GU Cancers: Best of ASCO

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Disclosures

- Research Funding
  - Pfizer, Merck, Acerta Pharma, Roche/Genentech, Bristol-Myers Squibb, Incyte, Seattle Genetics
- Consulting
  - BioClin Therapeutics

Lecture Objectives

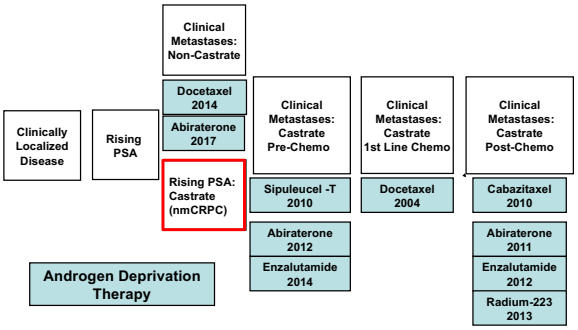
- Describe recent advances using antiandrogen therapy in patients with nonmetastatic castration-resistant prostate cancer (nmCRPC).
- Discuss the use of novel combination therapy approaches with immune checkpoint inhibitors in metastatic renal cell cancer.
- Review the evolving landscape of immunotherapy in patients with advanced bladder cancer.

Poll

Genitourinary cancers account for what percent of new cancer cases in the United States?

A. 60%
B. 40%
C. 20%
D. 5%

Prostate Cancer Clinical States

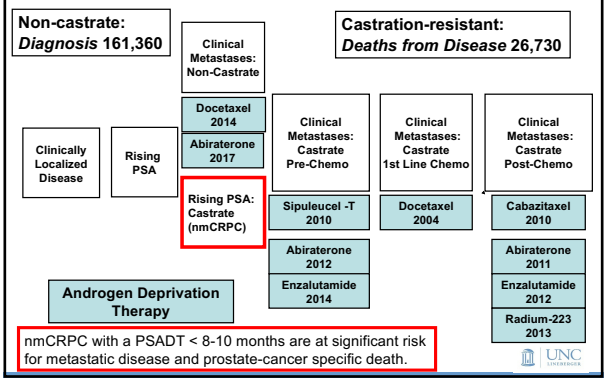


Poll

A shorter PSADT in nmCRPC is associated with which of the following?

A. Increased risk for metastasis
B. Increased risk for prostate cancer specific mortality
C. Decreased overall survival
D. A and B
E. All of the above

Prostate Cancer Clinical States



nmCRPC with a PSADT < 8-10 months are at significant risk for metastatic disease and prostate-cancer specific death.

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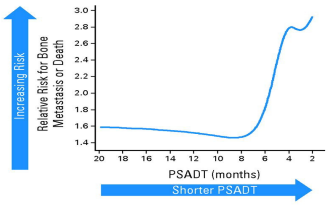
Rapid PSADT in nmCRPC



Smith at al. *J Clin Oncol*. 2013

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SPARTAN, a Phase 3 Double-Blind, Randomized Study of Apalutamide vs Placebo in Patients With Nonmetastatic Castration-Resistant Prostate Cancer

Eric J. Small,[1] Fred Saad,[2] Simon Chowdhury,[3] Boris A. Hadaschik,[4] Julie N. Graff,[5] David Olmos,[6] Paul N. Mainwaring,[7] Hiroji Uemura,[8] Angela Lopez-Gitlitz,[9] Géralyn C. Trudel,[9] Byron M. Espina,[9] Youyi Shu,[9] Youn C. Park,[9] Wayne R. Rackoff,[9] Margaret K. Yu,[9] Matthew R. Smith,[10] on behalf of the SPARTAN Investigators

[1]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA; [2]Centre Hospitalier de l'Université de Montréal, Université de Montréal, Montréal, Québec, Canada; [3]Guy's, King's and St. Thomas' Hospitals, Great Maze Pond, London, UK; [4]University of Duisburg-Essen, Essen, Germany; [5]VA Portland Health Care System, Portland, and Knight Cancer Institute, Oregon Health & Science University, Portland, OR; [6]Spanish National Cancer Research Centre (CNIO), Madrid, and Hospitales Universitarios Virgen de la Victoria y Regional de Málaga, Málaga, Spain; [7]Centre for Personalised Nanomedicine, University of Queensland, Brisbane, Australia; [8]Yokohama City University Medical Center, Yokohama, Japan; [9]Janssen Research & Development, Los Angeles, CA; [10]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA

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Presented By: Eric Small, MD, FASCO

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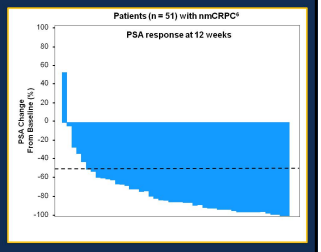
Background

- Androgen signaling inhibitors (ASI) prolong survival in men with mCRPC[1-4]
- Apalutamide is a next-generation ASI under development for the treatment of prostate cancer[5]
- In a phase 2 study, apalutamide led to a ≥ 50% PSA decline in 89% of high-risk nmCRPC patients[6]



1. de Bono JS, et al. *N Engl J Med*. 2011;364:1995-2005. 2. Scher HI, et al. *N Engl J Med*. 2012;367:1187-1197. 3. Ryan CJ, et al. *N Engl J Med*. 2013;368:138-148. 4. Beer TM, et al. *N Engl J Med*. 2014;371:424-433. 5. Clegg NJ, et al. *Cancer Res*. 2012;72:1494-1503. 6. Smith MR, et al. *Eur Urol*. 2016;70:963-970.

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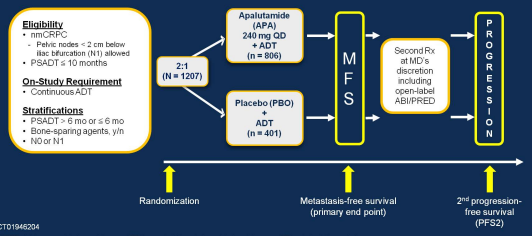
SPARTAN — Overall Study Design

Phase 3 Placebo-Controlled, Randomized International Study



NCT01946204

ABI/PRED, abiraterone acetate plus prednisone; nmCPRC, nonmetastatic castration-resistant prostate cancer; MFS, metastasis-free survival.

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Results

Patient Demographics and Disease Characteristics

	APA (n = 806)	PBO (n = 401)
Median age, yrs	74.0	74.0
Median time from initial diagnosis to randomization, yrs	7.95	7.85
Median PSADT, mos	4.40	4.50
PSADT, %		
≤ 6 mos	71	71
> 6 mos	29	29
Bone-sparing agent use, %		
Yes	10	10
No	90	90
Nodal status at study entry, %		
N0	83	84
N1	17	16
Prior prostate cancer therapy, %		
Definitive local therapy	77	77
GnRH agonist	97	97
First-generation antiandrogen	73	72

GnRH, gonadotropin-releasing hormone.

