Kidney and Bladder Cancer Updates

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COI

Hamid Emamekhoo, MD, has the following financial relationships to disclose:

- Exelixis: Consultant (advisory board)
- Seattle Genetics: Consultant (advisory board)

Objectives

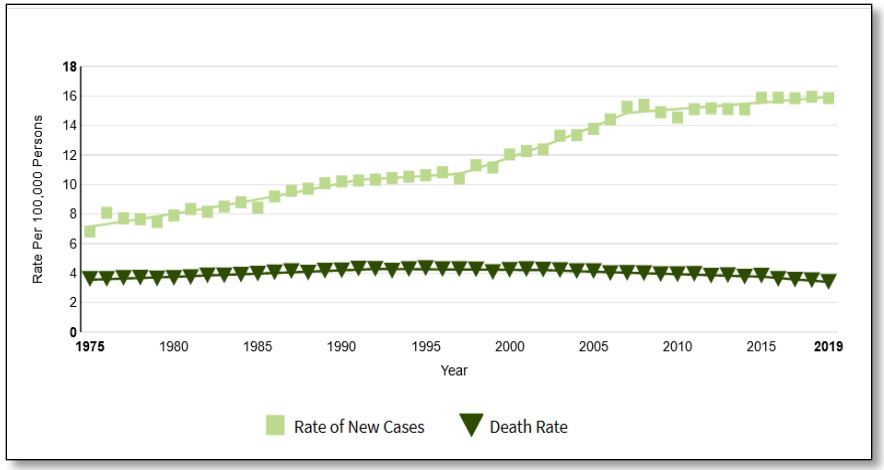
- **Kidney Cancer:**
  - List different treatment regimens approved for advanced renal cell carcinoma (aRCC)
  - Compare the outcomes associate with different combination regimens.
  - Select an appropriate adjuvant treatment option for a patient with high risk RCC post nephrectomy.

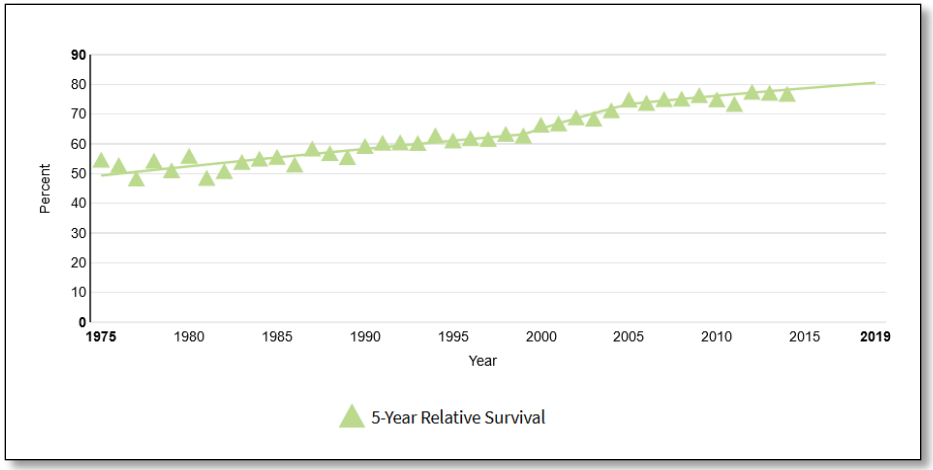
- **Bladder Cancer:**
  - Compare different treatment options approved for metastatic urothelial carcinoma (mUC) of bladder and select the optimal treatment regimen for each patient.
  - Identify the appropriate maintenance treatment approach after chemotherapy in mUC.
  - List available agents for second line and beyond in mUC.

Kidney Cancer

Kidney Cancer	2022	% of all cancers
Estimated new cases	79000	4.1%
Estimated deaths	13920	2.3%

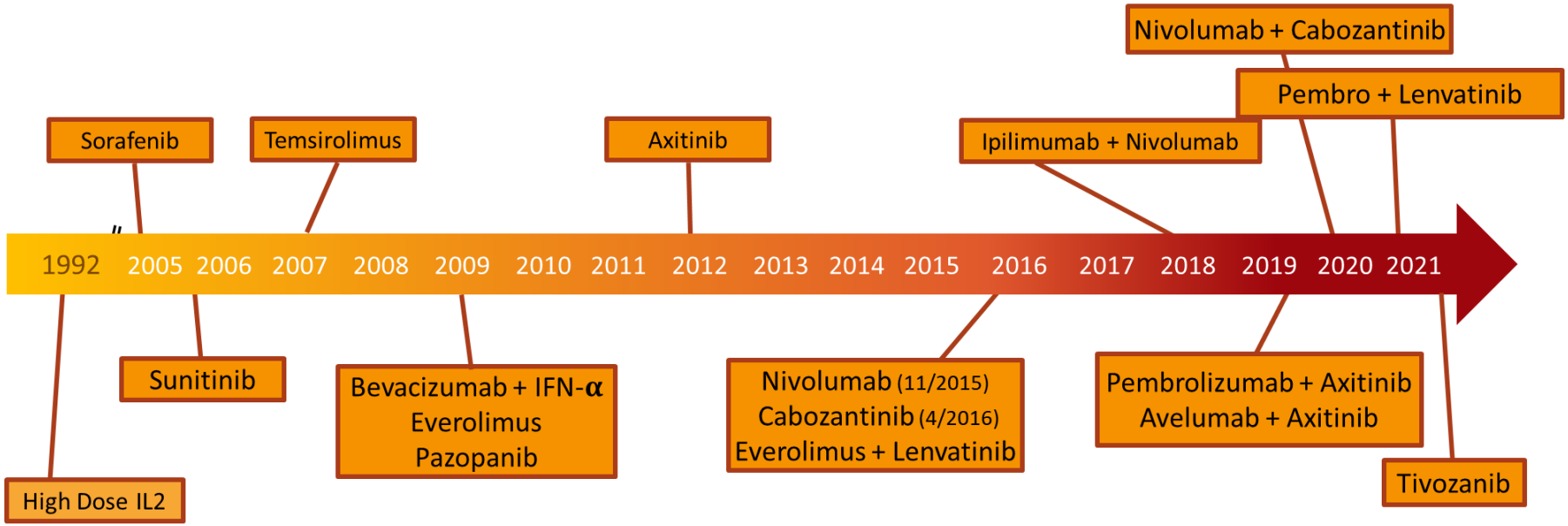
New Cases, Deaths and 5-year Relative Survival





https://seer.cancer.gov/statfacts/html/kidrp.html

Metastatic RCC: Treatment Evolution



NCCN Treatment Guidelines - RCC

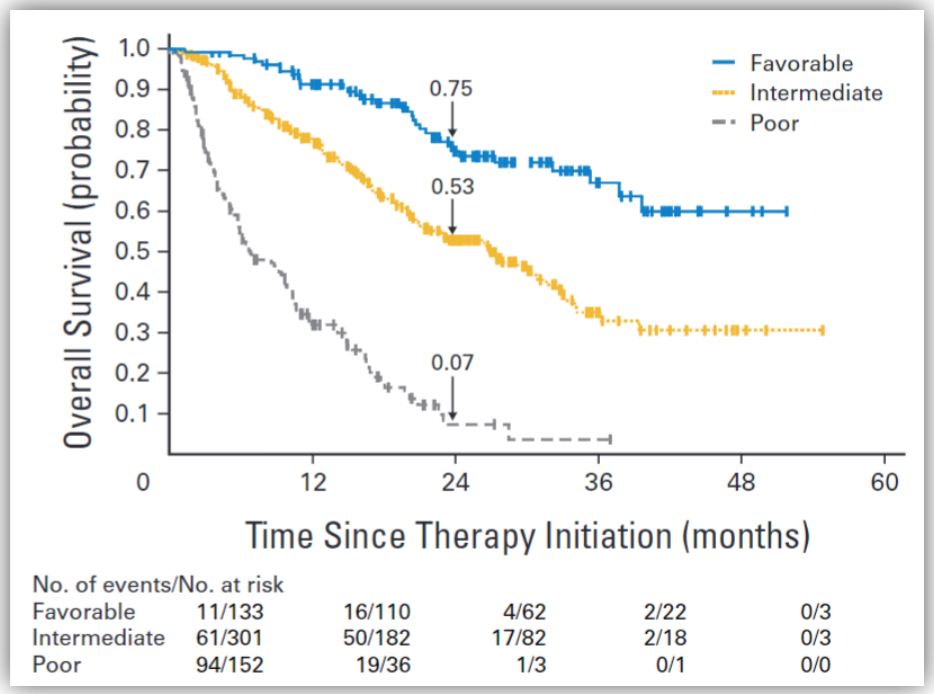
PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	**Preferred Regimens**	**Other Recommended Regimens**	**Useful in Certain Circumstances**
Favorable[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1)	• Axitinib + avelumab[b] • Cabozantinib (category 2B) • Ipilimumab + nivolumab[b] • Pazopanib • Sunitinib	• Active surveillance[c] • Axitinib (category 2B) • High-dose IL-2[d] (category 2B)
Poor/ intermediate[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Ipilimumab + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Cabozantinib	• Axitinib + avelumab[b] • Pazopanib • Sunitinib	• Axitinib (category 2B) • High-dose IL-2[d] (category 3) • Temsirolimus[e] (category 3)

