Alternate regimens (no comb chemo, studies, monotherapy, BSC)

NO

PS ≥ 2 and
GFR < 60 mL/min
(no comb chemo studies)

Monotherapy with either:
1. pembrolizumab
2. atezolizumab
Or
Best supportive care

Second-line treatment
independent of the time of progression after first-line treatment

PS 0-1

Progression (independent of the time interval after receiving first-line chemotherapy), adequate renal function

Standard regimens
1. pembrolizumab
2. atezolizumab
3. nivolumab
Or
1. Clinical trial
2. Comb chemotherapy
3. Monotherapies

Subsequent treatment
1. Chemotherapy
2. Immunotherapy, if not given as second-line treatment
3. Clinical trial
4. Best supportive care

PS ≥ 2

a. Consider immunotherapy
b. Clinical trial
c. Best supportive care

BSC = best supportive care; GC = gemcitabine plus cisplatin; GFR = glomular filtration rate; HD MVAC = (high-dose) methotrexate, vinblastine, adriamycin plus cisplatin; PCG = paclitaxel, cisplatin, gemcitabine; PS = performance status.

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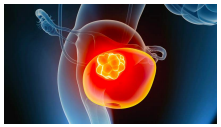

Bladder

European Association of Urology

BCG-refractory tumour:

- if T1 high-grade/G3, non-muscle-invasive papillary tumour is present at three months;
- if Ta high-grade/G3 or CIS (without concomitant papillary tumour) is present at both three and six months (after a second induction course or the first maintenance course of BCG);
- if high-grade tumour appears during BCG therapy [199];

BCG-relapsing tumour:

- recurrence of high-grade/ G3 (WHO 1973/2004) tumour after completion of BCG maintenance, despite an initial response).

BCG unresponsive:

- Bacillus Calmette-Guérin-refractory or T1 BCG relapse within six months or CIS within twelve months of last BCG exposure.

7.1.2 Guidelines for treatment failure of non-muscle-invasive bladder cancer

Recommendations	Strength rating
Discuss immediate radical treatment in all T1 tumours at high risk of progression (i.e., high grade, multifocality, carcinoma *in situ*, and tumour size, as outlined in the EAU Guidelines for Non-muscle-invasive Bladder Cancer).	Strong
Offer radical treatment to all T1 patients failing intravesical therapy.	Strong

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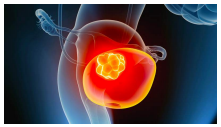
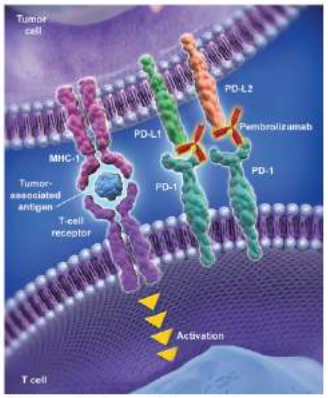


Phase 2 study of pembrolizumab in patients with bacillus Calmette-Guérin–unresponsive, high-risk, non–muscle-invasive bladder cancer: KEYNOTE-057

J. Bellmunt, M. De Santis, J. Boormans, A. Kamat, T. Choueiri, R. Dreicer, A. Siefker-Radtke, G. Sonpavde, K. Nam, R. Perini, S. Keefe, D. Bajorin

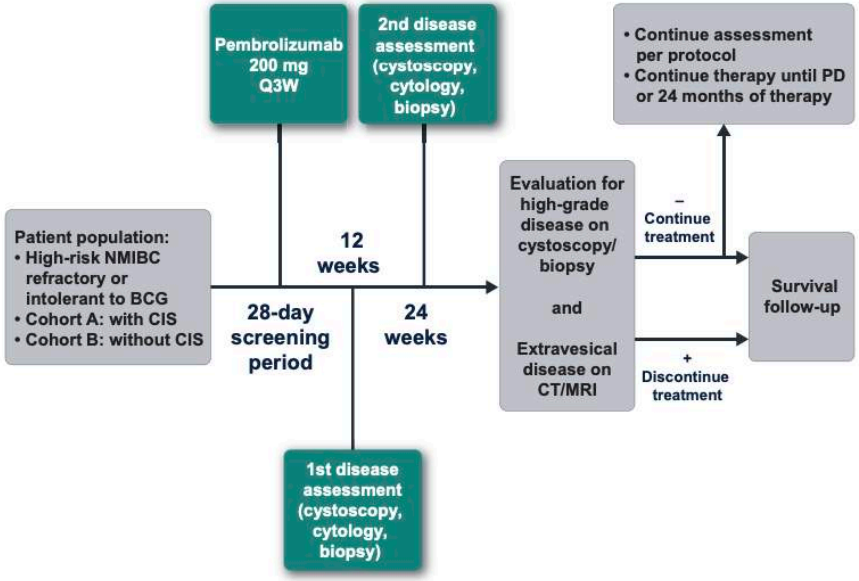
Figure 1. Pembrolizumab and the PD-1 pathway.