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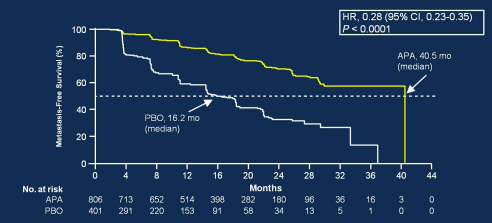
Primary End Point: Metastasis-Free Survival

72% risk reduction of distant progression or death



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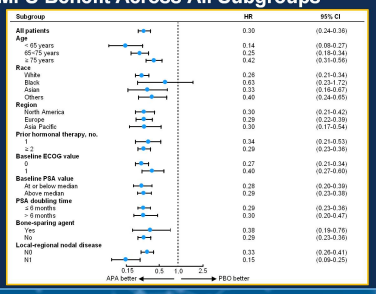
Consistent MFS Benefit Across All Subgroups



ECOG, Eastern Cooperative Oncology Group

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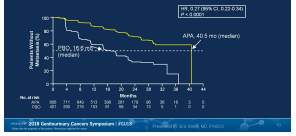
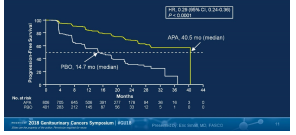
Secondary Endpoints

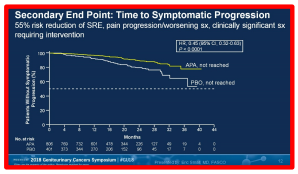
Secondary End Point: Time to Metastasis
73% risk reduction of distant progression



Secondary End Point: Progression-Free Survival
71% risk reduction of local progression, distant progression, or death



Secondary End Point: Time to Symptomatic Progression
55% risk reduction of SRE, pain progression/worsening sx, clinically significant sx requiring intervention



Secondary End Point: Overall Survival
30% risk reduction of death

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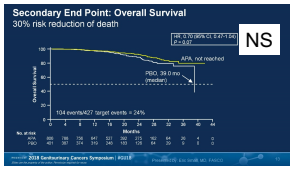

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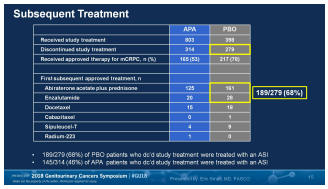

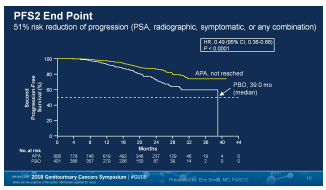

Apalutamide resulted in a 51% risk reduction in PFS2 even in the face of a high rate of secondary ASI use in the placebo arm.

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Results: All Adverse Events

	APA (n = 803)	PBO (n = 398)
Grade 3 or 4 AE	45%	34%
Any serious AE	25%	23%
Any AE leading to treatment discontinuation	11%	7%
Percent of patients remaining on treatment at the clinical cutoff date	61%	30%

AE, adverse event.

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Presented by: Eric Small, MD, FASCO
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PROSPER: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Enzalutamide in Men With Nonmetastatic Castration-Resistant Prostate Cancer

Maha Hussain,[1] Karim Fizazi,[2] Fred Saad,[3] Per Rathenborg,[4] Neal Shore,[5] Eren Demirhan,[6] Katharina Modelska,[6] De Phung,[7] Andrew Krivoshik,[7] and Cora N. Sternberg[8]

[1]Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL; [2]Institut Gustave Roussy, University of Paris Sud, Villejuif, France; [3]Centre hospitalier de l'Université de Montréal, Montreal, Canada; [4]Herlev Hospital, Herlev, Denmark; [5]Carolina Urologic Research Center, Myrtle Beach, SC; [6]Pfizer Inc., San Francisco, CA; [7]Astellas Pharma, Inc., Northbrook, IL; [8]San Camillo and Forlanini Hospitals, Rome, Italy

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Presented by: Maha Hussain, MD, FACP, FASCO

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Background, cont.

- Enzalutamide significantly improved OS and radiographic progression-free survival (rPFS) in men with chemotherapy-naïve M1 CRPC (PREVAIL trial)[1]
- Enzalutamide was superior to bicalutamide in improving rPFS in the subgroup of patients with chemotherapy-naïve M0 CRPC (STRIVE trial)[2]

Hypothesis:

Enzalutamide will delay metastases development in men with M0 CRPC and rapidly rising PSA (PSA doubling time ≤ 10 months)

1. Beer TM et al. *N Engl J Med*. 2014;371:424-33; 2. Penson DF et al. *J Clin Oncol*. 2016;34:2098-106.

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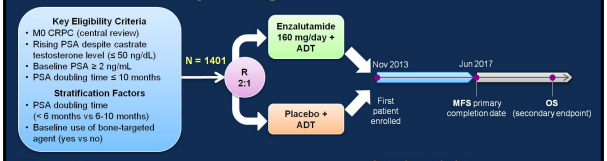
PROSPER Study Design



Primary endpoint

- MFS (defined as time from randomization to radiographic progression or death within 112 days of treatment discontinuation)

Statistical Design:

- Target difference in Kaplan-Meier estimated median MFS of 9 months (24 months vs 33 months)
- Target of 440 events provides 90% power to detect a target HR of 0.72

Secondary endpoints

- Safety
- Time to PSA progression
- Time to use of new antineoplastic therapy
- OS
- PSA response
- Quality of life

Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio; R, randomization.

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Baseline Patient Characteristics (N = 1401)

Characteristic	Enzalutamide + ADT (n = 933)	Placebo + ADT (n = 468)
Median age (range), y	74 (50-95)	73 (53-92)
ECOG PS, no. (%)		
0	747 (80%)	382 (82%)
1	185 (20%)	85 (18%)
Median serum PSA (range), ng/mL	11.1 (0.8-1071.1)	10.2 (0.2-467.5)
Median PSA doubling time (range), mo	3.8 (0.4-37.4)	3.6 (0.5-71.8)
PSA doubling time category, no. (%)		
< 6 mo	715 (77%)	361 (77%)
≥ 6 mo	217 (23%)	107 (23%)
Baseline use of bone targeting agent, no. (%)		
No	828 (89%)	420 (90%)
Yes	105 (11%)	48 (10%)

- Median duration of therapy was 18.4 (range, 0-41.9+) months for enzalutamide and 11.1 (range, 0-42.8+) months for placebo
- Patients on treatment as of 28 June 2017 (cutoff date): 634 patients (68%) on enzalutamide and 176 patients (38%) on placebo

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group Performance Status.

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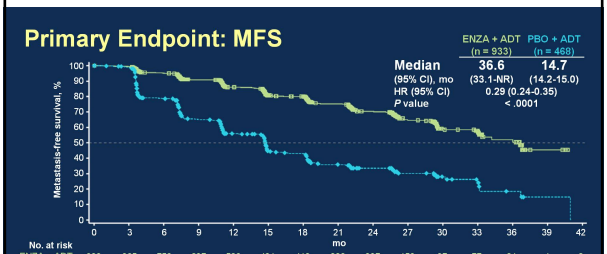
Primary Endpoint: MFS



- Median MFS was ≈ 22 months longer with enzalutamide than with placebo (71% reduction in relative risk of radiographic progression or death)

Abbreviations: CI, confidence interval; ENZA, enzalutamide; NR, not reached; PBO, placebo.