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Cabozantinib (category 1) • Lenvatinib + everolimus • Nivolumab[b] (category 1)	• Axitinib (category 1) • Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b] • Ipilimumab + nivolumab[b] • Lenvatinib + pembrolizumab[b] • Pazopanib • Sunitinib • Tivozanib[g] (category 1) • Axitinib + avelumab[b] (category 3)	• Everolimus • Bevacizumab[f] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Sorafenib (category 3) • Temsirolimus[e] (category 2B) • Belzutifan (category 2B)

IMDC Risk Groups

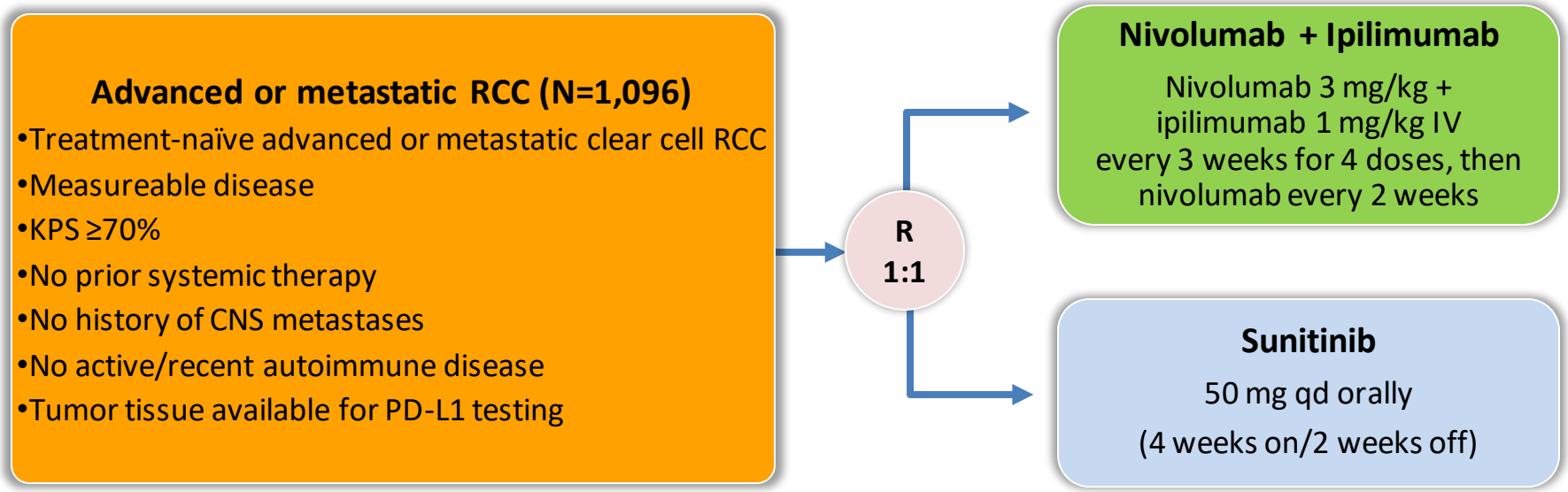
IMDC Criteria	Score
Karnofsky performance score < 80	1
Time from original diagnosis to initiation of systemic therapy <1 year	1
Hemoglobin < LLN	1
Serum calcium > ULN	1
Neutrophil count > ULN	1
Platelet count > ULN	1



Heng JCO 2009;27(34):5794-5799

Risk Group	Score
Good Risk	0
Intermediate Risk	1-2
Poor Risk	3-6

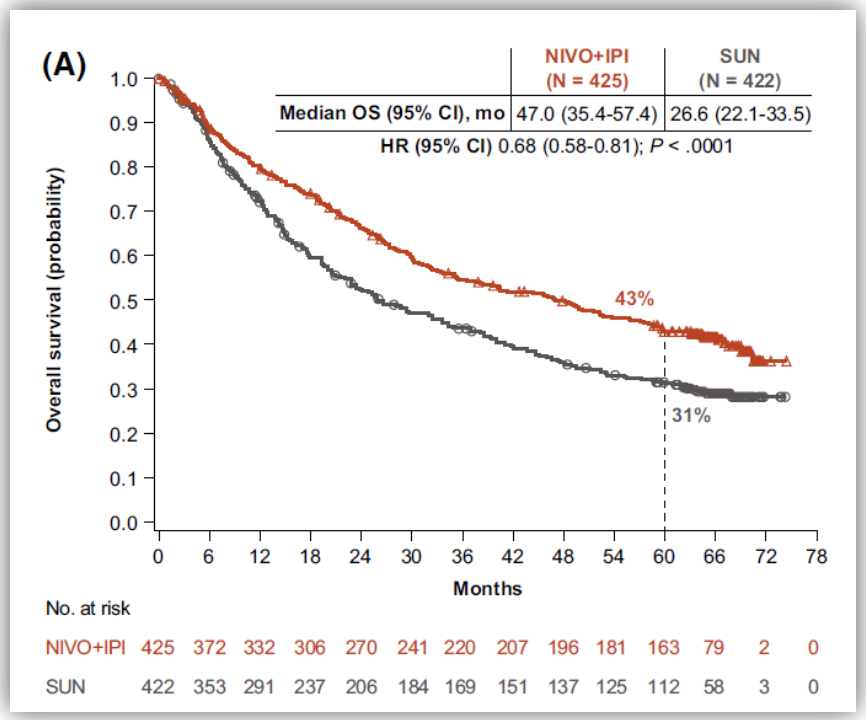
CheckMate 214 Study Design

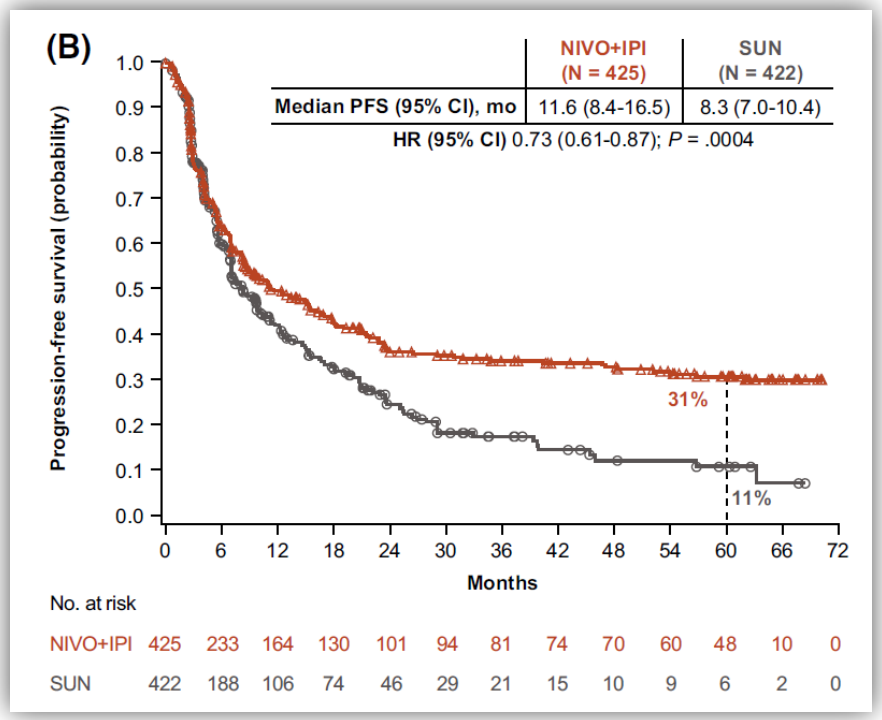


- **Stratification:** IMDC prognostic score (0 vs 1/2 vs 3-6)
- **Co-primary endpoints:** in IMDC intermediate- and poor-risk patients
  - ORR (per IRRC), PFS (per IRRC), and OS
- **Secondary endpoints:** in ITT patients
  - ORR, PFS, OS, and adverse event incidence rate (in all treated patients)