MHC-1 = major histocompatibility complex 1; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1; PD-L2 = programmed death ligand 2.

Figure 3. Countries with currently open sites of enrollment for KEYNOTE-057 (shown in green).

Figure 2. Study design.



BCG = Bacillus Calmette-Guérin; CIS = carcinoma in situ; CT = computed tomography; MRI = magnetic resonance imaging; NMIBC = non–muscle-invasive bladder cancer; PD = progressive disease; Q3W = every 3 weeks.

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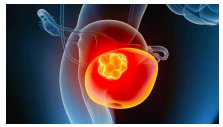

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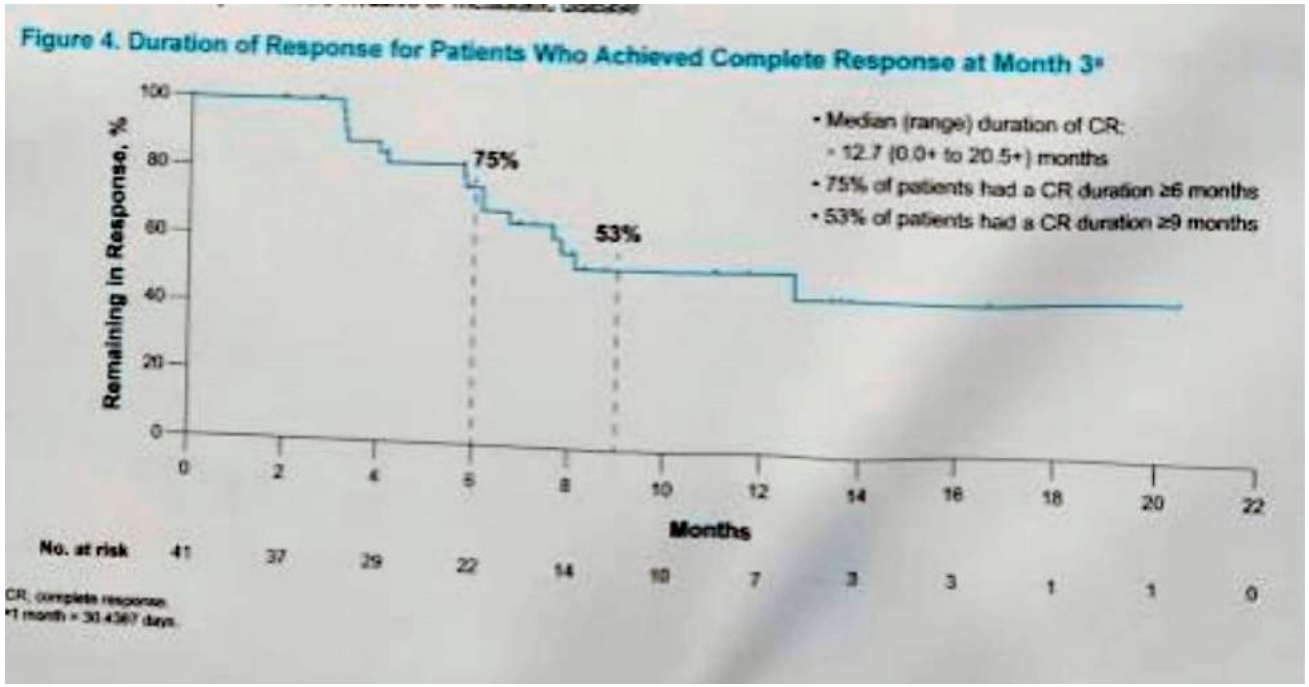

