Urothelial Carcinoma: Highlights 2019

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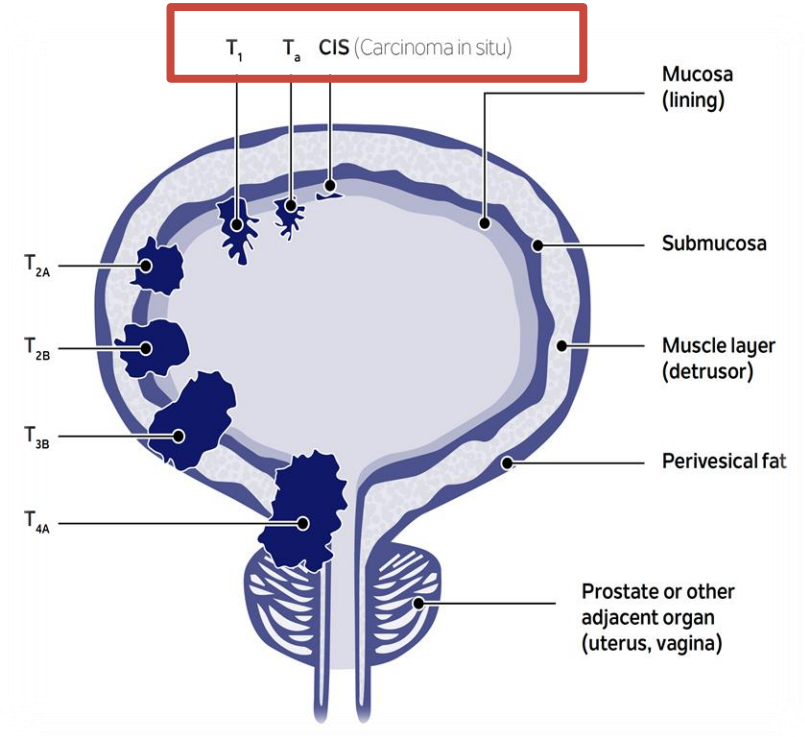
APS Associazione PaLiNUro

PAZIENTI LIBERI DALLE NEOPLASIE UROTELIALI

Goals of treatment and treatment options vary by type of disease at diagnosis

	Non-muscle-invasive disease	Muscle-invasive disease	Metastatic disease
Main goals of treatment	• Curative intent • Reduce recurrence • Prevent progression to more advanced stage	• Curative intent • Reduce recurrence • Prevent progression to more advanced stage	• Prolong quantity and quality of life
Current treatment options	• TURBT • Intravesical therapy • Cystectomy	• TURBT • Partial or radical cystectomy • Neoadjuvant and adjuvant chemo/immunotherapy • Radiotherapy	• Chemotherapy • Immunotherapy • Radiotherapy • Clinical trials



Non-Muscle Invasive BCa

From 2016 White Paper of Bladder Cancer
http://www.ecpc.org/da/pressroom/events/icalrepeat.detail/2016/04/20/60/119/launch-of-ecpc-paper-on-bladder-cancer

NMIBC – Overview

- Bladder carcinoma is the most common malignancy of the urinary tract
- 75-85% of patients present with non-muscle invasive bladder cancer (NMIBC) – disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1)
- Probability of recurrence and progression of NMIBC is proportional to
  - Grade
  - Stage
  - BCG unresponsiveness

Risk group stratification of NMIBC

Low-risk tumours	Primary, solitary, Ta, LG/G1, < 3 cm, no CIS
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low and high risk)
High-risk tumours	Any of the following: • T1 tumour • HG/G3 tumour • CIS • Multiple and recurrent and large (>3 cm) Ta G1G2 tumours (all conditions must be present in this point)

CIS = carcinoma *in situ*; HG = high grade; LG = low grade.

Babjuk M, et al. Eur Urol 2017;71:447-461

BCG failure

Whenever a MIBC is detected during follow-up.

BCG-refractory tumour:

1. If HG non–muscle-invasive papillary tumour is present at 3 mo. Further conservative treatment with BCG is associated with increased risk of progression (LE: 3).
2. If CIS (without concomitant papillary tumour) is present at both 3 and 6 mo. If patients with CIS present at 3 mo, an additional BCG course can achieve a complete response in > 50% of cases [11] (LE: 3).
3. If HG tumour appears during BCG therapy.*

HG recurrence after BCG. Recurrence of HG/grade 3 (WHO 2004/1973) tumour after completion of BCG maintenance, despite an initial response (LE: 3).

BCG intolerance

Severe side effects that prevent further BCG instillation before completing induction.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

EUROPEAN UROLOGY

Guidelines

EAU Guidelines on Non–Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016

Marko Babjuk[a,], Andreas Böhle[b], Maximilian Burger[c], Otakar Capoun[d,†], Daniel Cohen[e,f,†], Eva M. Compérat[g], Virginia Hernández[h,†], Eero Kaasinen[i], Joan Palou[j], Morgan Rouprêt[k,l], Bas W.G. van Rhijn[m], Shahrokh F. Shariat[n], Viktor Soukup[d,†], Richard J. Sylvester[o], Richard Zigeuner[p]*

Treatment recommendation:

Category	Treatment recommendation	GR
BCG-refractory tumour	1. Radical cystectomy 2. Bladder-preserving strategies in patients not suitable for cystectomy	B
HG/G3 recurrence after BCG	1. Radical cystectomy 2. Repeat BCG course 3. Bladder-preserving strategies	C
Non–HG/G3 recurrence after BCG for primary intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy 2. Radical cystectomy	C

BCG = bacillus Calmette-Guérin; GR = grade of recommendation.

BCG refractory NMIBC – Overview

- Compounds used in BCG-unresponsive high risk NMIBC

Author	Journal	Year	Intervention	Response	Timing of 1st eval
McKiernan	JCO	2006	Docetaxel	56% CR 11% PR 33% NR	10 weeks
McKiernan	J Urol	2014	Nab-paclitaxel	35.7% CR	12 weeks
Skinner	J Urol	2013	Gemcitabine	47% CR	3 mo
Steinberg	J Urol	2000	Valrubicin	21% CR 15% Ta residual	3 mo

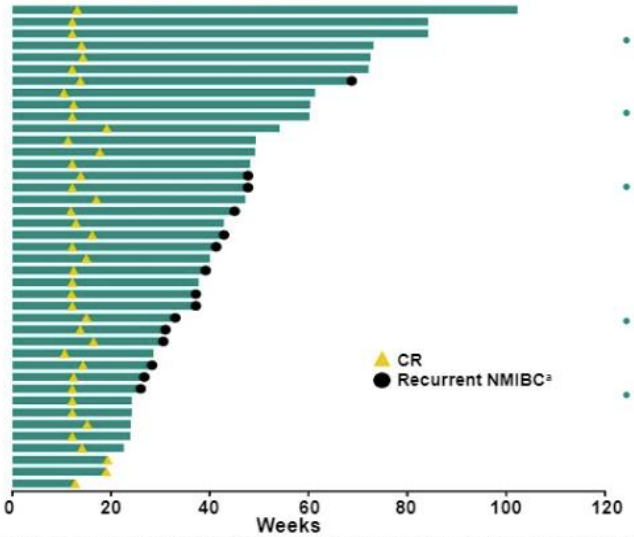
KEYNOTE-057: Single-Arm, Open-Label Phase 2 Study (NCT02625961)

Pati
- HR NMIBC patie to BCG who refu ineligible for cys
- Patients with pa must have fully at study entry
- Two cohorts
- Cohort A (n = 1 with out papilla (high-grade Ta
- Cohort B (n = 1 disease (high-g T1) without CIS

If no persistenc

If H

Time to CR and Development of Recurrent HR NMIBC



- Median follow-up for those in CR, 16.7 months (range, 5.9-28.2 months)
- 24 (58.5%) of complete responders had an ongoing response at time of data cutoff[b]
- 1 patient not represented in this figure was nonevaluable at week 12 but subsequently had confirmed CR beginning at week 24, with >12 months durability
- 15 (36.6%) of CRs subsequently experienced recurrent NMIBC after CR
- No patient developed muscle-invasive or metastatic disease

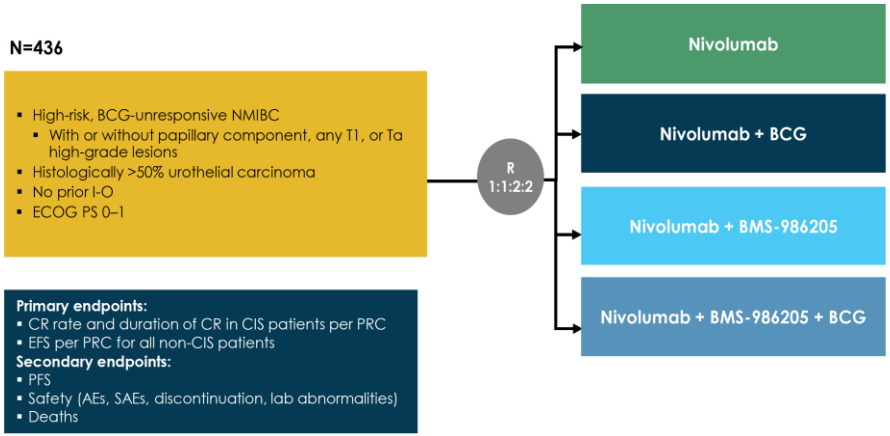
[a]Reappearance of HR NMIBC (CIS and/or high-grade Ta and/or T1 disease) after a disease-free interval (at each month or afterward). [b]One patient had ≥2 non-evaluable assessments. This patient discontinued after week 12 (censored at week 12) because of ongoing AEs and therefore did not complete the subsequent required efficacy assessments. Another patient with locally assessed CR underwent cystectomy. Database cutoff: September 14, 2018.

ation of ≥6 months

	Pembrolizumab (n=103)
	--
	--
	--
	38.8
	--
	NR (0+ to14.1+)
	63.1
	12.6
, %	5.8
	1.0*