Motzer R. *NEJM*, 2018. 378(14): 1277-1290

CheckMate 214: 5-yr Follow Up





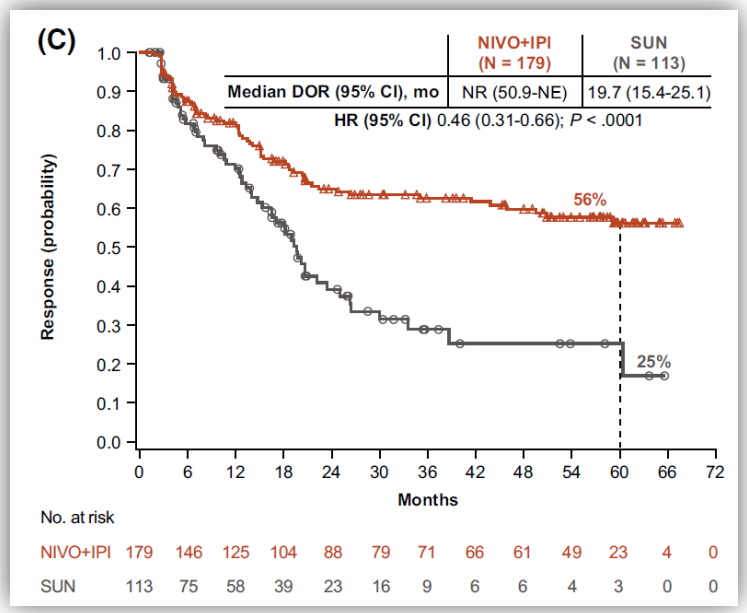
Motzer R, *Cancer* 2022. 128: 2085-2097

CheckMate 214: 5-yr Follow Up

Response assessment	ITT		Intermediate/Poor Risk	
	NIVO+IPI (N = 550)	SUN (N = 546)	NIVO+IPI (N = 425)	SUN (N = 422)
Confirmed ORR (95% CI), %	39.3 (35.2-43.5)	32.4 (28.5-36.5)	42.1 (37.4-47.0)	26.8 (22.6-31.3)
P	.0055		< .0001	
Best overall response, n (%)				
Complete response	64 (11.6)	17 (3.1)	48 (11.3)	9 (2.1)
Partial response	152 (27.6)	160 (29.3)	131 (30.8)	104 (24.6)
Stable disease	198 (36.0)	230 (42.1)	131 (30.8)	187 (44.3)
Progressive disease	97 (17.6)	77 (14.1)	82 (19.3)	71 (16.8)
Unable to determine	38 (6.9)	57 (10.4)	32 (7.5)	48 (11.4)
Not reported	1 (0.2)	5 (0.9)	1 (0.2)	3 (0.7)
Median time to response (Q1–Q3), months	2.8 (2.7-4.0)	4.0 (2.8-5.6)	2.8 (2.6-3.8)	3.1 (2.8-5.4)
Ongoing response, n (%)	N = 216 136 (63.0)	N = 177 89 (50.3)	N = 179 114 (63.7)	N = 113 56 (49.6)
Ongoing complete response, n (%)[a]	N = 64 54 (84.4)	N = 17 15 (88.2)	N = 48 41 (85.4)	N = 9 8 (88.9)

Abbreviations: IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IRRC, independent radiolo to-treat; NIVO+IPI, nivolumab plus ipilimumab; ORR, objective response rate; Q; quartile; RECIST, Response Evaluati sunitinib.

[a]Includes 1 patient in the NIVO+IPI arm and 2 patients in the SUN arm who were censored for progression after startin



Motzer R. *Cancer* 2022. 128: 2085-2097

1st Line mRCC Trials

Regimen/Study	ORR	CR Rate	PR Rate	Primary PD	OS	OS HR	PFS	Median f/u, mo	n
Nivolumab + ipilimumab (CheckMate-214)[1][2]	42% vs 27%	11%	31%	19%	43% vs 31% (in I/P) at 5-yr	0.68	31% vs 11% at 5-yr	67.7	1096
Pembrolizumab + Axitinib (KEYNOTE-426)[3][4]	57% vs 35%	9% [3]	53%	11%	51% vs 38% at 3.5-yr	0.64	38% vs 26% at 2-yr	42.8	861
Nivolumab + Cabozantinib (CheckMate 9ER)[5]	56% vs 28%	12%	43%	6%	70% vs 60% at 2-yr	0.70	40% vs 21% at 2-yr	32.9	651
Lenvatinib + Pembrolizumab (CLEAR)[6]	71% vs 36%	16%	55%	5%	70% vs 66% at 33-mon	0.72	50% vs 20% at 2-yr	33.7	1069
Nivolumab monotherapy (Hoosier group) [7]	34%	6.5%	27.6%	30%	--	--	25% at 2-yr	--	123
Pembrolizumab monotherapy (KEYNOTE-427)[8]	26.7%	4%	35.5%	28%	--	--	19% at 2-yr	--	68
TKIs	33%[9]	< 3%	23-40%	15-18%	--	--	--	--	--

Adapted from @brian_rini and @Uromigos

1. Motzer. *NEJM*. 2018. 2. Motzer, *Cancer* 2022. 3. Rini, ASCO 2021. 4. Powels, *Lancet* 2020. 5. Motzer, *Lancet* 2022.
6. Motzer, *NEJM* 2021. 7. Atkins, ASCO GU 2022. 8. McDermott, *JCO* 2021. 9. Choueiri, *JCO* 2016.

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Patient Characteristics

- Immune Checkpoint Inhibitor Warning/Precautions:
  - Active or significant history of autoimmune disorders
  - Chronic steroid therapy
  - Severe/uncontrolled diabetes mellitus
  - Recent/ongoing antibiotic treatment

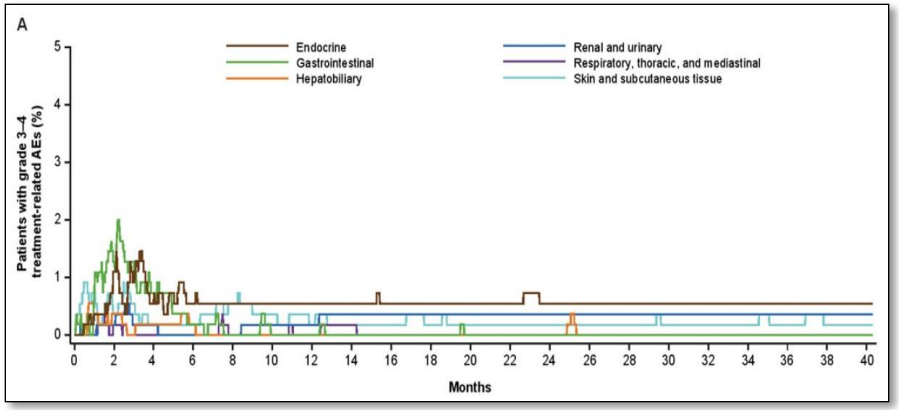
- TKI Warning/Precautions:
  - Uncontrolled hypertension
  - Hemorrhage risk
  - GI bleeding, perforations, or fistula
  - Recent major surgery or concerns for delayed wound healing
  - Proteinuria
  - Cytopenia