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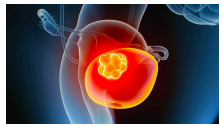

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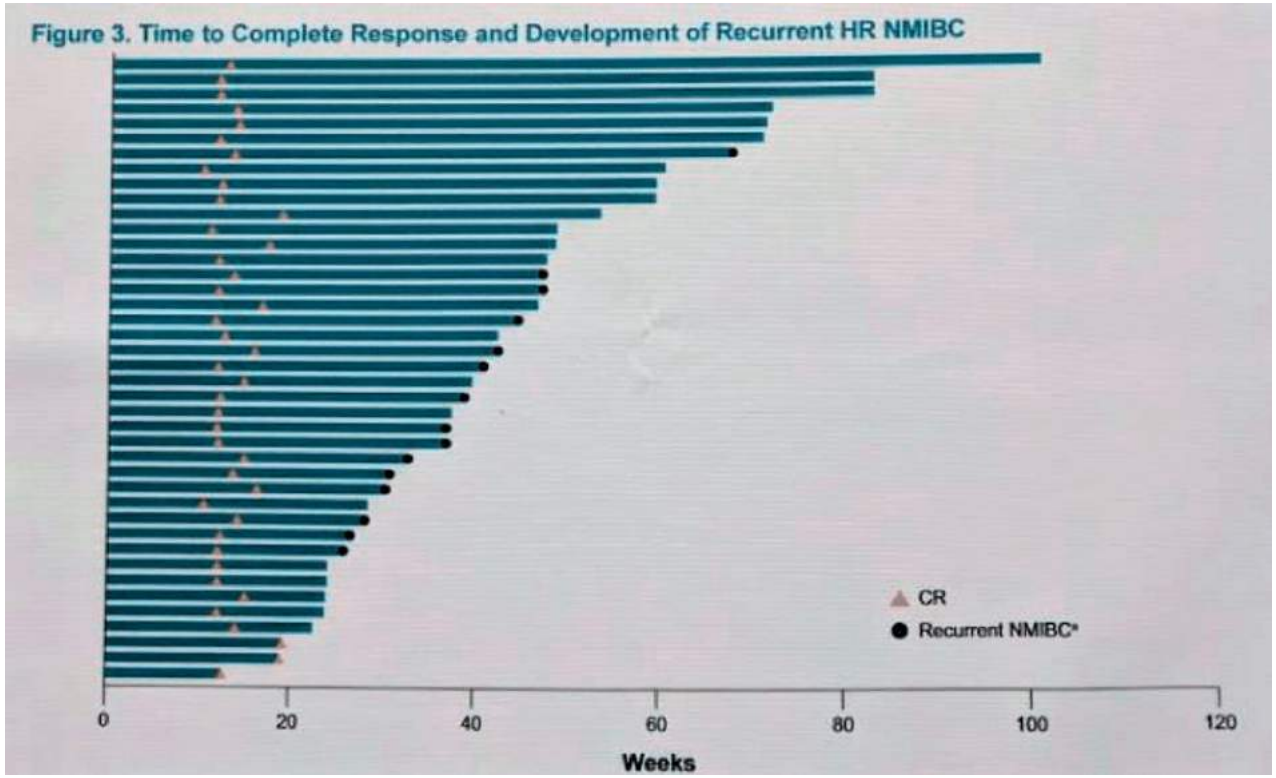
Figure 3. Time to Complete Response and Development of Recurrent HR NMIBC



ASCO GU 2019: Long-term Outcomes of Hypoxia Modification in Bladder Preservation: Update from BCON Trial

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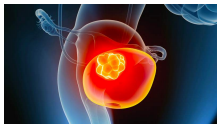


ASCO

Radiotherapy
+Carbogen (98% O_2, 2% CO_2)
+ Nicotinamide 40-60mg/kg daily
(Hypoxia modification)

Radiotherapy alone

N=333 pts
(T1G3- T2-4aN0M0)

- Local control
- F/U 10.3 years
- 5 year RFS 59.4% vs 50.7%
- 5 year OS 49.8% vs 39.9%

Figure 2 – Recurrence-free survival:

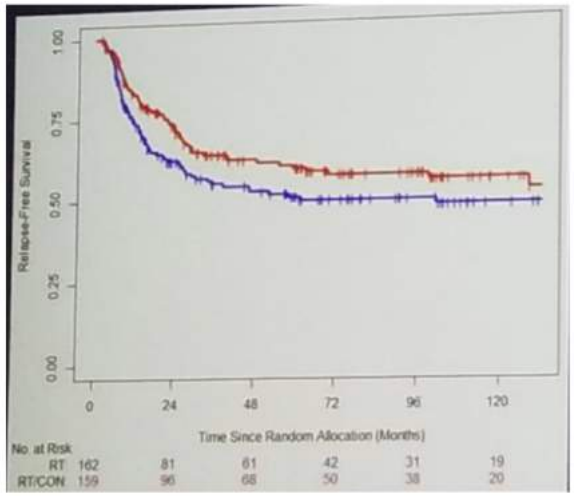
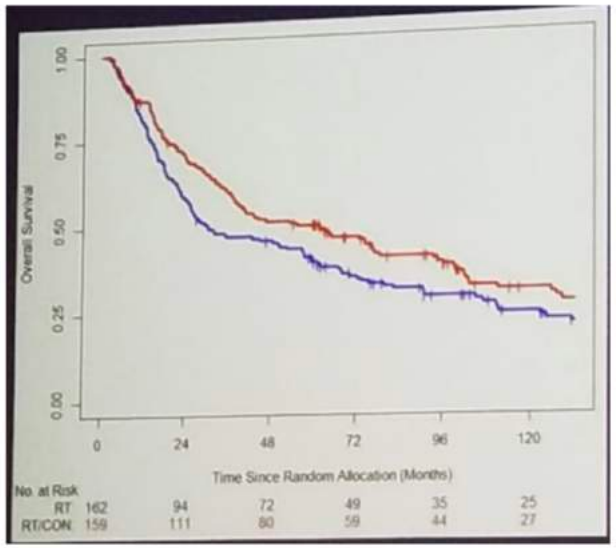


Figure 1 – Overall survival:



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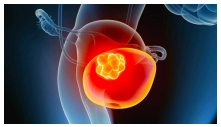

Single-arm Neoadjuvant Monotherapy Trials

Pembrolizumab (PURE-01)
- Phase II x3 cycles q3weeks
- Cisplatin-eligible or ineligible
- cT2-T3bN0-1M0
- Primary endpoint: pCR

Necchi et al, JCO 2018

Pembrolizumab (PURE-01)
N=50 evaluable

Pemprolizumab (PURE-01)
- pCR=42%
  - *PD-L1 + pCR 54.3%*
- *42% DDR genomic alterations*

ddMVAC N=1,093
pCR 27.8%

Zhu et al, Oncotarget 2017
(Meta-analysis of 10 studies)

Atezolizumab (ABACUS)
- Phase II
- 2 cycles q3 weeks
- Cisplatin-ineligible (or refuse)
- T2-4aN0M0
- Primary endpoint:
  - pCR>20% & increase CD8 count

Atezolizumab (ABACUS)
N=68 evaluable
- 12% had prior BCG
- 76% smoker/prior
- 71% T2

Atezolizumab (ABACUS)
- pCR= 29%
  - PD-L1+ pCR 40%
  - T2 pCR 35% (T3 15%)
- PD-L1 + increased 35%→73% post treatment
- CD8 expression increased post treatment (500→952 cells/mm^2)

Powles et al, ASCO 2018

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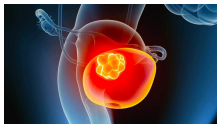
Phase III Checkpoint-Inhibitor Adjuvant Trials in Muscle Invasive Bladder Cancer



AMBASSADOR Alliance (NCT 03244384) High risk muscle invasive urothelial carcinoma of the bladder, ureter and renal pelvis	R (1:1) N=739	**Pemprolizumab** 200mg IV Q3W x 1 year **Observation**	Co-primary **DFS & OS**
Checkmate 274 (NCT 02632409) High Risk muscle invasive urothelial carcinoma of the bladder, ureter, and renal pelvis	R (1:1) N=640	**Nivolumab** 240mg IV Q2W x1 year **Placebo** Q2W	**DFS** • PD-L1 + • All
IMvigor 010 (NCT 02450331) High risk muscle invasive urothelial carcinoma of the bladder, ureter and renal pelvis	R (1:1) N=700	**Atezolizumab** 1200mg IV Q3W x 1 year **Observation**	**DFS**

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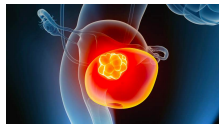
Where Do We Go from Here?