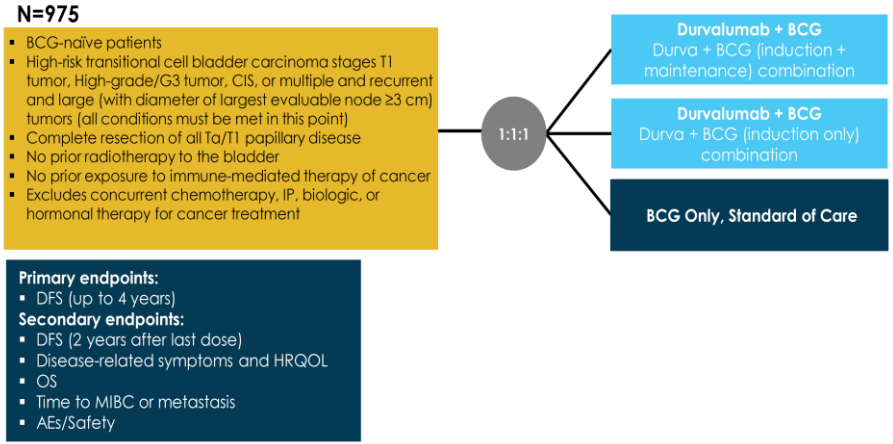
ASCO
American Society of Clinical Oncology
Genitourinary Cancers Symposium

Checkmate 9UT: Phase 2 Trial of Nivolumab ±BCG ±IDOi in High-Risk, BCG-Unresponsive NMIBC

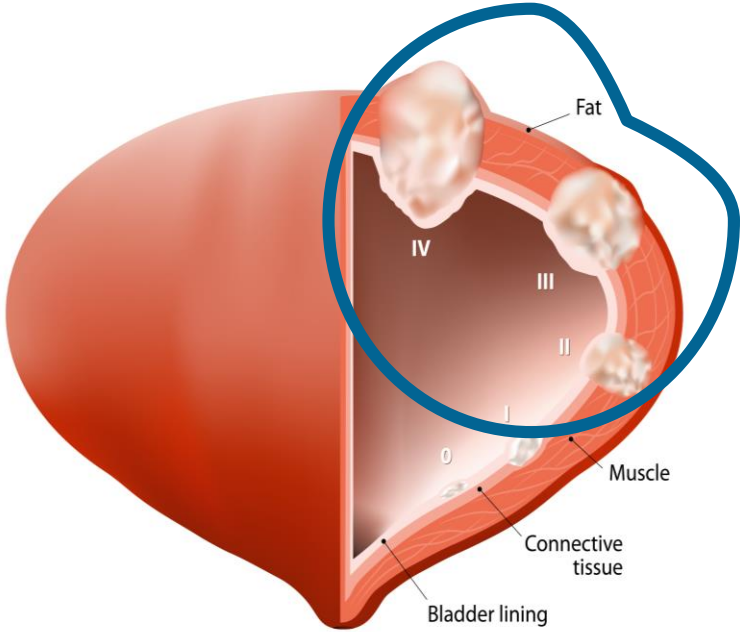


Clinicaltrials.gov. NCT03519256. Accessed October 5, 2018

POTOMAC: Durvalumab+ BCG in High-risk, Naïve NMIBC



Clinicaltrials.gov. NCT03528694. Accessed October 20, 2018



Muscle Invasive Bladder Cancer

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Guidelines

Updated 2016 EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer

Recommendation	GR
Treatment failure of NMIBC	
Consider immediate radical treatment in all T1 tumours at high risk of progression (ie, high grade, multifocality, carcinoma *in situ*, and tumour size, as outlined in the European Association of Urology Guidelines for NMIBC [34]).	C
Offer radical treatment to all T1 patients failing intravesical therapy.	B
Neoadjuvant chemotherapy	
Offer neoadjuvant chemotherapy for T2–T4a, cN0M0 bladder cancer.	A
Always use cisplatin-based combination therapy.	
Do not offer neoadjuvant chemotherapy to patients who are ineligible for cisplatin-based combination chemotherapy.	A
Pre- and postoperative radiotherapy	
Do not offer preoperative radiotherapy to improve survival.	A
Offer preoperative radiotherapy for operable MIBC because it can result in tumour downstaging after 4–6 wk.	C

GR = grade of recommendation; MIBC = muscle-invasive bladder cancer; NMIBC = non–muscle-invasive bladder cancer.

PURE-01: Neoadjuvant pembrolizumab before radical cystectomy for MIBC

- Fit and planned for cystectomy
- Predominant (i.e. 50% at least) UC histology
- cT≤3bN0 stage
- Residual disease after TURB (surgical opinion, cystoscopy or radiological presence)
- GFR ≥20 ml/min (Cockcroft – Gault formula)
- ECOG-PS 0-1

3×3 weekly cycles of pembrolizumab 200 mg IV

Additional DD-MVAC x 4 cycles in non-responding pts (investigator choice)

- Cystectomy
- Post-cystectomy management according to EAU guidelines
- Survival data collected until 2-y post cystectomy

Pre-post treatment tissue/blood sample collection for biomarker analyses

Pre-post treatment imaging: multiparametric bladder MRI (mpMRI); ^{18}FDG-PET/CT scan, T/A CT scan

- Pathologic complete response (pT0) in ITT population is the primary endpoint
- The H_1 is pT0 ≥25% and H_0 pT0≤15%
- **71 pts** will be enrolled, with **43 pts** at first stage according to MinMax design
- pT0 limits for H0 rejection: **6 (1st stage); 14 (2nd stage)**
- 80% power and a one-sided test of significance at the 10% level
- Data cut-off: May 10th, 2018: Median Follow-up: 8 months

2019 ASCO ANNUAL MEETING #ASCO19

JOURNAL OF CLINICAL ONCOLOGY RAPID COMMUNICATION

Pembrolizumab as Neoadjuvant Therapy Before Radical Cystectomy in Patients With Muscle-Invasive Urothelial Bladder Carcinoma (PURE-01): An Open-Label, Single-Arm, Phase II Study

Andrea Necchi, Andrea Anichini, Daniele Raggi, Alberto Briganti, Simona Massa, Roberta Lucianò, Maurizio Colecchia, Patrizia Giannatempo, Roberta Mortarini, Marco Bianchi, Elena Farè, Francesco Monopoli, Renzo Colombo, Andrea Gallina, Andrea Salonia, Antonella Messina, Siraj M. Ali, Russell Madison, Jeffrey S. Ross, Jon H. Chung, Roberto Salvioni, Luigi Mariani, and Francesco Montorsi

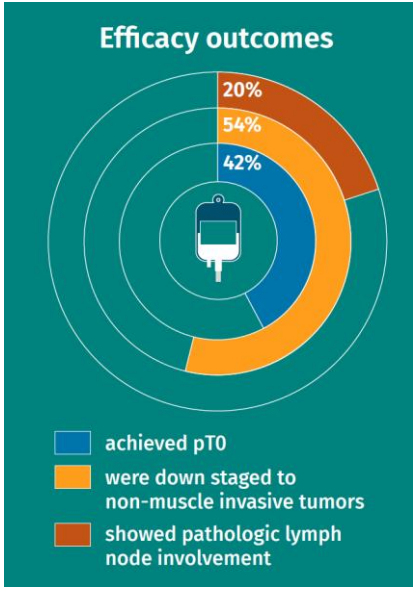


Table 3. Pathologic Response to Pembrolizumab

Response	All Treated Patients (N = 50)	PD-L1 CPS ≥ 10% (n = 35)	PD-L1 CPS < 10% (n = 15)
Primary end point			
Pathologic complete response, No. (%)	21 (42)	19 (54.3)	2 (13.3)
95% CI	28.2 to 56.8		
Secondary end point			
Pathologic downstaging to pT<2, No. (%)	27 (54)	23 (65.7)	4 (26.7)
95% CI*	39.3 to 68.2		
Treatment failure, No. (%)			
pT2N0	2 (3.8)		
pT3-4N0	6 (12)		
pTanyN+	10 (20)		
Additional MVAC chemotherapy†	5 (10)		
RECIST v1.1 PD	0		

Table 1. Baseline Characteristics (N = 50)

Characteristic	No. (%)
Time frame of accrual	Feb 2017 to Mar 2018
Median age, years (IQR)	66 (60-72)
Gender	
Male	41 (82)
Female	9 (18)
Smoking status	
Nonsmoker	19 (38)
Former smoker	22 (44)
Current smoker	9 (18)
Clinical T stage	
T2N0	21 (42)
T3N0	27 (54)
T2-3N1	2 (4)
Hydronephrosis	9 (18)
History of previous non–muscle-invasive UC	7 (14)
Previous BCG intravesical instillations	5 (10)
Histology	
Pure UC	41 (82)
UC and squamous cell carcinoma component	6 (12)
Micropapillary variant	2 (4)
Lymphoepithelioma-like variant	1 (2)
Concomitant carcinoma in situ component	3 (6)
Median bladder tumor volume, cm^3 (range)*	0.7 (0.4-1.5)
Cisplatin eligibility (Galsky criteria)	
Yes	46 (92)
No	4 (8)
No. of cycles of pembrolizumab administered	
1	1 (2)
2	2 (4)
3	47 (94)
Type of RC	
RARC	32 (64)
ORC	18 (36)
Type of urinary diversion	
Neobladder	23 (46)
Ileal conduit	26 (52)
Ureterocutaneostomy	1 (2)
Adjuvant chemotherapy post-RC	3 (6)
Median time from end pembrolizumab-RC, days (IQR)	22 (15-30)
Total treatment period†	
Median No. of days (IQR)	63 (57-70)

ABACUS: A phase II study investigating the safety and efficacy of neoadjuvant atezolizumab in muscle invasive bladder cancer