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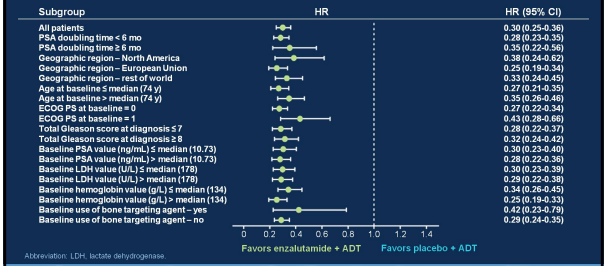
Subgroup Analysis of MFS



Abbreviation: LDH, lactate dehydrogenase.

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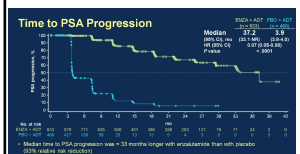
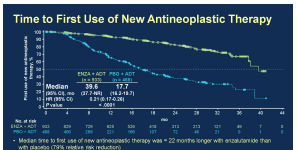
Secondary Endpoints

Time to PSA Progression



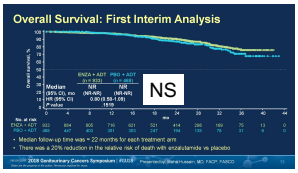
- Median time to PSA progression was ≈ 33 months longer with enzalutamide than with placebo (93% relative risk reduction)

Time to First Use of New Antineoplastic Therapy



- Median time to first use of new antineoplastic therapy was ≈ 22 months longer with enzalutamide than with placebo (79% relative risk reduction)

Overall Survival: First Interim Analysis



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- Median follow-up time was ≈ 22 months for each treatment arm
- There was a 20% reduction in the relative risk of death with enzalutamide vs placebo

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Conclusions

- APA and ENZA delay MFS in men with nmCRPC by two years.
- A delay in the onset of disease-related symptoms (SPARTAN) represents a clinical benefit.
- Side effects
  - More deaths from other causes within 3 months of progression on ENZA
  - Falls and fractures with APA
- No survival benefit (yet).
  - Is MFS a surrogate for OS in nmCRPC?

Poll

The use of novel antiandrogens in nmCRPC is associated with a significant benefit in which of the following?

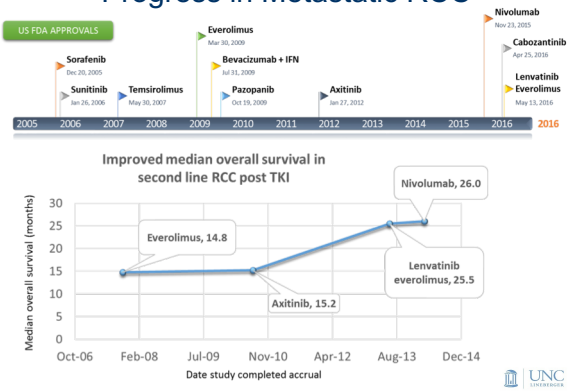
A. Metastasis-free survival

B. Time to PSA progression

C. Time to symptomatic progression

D. All of the above

Progress in Metastatic RCC



Poll

The use of combination VEGF targeted therapy is associated with which outcome in metastatic RCC?

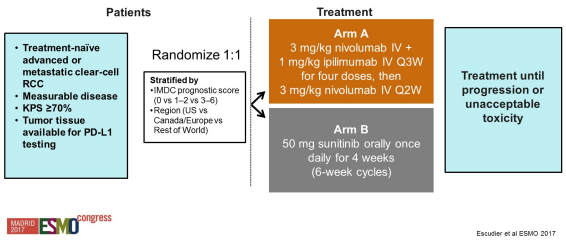
A. OS benefit
B. PFS benefit
C. Significant toxicity
D. All of the above

Emerging Therapeutic Strategies in Metastatic RCC

- Combination VEGF + PD-1 Pathway Inhibition
- Combination IDO + PD-1 Pathway Inhibition
- Combination CTLA4 + PD-1 Pathway Inhibition
- HIF2 alpha Inhibition

Plimack 2017

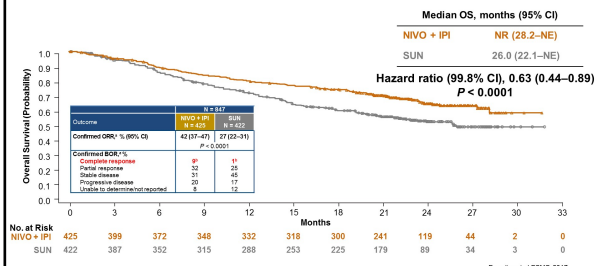
CheckMate 214: Study design



Escudier et al ESMO 2017

Co-primary endpoint

OS: IMDC intermediate/poor risk



Outcome	N = 847 NIVO + IPI N = 425	SUN N = 422
Confirmed ORR,[a] % (95% CI)	42 (37–47)	27 (22–31)
	P < 0.0001	
Confirmed BOR,[a] %		
Complete response	9[d]	1[e]
Partial response	32	25
Stable disease	31	45
Progressive disease	20	17
Unable to determine/not reported	8	12

Escudier et al ESMO 2017

Exploratory endpoint

ORR and PFS: IMDC favorable risk

Outcome	N = 249[a] NIVO + IPI N = 125	SUN N = 124
Confirmed ORR,[b] % (95% CI)	29 (21–38)	52 (43–61)
	P = 0.0002	
PFS,[c] median (95% CI), months	15.3 (9.7–20.3)	25.1 (20.9–NE)
	HR (99.1% CI) 2.18 (1.29–3.68) P < 0.0001	

Escudier et al ESMO 2017

Secondary endpoint

Treatment-related adverse events: All treated patients

Event, %	NIVO + IPI N = 547 Any grade	NIVO + IPI N = 547 Grade 3–5	SUN N = 535 Any grade	SUN N = 535 Grade 3–5[a]
Treatment-related adverse events in ≥25% of patients	93	46	97	63
Fatigue	37	4	49	9
Dysgeusia	6	0	33	<1
Stomatitis	4	0	28	3
Hypertension	2	<1	40	16
Mucosal inflammation	2	0	28	3
Palmar-plantar erythrodysesthesia syndrome	1	0	43	9
Treatment-related AEs leading to discontinuation, %	**22**	**15**	**12**	**7**
Treatment-related deaths	**n = 7[b]**		**n = 4[c]**	

60% of patients treated with NIVO + IPI required systemic corticosteroids for an adverse event

[a]Two patients had grade 5 cardiac arrest. [b]Pneumonitis, immune mediated bronchitis, lower GI hemorrhage, hemophagocytic syndrome, sudden death, liver toxicity, lung infection. [c]Cardiac arrest (n = 2), heart failure, multiple organ failure

