Tumore della vescica

Terapia, trattamenti e cure

Il ruolo dell’immunoterapia

18.11.21

Dr.ssa med. Kristin Feuerlein, FMH oncologia e medicina interna

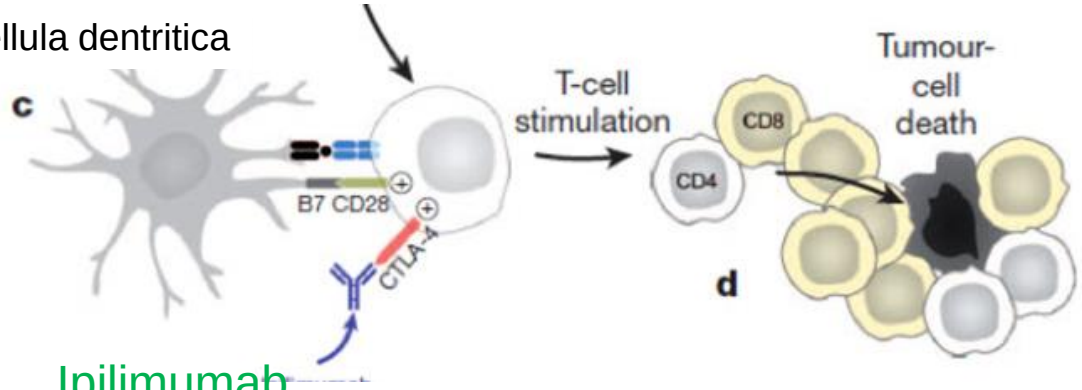
Centro Oncologico Mendrisio

Clinica Moncucco Lugano

CTLA-4-Immun-Checkpoint-Inhibitors

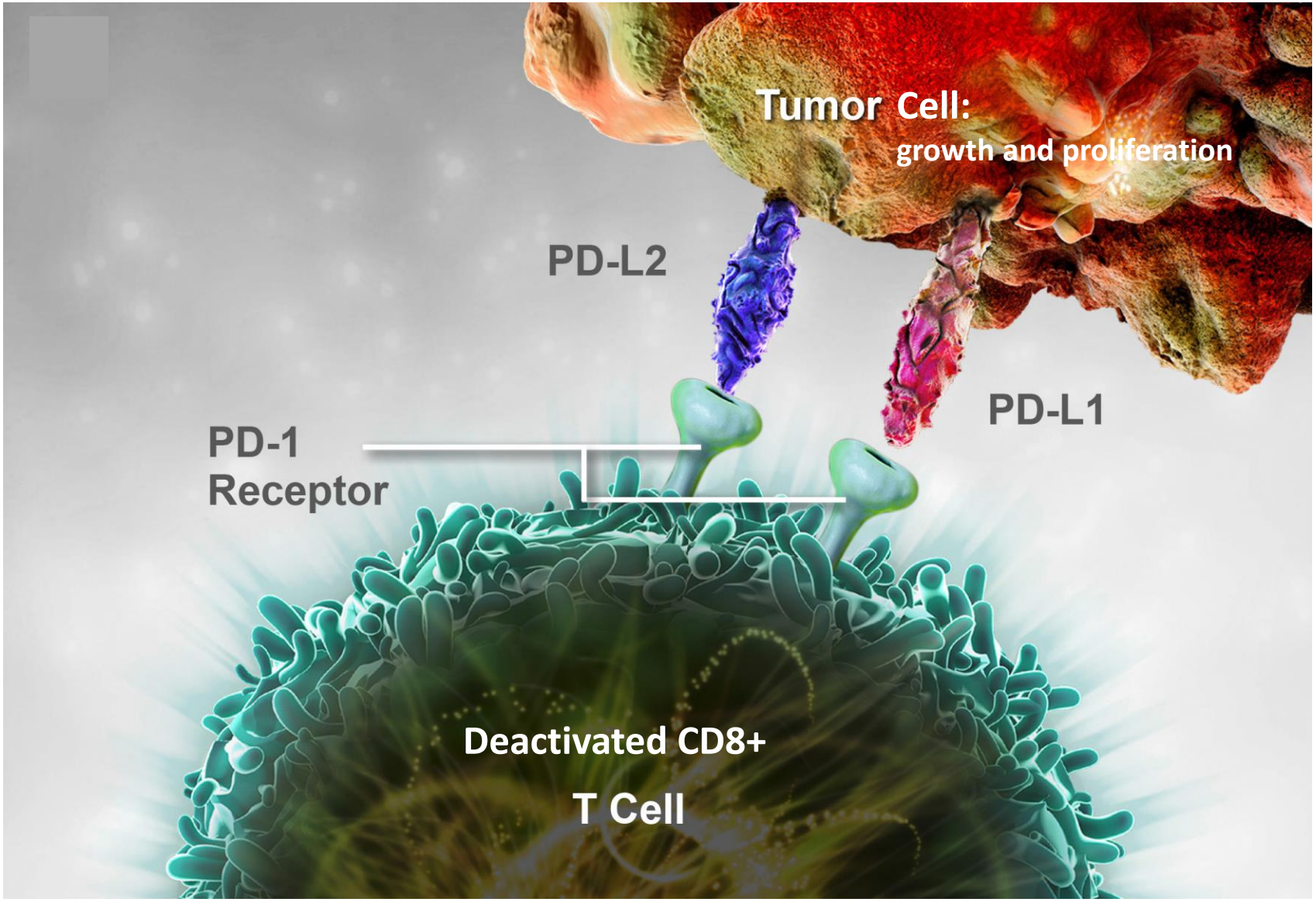
… fin'ora nessun ruolo nel carcinoma della vescica

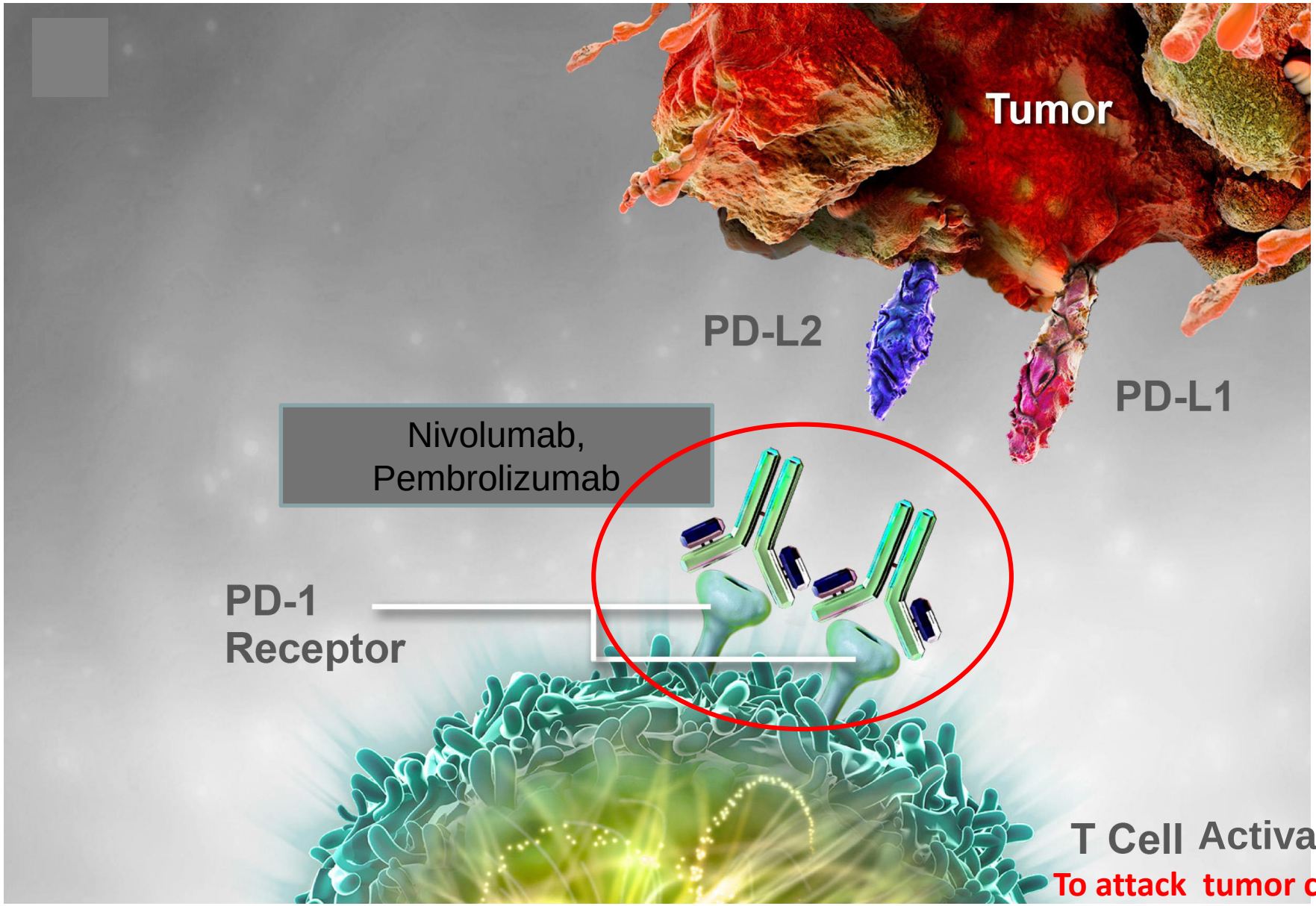
cellula dentritica

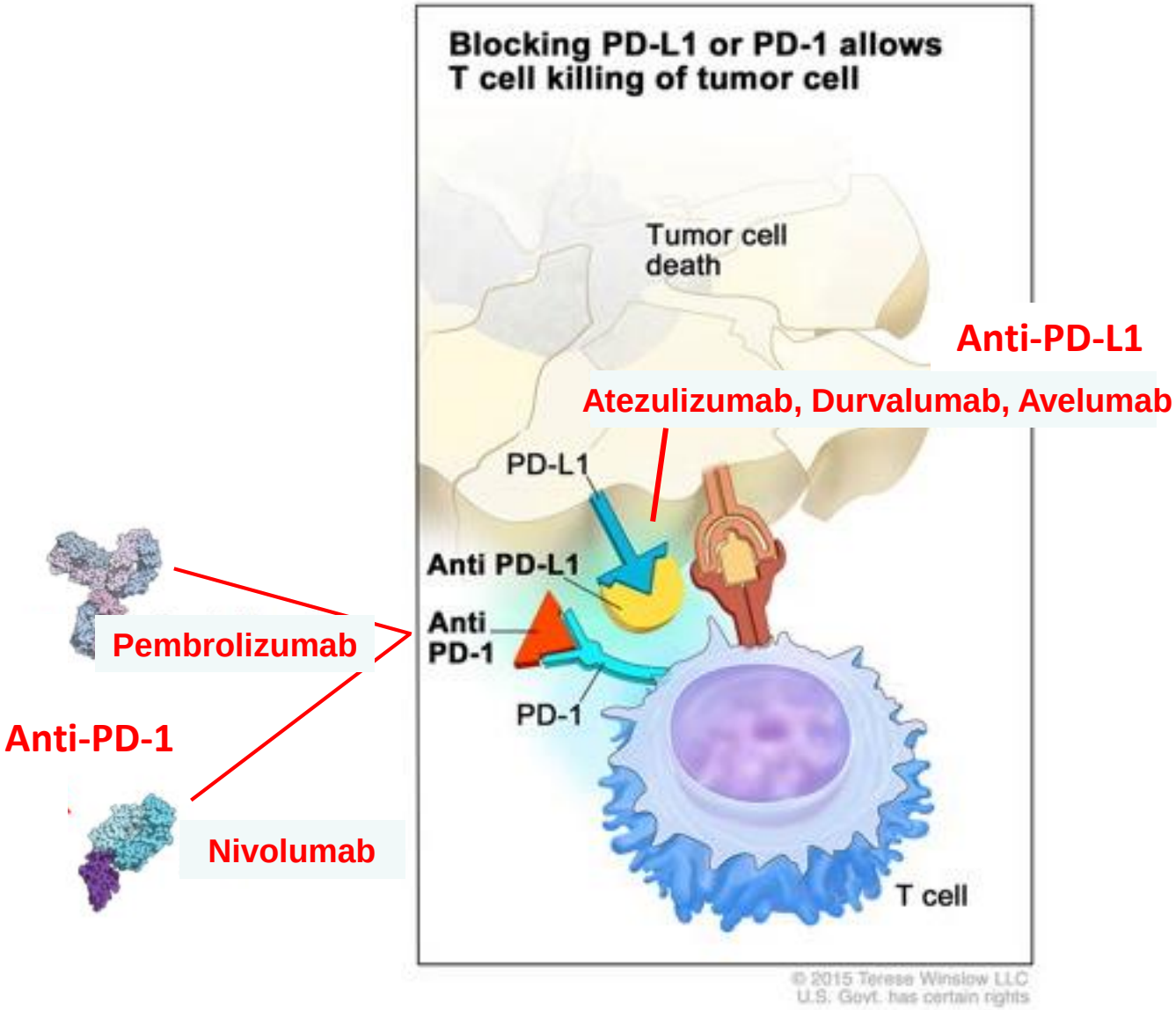


Ipilimumab
Tremelimumab

Anti PD-1 e anti PD-L1-anticorpi invece si..
(Nivolumab, Pembrolizumab, Atezolizumab)