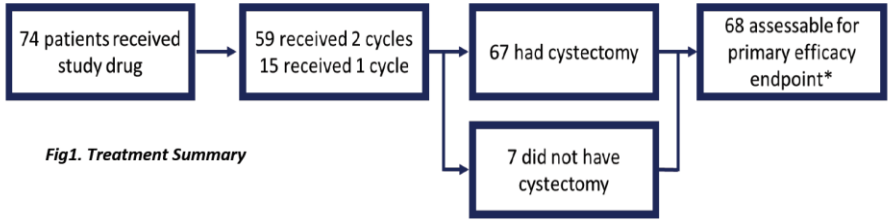
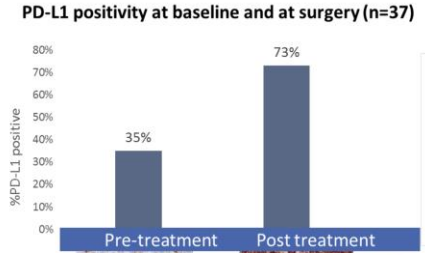
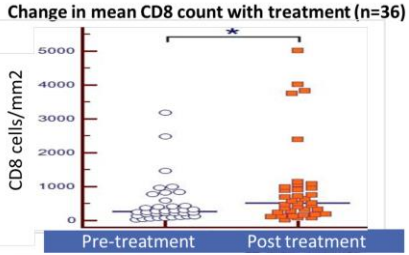
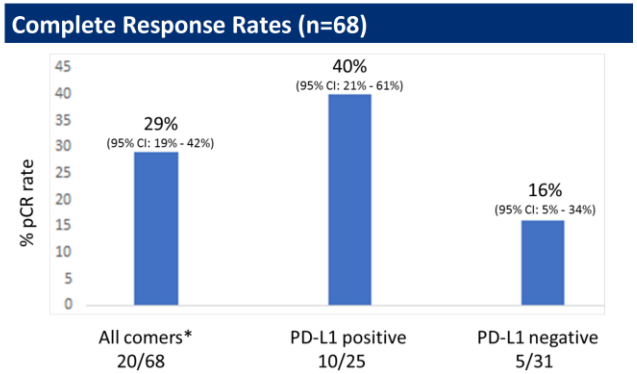


Fig1. Treatment Summary

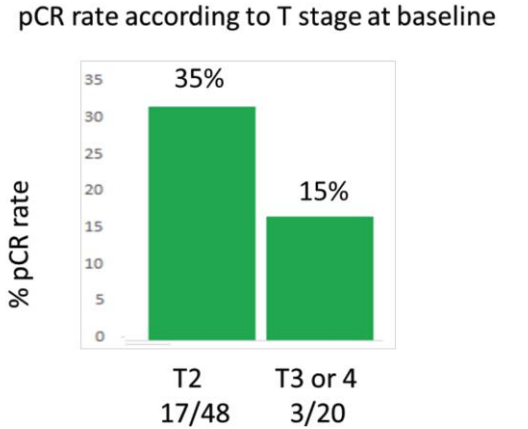






- 56/68 (82%) patients had PD-L1 analysis. Remainder ongoing assessment.
- 45% of 56 patients were PD-L1 positive at baseline (≥ 5% immune component with SP142 Ab)
- pCR= pT0 (n=16) and Tis (n=4)

** Patients who had cystectomy (n=67) or those who progresses prior to cystectomy (n=1).*



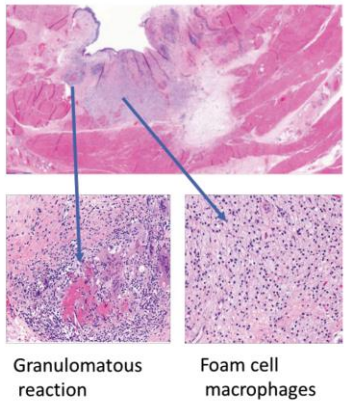
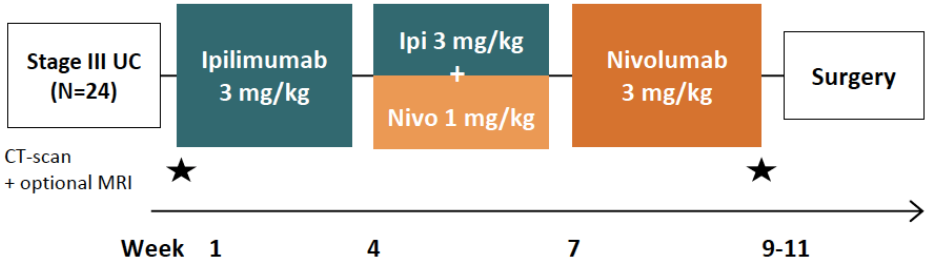


Fig3. Immune infiltration in a complete response post treatment surgical sample

Castellano D, et al. Annals of Oncology (2018) 29 (suppl_8): viii303-viii331. 10.1093/annonc/mdy283



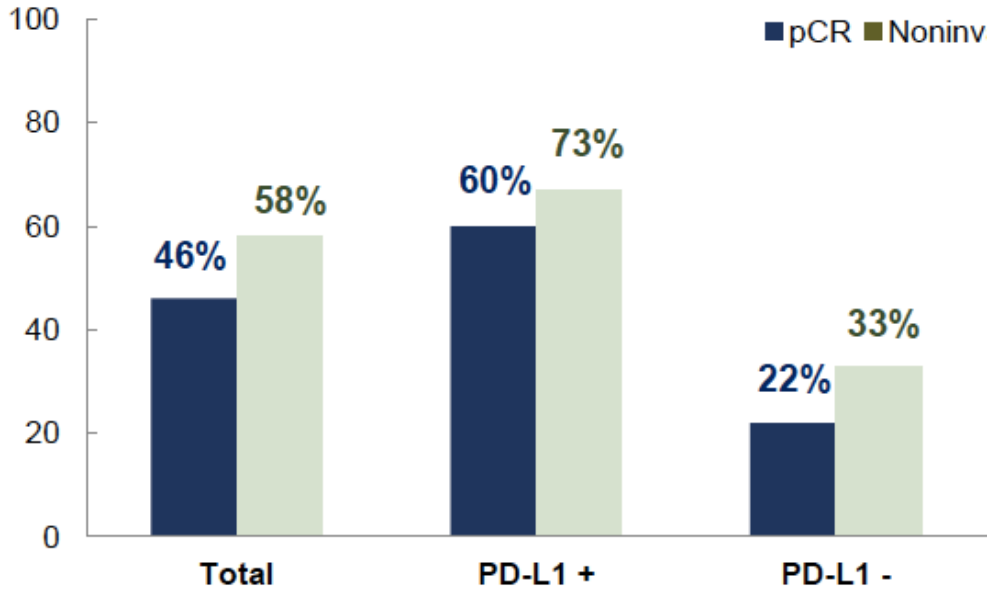
NABUCCO

Preoperative ipilimumab and nivolumab in locoregionally advanced, stage III, urothelial cancer

M.S. van der Heijden[1], N. van Dijk[1], L. Smit[2], K. Hendricksen[3], J.M. de Feijter[1], E. Bekers[2], E. Hooijberg[2], C.C.N. van Rooijen[4], A. Broeks[4], Y. Lubeck[2], K. Sikorska[5], T. Schumacher[6], P. Kvistborg[6], T. Boellaard[7], C.U. Blank[1,6], B.W. van Rhijn[3]

EFFICACY DATA

Pathological response	All pts (n=24)
pCR (secondary endpoint)	11 (46%)
Noninvasive disease (11 pCR, 2 CIS only, 1 pTa)	14 (58 %)
pCR per subgroup	
• PD-L1 CPS ≥ 10% (n=15)	9 (60%)
• PD-L1 CPS < 10% (n=9)	2 (22%)
• cN0 (n=14)	7 (50%)
• cN+ (n=10)	4 (40%)
Noninvasive disease per subgroup	
• PD-L1 CPS ≥ 10% (n=15)	11 (73%)
• PD-L1 CPS < 10% (n=9)	3 (33%)