Escudier et al ESMO 2017

Emerging Therapeutic Strategies in Metastatic RCC

- Combination VEGF + PD-1 Pathway Inhibition
- Combination IDO + PD-1 Pathway Inhibition
- Combination CTLA4 + PD-1 Pathway Inhibition
- HIF2 alpha Inhibition

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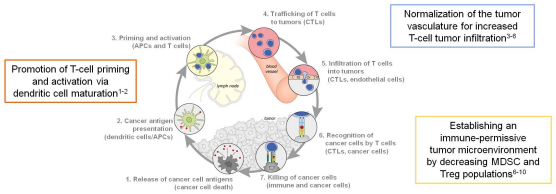
IMmotion151: A Randomized Phase III Study of Atezolizumab Plus Bevacizumab vs Sunitinib in Untreated Metastatic Renal Cell Carcinoma

Robert Motzer,[1] Thomas Powles,[2] Michael Atkins,[3] Bernard Escudier,[4] David McDermott,[5] Cristina Suarez,[6] Sergio Bracarda,[7] Walter M. Stadler,[8] Frede Donskov,[9] Jae Lyun Lee,[10] Robert Hawkins,[11] Alain Ravaud,[12] Boris Alekseev,[13] Michael Staehler,[14] Motohide Uemura,[15] Francis Donaldson,[16] Shi Li,[17] Mahrukh Huseni,[17] Christina Schiff,[17] Brian Rini[18]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Barts Health NHS Trust – St Bartholomew's Hospital, London, UK; [3]Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; [4]Gustave Roussy, Villejuif, France; [5]Beth Israel Deaconess Medical Center, Boston, MA; [6]Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain; [7]Ospedale San Donato, Arezzo, Italy; [8]The University of Chicago Medicine, Chicago, IL; [9]Department of Oncology, Aarhus University Hospital, Denmark; [10]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [11]The Christie NHS Foundation Trust, Manchester, UK; [12]CHU Hopitaux de Bordeaux – Hôpital Saint-André, Bordeaux, France; [13]P. Herzen Oncology Research Institute, Moscow, Russia; [14]Klinikum der Universität München, Campus Großhadern, München, Germany; [15]Department of Urology, Osaka University Graduate School of Medicine, Osaka, Japan; [16]Roche Products Ltd, Welwyn Garden City, UK; [17]Genentech, Inc., South San Francisco, CA; [18]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH

Rationale for Combining Atezolizumab + Bevacizumab



Normalization of the tumor vasculature for increased T-cell tumor infiltration[3-8]

Promotion of T-cell priming and activation via dendritic cell maturation[1-2]

Establishing an immune-permissive tumor microenvironment by decreasing MDSC and Treg populations[9-10]

- Atezolizumab's T-cell mediated cancer cell killing may be enhanced through bevacizumab's reversal of VEGF-mediated immunosuppression

1. Gabrilovich DI, et al. *Nat Med.* 1996. 2. Oyama T, et al. *J Immunol.* 1998. 3. Goel S, et al. *Physiol Rev.* 2011. 4. Motz GT, et al. *Nat Med.* 2014. 5. Hodi FS, et al. *Cancer Immunol Res.* 2014. 6. Wallin JJ, et al. *Nat Commun.* 2016. 7. Gabrilovich DI, Nagaraj S. *Nat Rev Immunol.* 2009. 8. Roland CL, et al. *PLoS One.* 2009. 9. Facciabene A, et al. *Nature.* 2011. 10. Voron T, et al. *J Exp Med.* 2015.
Figure adapted from Chen DS, Mellman I. *Immunity.* 2013.

Study Objectives

- A randomized Phase III study of atezolizumab + bevacizumab vs sunitinib was conducted in patients with treatment-naive advanced or metastatic RCC
- **Primary Endpoints**
  - PFS by investigator-assessment in PD-L1+ patients, defined as ≥ 1% expression on tumor-infiltrating immune cells (IC) as determined by immunohistochemistry (IHC)[a]
  - OS in ITT
- **Key Secondary Endpoints**
  - PFS in ITT
  - OS in PD-L1+
  - ORR and DOR
  - Independent radiology committee (IRC)-assessed PFS and ORR
  - Patient-reported outcomes
  - Safety

DOR, duration of response; ITT, intent-to-treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; [a] Using SP142 IHC assay.

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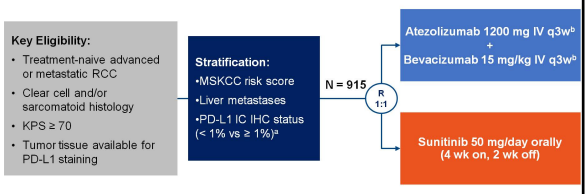
Study Design



[a] ≥ 1% IC: 40% prevalence using SP142 IHC assay. [b] No dose reduction for atezolizumab or bevacizumab.

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Baseline Characteristics

	PD-L1+ (n = 362)		ITT (N = 915)	
Characteristic	Atezo + Bev n = 178	Sunitinib n = 184	Atezo + Bev n = 454	Sunitinib n = 461
Age, median (range)	62 y (33-84)	59 y (23-80)	62 y (24-88)	60 y (18-84)
Male	67%	79%	70%	76%
KPS ≥ 80	95%	95%	91%	92%
Liver metastasis	17%	18%	17%	18%
Prior nephrectomy	84%	83%	74%	72%
Predominant clear cell histology	92%	87%	93%	92%
Sarcomatoid component	20%	27%	15%	16%
≥ 1% of IC expressing PD-L1 (PD-L1+)	-	-	39%	40%
MSKCC risk category				
Favorable (0)	17%	18%	20%	20%
Intermediate (1 or 2)	74%	73%	71%	70%
Poor (≥ 3)	8%	9%	10%	10%

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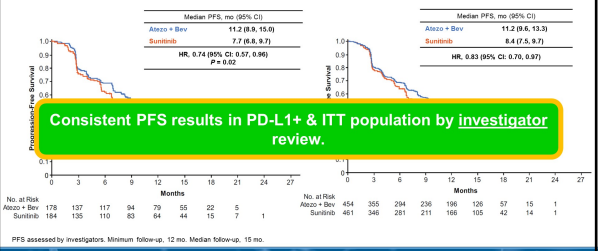
Co-Primary Endpoint

PFS (PD-L1+ & ITT)



Consistent PFS results in PD-L1+ & ITT population by investigator review.

PFS assessed by investigators. Minimum follow-up, 12 mo. Median follow-up, 15 mo.

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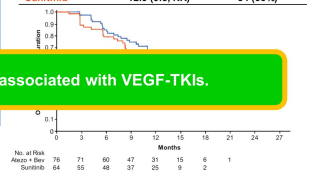
Secondary Endpoint

Objective Response Rate

	PD-L1+	
	Atezo + Bev n = 178	Sunitinib n = 184
Confirmed ORR, % 95% CI	43% (35, 50)	35% (28, 42)
Complete response	9%	4%
Pa		
St		
Pr		
Not evaluable[a]	7%	10%

PD-L1+	Median DOR, mo (95% CI)	Ongoing Responders, n (%)
Atezo + Bev	NR (12.4, NR)	49 (65%)
Sunitinib	12.9 (9.8, NR)	34 (53%)



Higher CR rates than associated with VEGF-TKIs.