Tumor Cell:
growth and proliferation
PD-L2
PD-L1
PD-1
Receptor
Deactivated CD8+
T Cell


Tumor
PD-L2
PD-L1
Nivolumab,
Pembrolizumab
PD-1
Receptor
T Cell Activation
To attack tumor cells


Blocking PD-L1 or PD-1 allows
T cell killing of tumor cell
Tumor cell
death
Anti-PD-L1
Atezulizumab, Durvalumab, Avelumab
PD-L1
Anti PD-L1
Anti
PD-1
PD-1
T cell
Pembrolizumab
Anti-PD-1
Nivolumab
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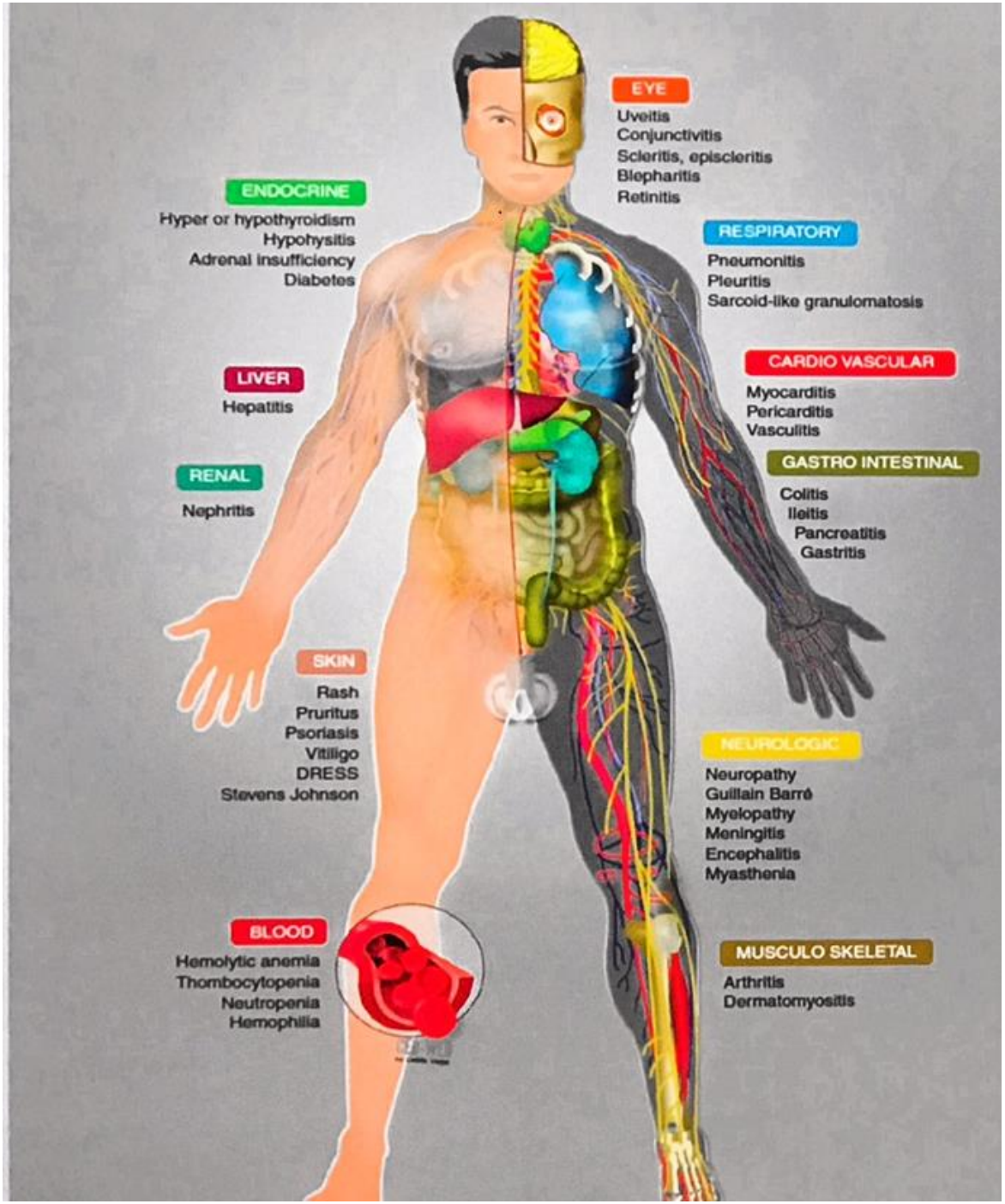
Tossicità dell’immunoterapia



Champiat et al. Ann Oncol 2016

Rare Side Toxicities: Long Tail of irAE

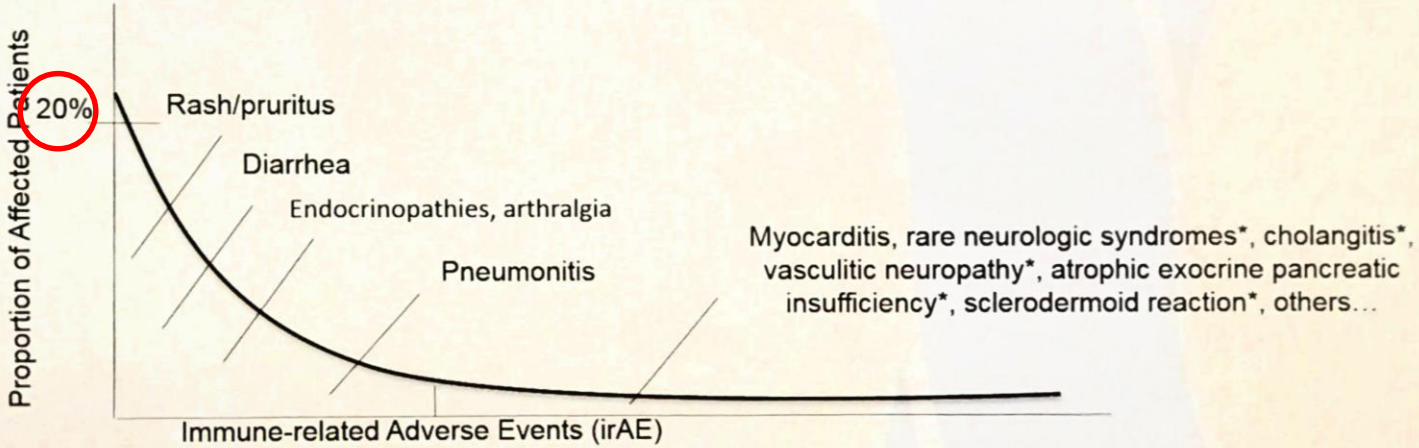


Figure legend: Approximate proportion of patients affected by immune-related adverse events of any grade upon treatment with single-agent PD-1 blockade.

Friedman and Snyder, Annals of Oncology 2017

Linee guidee

ESMO GUIDELINES TOXICITIES FROM IMMUNOTHERAPY

Tossicità di alto grado (grado 3-4)

Cortisone in vena: (Methyl)prednisolon 1-2mg/kg

Tossicità refrattaria a Cortisone

Ulteriore terapia immunosoppressiva: Mofetil (Cellcept) se tossicità epatica,

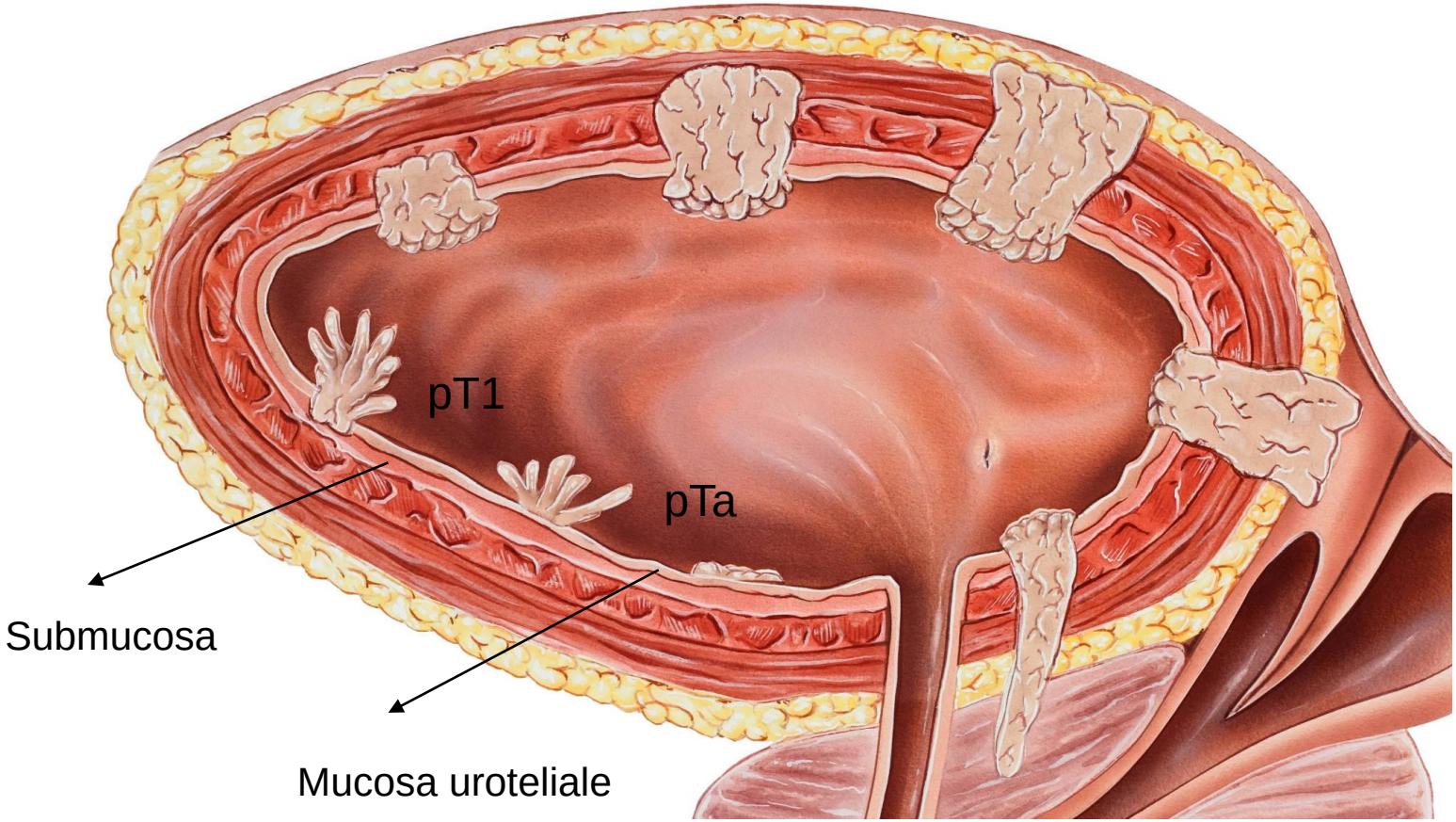
Infliximab (Remicade) per tossicità in altri organi