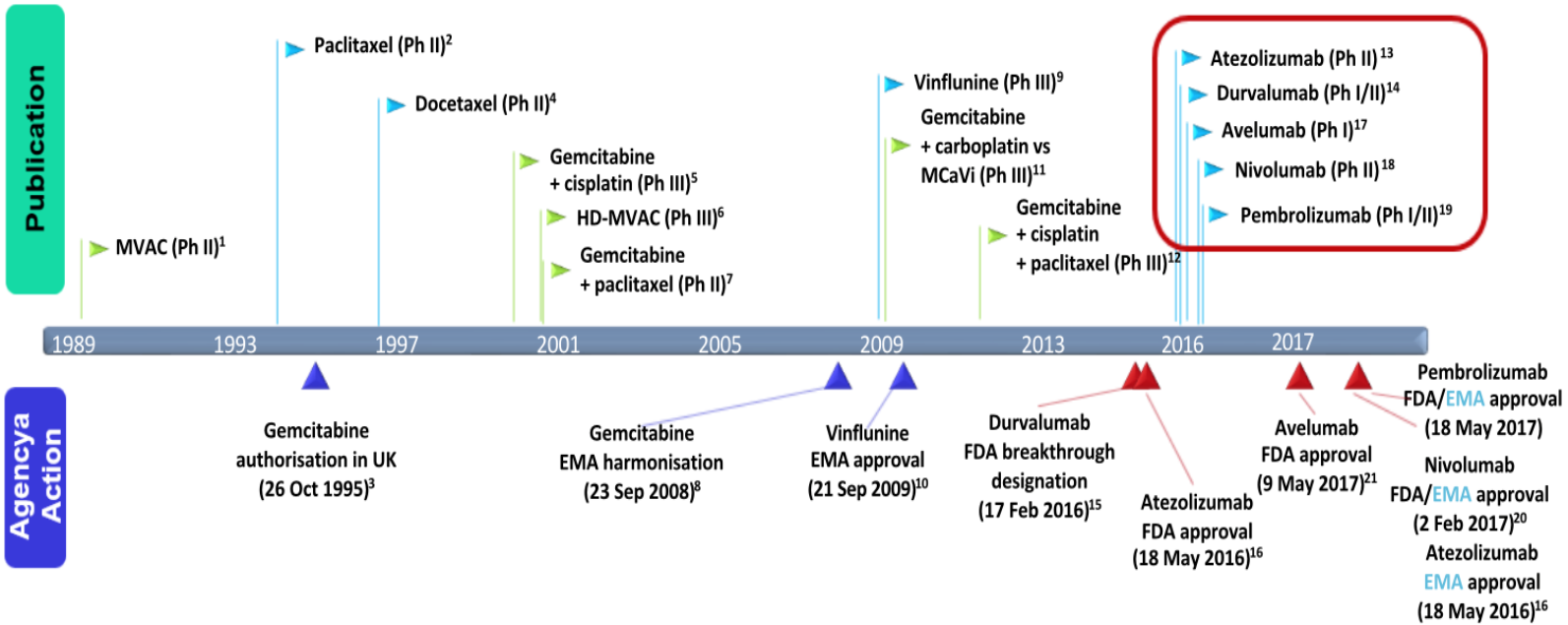


Overview of Ongoing Selected Neoadjuvant Trials in MIBC

Single-Agent Therapy	Country	Eligibility	Cisplatin Eligibility	Trial Identifier	Status
• Pembrolizumab (PURE-01)	Italy	T2-3aN0M0	Yes	NCT02736266	Has results
• Pembrolizumab (PANDORE)	France	T2-4N0 or Nx	No	NCT03212651	Enrolling
• Atezolizumab	South Korea	T2-4aN0M0	N/A	NCT03577132	Enrolling
• Atezolizumab	United States	T<2, T2-4N0M0	No	NCT02451423	Enrolling
• Avelumab (BL-AIR)	United States	T2-4aN0M0	No	NCT03498196	Enrolling
• Atezolizumab (ABACUS)	Europe	T2-4aN0M0	No	NCT02662309	Has results
Immune Combination Therapy					
• Nivolumab/urelumab	United States	T2-4aN0M0	No	NCT02845323	Enrolling
• Nivolumab/ipilimumab (NABUCCO)	Netherlands	T3-4N0 or N+	No	NCT03387761	Enrolling
• Durvalumab/tremelimumab vs. chemotherapy (DUTRENEO)	Spain	T2-4N0 or N1	Yes	NCT03472274	Enrolling
• Durvalumab/tremelimumab (NITIMIB)	Switzerland	T2-4N0 or N+	No	NCT03234153	Enrolling
• Durvalumab/tremelimumab	MDACC	T2-4aN0M0	No	NCT02812420	Enrolling
• Nivolumab ± ipilimumab (CA209-9DJ)	MSKCC	T2-4aN0M0	No	NCT03520491	Enrolling
• Durvalumab + olaparib (NEODURVARIB)	Spain	T2-4aN0M0	No	NCT03534492	Enrolling
Chemoimmunotherapy Combinations					
• Nivolumab + gemcitabine/cisplatin (BLASST-1)	United States	T2-4aN0M0	Yes	NCT03294304	Enrolling
• Avelumab (AURA) ± chemotherapy	Belgium	T2-4N0 or N+	Yes/No	NCT03674424	Enrolling
• Pembrolizumab + gemcitabine/cisplatin	United States	T2-4N0 or Nx	Yes	NCT02690558	Enrolling
• Pembrolizumab + gemcitabine/cisplatin	Indiana University	T2-4aN0M0	Yes	NCT02365766	Has results
• Nivolumab + gemcitabine/cisplatin	Hoosier Cancer Research Network	T2-4aN0M0	Yes	NCT03558087	Enrolling
• Chemotherapy vs. chemotherapy + nivolumab, ± BMS-986205 (CA017-078)	Multicenter international	T2-4aN0M0	Yes	NCT03661320	Enrolling
• Durvalumab + tremelimumab + dose-dense MVAC (NEMIO)	French multicenter	T2-4aN0-1M0	Yes	NCT03549715	Not yet enrolling

1L metastatic setting

Systemic therapy for urothelial cancer - 5 new immunotherapeutic agents



1. Sternberg CN et al. Cancer 1989;64:2448–2458; 2. Roth BJ et al. J Clin Oncol 1994;12:2264–2270; 3. Eli Lilly. SmPC Gemzar® 01 Jul 2014. Available at: http:// www.medicines.org.uk; 4. McCaffrey JA et al. J Clin Oncol 1997;15:1853–1857; 5. Von der Maase H et al. J Clin Oncol 2000;18:3068–3077; 6. Sternberg CN et al. J Clin Oncol 2001;19:2638–2646; 7. Meluch AA et al. J Clin Oncol 2001;19:3018–3024; 8. EMA. EMEA/CHMP/512295/2008; 24 Sep 2008. Available at: http:// www.ema.europa.eu; 9. Bellmunt J et al. J Clin Oncol 2009;27:4454–4461; 10. EMA. EMEA/H/C/000983; 2012. Available at: http:// www.ema.europa.eu; 11. De Santis M et al. J Clin Oncol 2009;27:5634–5639; 12. Bellmunt J et al. J Clin Oncol 2012;30:1107–1113; 13. Rosenberg JE et al. Lancet 2016;387:1909–1920; 14. Massard C et al. ASCO 2016. Abstract #4502 and oral presentation; 15. AstraZeneca. Press release 17 Feb 2016. Available at: http:// www.astrazeneca.com; 16. FDA. Press release 18 May 2016. Available at: http:// www.fda.gov); 17. Apolo AB et al. ASCO 2016. Abstract #4514 and poster; 18. Galsky MD et al. ESMO 2016. Abstract #LBA31_PR; 19. Balar A et al. ESMO 2016. Abstract #LBA32_PR; 20. FDA. Press release 2 Feb 2017. Available at http://www.fda.gov; 21. FDA. Press release 9 May 2017. Available at http://www.fda.gov.

Phase II IN

bjectives

- Inoperable locally advanced or metastatic UC
- Predominantly UC histology
- Tumor tissue evaluable for PD-L1 testing[a]

FDA alert May 18, 2018

"FDA issued an alert that preliminary data analysis shows a decrease in **survival** for bladder cancer patients with low PDL1 receiving mono- immunotherapy with pembrolizumab in KN 361or atezolizumab in Imvigor 130 versus chemotherapy as first-line therapy". EMA announced restrictive use in first line PDL1 low

Cis eligible patients: CIS

Cis Ineligible pts

PDL1

Low → chemo

High → CPI

	ORR	
Keynote 045- Prior Platinum CPS>10%	21% vs 11.4% 21.6% vs 6.7%	
Keynote 052- Platinum Ineligible CPS>10% CPS-1-10% CPS <1%	 24% 39% 20% 11%	 OS: 18.5 vs 10 CPS>10 vs <10
Imvigor 210- Platinum Ineligible IC0 IC1 IC2/3	 23% 21% 21% 24%	 OS: 12.3 vs 19.1 mos >5% vs <5%

Need more data-
Difference in liver metastases, hemoglobin, PS differences

- Key cohort 1 inclusi
  - No prior trea
- En

- Pembrolizumab is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing therapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 10] (using 22C3 antibody), or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status
- Atezolizumab is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:
  - Are not eligible for cisplatin-containing therapy, and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥5% of the tumor area) (using SP142 antibody), or
  - Are not eligible for any platinum-containing therapy regardless of level of tumor PD-L1 expression

:67-76
0602-2

Clinical Trials: First-Line Metastatic Bladder Cancer

Study	Agent	Phase and Type	Primary Endpoint
MK3475-361/ KEYNOTE-361[1]	Pembrolizumab +/- chemotherapy[a] vs chemotherapy	3 Randomised, controlled	PFS, OS
IMvigor130[2]	Atezolizumab +/- chemotherapy[a] vs chemotherapy	3 Randomised, controlled	PFS, OS, % with AEs
DANUBE[3]	Durvalumab +/- tremelimumab vs SOC chemotherapy	3 Randomised, open label	PFS, OS
CheckMate901[4] *Galsky MD et al. TPS 539*	Nivolumab+Ipilimumab vs chemotherapy +/- IO	3 Randomised, open label	PFS, OS
NILE	Durvalumab +/- tremelimumab + chemo vs chemo	3 Randomised, open label	PFS, OS

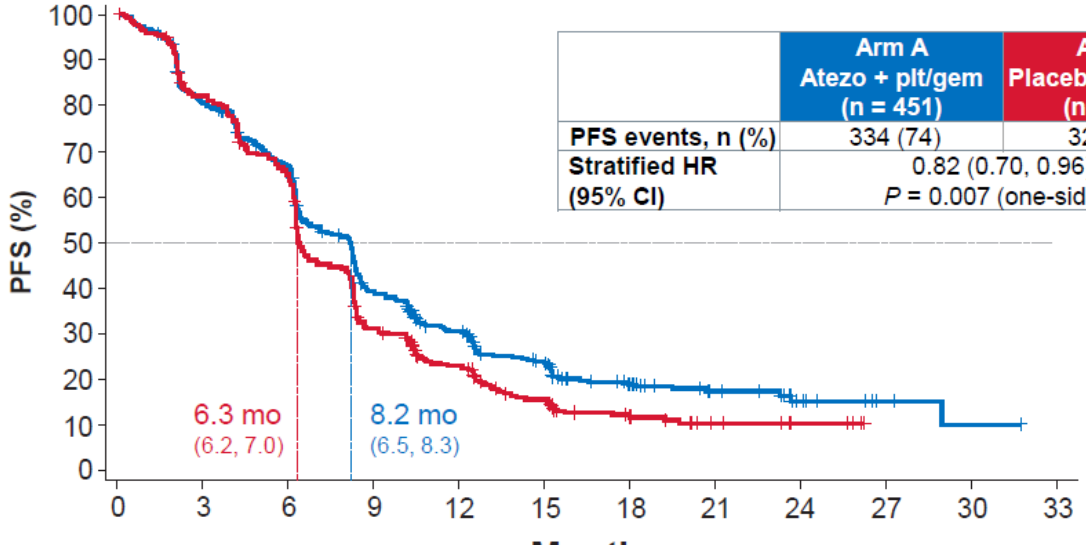
IMvigor130: a phase III study of atezolizumab with or without platinum-based chemotherapy in previously untreated metastatic urothelial carcinoma