Treatment Characteristics & TRAEs

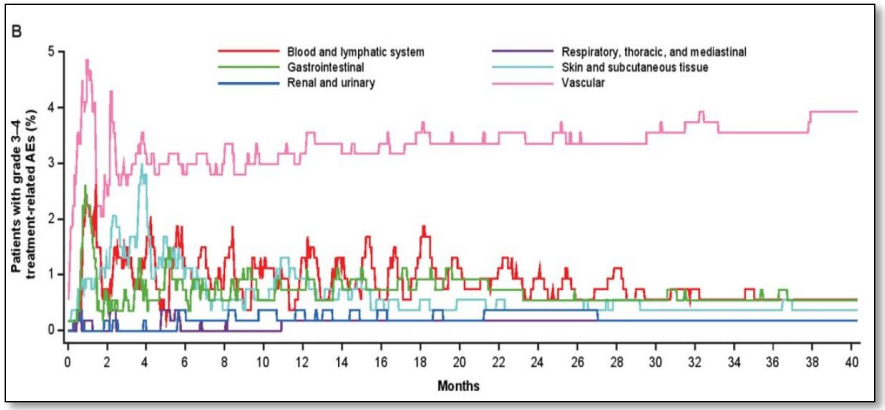
- CheckMate 214:

  Common G3/4 TRAEs over time by system organ class in all treated patients

Ipi/Nivo



Sunitinib



1. Tannir N. ASCO GU 2019

Sarcomatoid Differentiation (sRCC)

- An aggressive form of kidney cancer with poor prognosis
- Sarcomatoid differentiation can lead to loss of RCC markers (CAIX, CD10, PAX8)
- Doxorubicin-based chemo has been used with limited response.
- TKIs or mTOR-inh alone or in combination with chemo has not been more effective.
- sRCC is an inflamed tumor and an immune responsive disease.
- Treatment of sRCC should include ICIs if it is not contraindicated.
- Ipi/Nivo is my preferred regimen if the patient is not very symptomatic.

Table 3

Post hoc analysis of Phase III trials on Immunotherapy combination for Sarcomatoid Renal Cell Carcinoma

Study	Investigational therapy	Comparator arm	*N* (% sRCC)	ORR (CR)	12-month OS	PFS	OS
CheckMate 214 [69]	Ipilimumab + Nivolumab	Sunitinib	74 (18.2%)	61% (19%)	84%	26.5 months	Not reached
KEYNOTE 426 [72]	Axitinib + Pembrolizumab	Sunitinib	51 (18.2%)	59% (12%)	83%	Not reached	Not reached
JAVELIN Renal 101 [75]	Axitinib + Avelumab	Sunitinib	47 (12.2%)	47% (4%)	83%	7 months	NR
IMmotion 151 [76]	Atezolizumab + Bevacizumab	Sunitinib	68 (16%)	49% (10%)	56 %	8.3 months	21.7 months
Checkmate 9ER [77]	Nivolumab + Cabozantinib	Sunitinib	75 (11.5%)	55.9% (CR not reported)	NR	10.9 months	Not reached

ORR: Overall response rate; CR: Complete response; PFS: progression free survival; OS: overall survival; %: percentage of overall population; NR: Not reported.

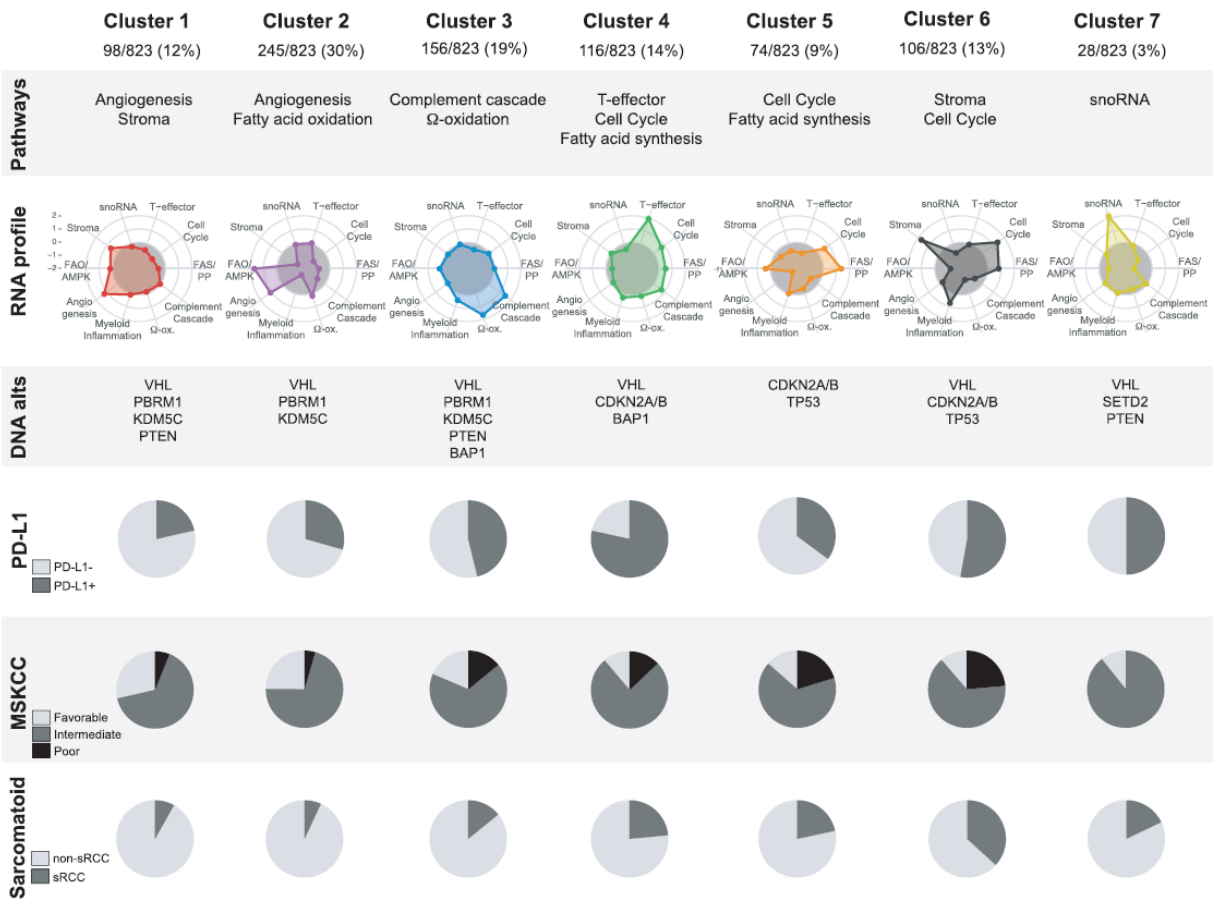
Candelario , *Kidney Cancer* 2021. 167-179

Treatment Selection for mRCC

- Combination regimens (IO/IO or IO/TKI) should be used in the first line setting unless it is contraindicated.
- IO/IO and IO/TKI are all great options for first-line treatment in mRCC.
- The longest duration of follow up (67.7 months) is available for Ipi/Nivo.
- Ipi/Nivo has an impressive 5-year PFS of 31% and OS of 43%for Ipi/Nivo.
- IO/TKI combinations have a higher ORR and a lower primary PD rate which makes them a very suitable option for patients with high volume and symptomatic disease.
- Presence of sarcomatoid features (sRCC) corelate with good response to ICIs and these agents should be a part of treatment regimen.
- Subgroup of patients with sRCC had an outstanding ORR and CR with Ipi/Nivo
- Patient characteristics, treatment related side effects, and impact on QoL should be considered in the process of selecting the best treatment regimen for each patient.
- Predictive biomarkers are needed to guide our treatment selection for patients with mRCC.