NR, not reached. [a] Including patients with no post-baseline tumor assessment. ORR assessed by investigators in patients with measurable disease at baseline. Minimum follow-up, 12 mo. Median follow-up, 15 mo.

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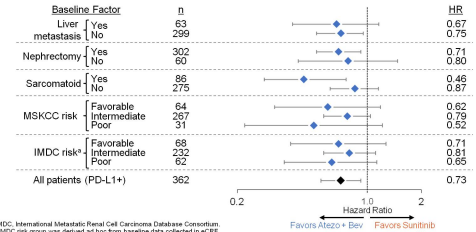
Subgroup Analysis

PFS in Key Subgroups (PD-L1+)

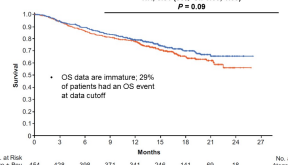


IMDC, International Metastatic Renal Cell Carcinoma Database Consortium. [a]IMDC risk group was derived ad hoc from baseline data collected in eCRF. PFS assessed by investigators.

Overall Survival in ITT & PD-L1+

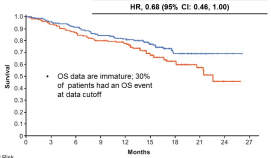
Co-Primary Endpoint

ITT Median OS, mo (95% CI)	
Atezo + Bev	Not reached
Sunitinib	Not reached
HR, 0.81 (95% CI: 0.63, 1.03)	
P = 0.09	



No. at Risk									
Atezo + Bev	454	428	398	371	341	246	141	69	18
Sunitinib	461	422	384	357	331	227	126	65	15

PD-L1+ Median OS, mo (95% CI)	
Atezo + Bev	Not reached
Sunitinib	23.3 (21.3, NR)
HR, 0.68 (95% CI: 0.46, 1.00)	



No. at Risk									
Atezo + Bev	178	169	160	147	139	109	55	26	6
Sunitinib	184	169	154	141	134	96	51	27	6

Minimum follow-up, 12 mo. Median of follow-up, 15 mo. Event/patient ratio: 27% for atezo + bev, 31% for sunitinib.
The OS analysis did not pass the *P* value boundary of alpha = 0.0009 at the first interim analysis.

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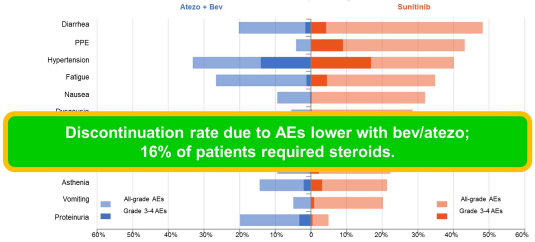
Treatment-related AEs

> 5% difference between arms and ≥ 20% frequency in either arm

Secondary Endpoint



Discontinuation rate due to AEs lower with bev/atezo; 16% of patients required steroids.

PPE, palmar-plantar erythrodysesthesia.

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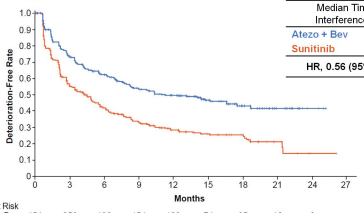
Time to Symptom Interference With Activities of Daily Living in ITT

Secondary Endpoint

Median Time to Symptom Interference, mo (95% CI)	
Atezo + Bev	11.3 (8.3, 17.5)
Sunitinib	4.3 (3.1, 5.6)
HR, 0.56 (95% CI: 0.46, 0.68)	



No. at Risk									
Atezo + Bev	454	256	196	154	128	74	35	12	3
Sunitinib	461	178	119	87	60	38	25	7	1

Per the MD Anderson Symptom Interference Scale, event defined as a ≥ 2-point score increase (on a 10-point scale) from baseline.

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Secondary Endpoint

PFS and ORR by IRC

	PD-L1+		PD-L1-[a]		ITT	
	Atezo + Bev n = 178	Sunitinib n = 184	Atezo + Bev n = 276	Sunitinib n = 277[b]	Atezo + Bev n = 454	Sunitinib n = 461
Median PFS, mo (95% CI)	8.9 (6.9, 12.5)	7.2 (6.1, 11.1)	11.0 (8.3, 13.3)	8.4 (7.4, 10.1)	9.6 (8.3, 11.5)	8.3 (7.0, 9.7)
Stratified HR (95% CI)	0.93 (0.72, 1.21)		0.84 (0.67, 1.04)		0.88 (0.74, 1.04)	

What could drive discordance between investigator and central review?

- IRC and INV assessment of PFS benefit was generally consistent in the ITT population; however, results differed from INV assessment in patients with PD-L1+ disease
- Investigators, IRC reviewers and the sponsor were blinded to PD-L1 status

[a] PD-L1 negative tumors had a PD-L1 IC IHC expression < 1%. [b] n = 276 for ORR.

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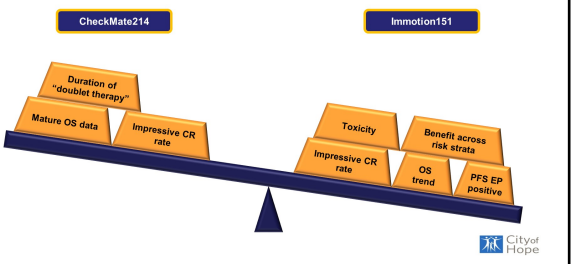
Immotion151 vs CheckMate214



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Abstract 579

Safety and efficacy of axitinib in combination with pembrolizumab in patients with advanced renal cell cancer

Michael B Atkins, MD[1], Elizabeth R Plimack, MD[2], Igor Puzanov, MD[3,4], Mayer N Fishman, MD[5], David F McDermott, MD[6], Daniel C Cho, MD[7], Ulka Vaishampayan, MD[8], Saby George, MD[4], Thomas E Olencki, DO[9], Jamal C Tarazi, MD[10], Brad Rosbrook, MS[10], Kathrine C Fernandez, MPH[11], Mariajose Lechuga, MD[12], and Toni K Choueiri, MD[13]

[1]Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC, USA; [2]Fox Chase Cancer Center, Philadelphia, PA, USA; [3]Vanderbilt University Medical Center, Nashville, TN, USA; [4]Roswell Park Cancer Institute, Buffalo, NY, USA; [5]Moffitt Cancer Center, Tampa, FL, USA; [6]Beth Israel Deaconess Medical Center, Boston, MA, USA; [7]NYU Langone Medical Center, New York, NY, USA; [8]Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA; [9]The Ohio State University, Wexner Medical Center, Columbus, OH, USA; [10]Pfizer Oncology, San Diego, CA, USA; [11]Pfizer Oncology, Cambridge, MA, USA; [12]Pfizer S.r.L, Milan, Italy; [13]Dana-Farber Cancer Institute, Boston, MA, USA

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Study Design and Endpoints

- This open-label phase Ib, multicenter study* consisted of 2 phases:
  - Dose-finding phase to estimate the maximum tolerated dose (MTD)
  - Dose-expansion phase

Primary endpoint (dose-finding phase)
- Dose-limiting toxicity during the first 2 cycles (6 weeks)

Secondary endpoints (dose-expansion phase)
- Safety, objective response rate, progression-free survival, overall survival, pharmacokinetics, and biomarkers

* ClinicalTrials.gov identifier: NCT02133742.