IMvigor130 study

- Locally advanced or mUC
- No prior systemic therapy i setting
- ECOG PS ≤ 2
- 1L platinum-eligible
- N = 1200
- Randomised 1:1:1

Stratification factors:
- PD-L1 IC status (IC0 vs IC1
- Bajorin risk factor score inclu ≥ 80% and presence of visce (0 vs 1 vs 2 and/or patients v
- Investigator choice of plt/ger (cisplatin + gem or carboplat

Final PFS: ITT (Arm A vs Arm C)



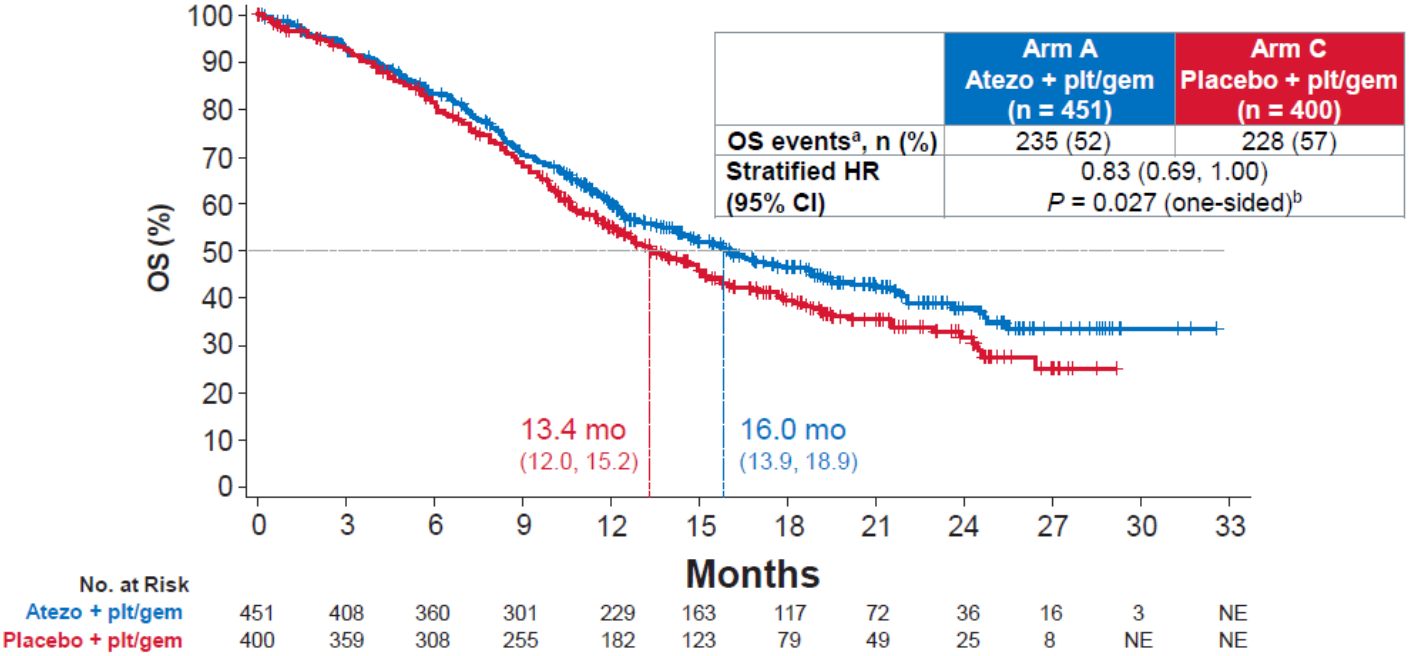
	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
PFS events, n (%)	334 (74)	326 (82)
Stratified HR (95% CI)	0.82 (0.70, 0.96) *P* = 0.007 (one-sided)	

No. at Risk												
Atezo + plt/gem	451	345	282	160	111	74	42	22	10	4	2	NE
Placebo + plt/gem	400	317	246	116	73	40	18	11	4	NE	NE	NE

NE, not estimable. Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients).

IMvigor130: a phase III study of atezolizumab with or without platinum-based chemotherapy in previously untreated metastatic urothelial carcinoma

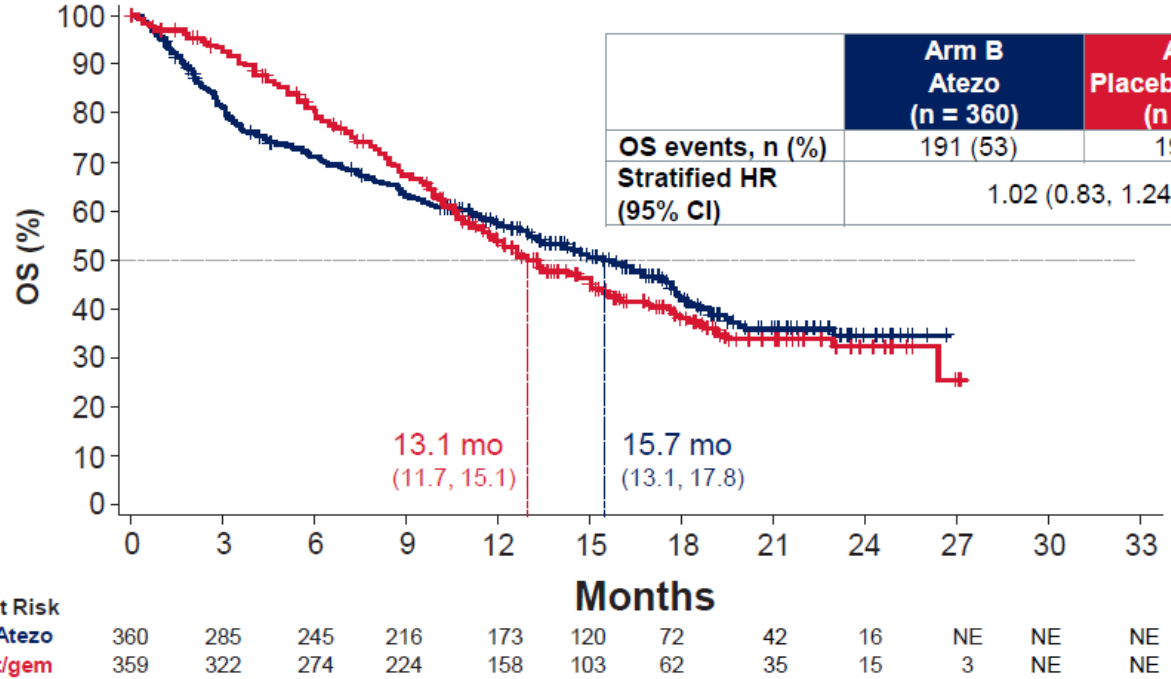
Interim OS: ITT (Arm A vs Arm C)



	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
OS events[a], n (%)	235 (52)	228 (57)
Stratified HR (95% CI)	0.83 (0.69, 1.00) *P* = 0.027 (one-sided)[b]	

IMvigor130: a phase III study of atezolizumab with or without platinum-based chemotherapy in previously untreated metastatic urothelial carcinoma

Interim OS for Monotherapy: ITT (Arm B vs Arm C)

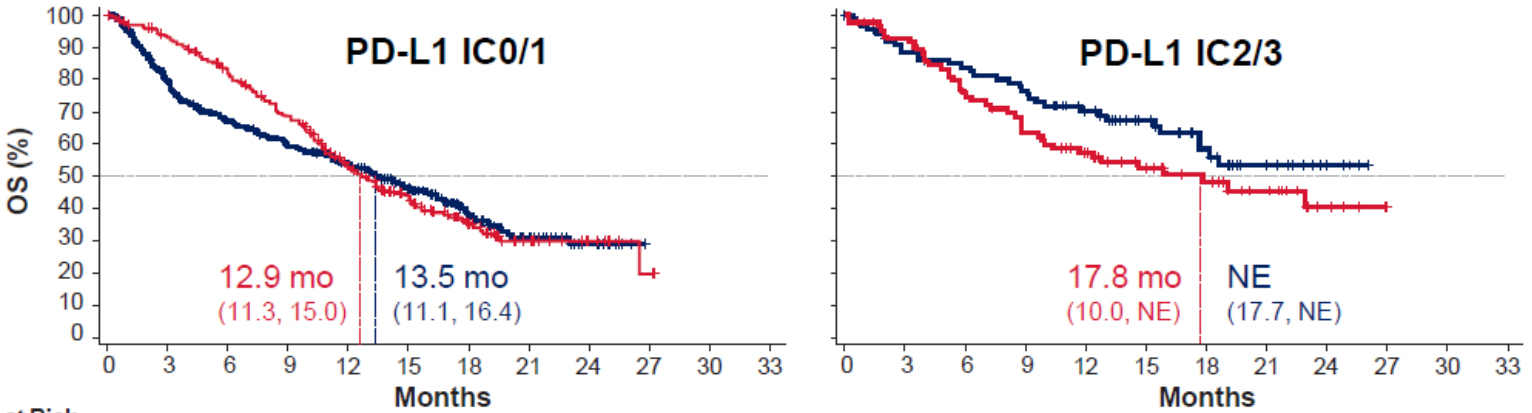


	Arm B Atezo (n = 360)	Arm C Placebo + plt/gem (n = 359)[a]
OS events, n (%)	191 (53)	198 (55)
Stratified HR (95% CI)	1.02 (0.83, 1.24)	

No. at Risk												
Atezo	360	285	245	216	173	120	72	42	16	NE	NE	NE
Placebo + plt/gem	359	322	274	224	158	103	62	35	15	3	NE	NE

IMvigor130: a phase III study of atezolizumab with or without platinum-based chemotherapy in previously untreated metastatic urothelial carcinoma

Interim OS: PD-L1 status (Arm B vs Arm C)



	Arm B Atezo (n = 272)	Arm C Placebo + plt/gem (n = 274)
OS events, n (%)	158 (58)	156 (57)
Unstratified HR (95% CI)	1.07 (0.86, 1.33)	

	Arm B Atezo (n = 88)	Arm C Placebo + plt/gem (n = 85)
OS events, n (%)	33 (38)	42 (49)
Stratified HR (95% CI)	0.68 (0.43, 1.08)	