Biomarker Development

- Biomarker studies based on specimens from 823 tumors from aRCC patients enrolled in IMmotion151 trial (Atezolizumab + Bevacizumab vs Sunitinib)

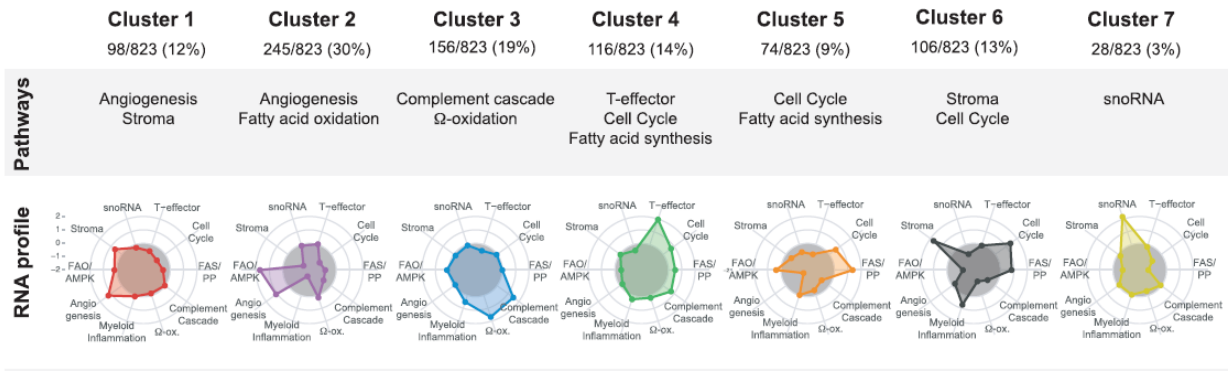


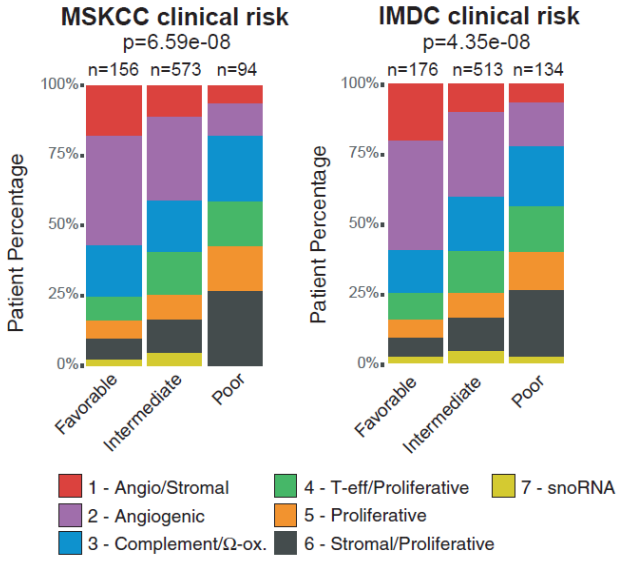
Motzer R. *Cancer Cell*, 2020

Biomarker Development

- Biomarker studies based on specimens from 823 tumors from aRCC patients enrolled in IMmotion151 trial (Atezolizumab + Bevacizumab vs Sunitinib)

- There is significant heterogeneity in clinical risk groups





Motzer R. *Cancer Cell*, 2020

Metastatic Papillary RCC

- SWOG 1500: Phase II trial comparing Sunitinib with Cabozantinib, Crizotinib, and Savolitinib
- Sunitinib 50 mg PO 4/2 w schedule
- Cabozantinib 60 mg PO daily
- Assignment to the savolitinib (29 patients) and crizotinib (28 patients) groups was halted after a prespecified futility analysis.

Outcome, %	Cabozantinib (n = 44)	Sunitinib (n = 46)
ORR*	23	4
▪ CR	5	0
▪ PR	18	4
▪ Unconfirmed PR	5	2
▪ SD	51	50
▪ PD	9	24
PFS*		
▪ Median PFS, mos	9.0	5.6
▪ 95% CI	6.0-12.0	3.0-7.0
OS		
▪ Median OS, mos	20.0	16.4
▪ 95% CI	11.0-NR	13.0-22.0

1. Pal S. ASCO GU 2021 2. Pal S. *Lancet* 2021. 695-703

Trials in Progress

- COSMIC-313:
  - NCT03937219
  - Ipi/Nivo/Cabo vs Ipi/Nivo
  - Press release: Met the primary endpoint of PFS

- PDIGREE (A031704):
  - NCT03793166
  - An adaptive, randomized, phase III trial
  - Ipi/Nivo x 4 → Patients with PR or SD will be randomized to Nivo vs Cabo/Nivo

Belzutifan (HIF-2α inhibitor)

- Pathogenic VHL variants reduce VHL protein activity which results in stabilization of HIF subunits, independent of oxygen concentrations.
- HIF-mediate transcription facilitates VEGF gene expression.
- HIF inhibition will inhibit tumor growth in RCC
- FDA approved Belzutifan in 2021 for patients with VHL associated RCC.

Ongoing phase III clinical trials in advanced RCC:

Status	Study Title	Conditions	Interventions
Active, not recruiting	A Study of **Belzutifan** (**MK-6482**) Versus Everolimus in Participants With Advanced **Renal Cell Carcinoma** (**MK-6482**-005)	• **Carcinoma**, **Renal Cell**	• Drug: **Belzutifan** • Drug: Everolimus
Recruiting	A Study of **Belzutifan** (**MK-6482**) in Combination With Lenvatinib Versus Cabozantinib for Treatment of **Renal Cell Carcinoma** (**MK-6482**-011)	• **Carcinoma**, **Renal Cell**	• Drug: **Belzutifan** • Drug: Lenvatinib • Drug: Cabozantinib
Recruiting	A Study of Pembrolizumab (MK-3475) in Combination With **Belzutifan** (**MK-6482**) and Lenvatinib (MK-7902), or Pembrolizumab/Quavonlimab (MK-1308A) in Combination With Lenvatinib, Versus Pembrolizumab and Lenvatinib, for Treatment of Advanced Clear **Cell Renal Cell Carcinoma** (**MK-6482**-012)	• **Carcinoma**, **Renal Cell**	• Biological: Pembrolizumab • Drug: **Belzutifan** • Biological: Pembrolizumab/Quavonlimab • Drug: Lenvatinib

Adjuvant Therapy for Renal Cell Carcinoma

- Radical nephrectomy is the standard of care treatment for localized RCC.
- Rate of disease recurrence after nephrectomy is about 50%.
- Adjuvant therapy with VEGR-receptor TKIs has not shown a consistent benefit.
  - ASSURE
  - S-TRAC*
  - PROTECT
  - SORCE
  - EVEREST
  - ATLAS

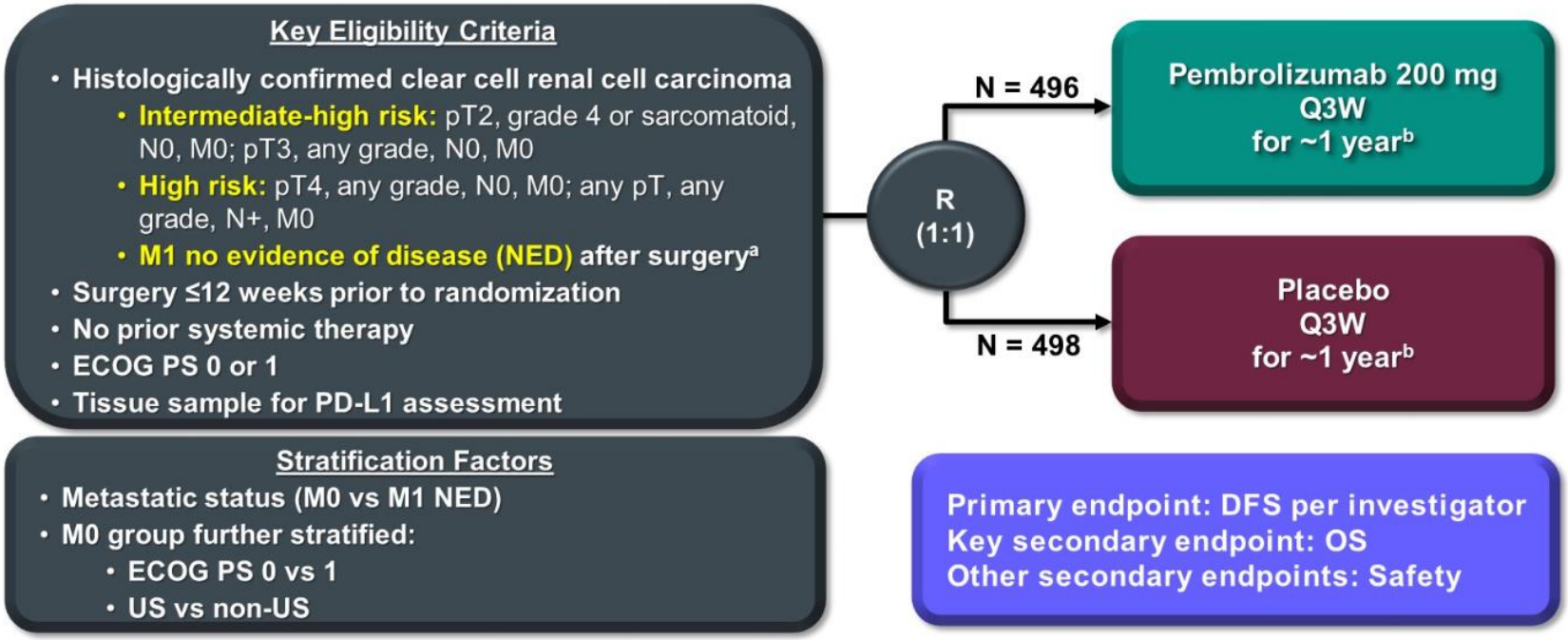
- Studies evaluating the role of immune checkpoint inhibitors:
  - KEYNOTE-564*
  - PROSPER RCC
  - IMmotion 010
  - CheckMate 914
  - RAMPART