Annals of Oncology 28 (Supplement 4): i119–i142, 2017
doi:10.1093/annonc/mdx225

Standard nella terapia curativa

Carcinoma della vescica senza metastasi a distanza

Malattia localizzata

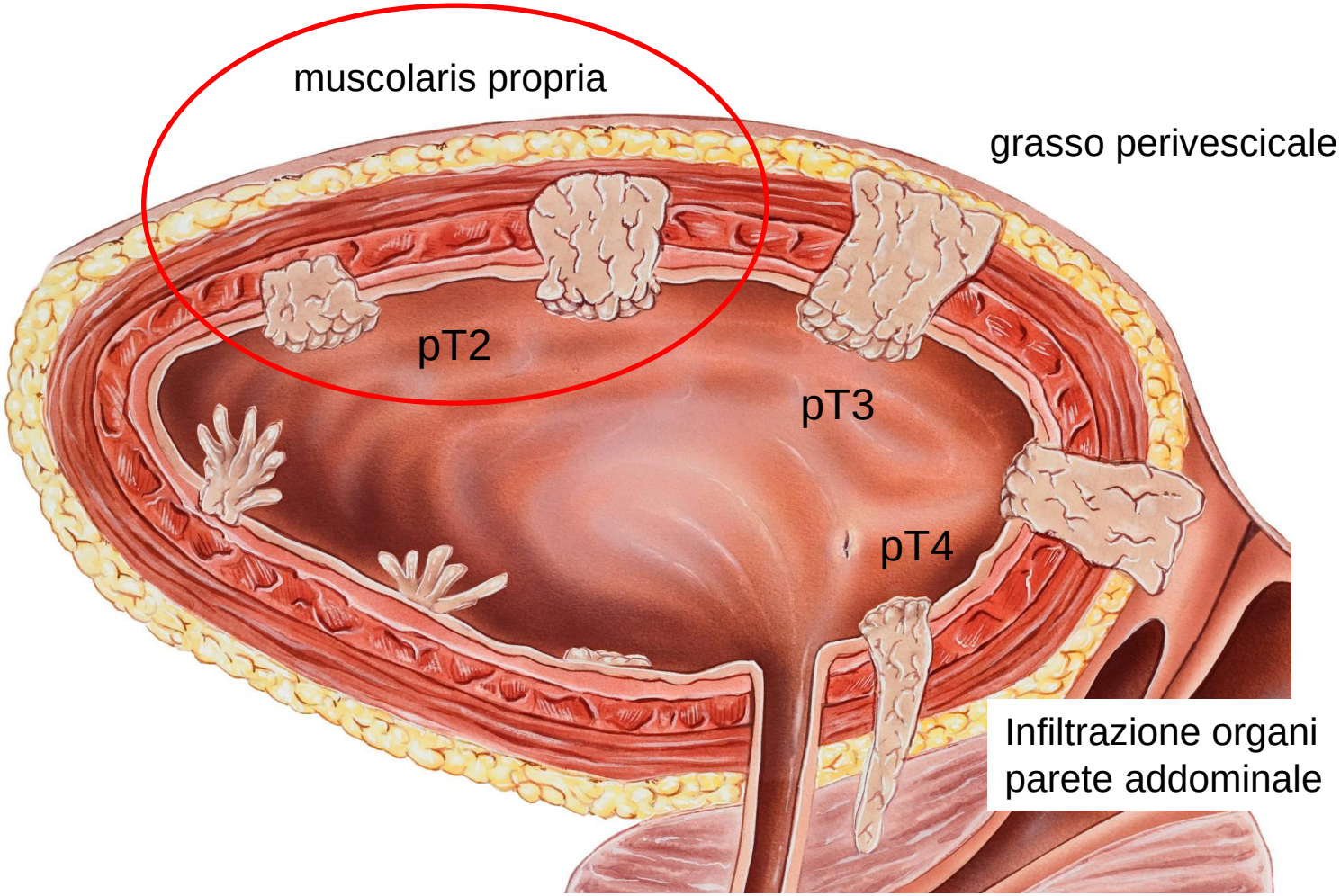

pT1
pTa
Submucosa
Mucosa uroteliale

pTa pT1

Resezione endovescicale (TUR-V), evtl seguita da terapia intravescicale

Se carcinoma recidivante, tumori multipli, T1 G3 +CIS, sede urethrale,

invasione vascolare / linfatica, refrattaria a terapia intravescicale ***cistectomia***


muscolaris propria
grasso perivescicale
pT2
pT3
pT4
Infiltrazione organi
parete addominale

≥ pT2 (invasione muscolare) = pT2–4 N+

Cisplatino e Gemcitabina 3-4 cicli, seguiti da cistectomia e linfadenectomia (se non dato neoadiuvante, considerare terapia adiuvante)

→ **Carboplatino non è una sostituzione per Cisplatino !**

se non candidato per cisplatino direttamente ad OP

→ se non operabile radio-/chemioterapia con Cisplatino o con MMC/5FU o Gemcitabina dopo TUR-V massimale

Vesper Phase III trial, ESMO 2021

Standard

- CISPLATIN 70 mg/m2: Day 1 ***Every 3 weeks, for a total of 4 cycles***
- GEMCITABINE 1250 mg/m2: Day 1 and Day 8

Experimental Arm B: dd-MVAC .

- METHOTREXATE 30 mg/m2: Day 1
- VINBLASTINE 3 mg/m2: Day 2
- DOXORUBICIN 30 mg/m2: Day 2 ***Every 2 weeks, for a total of 6 cycles***
- CISPLATIN 70 mg/m2: Day 2
- ***G-CSF: Day 3 to Day 9***

Vesper Phase III trial, ESMO 2021

- dd MVAC aumenta DFS e ypN0, trend per OS (troppo presto)
- dd MVAC molto piu' tossico (astenia, nausea, neutropenia, 3 morti)

→ solo 60% hanno potuto completare i 6 cicli di terapia

Consiglio

- dd MVAC solo se pazienti top – fit, giovani e fattori di rischi (N+)
- solo 4 cicli e non 6 cicli

Immunoterapia non ancora nessun ruolo nel setting neoadiuvante

→ Potrebbe cambiare presto

→ Studi in corso

- in combinazione con chemioterapia
- senza chemioterapia

Primi dati per immunoterapia nel setting adiuvante (1 anno)

- 1 studio di fase III (Nivolumab) positivo
- 1 studio di fase III (Atezolizumab) negativo

The NEW ENGLAND JOURNAL of MEDICINE

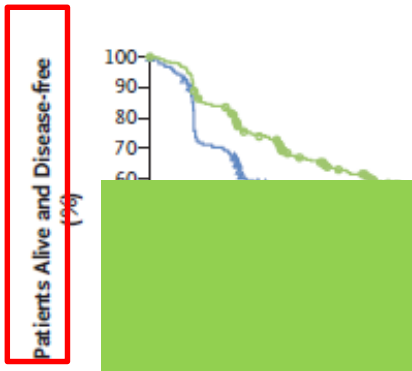
ORIGINAL ARTICLE

Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma

D.F. Bajorin, J.A. Witjes, J.E. Gschwend, M. Schenker, B.P. Valderrama, Y. Tomita, A. Bamias, T. Lebret, S.F. Shariat, S.H. Park, D. Ye, M. Agerbaek, D. Enting, R. McDermott, P. Gajate, A. Peer, M.I. Milowsky, A. Nosov, J. Neif Antonio, Jr., K. Tupikowski, L. Toms, B.S. Fischer, A. Qureshi, S. Collette, K. Unsal-Kacmaz, E. Broughton, D. Zardavas, H.B. Koon, and M.D. Galsky

N Engl J Med 2021;384:2102-14.

A Intention-to-Treat Population



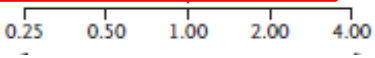
	No. of Events/ No. of Patients	Disease-free Survival at 6 Mo (95% CI)	Disease-free Survival at 12 Mo (95% CI)
		%	
Nivolumab	170/353	74.9 (69.9–79.2)	62.8 (57.3–67.8)
Placebo	204/356	60.3 (54.9–65.3)	46.6 (41.1–51.9)

ase recurrence or death,
.55–0.90)

Mancano i dati per la sopravvivenza

No. at Risl
Nivolumab
Placebo

Not rep				NA
Previous r				
Yes	308	70/153	100/155	0.52 (0.38–0.71)
No	401	100/200	104/201	0.92 (0.69–1.21)
Any previous neoadjuvant systemic therapy				
Yes	319	75/160	104/159	0.53 (0.39–0.72)
No	390	95/193	100/197	0.91 (0.69–1.21)
Days from surgery to randomization				
0–30	5	0/2	2/3	NA
>30–60	149	43/79	40/70	0.66 (0.40–1.06)
>60–90	342	78/165	93/177	0.76 (0.55–1.03)
>90–120	198	47/103	62/95	0.67 (0.44–1.00)
>120	15	2/4	7/11	NA
Smoking status				
Current or former smoker	484	116/237	141/247	0.70 (0.55–0.90)
Never smoked	215	53/111	61/104	0.67 (0.45–0.98)
Unknown	10	1/5	2/5	NA
PD-L1 expression level at baseline				
≥1%	280	55/139	79/141	0.56 (0.40–0.80)
<1%	419	114/210	120/209	0.82 (0.63–1.06)
Indeterminate or not able to be evaluated	8	1/3	4/5	NA
Not reported	2	0/1	1/1	NA



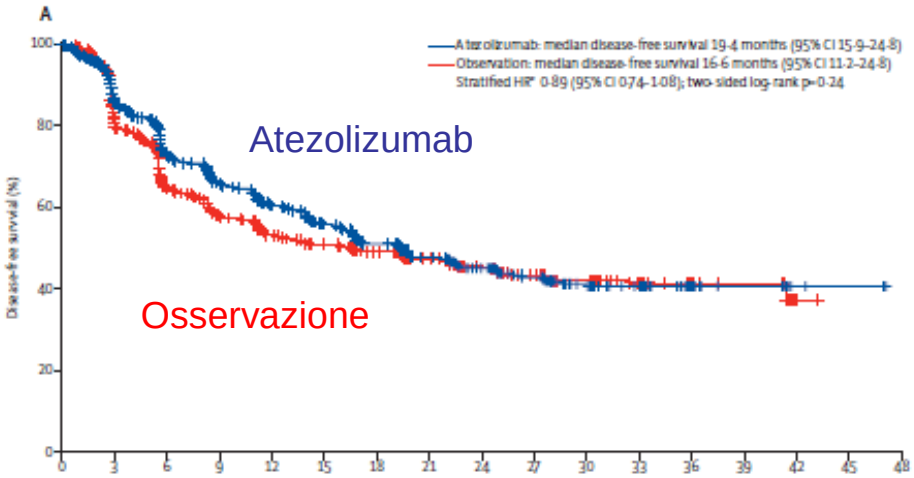
N Engl J Med 2021;384:2102-14.

Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial

*Joaquim Bellmunt, Maha Hussain, Jürgen E Gschwend, Peter Albers, Stephane Oudard, Daniel Castellano, Siamak Daneshmand, Hiroyuki Nishiyama, Martin Majchrowicz, Viraj Degaonkar, Yi Shi, Sanjeev Mariathasan, Petros Grivas, Alexandra Drakaki, Peter H O'Donnell, Jonathan E Rosenberg, Daniel M Geynisman, Daniel P Petrylak, Jean Hoffman-Censits, Jens Bedke, Arash Rezazadeh Kalebasty, Yousef Zakharia, Michiel S van der Heijden, Cora N Sternberg, Nicole N Davarpanah, Thomas Powles, for the IMvigor010 Study Group**

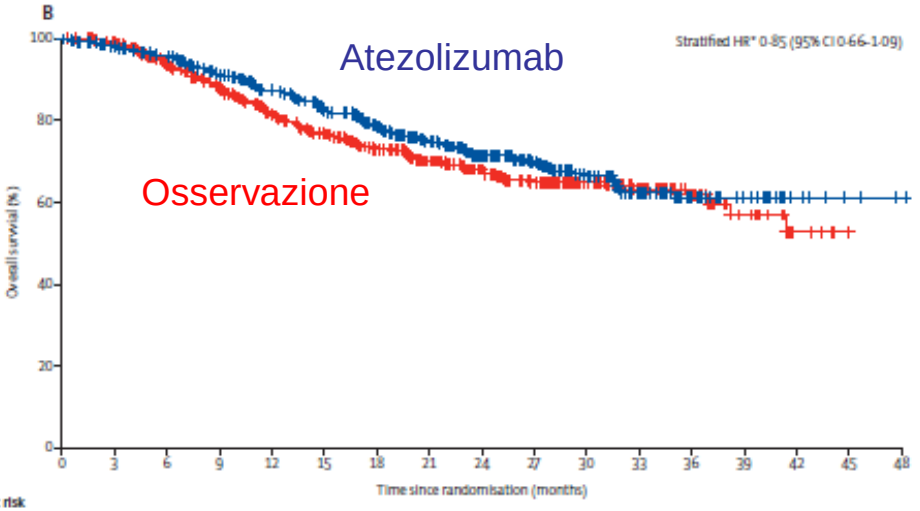
Lancet Oncol 2021; 22: 525–37

Disease free survival



Number at risk (number censored)																	
Atezolizumab	406	332	281	248	233	201	169	142	115	92	67	52	15	10	3	2	--
	(0)	(19)	(19)	(26)	(31)	(36)	(52)	(68)	(88)	(106)	(128)	(142)	(179)	(184)	(191)	(192)	--
Observation	403	305	240	211	188	177	156	131	109	87	67	42	17	12	2	-	--
	(0)	(24)	(31)	(33)	(40)	(43)	(58)	(78)	(95)	(112)	(130)	(154)	(179)	(184)	(193)	-	--

Overall survival



Number at risk (number censored)																	
Atezolizumab	406	383	369	350	328	306	267	229	185	144	100	72	35	22	8	4	2
	(0)	(16)	(21)	(23)	(30)	(33)	(59)	(85)	(119)	(156)	(195)	(217)	(253)	(266)	(280)	(284)	(286)
Observation	403	377	345	318	289	270	235	199	163	134	100	65	36	20	6	1	--
	(0)	(23)	(35)	(40)	(46)	(49)	(71)	(98)	(129)	(151)	(185)	(218)	(246)	(260)	(273)	(278)	--

Ruolo dell’immunoterapia nel setting adiuvante

ancora da definire

Malattia metastatica

J. S. 21.08.1980

Anamnesi

Ematuria macroscopica

Diagnosi collaterali

Nessuna

Non fuma e non ha mai fumato .