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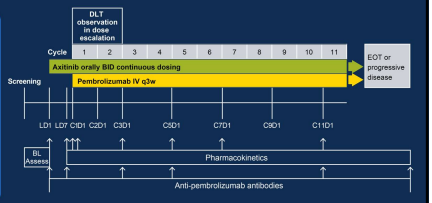
Study Design

Key inclusion criteria
- Clear-cell advanced RCC with primary tumor resected
- Mandatory archival tumor biospecimen
- ≥1 measureable lesion, as defined by RECIST v1.1
- ECOG PS 0 or 1
- Controlled hypertension

Key exclusion criteria
- Prior systemic therapy for advanced RCC



Arrows indicate dosing.
BID=twice daily; BL assess=baseline assessment; C=cycle; D=day; DLT=dose-limiting toxicity; ECOG PS=Eastern Cooperative Oncology Group performance status; EOT=end of treatment; IV=intravenous; LD1=lead-in Day 1; LD7=lead-in Day 7; q3w=every 3 weeks; RCC=renal cell carcinoma; RECIST=Response Evaluation Criteria in Solid Tumors

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Results: DLTs

- 11 patients were treated during the dose-finding phase, all at DL1.
- 3 DLTs were reported
  - 1 patient had transient ischemic attack
  - 2 patients were unable to complete ≥75% of planned axitinib dose due to treatment-related toxicity (grade 2/3 headache; and grade 2 headache, fatigue, asthenia, and dehydration)
- MTD was estimated to be axitinib 5 mg BID + pembrolizumab 2 mg/kg q3w
- These 11 patients were included in the dose-expansion analysis

BID=twice daily; DLT=dose-limiting toxicity; q3w=every 3-week cycle ; MTD=maximum tolerated dose

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Baseline Characteristics

- 52 treatment-naïve patients with advanced RCC were enrolled and received treatment:
  - 11 patients in the dose-finding phase
  - 41 patients in the dose-expansion phase

Characteristic, n (%)	Axitinib + Pembrolizumab N=52
Age, median (range) years	63.0 (28–75)
Male / Female, n (%)	41 (78.8) / 11 (21.2)
ECOG PS, n (%)	
0	39 (75.0)
1	10 (19.2)
Not reported	3 (5.8)

IMDC Criteria risk group, n (%)	
Favorable	24 (46.2)
Intermediate	23 (44.2)
Poor	3 (5.8)
Unknown	2 (3.8)
Fuhrman grade, n (%)	
1	2 (3.8)
2	12 (23.1)
3	18 (34.6)
4	14 (26.9)
Not done	6 (11.5)
Duration since initial pathologic diagnosis	
n	46
Mean, months	43.6
Median, months (range)	20.3 (0.8–166.6)
Unspecified, n	6

ECOG PS=Eastern Cooperative Oncology Group performance status; IMDC=International Metastatic Renal Cell Carcinoma Database

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Adverse Events, Safety Analysis Set (N=52)

Adverse Event, n (%)	Treatment-related* AE Grade ≥3 in ≥2 Patients	Immune-related AE Grade ≥3
Any AE	34 (65.4)	11 (21.1)
Hypertension	12 (23.1)	0
Fatigue	5 (9.6)	2 (3.8)
Diarrhea	5 (9.6)	4 (7.7)
ALT increased	4 (7.7)	2 (3.8)
AST increased	2 (3.8)	2 (3.8)
γ-glutamyltransferase increased	2 (3.8)	0
Headache	2 (3.8)	0
Hypophosphatemia	2 (3.8)	0
Lymphocyte count decreased	2 (3.8)	1 (1.9)
PPE	2 (3.8)	0
Weight decreased	2 (3.8)	1 (1.9)

* Related to axitinib and/or pembrolizumab. One (1.9%) patient had grade 4 hyperuricemia event. No grade 5 treatment-related AEs were reported.
6 patients received steroids for presumed immune-related AEs.
AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; PPE=palmar-plantar erythrodysesthesia

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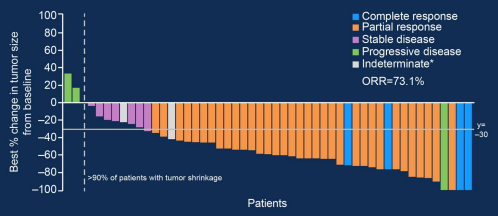
Tumor Response



* Stable disease or partial response not confirmed, or no follow-up scans available.
ORR=objective response rate

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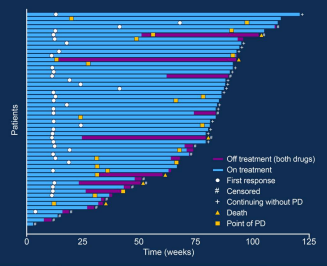
Swimmer's Plot

- Median time to response was 2.8 months (range 0.7–15.2)
- Median duration of tumor response was 18.6 months (95% CI 15.1–not reached)
- 10 patients who discontinued both drugs due to toxicity were censored even though their disease had not progressed
  - 5 were still responding to treatment



CI=confidence interval; PD=progressive disease

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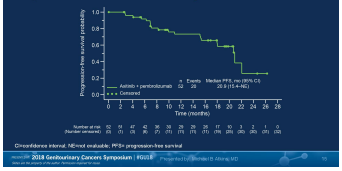
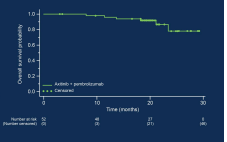
Kaplan–Meier Estimate of Progression-free Survival



CI=confidence interval; NE=not evaluable; PFS= progression-free survival

Kaplan–Meier Estimate of Overall Survival

- Median OS was not reached at minimum follow-up period of 17.6 months
- 6 deaths were reported:
  - Disease under study (n=4)
  - Other reason (n=2)
    - Cardiac arrest during cardiac cath
    - unknown



cath=catheterization; OS=overall survival

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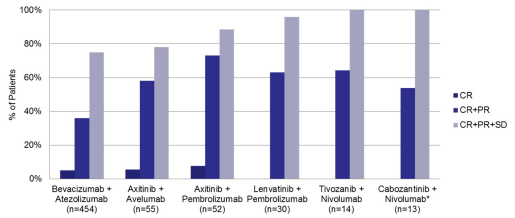
The current landscape …