Objective Response Rate (RECIST 1.1)

Characteristic	Placebo (n=52)	Pembrolizumab (n=55)
Not evaluable (baseline CR)	10	9
Overall response	12%	22%
Partial response	12%	13%
Complete response	0	9%
Stable disease	29%	35%
Progressive disease	54%	33%
Unknown	5%	10%

Randomized double-blind phase II study of maintenance pembrolizumab versus placebo after first-line chemotherapy in patients with metastatic urothelial cancer: HCRN GU14-182

Matthew D. Galsky, Sumanta K. Pal, Amir Mortazavi, Matthew I. Milowsky, Saby George, Sumati Gupta, Mark T. Fleming, Long H. Dang, Daniel M. Geynisman, Radhika Walling, Robert S. Alter, Erwin L. Robin, Jue Wang, Shilpa Gupta, David D. Chism, Joel Picus, George Philips, David I. Quinn, Noah M. Hahn, Menggang Yu

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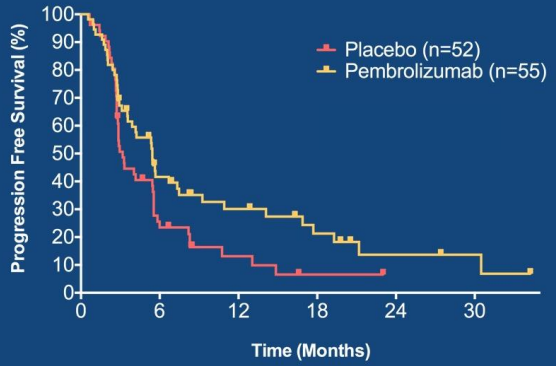
HCRN GU14-182

Metastatic UC
At least stable disease
≤ 8 cycles of platinum-based chemotherapy

Random
Stratifica
Lymph-nod
metastases
Response to
chemo (CR/P

Progression-free Survival



Number at Risk

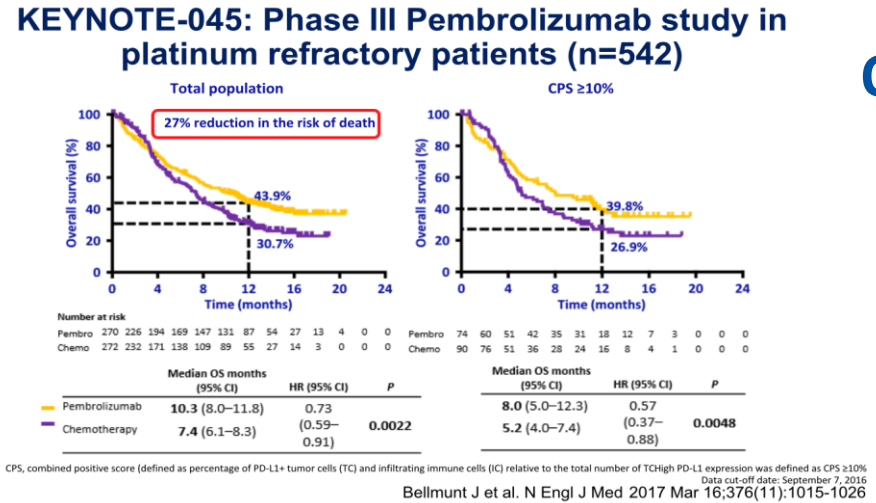
Placebo	52	12	4	1	0	0
Pembrolizumab	55	20	12	7	3	2

Median PFS and 95% CI
Placebo: 3.2 (2.8, 5.5)
Pembrolizumab: 5.4 (3.6, 9.2)

Hazard Ratio: 0.64 (0.41, 0.98)

Log rank $p = 0.038$

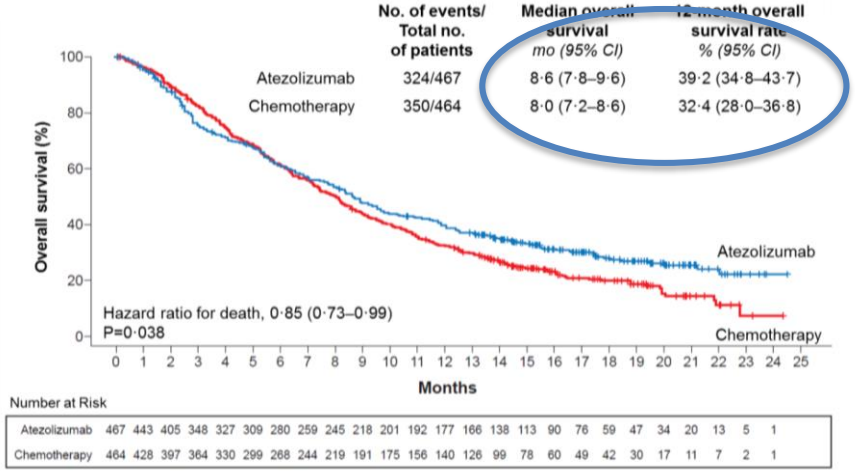
≥2L metastatic setting



Outcomes of Keynote-045 - Efficacy

US FDA and EMA approval for Pembrolizumab in platinum-treated, advanced UC

Bellmunt J. et al, NEJM 2017 & GU-ASCO 2019



Outcomes of IMvigor211 - Efficacy

US FDA and EMA approval for Atezolizumab in platinum-treated, advanced UC

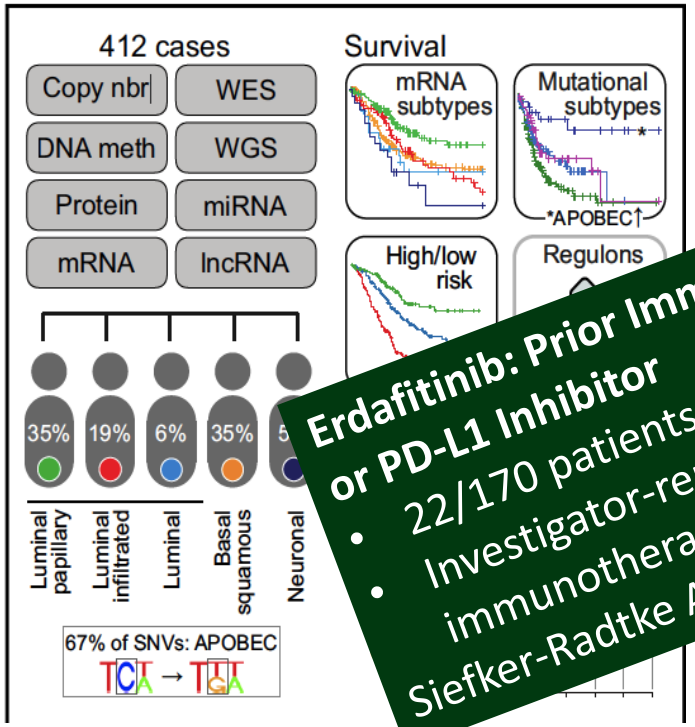
Powles T. et al, Lancet 2017 & GU-ASCO 2018

Immune checkpoint inhibitors in the platinum-refractory setting (no Head to Head comparisons)

	Atezolizumab[1,6]	Nivolumab[2]	Pembrolizumab[3]	Avelumab[4]	Durvalumab[5]
Phase	Phase II single arm Phase III randomized	Phase II single arm	Phase III randomized	Phase Ib	Phase I/II
Number of patients	310[1] 467[6]	265	270	249	191
Dosing	1200 mg q3w	3 mg/kg q3w	200 mg q3w	10 mg/kg q2w	10 mg/kg q2w
ORR	15%; IC2/3 23%	19.6%	21.1%	17%	17.8%
Duration of response	84% ongoing at median follow-up of 11.7 months/15.9months[6]	77% ongoing at median follow-up of 7.0 months	72% ongoing at median follow-up of 14.1 months	64% ongoing at data cut	Not reached at data cut
Median OS	7.9/11.1 months	8.7 months	10.3 months	7.7 months	18.2 months
Median PFS	2.1 months	2.0 months	2.1 months	1.5 months	1.5 months
Grade 3/4 TRAEs	16%[1]/20%[6]	18%	15% G3–5	10.8% G3–5	6.8%

1. Rosenberg JE et al. Lancet 2016;387:1909–1920; 2. Sharma P et al. Lancet Oncol 2017;18:312–322 ; 3. Bellmunt J et al. N Engl J Med 2017 2017;376:1015–1026; 4. . Patel MR et al, Lancet Oncol 2018 Jan 19 (1): 51-64 and Apolo AB et al. J Clin Oncol 2017 Jul 1;35(19):2117-2124 5. Powles T et al. JAMA Oncol. doi:10.1001/jamaoncol.2017.2411. 6. Powles T et al The Lancet 2018

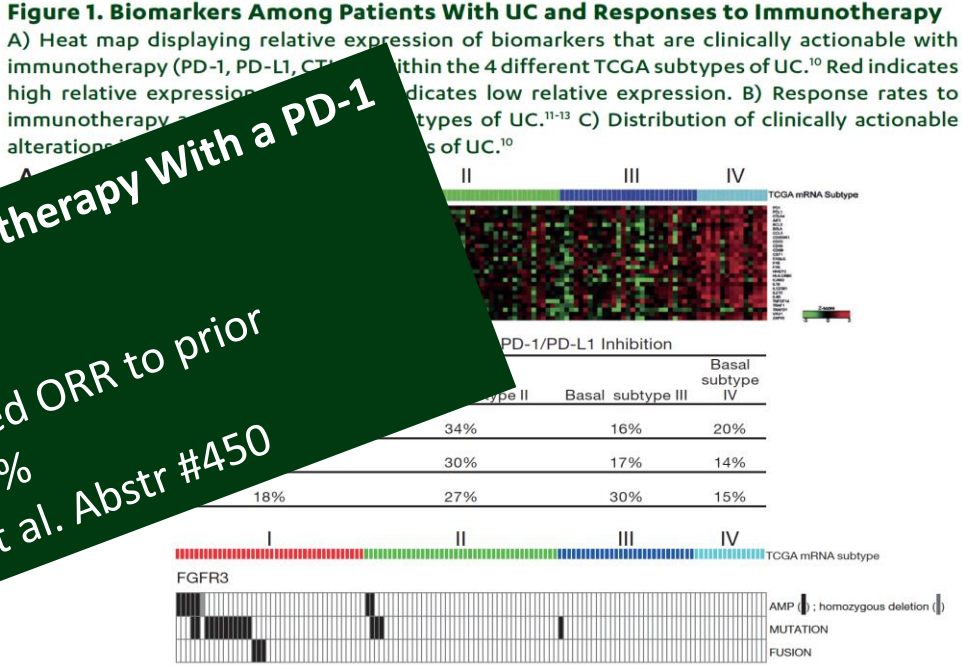
Is FGFR Mut/Fus a favorable feature in mBCa?