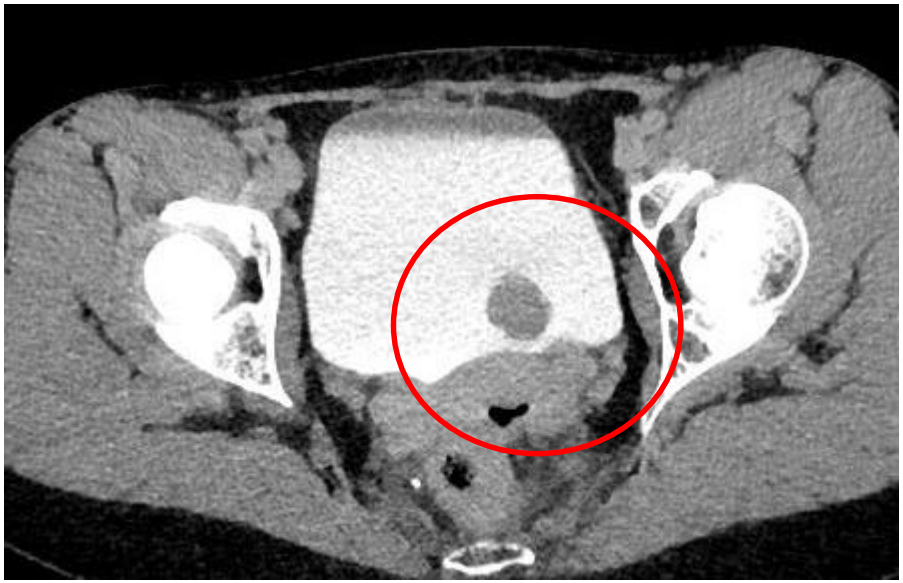
Anamnesi sociale

5 figli, l’ultimo nato 2 mesi prima della comparsa di ematuria

Anamnesi familiare

Padre forte fumatore. Carcinoma del colon a 40 anni

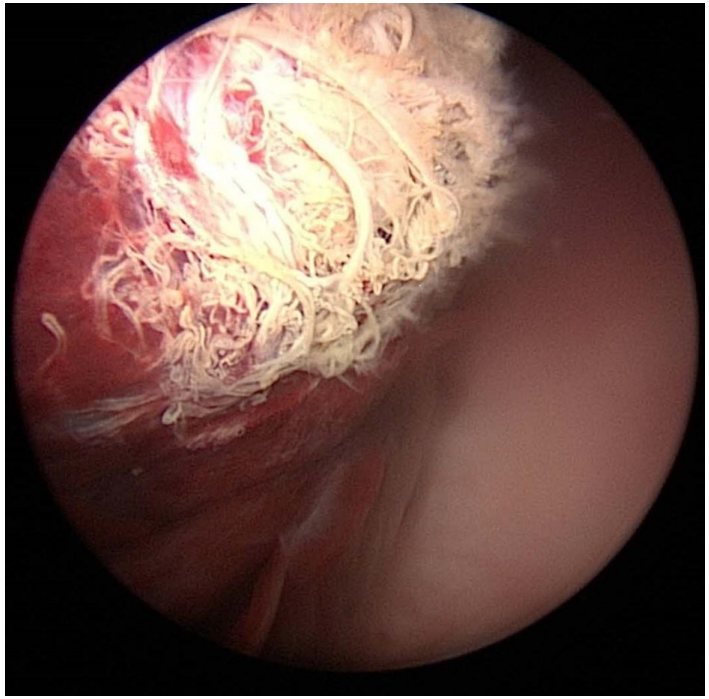
Uro-TAC 29.01.18



Uro-TAC 29.01.18

Neoformazione (6x3.9x2.3cm) dell’uretere sx con idronefrosi IV grado

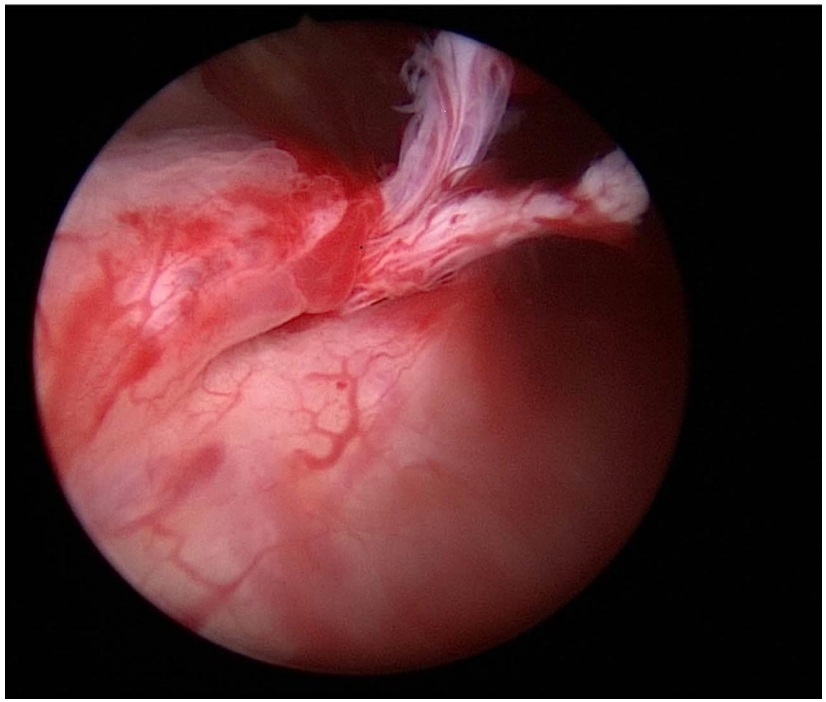
TUR-V diagnostica 12.02.2018



Tumefazione vescicale

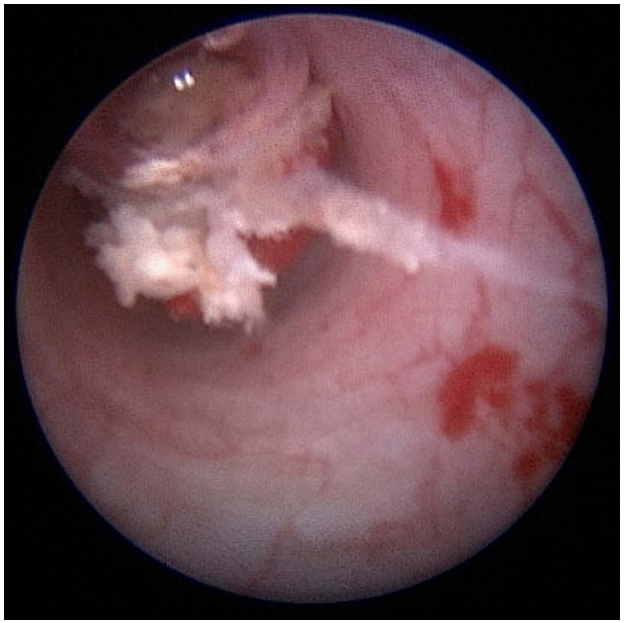
Foto Dr. Castelnuovo / Dr. Villani

TUR-V diagnostica 12.02.2018



Peduncolo fuoriuscente dal meato ureterale sx

Ureteroscopia sinistra



Tumefazione dell’uretere medio

Foto Dr. Castelnuovo / Dr. Villani

Pielografia retrograda a sinistro

Neoformazione ostruttiva a livello dell’uretere medio

Foto Dr. Castelnuovo / Dr. Villani

Nefro-ureterectomia sinistra il 26.03.19

Foto Dr. Castelnuovo / Dr. Villani

Diagnosi oncologica

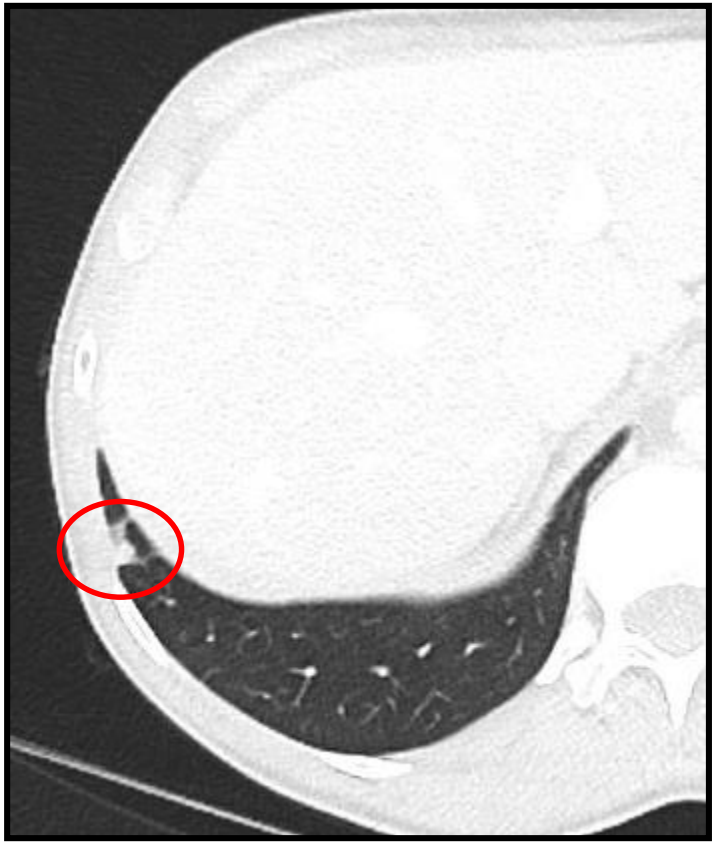
- Carcioma uroteliale della vescica, stadio pT1 G2

- Carcinoma uroteliale papillare e solido dell’uretere sinistro, stadio pT2 cN0 L0 G3 R0

- Carcinoma uroteliale papillare e focalmente solido del bacinetto renale sinistro (plurimi focolai del diametro massimo di 3 cm), stadio pT3 cN0 L1 G3 R0