Motzer et al ASCO GU 2018; Lee et al ESMO 2017; Choueiri et al ASCO 2017; Atkins et al ASCO GU 2018; Nadal et al ASCO GU 2018

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Phase III Assessments of VEGF + CPI Combinations in RCC

Control	Comparator
Sunitinib	Nivolumab/Ipilimumab
Sunitinib	Bevacizumab + Atezolizumab
Sunitinib	Axitinib + Pembrolizumab
Sunitinib	Lenvatinib + Everolimus *vs* Lenvatinib/Pembrolizumab
Sunitinib	Axitinib + Avelumab
Sunitinib	Cabozantinib/Nivolumab

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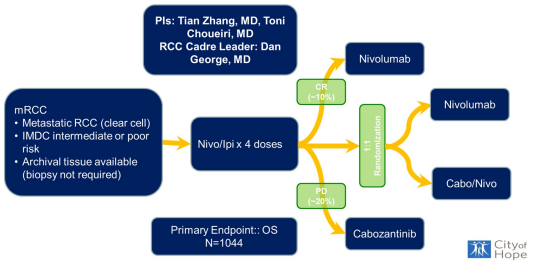
Forthcoming Phase III Trials



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Poll

Novel investigational approaches in metastatic RCC include?

A. Immunotherapy-immunotherapy
B. Immunotherapy-VEGF targeted therapy
C. HIF2 alpha inhibition
D. All of the above

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Poll

Recent advances in the treatment of advanced bladder cancer include the approval of which of the following agents?

A. Pembrolizumab
B. Bevacizumab
C. Everolimus
D. Ramucirumab

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Systemic Therapy for Bladder Cancer: pre-2016

Non-muscle Invasive	Neoadjuvant Adjuvant	First Line Metastatic	Next Line Metastatic
No systemic therapy	Gem/cisplatin or A-MVAC (Cisplatin)	Gem/cisplatin A-MVAC (cisplatin) or gem/carboplatin	▪ Paclitaxel/docetaxel ▪ Vinflunine*

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Systemic Therapy for Bladder Cancer: Now

Non-muscle Invasive	Neoadjuvant Adjuvant	First Line Metastatic	Second Line Metastatic	Next Line Metastatic
No systemic tx	Gem/cisplatin or A-MVAC (cisplatin)	Gem/cisplatin A-MVAC (cisplatin) or gem/carboplatin **PD-1/PD-L1 inhibitors (2)**	**PD-1/PD-L1 inhibitors (5)**	▪ Paclitaxel or docetaxel ▪ Vinflunine*

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Two-year follow-up from the phase 3 KEYNOTE-045 trial of pembrolizumab versus investigator's choice (paclitaxel, docetaxel, or vinflunine) in recurrent, advanced urothelial cancer

Joaquim Bellmunt,[1] Ronald de Wit,[2] David J. Vaughn,[3] Yves Fradet,[4] Jae Lyun Lee,[5] Lawrence Fong,[6] Nicholas J. Vogelzang,[7] Miguel A. Climent,[8] Daniel P. Petrylak,[9] Toni K. Choueiri,[1] Andrea Necchi,[10] Winald Gerritsen,[11] Howard Gurney,[12] David I. Quinn,[13] Stéphane Culine,[14] Cora N. Sternberg,[15] Kijoeng Nam,[16] Tara Frenkl,[16] Rodolfo F. Perini,[16] Dean F. Bajorin[17]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Erasmus MC Cancer Institute, Rotterdam, Netherlands; [3]Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA, USA; [4]CHU de Quebec-Universite Laval, Quebec City, QC, Canada; [5]Asan Medical Center and University of Ulsan College of Medicine, Seoul, Republic of Korea; [6]University of California, San Francisco, San Francisco, CA, USA; [7]Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [8]Fundacion Instituto Valenciano de Oncologia, Valencia, Spain; [9]Smilow Cancer Hospital at Yale University, New Haven, CT, USA; [10]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [11]Radboud University Medical Center, Nijmegen, Netherlands; [12]Westmead Hospital and Macquarie University, Sydney, NSW, Australia; [13]University of Southern California Norris Comprehensive Cancer Center and Hospital, Los Angeles, CA, USA; [14]Hôpital Saint-Louis, Paris, France; [15]San Camillo Forlanini Hospital, Rome, Italy; [16]Merck & Co., Inc., Kenilworth, NJ, USA; [17]Memorial Sloan Kettering Cancer Center, New York, NY, USA

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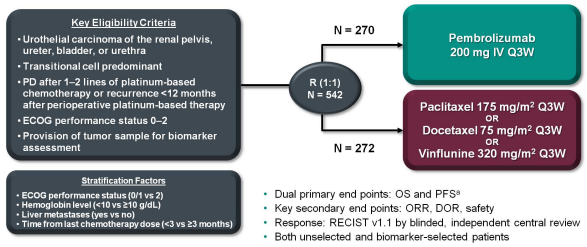
KEYNOTE-045 Study Design (NCT02256436)



- Dual primary end points: OS and PFS[a]
- Key secondary end points: ORR, DOR, safety
- Response: RECIST v1.1 by blinded, independent central review
- Both unselected and biomarker-selected patients

[a]In total ITT population and in patients with combined positive score ≥10%.

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Baseline Characteristics

n (%)	Pembro (N = 270)	Chemo (N = 272)
Age, median (range), y	67 (29-88)	65 (26-84)
Men	200 (74.1)	202 (74.3)
Upper tract disease	38 (14.1)	37 (13.6)
Lower tract disease	232 (85.9)	235 (86.4)
ECOG PS[a]		
0	120 (44.4)	106 (39.0)
1	142 (52.6)	158 (58.1)
2	3 (1.1)	4 (1.5)
Visceral disease	241 (89.3)	235 (86.4)
Disease in lymph node only	28 (10.4)	37 (13.6)

n (%)	Pembro (N = 270)	Chemo (N = 272)
Liver metastases	91 (33.7)	95 (34.9)
Hemoglobin <10 g/dL[b]	43 (15.9)	44 (16.2)
Time since completion of most recent prior therapy		
≥3 months	167 (61.9)	168 (61.8)
<3 months	103 (38.1)	104 (38.2)
Setting of most recent prior therapy		
Neoadjuvant	19 (7.0)	22 (8.1)
Adjuvant	12 (4.4)	31 (11.4)
First line	184 (68.1)	158 (58.1)
Second line	55 (20.4)	59 (21.7)
Third line	0	2 (0.7)

[a]Missing for 5 patients in the pembrolizumab arm and 4 patients in the chemotherapy arm. [b]Missing for 7 patients in the pembrolizumab arm and 4 patients in the chemotherapy arm. Data cutoff date: October 26, 2017.