Erdafitinib: Prior Immunotherapy With a PD-1 or PD-L1 Inhibitor

- 22/170 patients
- Investigator-reported ORR to prior immunotherapy: 5%

Siefker-Radtke AO, et al. Abstr #450



Robertson et al., 2017, Cell 171, 1–17

McConkey D, et al. *Hematol Oncol Clin North Am*. 2015;29:377-394; Sharma P, et al. *Lancet Oncol*. 2017;18:312-322; Rosenberg JE, et al. *Lancet*. 2016;387:1909-1920; Balar AV, et al. *Lancet*. 2017;389:67-76; Siefker-Radtke AO, et al. 2018 Genitourinary Cancers Symposium, Abstr 450

The NEW ENGLAND JOURNAL of MEDICINE

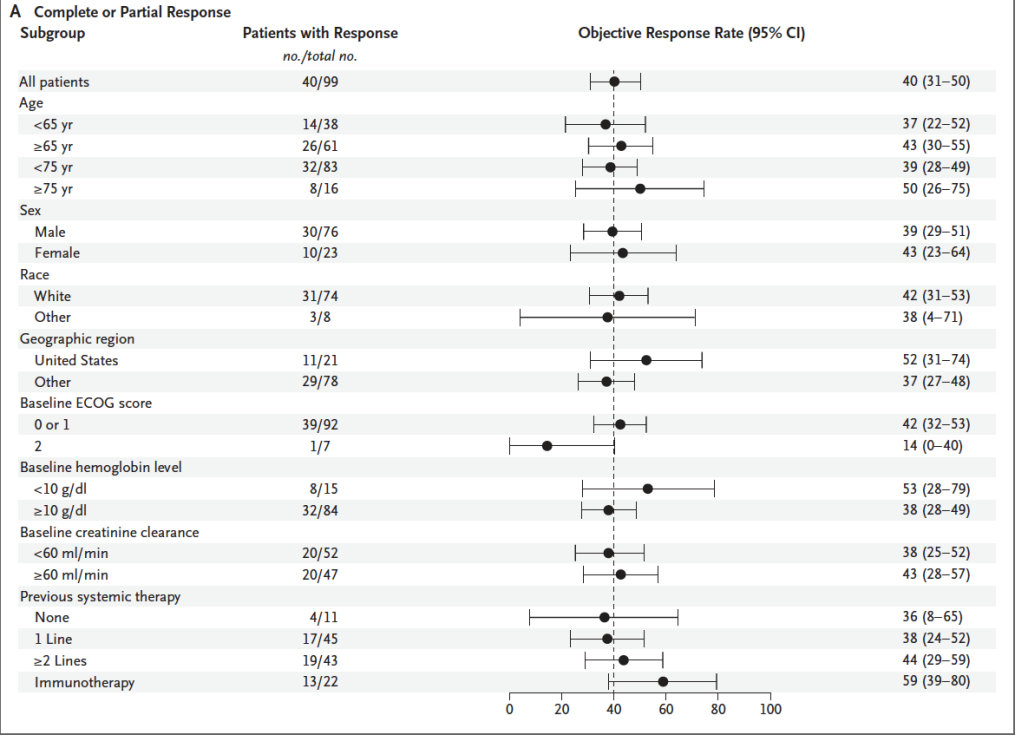
ORIGINAL ARTICLE

Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma

Y. Loriot, A. Necchi, S.H. Park, J. Garcia-Donas, R. Huddart, E. Burgess, M. Fleming, A. Rezazadeh, B. Mellado, S. Varlamov, M. Joshi, I. Duran, S.T. Tagawa, Y. Zakharia, B. Zhong, K. Stuyckens, A. Santiago-Walker, P. De Porre, A. O'Hagan, A. Avadhani, and A.O. Siefker-Radtke, for the BLC2001 Study Group*

Variable	Value	Rate of Response (95% CI)
		percent
Response per investigator assessment — no. of patients†		
Any objective response	40	40 (31–50)
Complete response	3	3
Partial response	37	37
Stable disease	39	39
Progressive disease	18	18
Could not be evaluated or unknown		
Median time to response — mo		
Median duration of response (95% CI)		
Response per independent radiologic a		
Objective response		
Complete response		
Partial response		

A Complete or Partial Response



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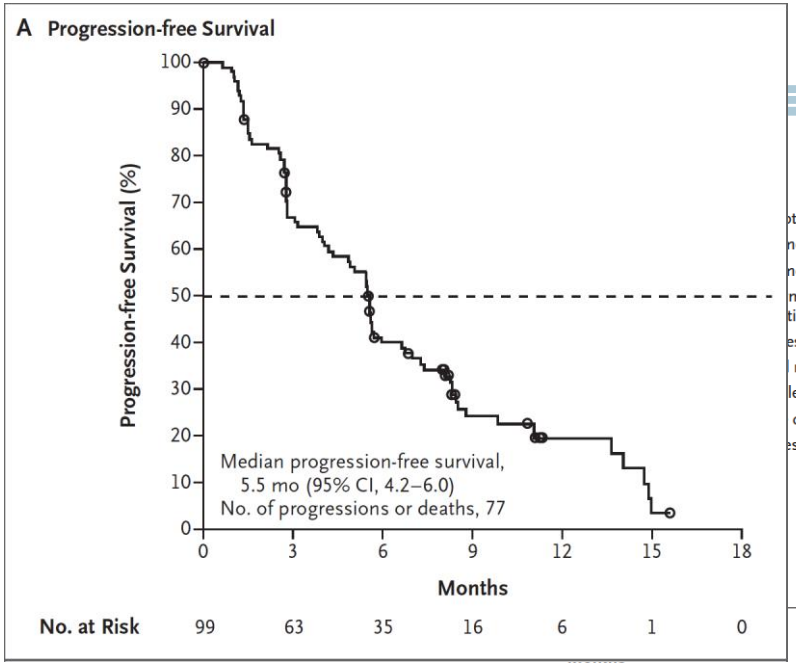
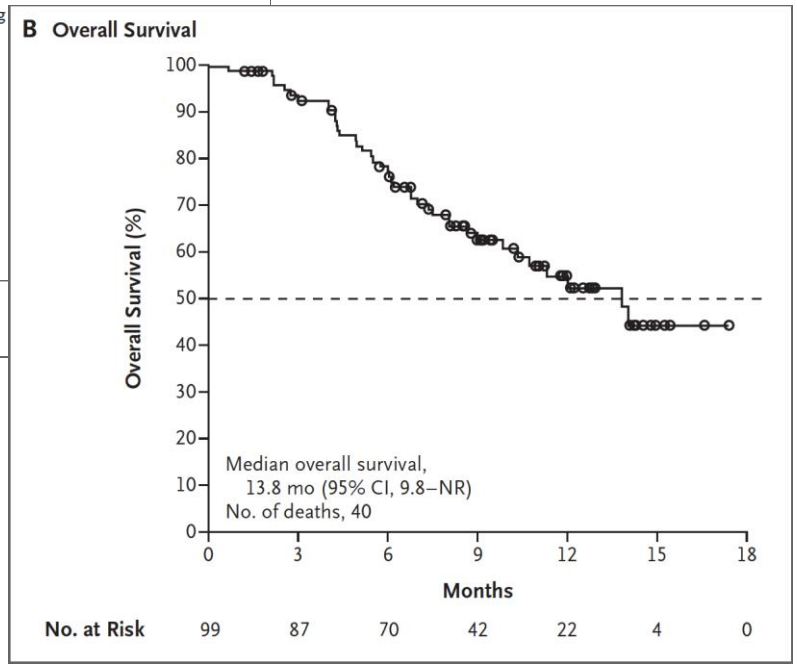




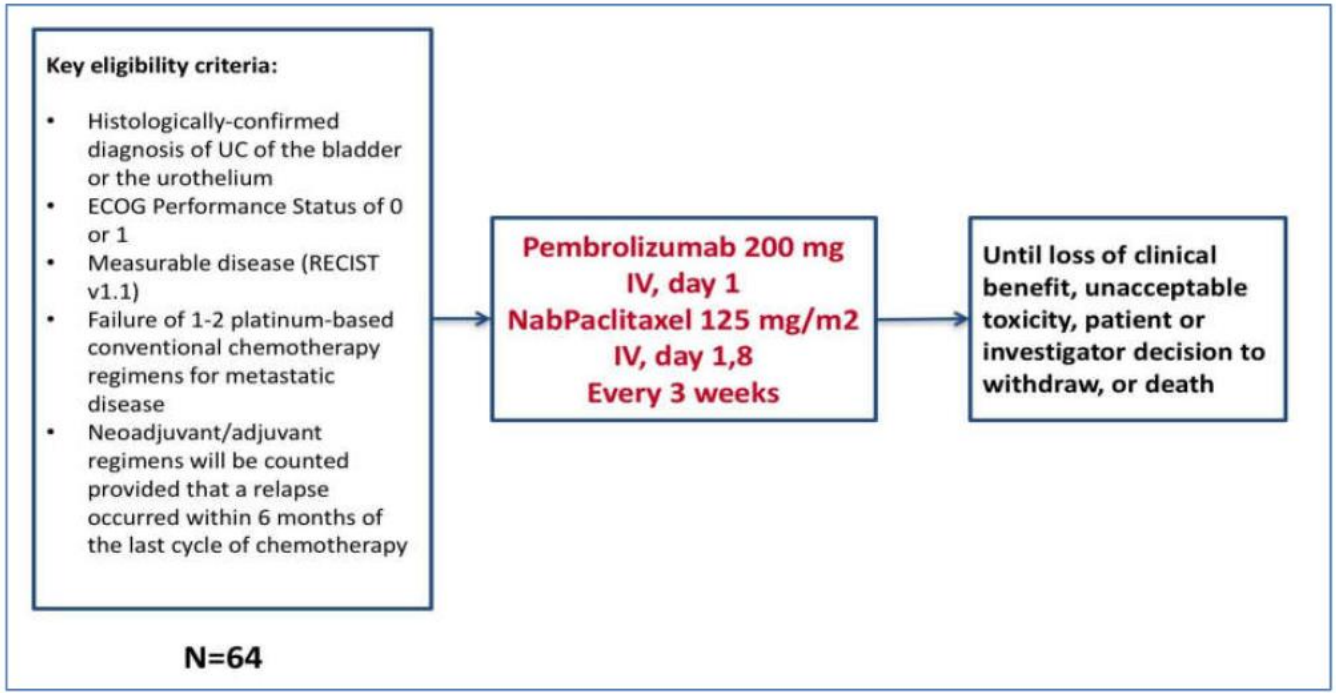
Fondazione IRCCS Istituto Nazionale dei Tumori