Staging

TAC torace addome il 24.04.18



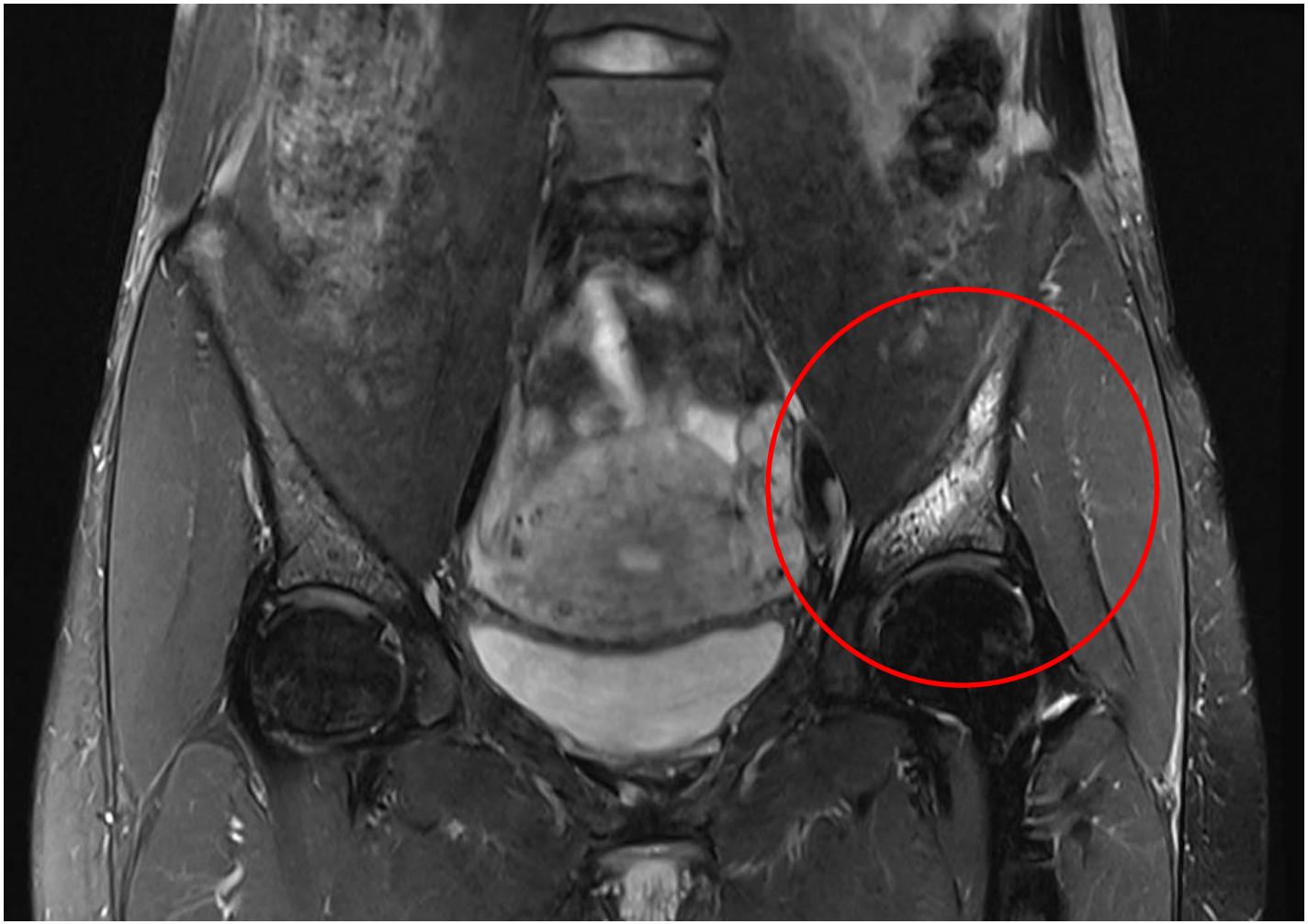
Piccolo nodulo polmonare sub-pleurico al III segmento destro di 2mm

e in sede apico-dorsale destro di 7.4mm

Scintigrafia ossea del 25.04.18

Iperfissazione del tracciante a livello dell’ala iliaca sinistra in sede sovra-acetabolare

RM bacino nativo e con mezzo di contrasto del 30.04.18



Alterazione della trabecolatura ossea dell’osso iliaco sinistro

Malattia metastatica

- Metastasi ossea unica a livello dell’osso iliaco sinistro (biopsia del 07.05.2018)
- 2 micronoduli polmonari a destro DD esiti cicatriziali

Terapia oncologica

- 6 cicli di chemioterapia con Carboplatino (non Cisplatino per insufficienza renale) e Gemcitabina dal 30.05.18 al 13.11.2018: stabilità di malattia

  → Effetti collaterali: leucopenia G3 e trombocitopenia G2 prolungata

- Radioterapia su metastasi ossea unica con 10x3Gy, in totale 30Gy 09.2019 *(discusso al Tumorboard interdisciplinare del 08.08.19)*

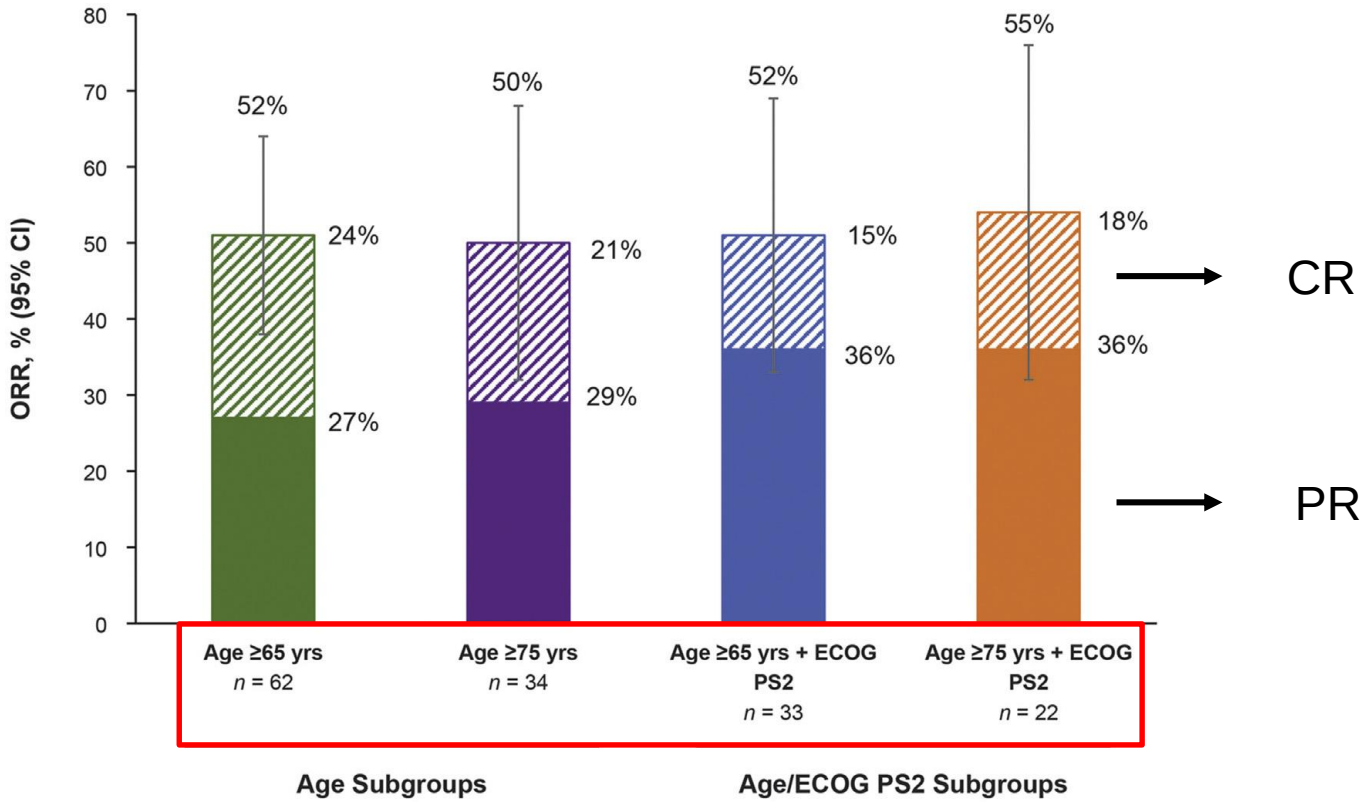
Standard di terapia di 1° linea nella malattia metastatica

Cisplatino iv d1 e Gemcitabina iv d1 + d8 q 21 4- 6 cicli

Pembrolizumab as First-line Therapy in Cisplatin-ineligible Advanced Urothelial Cancer (KEYNOTE-052): Outcomes in Older Patients by Age and Performance Status

Petros Grivas[a,], Elizabeth R. Plimack[b], Arjun V. Balar[c], Daniel Castellano[d], Peter H. O'Donnell[e], Joaquim Bellmunt[f], Thomas Powles[g], Noah M. Hahn[h], Ronald de Wit[i], Dean F. Bajorin[j], Misoo C. Ellison[k], Tara L. Frenkl[k], James L. Godwin[k], Jacqueline Vuky[l]*

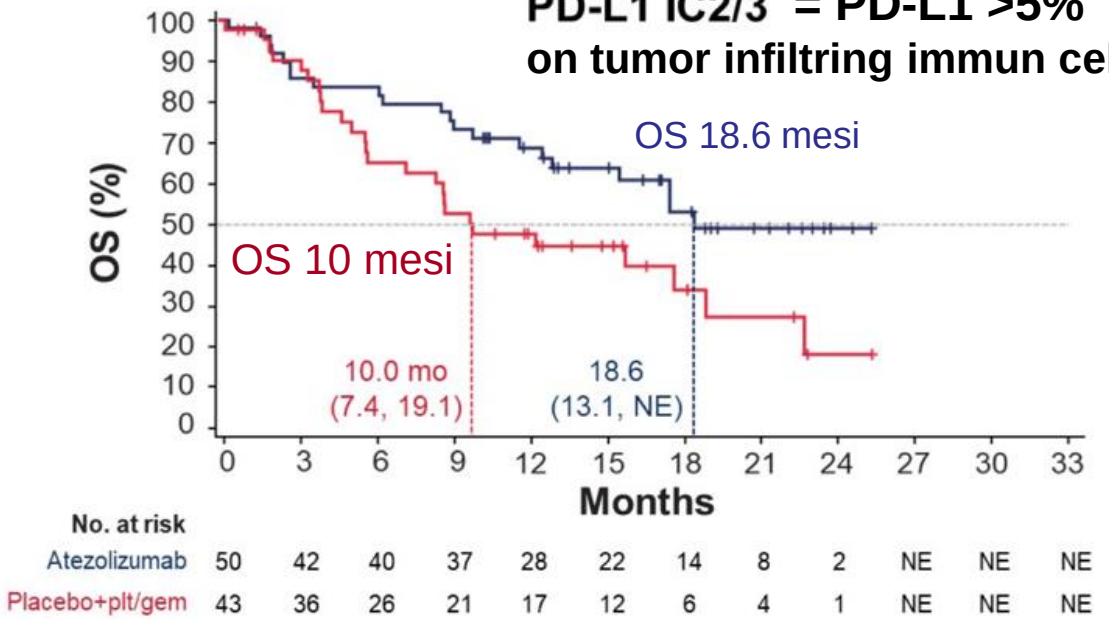
CPS score
≥ 10%
(PD-L1 pos cells/ total tumor cells)



EUROPEAN UROLOGY ONCOLOGY 3 (2020) 351–359

ASCO GU 2021: Atezolizumab Monotherapy vs Chemotherapy in Previously Untreated Locally Advanced or Metastatic Urothelial Carcinoma: Clinical Outcomes by PD-L1 Status In Cisplatin-Ineligible Patients From the Phase III IMvigor130 Study

PD-L1 IC2/3 = PD-L1 >5%
on tumor infiltring immun cells



	Atezolizumab (Arm B) (n=50)	Placebo + plt/gem (Arm C) (n=43)
OS events	21	26
OS HR (95% CI)	0.53 (0.30, 0.94)	
ORR (95% CI), %	38 (25, 53)	33 (19, 49)

Zachary Klaassen, MD, MSc, American Society of Clinical Oncology Genitourinary Cancers Symposium (#GU21); February 11th-February 13th, 2021

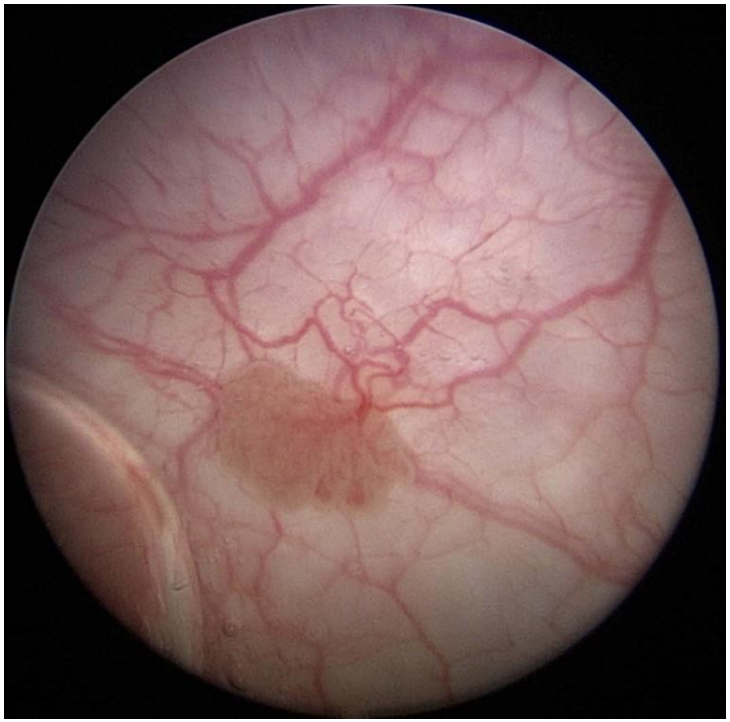
Standard di terapia di 1° linea nella malattia metastatica