Peri-operative ICI Therapy in RCC

	KEYNOTE-564*	PROSPER RCC	IMmotion 010	CheckMate 914	RAMPART (UK based)
ICI	Pembrolizumab	Nivolumab	Atezolizumab	Nivo Ipi + Nivo	Druva Durva + Treme
Comparator arm	Placebo	Observation	Placebo	Placebo	Observation
Eligibility	T2 (G4) N0 M0 T3 (Gx) N0 M0 T4 (G any) N0 M0 Tx (G any), N+ M0 M1-NED	T2-4 Nx M0 Tx N1-2 M0 *M1-NED (added later)	T2 (G4) N0 M0 T3a (G3-4) N0 M0 T3b-4 (G any) N0 M0 Tx (G any) N+ M0 M1-NED	T2a (G3-4) N0 M0 T2b-4 (G any) N0 Tx (G any) N1 M0	Leibovich score 3-11 pT2 or higher Resected Adrenal met allowed
Histology	Clear cell	Any	Clear cell	Clear cell	Any
Patient #	994	805	664	800	1750
Primary endpoint	DFS	DFS	DFS	DFS	DFS and OS

Adjuvant Treatment in RCC

KEYNOTE-564 (NCT03142334) Study Design

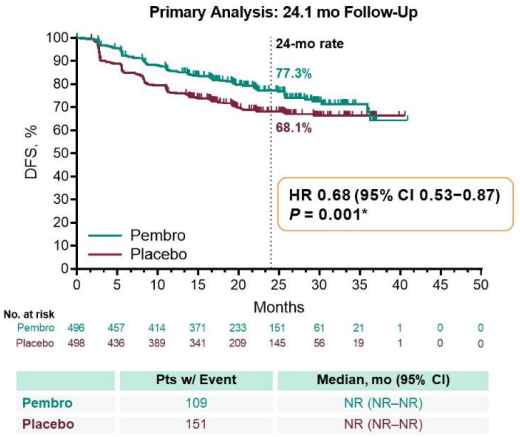


- Median (range) time from randomization to cutoff: 30.1 (20.8–47.5) months

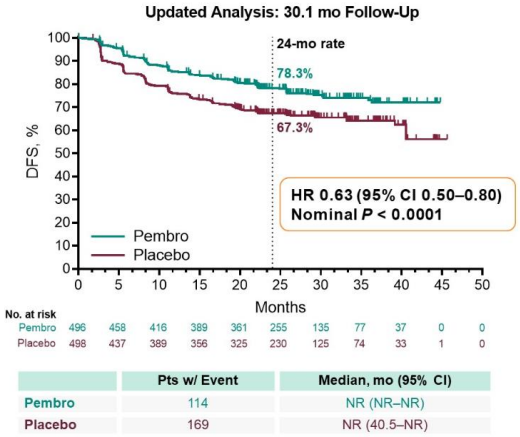
Q3W, every 3 weeks.
[a]M1 NED: no evidence of disease after primary tumor + soft tissue metastases completely resected ≤1 year from nephrectomy; [b]≤17 cycles of treatment were equivalent to ~1 year.
Data cutoff date: June 14, 2021.

KEYNOTE-564: 30-months Results

Primary Endpoint: DFS, ITT Population

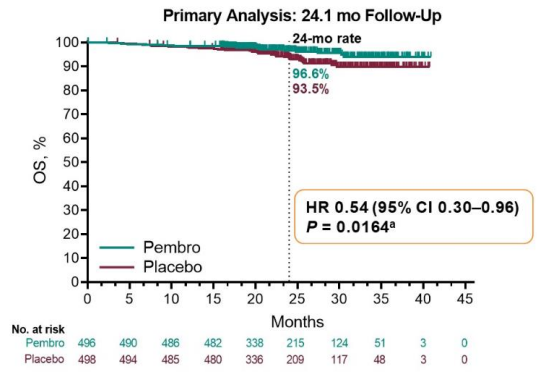


	Pts w/ Event	Median, mo (95% CI)
Pembro	109	NR (NR–NR)
Placebo	151	NR (NR–NR)

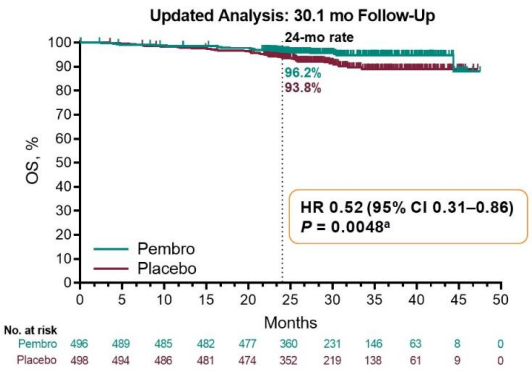


	Pts w/ Event	Median, mo (95% CI)
Pembro	114	NR (NR–NR)
Placebo	169	NR (40.5–NR)

Key Secondary Endpoint: OS, ITT Population



	Pts w/ Event	Median, mo (95% CI)
Pembro	18	NR (NR–NR)
Placebo	33	NR (NR–NR)