Sistema Socio Sanitario Regione Lombardia

SPONSOR: Fondazione IRCCS Istituto Nazionale dei Tumori

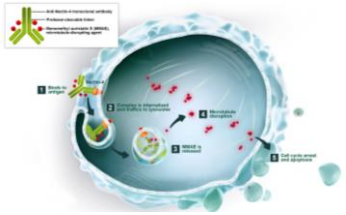
An open label, single-arm, phase 2 study of pembrolizumab and nanoparticle albumin-bound paclitaxel in patients with metastatic urothelial carcinoma after chemotherapy failure; the PEANUT study

EudraCT NUMBER: 2017-000579-10



ASCO American Society of Clinical Oncology

Genitourinary Cancers Symposium



EV-201: Results of Enfortumab Vedotin Monotherapy for Locally Advanced or Metastatic Urothelial Cancer Previously Treated with Platinum and Immune Checkpoint Inhibitors (NCT03219333)

Daniel P. Petrylak, Arjun V. Balar, Peter H. O'Donnell, Bradley A. McGregor, Elisabeth I. Heath, Evan Y. Yu, Matthew D. Galsky, Noah M. Hahn, Elaina M. Gartner, Juan M. Pinelli, Shang-Ying Liang, Amal Melhem-Bertrandt, and Jonathan E. Rosenberg

EV-201: Single-Arm, Pivotal Phase 2 Trial

Screening and enrollment
51 global sites

Previously treated locally advanced or metastatic urothelial cancer

Cohort 1
Prior PD-1/L1 inhibitor and platinum-based therapy

Enrollment completed
July 2018
N=128[1]

Cohort 2
Prior PD-1/L1 inhibitor, platinum naive, cisplatin ineligible

Enrollment ongoing

Enfortumab vedotin

1.25 mg/kg IV on days 1, 8, and 15 of each 28-day cycle

Primary endpoint:
ORR per RECIST v1.1 as determined by BICR

Select secondary endpoints:
DOR
PFS
OS
Safety

[1] 3 patients did not receive enfortumab vedotin treatment:
one each due to clinical deterioration, patient decision, and low hemoglobin after enrollment

BICR=blinded independent central review; DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

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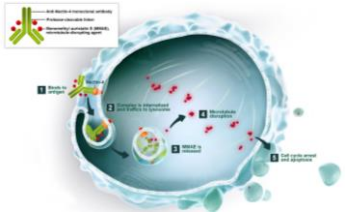

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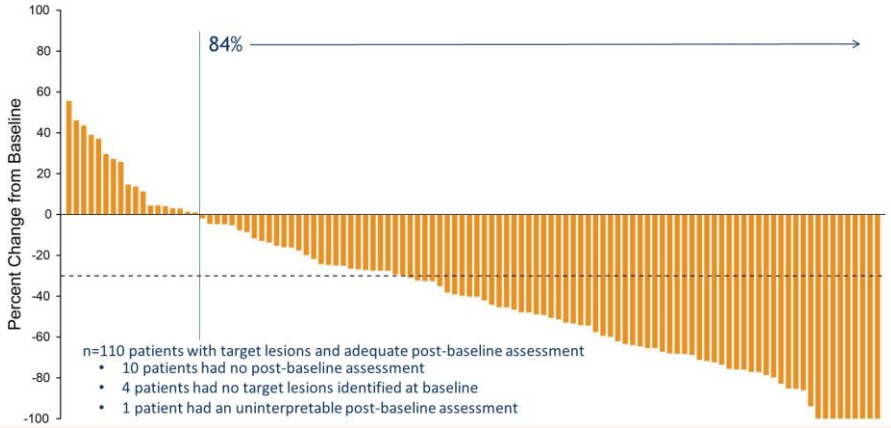
EV-201: Cohort 1 Objective Response Rate with Enfortumab Vedotin

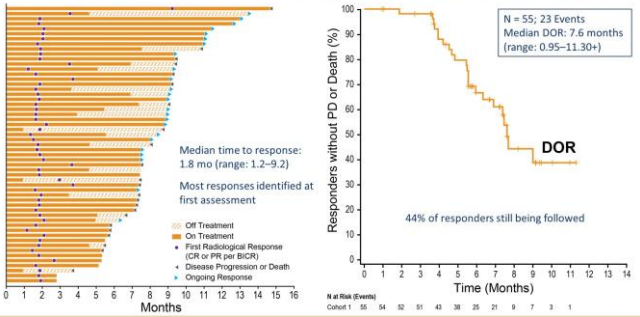
ORR per RECIST v 1.1 assessed by BICR	Patients (N=125) n (%)
Confirmed objective response rate	55 (44)
95% confidence interval[1]	(35.1, 53.2)
Best overall response per RECIST v. 1.1, n (%)	
Complete response	15 (12)
Partial response	40 (32)
Stable disease	35 (28)
Progressive disease	23 (18)
Not evaluable[2]	12 (10)

[1] Computed using the Clopper-Pearson method
[2] Includes 10 patients who discontinued study prior to post-baseline response assessment, 1 patient who had uninterpretable post-baseline assessment, and 1 post-baseline assessment did not meet the minimum interval requirement for stable disease

EV-201: Cohort 1 Change in Tumor Measurements per BICR



EV-201: Cohort 1 Duration of Response with Enfortumab Vedotin



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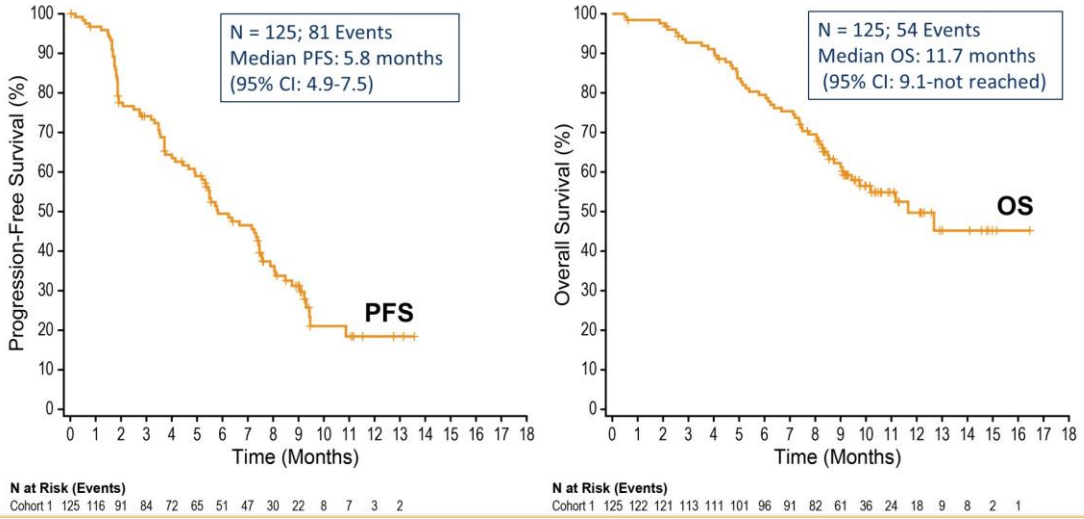
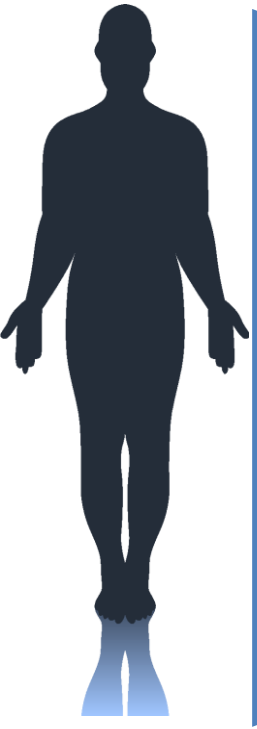
EV-201: Cohort 1 Kaplan-Meier Estimates of Survival



Patient journey and therapeutic options across the clinical stages



MIBC/1L metastatic

- Neoadjuvant IO/Adjuvant IO/1L Cisplatin-base chemo first

Cis-ineligible/treated pts, FGFR-mut/fus^{+} tumor

Erdafitinib or pan-FGFR inhibitor-first

Cis-ineligible/treated pts, FGFR wild-type tumors

ICI first option

(IO combo?)

ICI progression, FGFR wild-type

Enfortumab Vedotin[1]

Continue ICI

Salvage chemo

FGFR: fibroblas growth-factor receptor; ICI: immune checkpoint inhibitors; IO: immune-oncology; MIBC: muscle-invasive bladder cancer

1. Petrylak DP, et al. ASCO Annual Meeting 2019

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@DanieleRaggi83