Non fit for Cisplatino

- PD-L1 CPS score > 10% Pembrolizumab
- PD-L1 score > 5% Atezolizumab

→ se PD- L1 negativo Carboplatino / Gemcitabina (immunoterapia)

TUR-V del 10.12.19 (a 1 mese dopo la fine della chemioterapia)



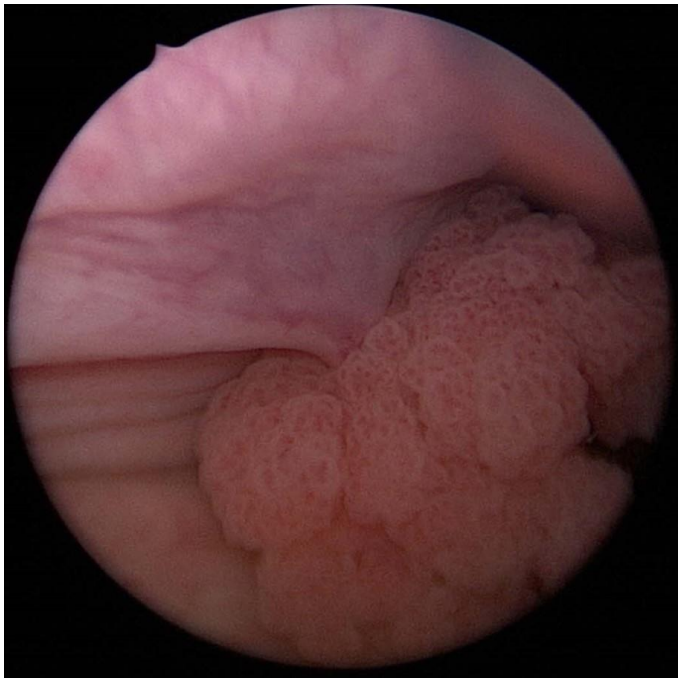
1. recidiva vescicale

Carcinoma uroteliale papillare. Stadio pTa, basso grado

Foto Dr. Castelnuovo / Dr. Villani

TUR-V del 08.04.19 e 23.05.21 (a 4 e 5 mesi dall'ultima cistoscopia)

2. recidiva (2 tumori)



Carcinoma uroteliale papillare e solido

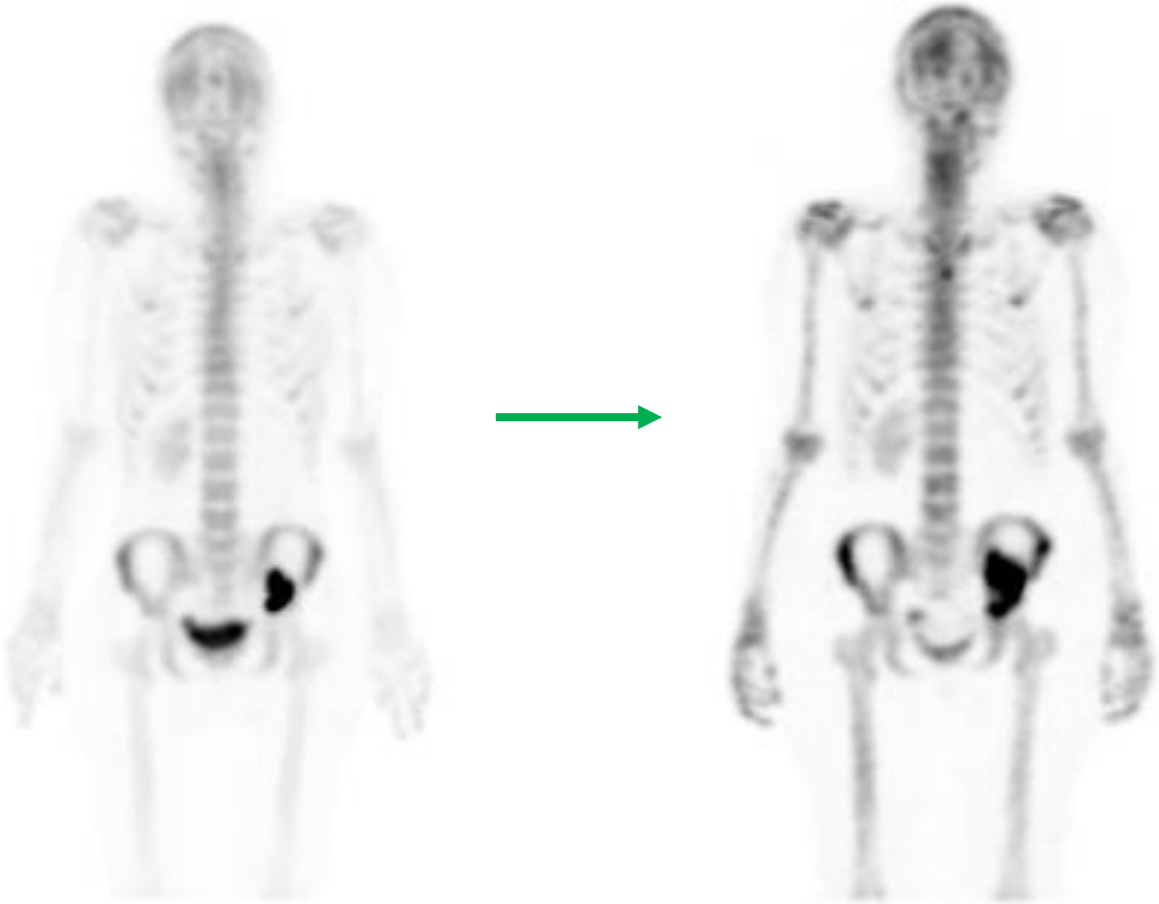
Stadio pT1 G2

Carcinoma uroteliale papillare

Stadio pTa basso grado

Foto Dr. Castelnuovo / Dr. Villani

4 mesi dopo la fine della chemioterapia



2018 **03.2019**

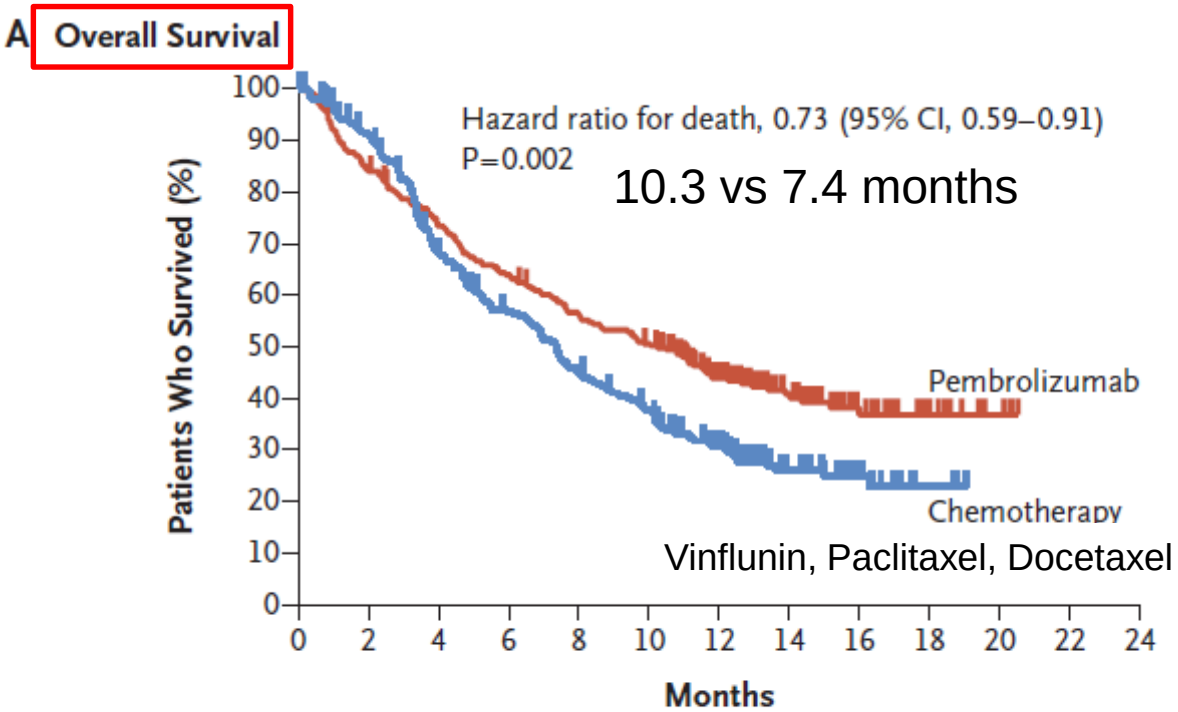
→ Nuova biopsia e cementoplastica, Dr. Cianfoni, 02.05.2019

Standard di terapia di 2° linea nella malattia metastatica

- Pembrolizumab o Atezolizumab
- Se passati > 6 mesi ripetizione schema Platino / Gemcitabina

Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma

J. Bellmunt, R. de Wit, D.J. Vaughn, Y. Fradet, J.-L. Lee, L. Fong, N.J. Vogelzang, M.A. Climent, D.P. Petrylak, T.K. Choueiri, A. Necchi, W. Gerritsen, H. Gurney, D.I. Quinn, S. Culine, C.N. Sternberg, Y. Mai, C.H. Poehlein, R.F. Perini, and D.F. Bajorin, for the KEYNOTE-045 Investigators*



No. at Risk

Pembrolizumab	270	226	194	169	147	131	87	54	27	13	4	0	0
Chemotherapy	272	232	171	138	109	89	55	27	14	3	0	0	0

N Engl J Med 2017;376:1015-26.

J.S. 21.08.1980

- Immunoterapia con l’**anticorpo anti-PD 1 Keytruda (Pembrolizumab) dal 06.05.19**

  ottima risposta e qualità di vita

- Cistoscopie ogni 6 mesi negative

ORIGINAL ARTICLE

Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma

T. Powles, S.H. Park, E. Voog, C. Caserta, B.P. Valderrama, H. Gurney, H. Kalofonos, S. Radulović, W. Demey, A. Ullén, Y. Loriot, S.S. Sridhar, N. Tsuchiya, E. Kopyltsov, C.N. Sternberg, J. Bellmunt, J.B. Aragon-Ching, D.P. Petrylak, R. Laliberte, J. Wang, B. Huang, C. Davis, C. Fowst, N. Costa, J.A. Blake-Haskins, A. di Pietro, and P. Grivas