Select Ongoing/ Completed Trials in Bladder Cancer

Non-Muscle Invasive

KEYNOTE-057 (Ph 2):
- Pembrolizumab in BCG unresponsive NMIBC

NCT02792192 (Ph 1/2):
- Atezolizumab ± BCG in high risk NMIBC

Muscle Invasive

CheckMate 274 (Ph 3):
- Nivolumab vs placebo postsurgery MIBC

IMvigor 010 (Ph 3):
- Atezolizumab vs observation postsurgery PD-L1+ MIBC

Pembrolizumab (PURE-01)

Atezolizumab (ABACUS)

Treatment naïve Metastatic

DANUBE (Ph 3):
- Durvalumab ± Tremelimumab vs chemo Tx-naïve, unresectable, urothelial carcinoma

KEYNOTE-052 (Ph 2):
- Pembrolizumab Tx-naïve, cisplatin ineligible, locally advanced mUC

KEYNOTE-361 (Ph 3):
- Pembrolizumab ± chemo vs chemo in Tx-naïve advanced or mUC

IMvigor 130 (Ph 3):
- Atezolizumab gem-cis vs gem-cis in untreated advanced or mUC

Pretreated Metastatic

CheckMate 275 (Ph 2):
- Nivolumab for locally advanced or mUC after Pt failure

IMvigor 211 (Ph 3):
- Atezolizumab vs chemo in locally adv or mUC, after Pt failure

KEYNOTE-045 (Ph 3):
- Pembrolizumab vs chemo in locally adv or mUC, after Pt failure

JAVELIN Bladder 100 (Ph 3):
- Avelumab as maintenance vs BSC for locally advanced mUC

Bellmunt J, et al. *Cancer Treat Rev.* 2017

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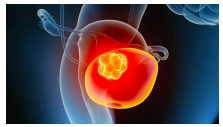

Phase III trials on the horizon

Pembrolizumab in combination with platinum-containing regimen in first line treatment of advanced bladder cancer

Eligibility

- 1L urothelial carcinoma
- Archival or Fresh Biopsy
- Measurable Disease
- ECOG Status 0, 1 and 2
- Hemoglobin >9 g/dL

Randomization 1:1:1

- Pembro
- Pembro + Cis-/carboplatin + gemcitabine
- Cis-/carboplatin + gemcitabine

Pembro up to 2 yrs

6 cycles chemo

Target enrollment: 990

Primary endpoint

- PFS + OS

Secondary endpoints

- DOR
- DCR
- Safety

Exploratory endpoints

- PKPD
- Biomarkers and genomics
- PRO

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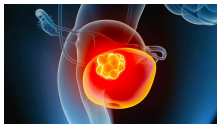

Συμπερασματικά

- Ασθενείς που δύναται να λάβουν Cisplatin πρέπει να λαμβάνουν συνδυασμένη χημειοθεραπεία με Cisplatin **(Standard of Care)**
- Pembro η Atezo μπορεί να λάβουν ασθενείς που δεν είναι υποψήφιοι για Cisplatin ως πρώτης γραμμής θεραπεία.
- Πρόκληση αποτελεί η πρόσβαση σε εξειδικευμένα διαγνωστικά κέντρα
- Αναμονή των μελετών Phase III για το συνδυασμό ανοσοθεραπείας με χημειοθεραπεία που φαίνεται ότι θα αλλάξει την ιατρική πρακτική