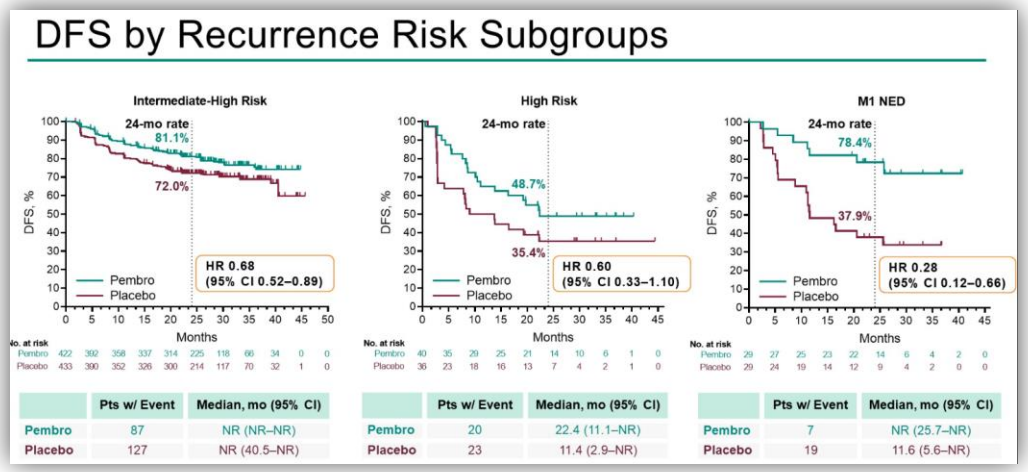


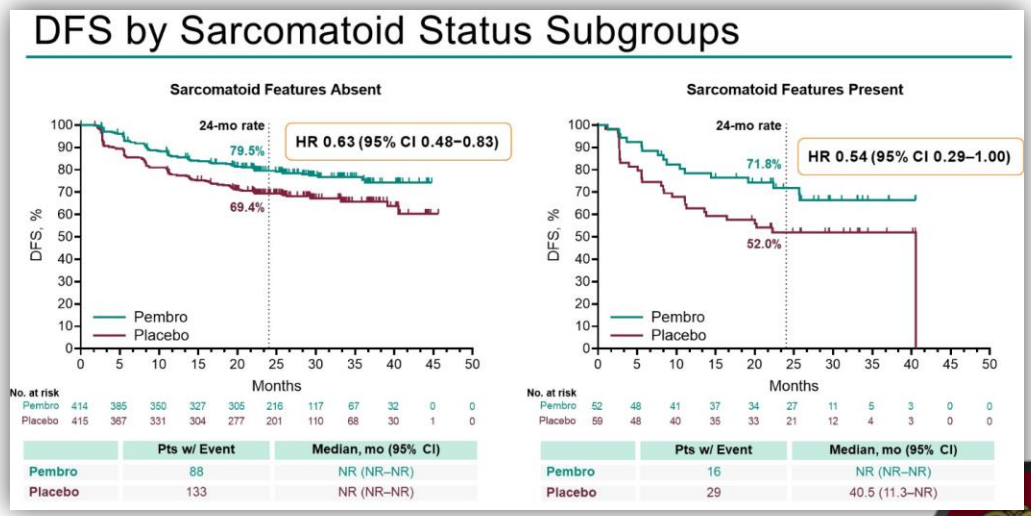
	Pts w/ Event	Median, mo (95% CI)
Pembro	23	NR (NR–NR)
Placebo	43	NR (NR–NR)

KEYNOTE-564: DFS in Subgroups

- **Intermediate-high risk:**
  pT2, G4 or Sarcomatoid, N0, M0,; pT3, any grade, N0, M0
- **High risk:**
  pT4, any grade, N0, M0,; any pT, any grade, N+, M0
- **M1-NED:**
  mets resected ≤ 1yr form nephrectomy

- Presence of Sarcomatoid features





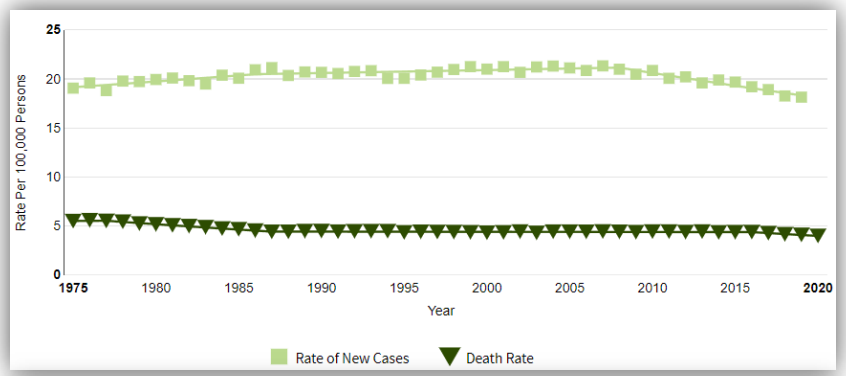
RCC Take Home Points

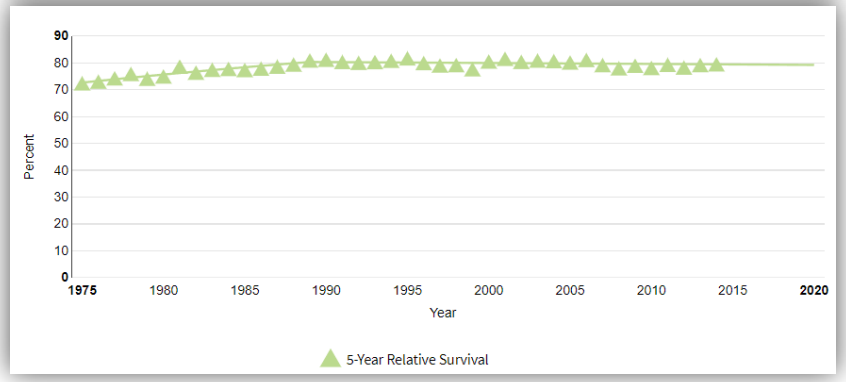
- Immunotherapy/Immune checkpoint inhibitors have revolutionized the treatment of mRCC.
- Combination regimens should be used in the first line setting unless it is contraindicated.
- IO/IO and IO/TKI combinations are all great options for first-line treatment in mRCC.
- Presence of sarcomatoid features seems to corelate with good response to immune checkpoint inhibitors and ICIs should be a part of treatment regimen.
- I (personal opinion) prefer TKI/IO combination for patients with higher volume, symptomatic, or rapidly progressing disease.
- Predictive biomarkers are needed and should be included in all prospective trial designs.
- Appropriate/relevant regimens should be considered as control arm (Sunitinib is NOT considered 1st-line SOC anymore!)
- Treatment free survival should be considered in the design of future clinical trials.
- Development of predictive biomarkers should be a priority.
- Adjuvant pembrolizumab is FDA approved for int/high and high risk disease post nephrectomy.
- Three other peri-operative or adjuvant trials didn't meet their primary endpoints.

Bladder Cancer

- Bladder cancer 2022 estimates[1]:
  - New cases: 81180 (4.2% of all new cancer cases)
  - Death from bladder cancer: 17100
- Urothelial carcinoma is the predominant histologic type (>90%)

- Rates for new bladder cancer cases have been falling on average 1.3% each year over 2010–2019.
- Age-adjusted death rates have been falling on average 1.1% each year over 2011–2020.
- 5-year survival rates have remained stable in the range of 79-80% since 1988.





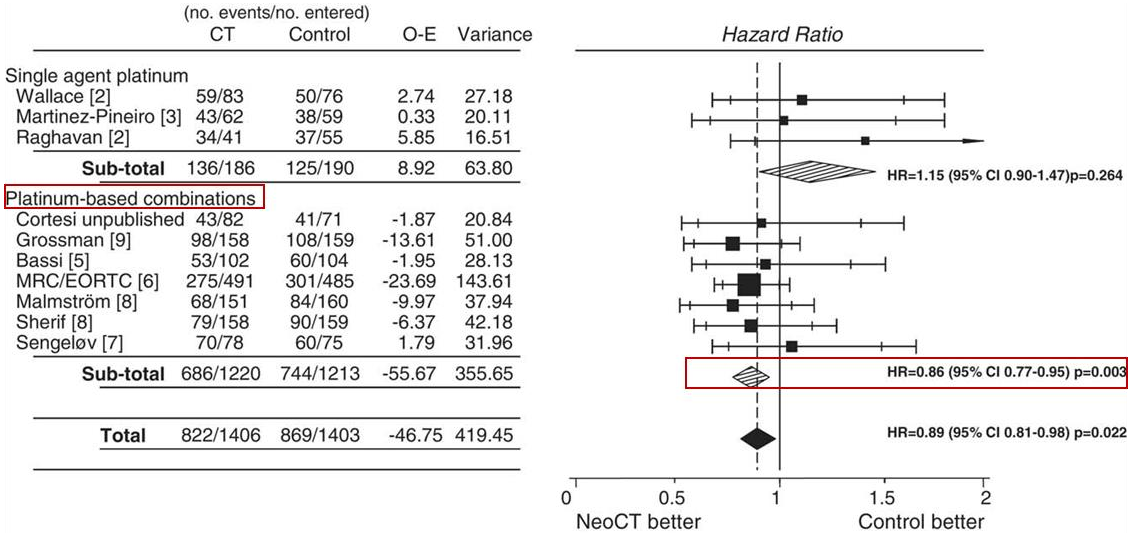
1. https://seer.cancer.gov/statfacts/html/urinb.html