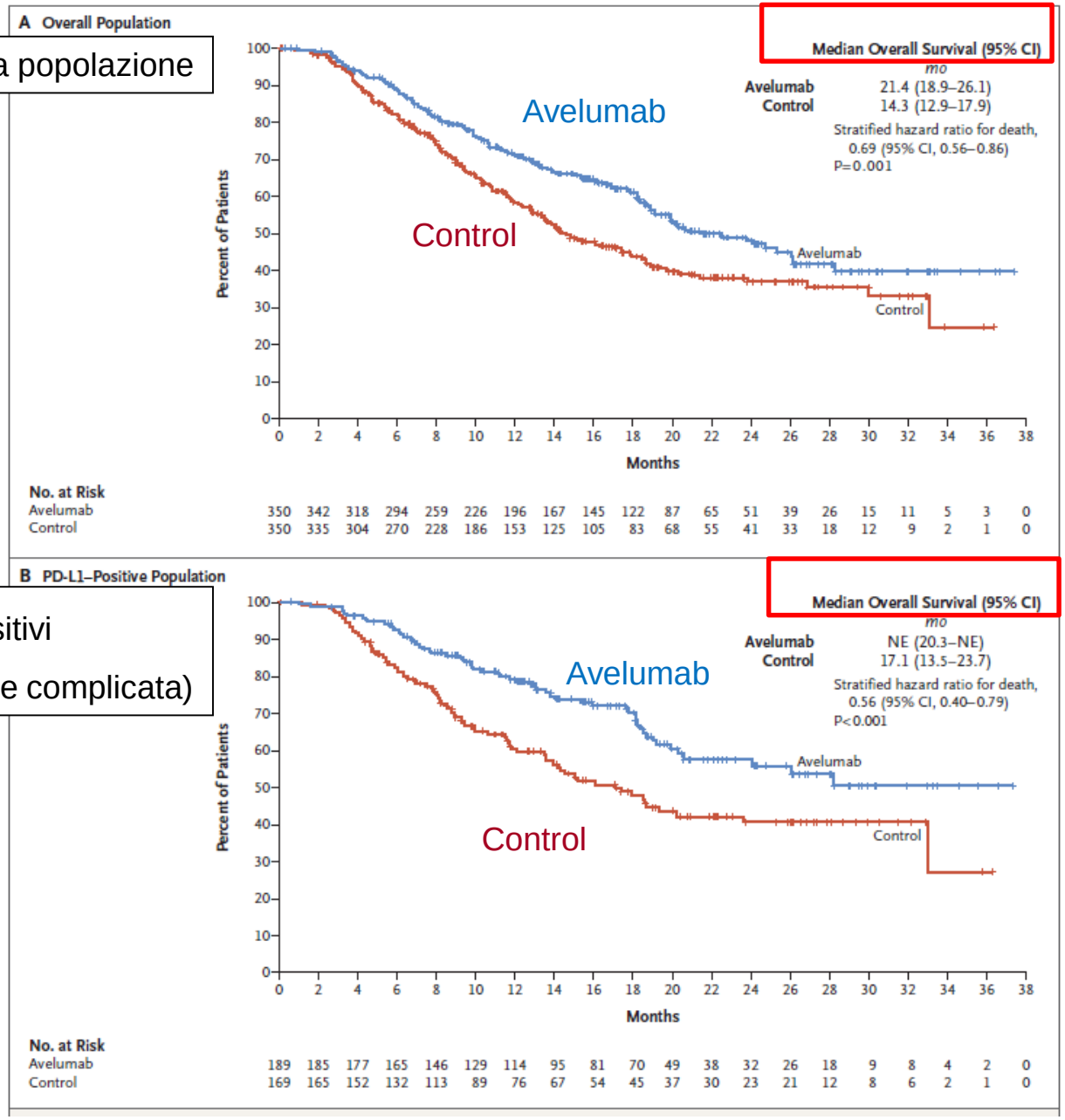
- Studio di fase III
- Nessuna progressione dopo 4-6 cicli di chemioterapia *(Cisplatino/Carboplatino + Gemcitabina)*
- Avelumab 10mg/kg ogni 2 settimane di mantenimento vs osservazione

N Engl J Med 2020;383:1218-30.

Tutta la popolazione

PD-L1 positivi

(definizione complicata)



N Engl J Med 2020;383:1218-30.

Nuovo standard di terapia di 1° linea nella malattia metastatica

Mantenimento con Avelumab (Bavencio) per pazienti senza progressione

dopo 4-6 cicli di chemioterapia con Platino e Gemcitabina

Standard di terapia di 2°/3° linea nella malattia metastatica (dopo chemioterapia e immunoterapia)

- Erdafitinib (inibitore della tirosin-chinasi FGFR 1-4) per os
- Enfortumab vedotin (anticorpo con doppia funziona) in vena

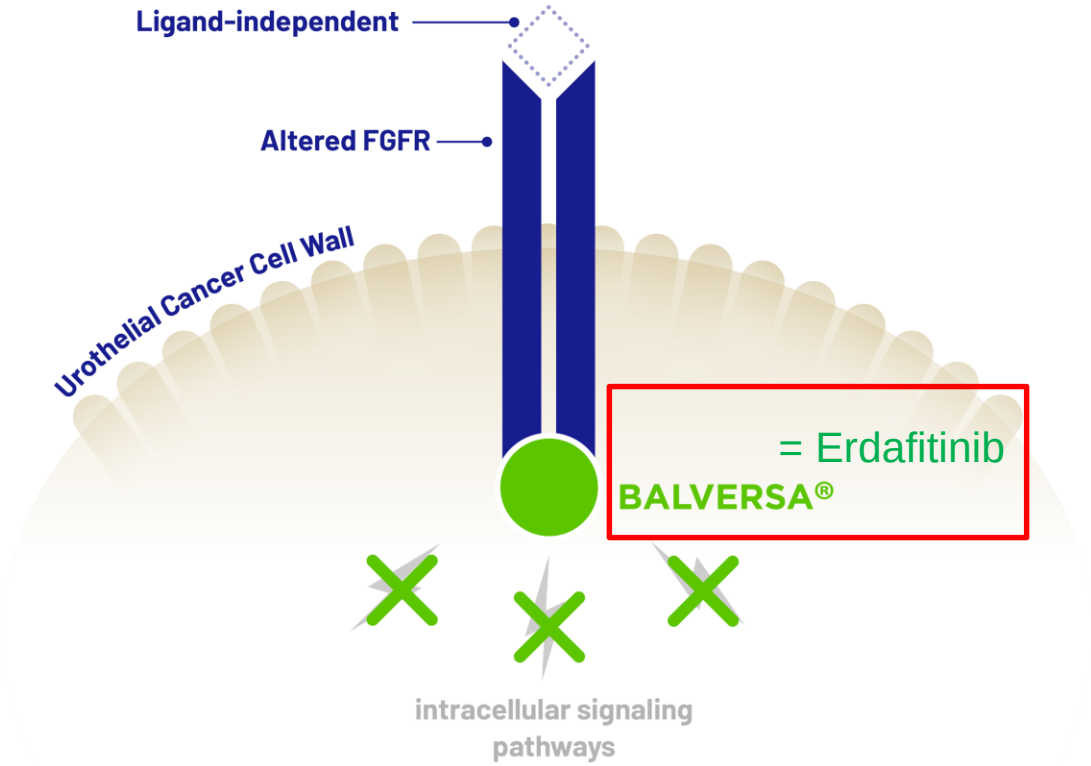
ORIGINAL ARTICLE

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*

- Studio fase II open label
- **Almeno una mutazione a livello del gene FGFR 3 o una fusione FGFR 2/3 (20% dei pazienti)**

N Engl J Med 2019;381:338-48.


Ligand-independent
Altered FGFR
Urothelial Cancer Cell Wall
= Erdafitinib
BALVERSA®
intracellular signaling pathways

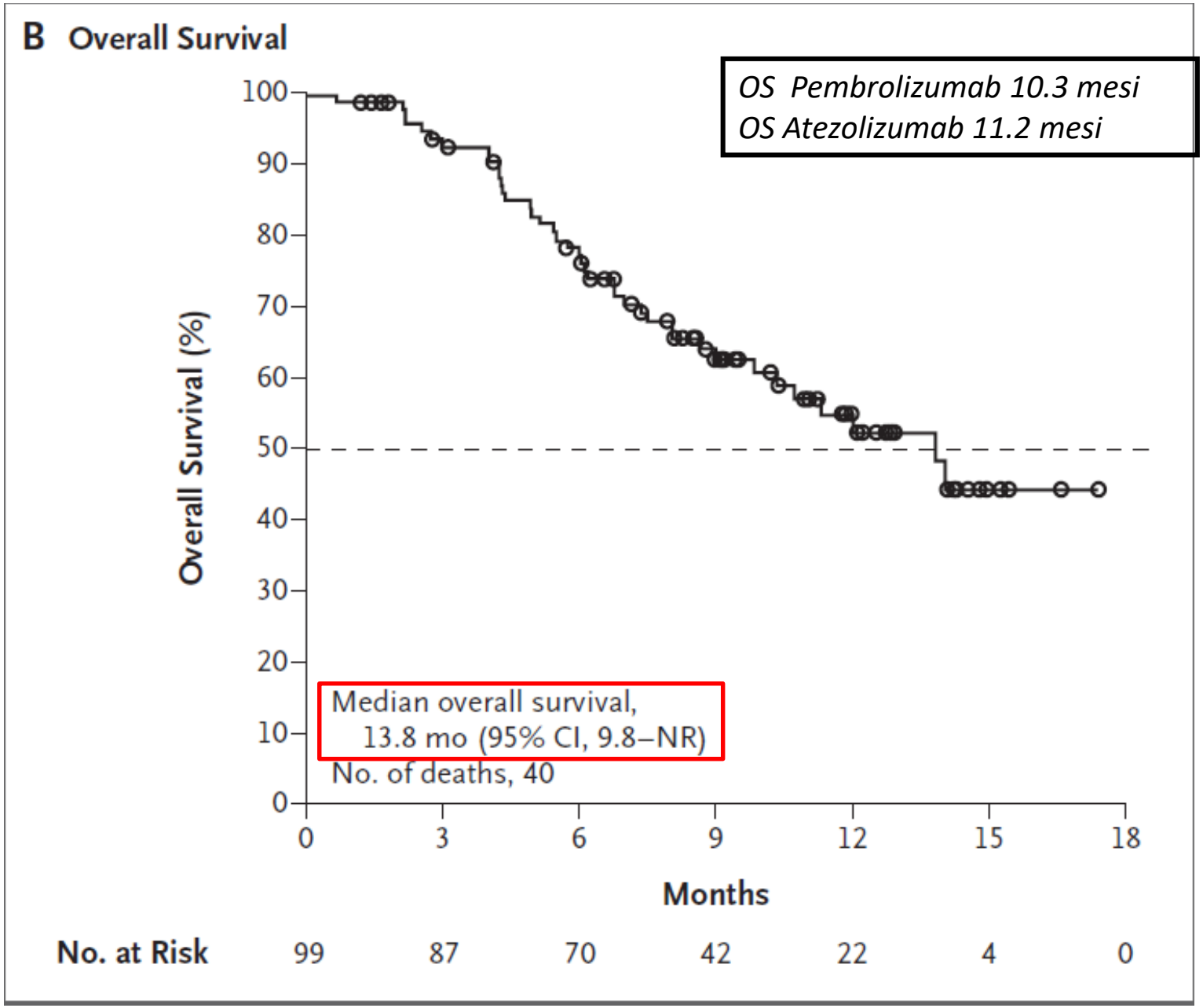
99 patients

Variable	Value	Rate of Response (95% CI)
		percent
Response per investigator assessment — no. of patients†		
Any objective response	40	40 (31–50)
C		3
P		37
Stabl		39
Progr		18
Coul		2
Median t		
Median c		
Response per independent radiologic assessment — no. of patients†		
Objective response	34	34 (25–44)
Complete response	3	3
Partial response	31	31

Probabilità di risposta superiore a

- Single agent chemotherapy (Vinflunine, taxanes) 10%
- Immunotherapy 13-21%

N Engl J Med 2019;381:338-48.



N Engl J Med 2019;381:338-48.

Table 3. Adverse Events in the 99 Patients in the Selected-Regimen Group.*

Adverse Event	Any Grade	Grade 1	Grade 2	Grade ≥3
		number of patients (percent)		
Hyperphosphatemia	76 (77)	53 (54)	21 (21)	2 (2)
Stomatitis	57 (58)	21 (21)	26 (26)	10 (10)
Diarrhea	50 (51)	31 (31)	15 (15)	4 (4)
Dry mouth	45 (46)	34 (34)	11 (11)	0
Decreased appetite	38 (38)	18 (18)	20 (20)	0
Dysgeusia	37 (37)	23 (23)	13 (13)	1 (1)
Fatigue	32 (32)	12 (12)	18 (18)	2 (2)
Dry skin	32 (32)	24 (24)	8 (8)	0
Alopecia	29 (29)	23 (23)	6 (6)	0
Constipation	28 (28)	19 (19)	8 (8)	1 (1)
Hand-foot syndrome	23 (23)	6 (6)	12 (12)	5 (5)
Ar				
As				
Na				
Dr				
Oi				
Al				
Pa				
Blurred vision	17 (17)	10 (10)	7 (7)	0
Nail dystrophy	16 (16)	5 (5)	5 (5)	6 (6)
Urinary tract infection	16 (16)	0	11 (11)	5 (5)
Vomiting	13 (13)	10 (10)	1 (1)	2 (2)
Hyponatremia	12 (12)	1 (1)	0	11 (11)
Hematuria	10 (10)	7 (7)	1 (1)	2 (2)
Dyspnea	8 (8)	4 (4)	2 (2)	2 (2)
Nail disorder	8 (8)	4 (4)	1 (1)	3 (3)
Acute kidney injury	6 (6)	2 (2)	2 (2)	2 (2)
Cataract	6 (6)	3 (3)	1 (1)	2 (2)
Colitis	5 (5)	1 (1)	2 (2)	2 (2)
General deterioration in physical health	5 (5)	0	1 (1)	4 (4)
Keratitis	5 (5)	0	2 (2)	3 (3)
Aphthous ulcer	4 (4)	2 (2)	0	2 (2)
Increase in γ-glutamyltransferase	3 (3)	1 (1)	0	2 (2)
Urosepsis	3 (3)	0	0	3 (3)

46% effetti collaterali G3 +

55% riduzione del dosaggio

13% interruzione della terapia

N Engl J Med 2019;381:338-48.