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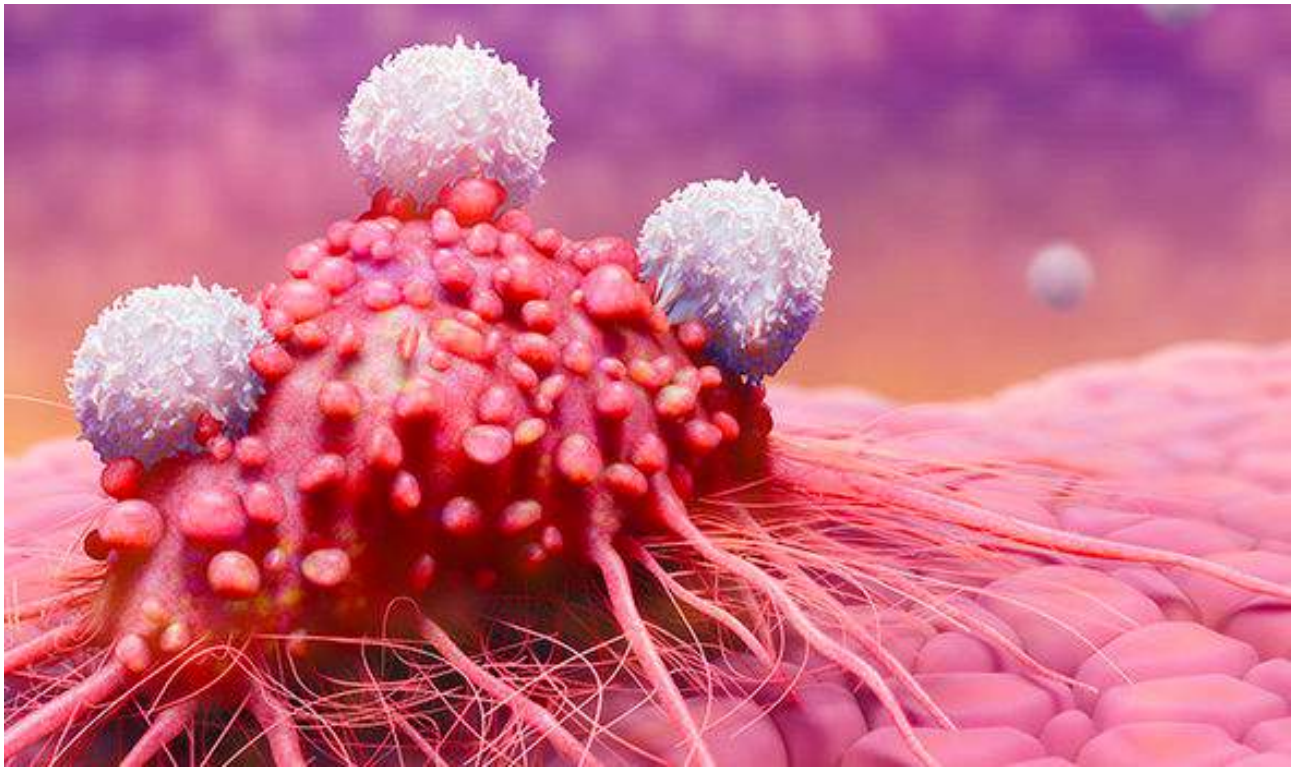
Penile Cancer



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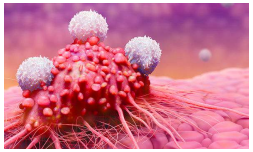
Ongoing Trials of Immune Checkpoint Inhibitors in Penile Cancer



NCT02837042 Phase II Pembrolizumab 2nd line following chemotherapy	N=35	**Pemprolizumab** 200mg IV Q3W x until progression	***Objective Response rate***
NCT02721732 Phase II Pembrolizumab patients different rare cancers after treatment failure	N=250	**Pembrolizumab** 200mg IV Q3W x1	**Non Progression rate**
NCT02834013 Phase II Combo treatment advanced rare cancers including Penile SCC	N=334	**Nivolumab+Ipilimumab**	***Response Rate RECIST***

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Costs

Corrected drug price calculations for cancer immunotherapies

Drug	Flat dose (US label)	Drug price/mg	Source of price	Price/cycle	Median cycles (Aguiar et al. [1])
Nivolumab (squamous)	240 mg Q2W	$26.064/mg	CMS limit (October 2016)	$6088.8	15 cycles
Nivolumab (non-squamous)	240 mg Q2W	$26.064/mg	CMS limit (October 2016)	$6088.8	14 cycles
Pembrolizumab	200 mg Q3W	$46.495/mg	CMS limit (October 2016)	$9139	9 cycles
Atezolizumab	1200 mg Q3W	$7.183/mg	WAC (November 2016)	$8620	8 cycles


THERE IS NOTHING
WRONG WITH CHANGE,
IF IT IS IN THE RIGHT
DIRECTION.
- WINSTON CHURCHILL