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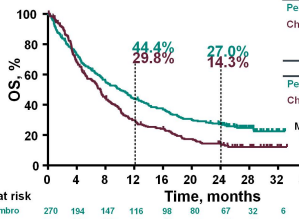
Overall Survival: Total



14.1 months of follow-up[1]

	Events, n	HR (95% CI)[a]	*P*[b]
Pembro	155	0.73 (0.59–0.91)	0.0022
Chemo	179		

27.7 months of follow-up

	Events, n	HR (95% CI)[a]	*P*[b]
Pembro	199	0.70 (0.57–0.85)	0.00017
Chemo	218		

Median (95% CI):
10.3 months (8.0–12.3)
7.3 months (6.1–8.1)

60.6% at 24 months in the chemotherapy arm received an immunotherapeutic agent, including those who received pembrolizumab as part of the cross over.

[a]Based on Cox regression model with treatment as a covariate stratified by ECOG performance status (0/1 vs 2), liver metastases (yes vs no), hemoglobin (<10 vs ≥10 g/dL), and time from completion of chemotherapy (<3 vs ≥3 months). [b]One-sided *P* value based on stratified log-rank test.
Data cutoff date: October 26, 2017.
1. Bellmunt J et al. *N Engl J Med*. 2017;376:1015-1026.

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Summary

- The OS benefit and superior safety of pembrolizumab over chemotherapy in 2L locally advanced or recurrent urothelial cancer is maintained after over 2 years of follow-up
  - Median OS, 10.3 versus 7.3 months; HR, 0.70; *P* = 0.00017; median follow-up, 27.7 months
  - OS at 12 months (44.4% vs 29.8%) and **24 months (27.0% vs 14.3%)**
- ORR and DOR continues to be greater with pembrolizumab than with chemotherapy
  - ORR, 21% vs 11%
  - DOR, **not reached** vs 4.4 months
- Results in patients with PD-L1–expressing tumors (CPS ≥10) or non–PD-L1 expressing tumors (CPS <10) were consistent with the intention to treat population

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Atezolizumab vs Chemotherapy in Platinum-Treated Locally Advanced or Metastatic Urothelial Carcinoma: Immune Biomarkers, Tumor Mutational Burden and Clinical Outcomes From the Phase III IMvigor211 Study

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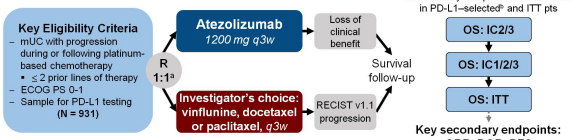
Phase III IMvigor211 Trial Design



- **Key exploratory endpoint:** relationship between tumor immune specific– or disease-related biomarkers and efficacy
- ***Objectives of this analysis:*** *compare clinical outcomes in ITT and PD-L1 subgroups vs those defined by tumor gene expression (tGE) signatures and tumor mutational burden (TMB)*

ClinicalTrials.gov ID, NCT02302807. IC, tumor-infiltrating immune cell.
[a] Stratification factors: 0 vs 1/2/3 risk factors (time from prior chemotherapy < 3 mo, ECOG PS > 0 and hemoglobin < 10 g/dL), yes vs no liver metastases, PD-L1 IC0/1 vs IC2/3 status, vinflunine vs taxane selection. [b] PD-L1 expression on IC assessed per VENTANA SP142 IHC assay: scored as IC3 (≥ 10%), IC2 (≥ 5% and < 10%).

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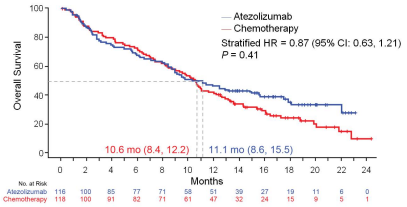
OS Analysis in PD-L1 IC2/3 Population



OS: IC2/3 → OS: IC1/2/3 → OS: ITT

- Based on OS results in the PD-L1 IC2/3 population, the primary endpoint was not met

Powles Lancet, 2017. Median follow-up duration: 17.3 mo (range 0-24.5 mo).
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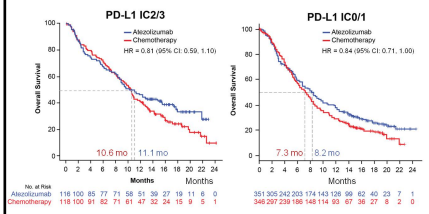
OS by PD-L1 IC Status



- In our study design, we hypothesized that efficacy was associated with PD-L1 status
- Unexpectedly, PD-L1 overexpression resulted in favorable outcomes in both arms
- Subsequent biomarker analyses focused on the ITT population

Unstratified HRs are displayed. Reprinted in part from *The Lancet*, Powles T, et al. 2017 Dec 18. [Epub]. © 2017, with permission requested from Elsevier.

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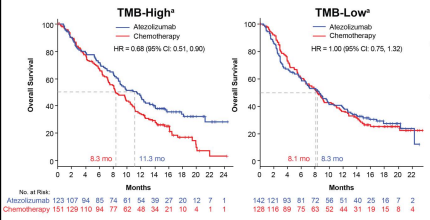
OS by TMB



- In the TMB-high subgroup, mOS was numerically longer with atezolizumab
- Complete and partial responses and prolonged OS were observed in subgroups of patients with TMB-low tumors in both arms

Unstratified HRs are displayed. [a] Median scores were used to define assessment cutoffs: TMB-high (≥ median) or TMB-low (< median). Median TMB in the biomarker-evaluable population was 9.65 mutations/Mb. Reprinted from *The Lancet*, Powles T, et al. 2017 Dec 18. [Epub]. © 2017, with permission requested from Elsevier.

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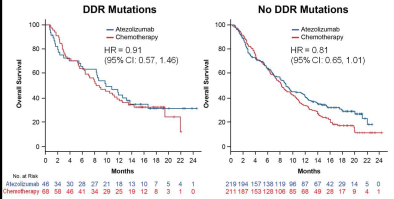
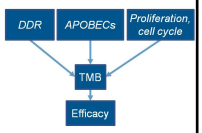
DDR Mutations and Efficacy



- However, tumors with DDR mutations did not enrich for increased efficacy in the atezolizumab arm
- Multiple factors contribute to TMB
  - e.g., DDR, APOBECs, proliferation



Based on TMB-evaluable population (n = 544). Unstratified HRs are displayed.

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Poll

Which of the following biomarkers should be used to select patients with advanced bladder cancer for immunotherapy?

A. PDL1 expression

B. TMB

C. RNA subtype

D. None of the above

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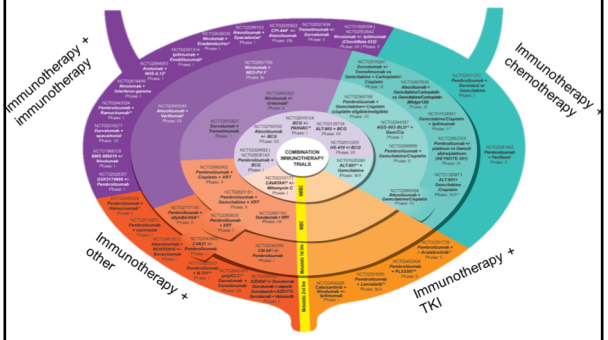
Immunotherapy Clinical Trials in Bladder Cancer



Davarpanah NN, et al. Curr Opin Oncol. 2017