→ *In studio Erdafitinib in 1° linea assieme a immunoterapia*

ORIGINAL ARTICLE

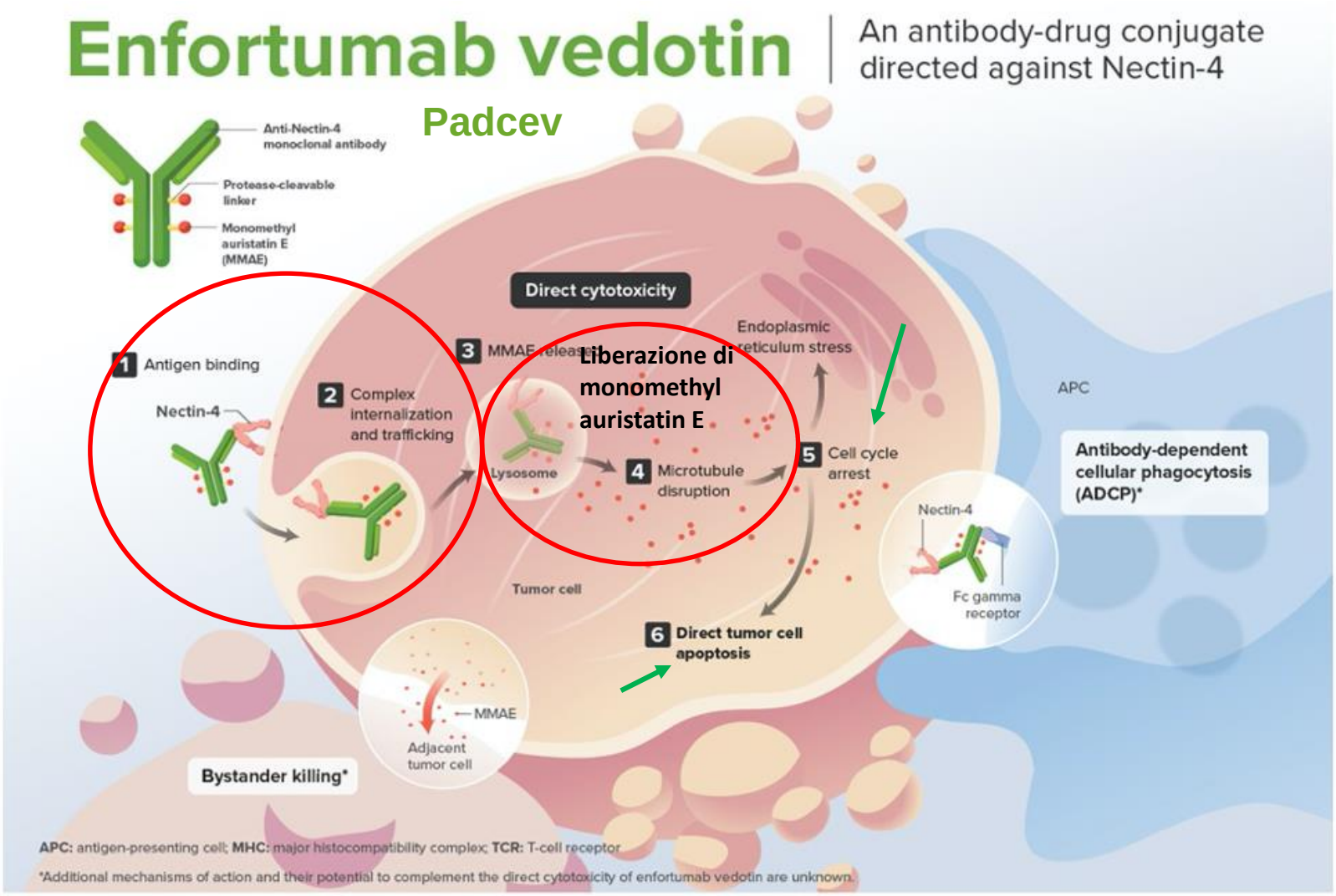
Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma

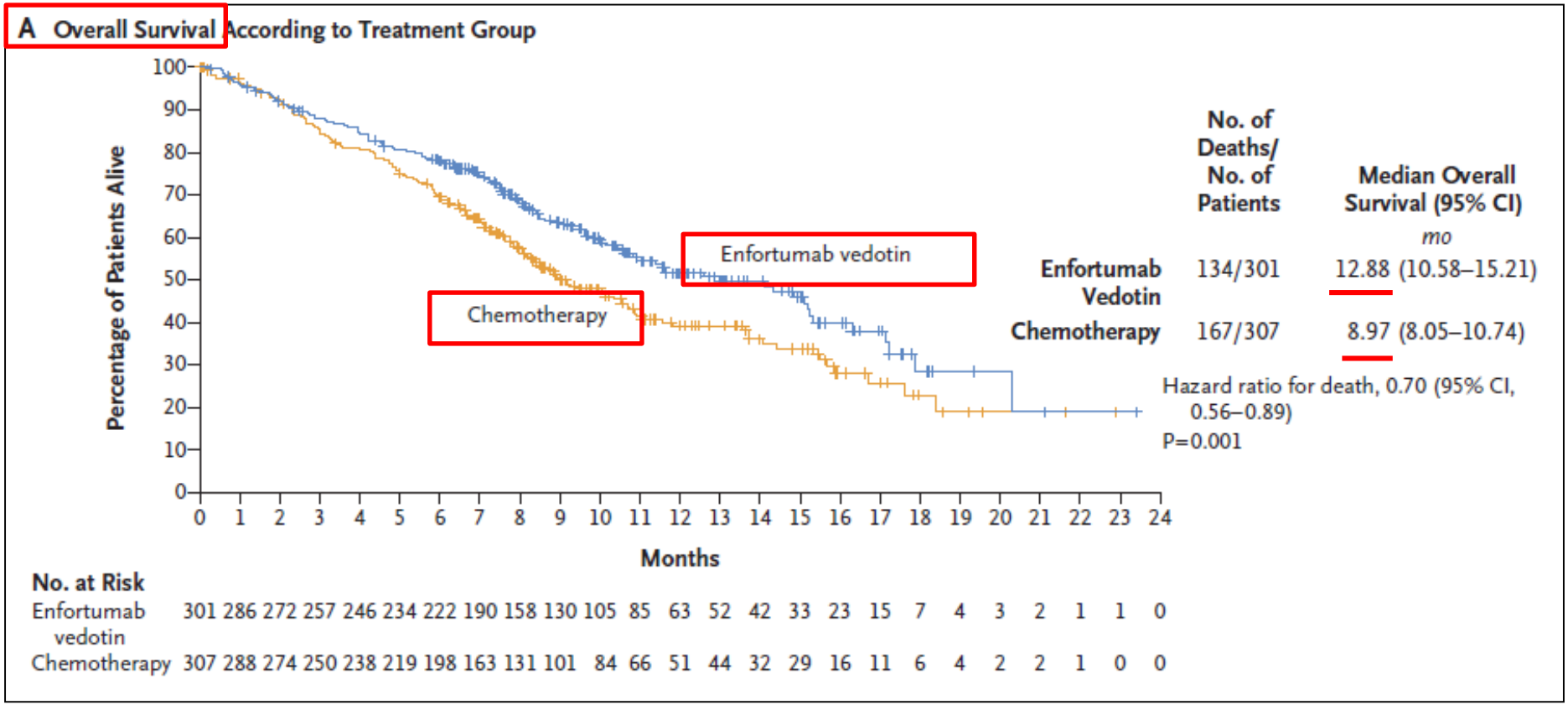
Thomas Powles, M.D., Jonathan E. Rosenberg, M.D., Guru P. Sonpavde, M.D., Yohann Loriot, M.D., Ph.D., Ignacio Durán, M.D., Ph.D., Jae-Lyun Lee, M.D., Ph.D., Nobuaki Matsubara, M.D., Christof Vulsteke, M.D., Ph.D., Daniel Castellano, M.D., Chunzhang Wu, Ph.D., Mary Campbell, M.D., Maria Matsangou, M.B., Ch.B., M.D., and Daniel P. Petrylak, M.D.

- Studio di fase III
- **Enfortumab Vedotin 1.25mg/m2 iv d1, 8 e 15 ogni 28 giorni vs chemioterapia di scelta (docetaxel, paclitaxel, vinflunine) d1 q 21 giorni**

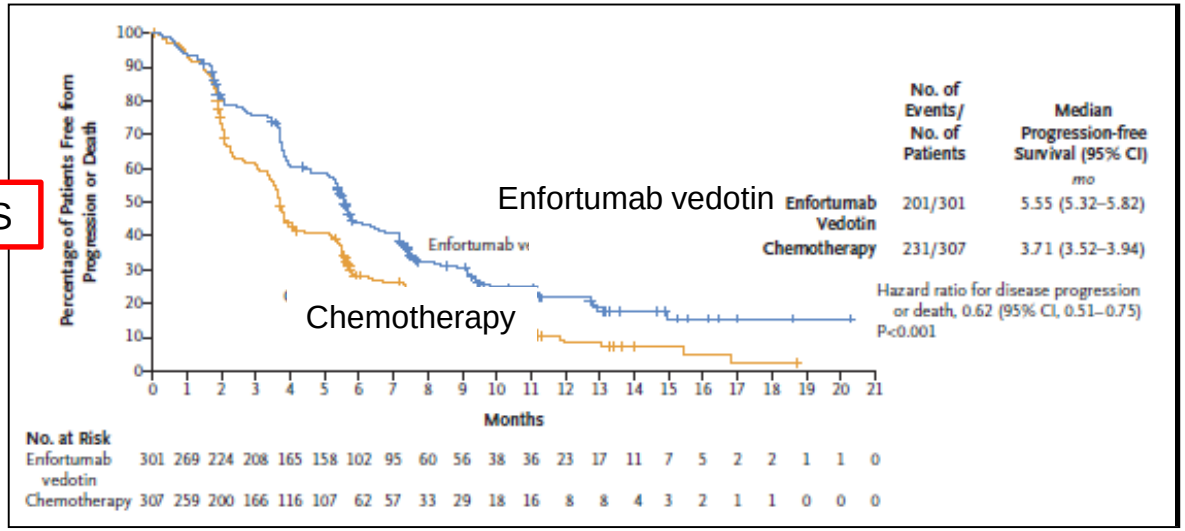
N Engl J Med 2021;384:1125-35.

Anticorpo con doppio funziona





PFS



N Engl J Med 2021;384:1125-35.

Table 2. Treatment-Related Adverse Events (Safety Population).*

Adverse Event	Enfortumab Vedotin Group (N=296)		Chemotherapy Group (N=291)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	278 (93.9)	152 (51.4)	267 (91.8)	145 (49.8)
Alopecia	134 (45.3)	0	106 (36.4)	0
Peripheral sensory neuropathy†	100 (33.8)	9 (3.0)	62 (21.3)	6 (2.1)
Pruritus	95 (32.1)	4 (1.4)	13 (4.5)	0
Fatigue	92 (31.1)	19 (6.4)	66 (22.7)	13 (4.5)
Decreased appetite	91 (30.7)	9 (3.0)	68 (23.4)	5 (1.7)
Diarrhea	72 (24.3)	10 (3.4)	48 (16.5)	5 (1.7)
Dysgeusia	72 (24.3)	0	21 (7.2)	0
Nausea	67 (22.6)	3 (1.0)	63 (21.6)	4 (1.4)
Maculopapular rash	48 (16.2)	22 (7.4)	5 (1.7)	0
Anemia	34 (11.5)	8 (2.7)	59 (20.3)	22 (7.6)
Decreased neutrophil count	30 (10.1)	18 (6.1)	49 (16.8)	39 (13.4)
Neutropenia	20 (6.8)	14 (4.7)	24 (8.2)	18 (6.2)
Decreased white-cell count	16 (5.4)	4 (1.4)	31 (10.7)	20 (6.9)
Febrile neutropenia	2 (0.7)	2 (0.7)	16 (5.5)	16 (5.5)

In 75% reversibile fino a G1

Iperglicemia

N Engl J Med 2021;384:1125-35.

Immunoterapia ha cambiato e sta cambiando l'oncologia

→ *per il carcinoma della vescica in attesa i dati per la terapia neoadiuvante*

Grazie per l’attenzione

Jimmy Carter