Peri-Operative Treatment in MIBC

- Radical cystectomy remains the gold standard curative intent treatment for MIBC
- The risk of recurrence in MIBC treated with RC alone is high and stage-dependent

➢ **Neoadjuvant Chemotherapy:**

- EORTC trial[1]: 976 pts, CMV x 3 vs no chemo, absolute diff in 10-yr survival of 6%
- Intergroup trial[2,3]: 317 pts, MVAC x 3 vs no chemo, absolute diff in 5-yr survival of 14%
- Meta analysis[4]: 3005 pts from 11 randomized trials, absolute diff in 5-yr survival of 5%



1. EORTC. J Clin Oncol, 2171-7, (2011)
2. Grossman, H. B. N Engl J Med 349, 859-866, doi:10.1056/NEJMoa022148 (2003).
3. Sonpavde, G. Cancer 115, 4104-4109, doi:10.1002/cncr.24466 (2009)
4. Eur Urol 48, 202-205; discussion 205-206, (2005)

Peri-Operative Treatment in MIBC

- **Neoadjuvant Chemotherapy; MVAC vs Gem/Cis**:
  - ✓ Retrospective studies:
    - MSKCC retrospective study2:
      - GC Q3w x 4 compared to historical cohort treated with MVAC
      - pT0: 26% in GC treated pts vs 28% in MVAC historical cohort
    - Retrospective international trial3:
      - 212 pts treated with GC (n=146) or MVAC (n=66)
      - pCR: 31% in GC vs 29% in MVAC cohort
    - Retrospective international trial4:
      - 935 pts. GC (n=602), MVAC (n=183), Other regimens (n=144)
      - pT0N0: 23.9 % in GC vs 24.5% in MVAC cohort

No significant difference between MVAC and GC.

1. Dash, A. Cancer 113, 2471-2477, (2008)
2. Galsky, M. D. Cancer 121, 2586-2593, (2015)
3. Zargar, H. Eur Urol 67, 241-249, (2015)

Peri-Operative Treatment in MIBC

- **Neoadjuvant Chemotherapy; MVAC vs Gem/Cis**:
  - ✓ Prospective studies:

    - SWOG1314:[1]
      - Phase 2 randomized trial, GC x4 (82 pts) vs ddMVAC x4 (85 pts)
      - Primary endpoint to evaluate the role of COXEN score in treatment selection
      - The COXEN score was not able to predict benefit in selecting the best regimen.
      - Trial was NOT powered to compare ddMVAC vs GC
      - The proportion of pCR was comparable in both arms (30% vs 28%)

    - VESPER trial:[2]
      - Phase 3 randomized trial, GC vs ddMVAC, allowed both neoadjuvant or adjuvant treatment
      - 12 weeks of treatment duration with either regimen
      - 437 pts had NAC with GC (219) and ddMVAC (218)
      - 3-yr PFS was better but didn't meet the prespecified primary endpoint significance
      - 3-yr PFS was higher with ddMVAC for the NAC group but this wasn't the primary endpoint.
      - OS results are not mature at this time but might indicate benefit.
      - Is the improvement in PFS due to added drugs or greater number of cycles?

1. Flaig T. *Clinical Cancer Research* 27, 2435–2441 (2021)
2. Pfister S. *JCO* 40, 2013–2022 (2022)

Peri-Operative Treatment in MIBC

- **Adjuvant Chemotherapy**:
  - ✓ Prospective studies:
    - Multiple trials stopped early due to slow accrual
    - EORTC 30994:[1] stopped after enrolling 284 of planned 660 pts. 5-yr PFS 47.6% vs 31.8%
  - ✓ Meta-Analysis:
    - 2004 Meta-analysis:[2]
      - 491 pts from 6 trials
      - HR for survival of 0.75
    - 2014 Meta-analysis:[3]
      - 945 pts from 9 trials
      - HR for survival of 0.77

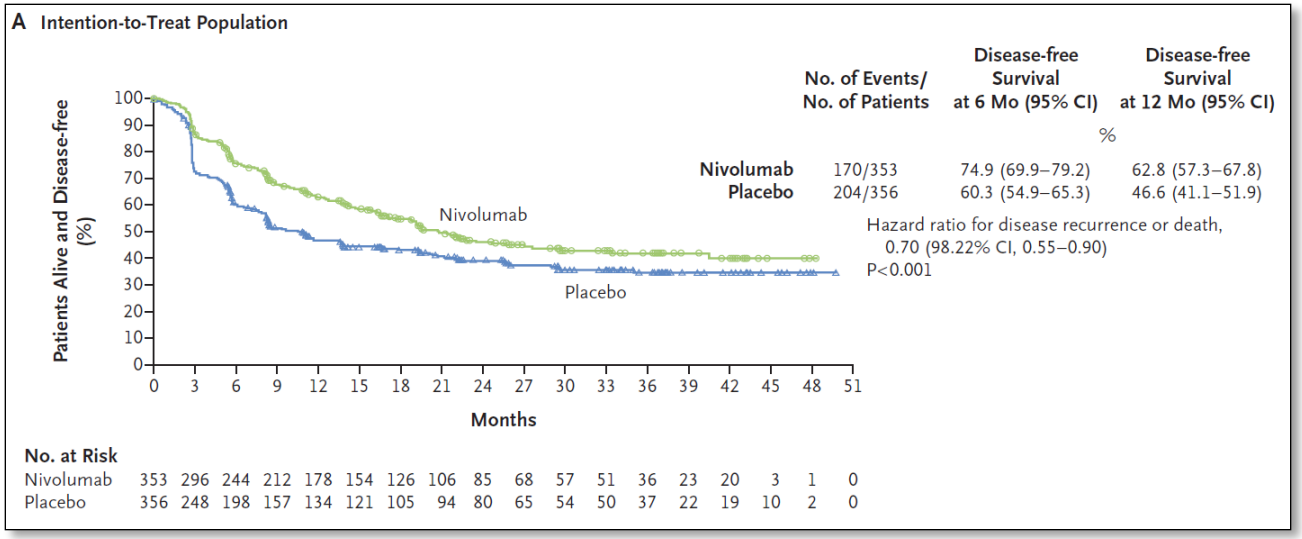
1. Sternberg C. *Lancet* 16(1):76-86 (2015)
2. ABC Meta-analysis, *Eur Urol* 48: 189-199, (2005)
3. Leow, J.J. *Eur Urol* 66: 42-54, (2014)

Peri-Operative Treatment in MIBC

- **Adjuvant immunotherapy**:
  - CheckMate-274 trial:

✓ FDA approved August 2021

    - Phase 3 randomized, Nivolumab vs placebo for up to 1 year
    - High-risk MIBC post RC:
      - ypT2-ypT4a or ypN+ who received NAC
      - pT3-pT4a or pN+ who did not receive NAC and were ineligible for/refused adj Cis chemo
    - Primary endpoint: DFS in ITT
    - Results: DFS 21 vs 11 mon (HR 0.7 CI: 0.54-0.89)



1. Bajorin D. *NEJM* 2021; 384: 2102-14

Systemic Treatment of met UC

Cytotoxic Chemotherapy for Platinum Fit Patients:

- Cisplatin fit patient:
  - GC (Gemcitabine, Cisplatin)
  - ddMVAC
  - MVAC (Methotrexate, Vinblastine, Doxorubicin, Cisplatin)
  - TCG (Taxol, Cisplatin, Gemcitabine)

- Cisplatin unfit patient:
  - Gemcitabine + Carboplatin
  - Atezolizumab
  - Carboplatin + Paclitaxel

Immune Checkpoint Inhibitors (ICI)

Platinum unfit – 1st line

ICI	Phase	n	Obj RR (%)	Med OS	Med Duration of Resp
Pembrolizumab	II	370	29% (CR=9%)	11.3 mon (3-yr OS=22%)	33 mon
Atezolizumab	II	119	23% (CR=9%)	16 mon	--

Platinum refractory – 2nd line

ICI	Trial/Phase	n	Obj RR (%)	Med OS
Pembrolizumab[1]	KN-045: Ph III	542	21.1% (CR: 9.3%)	10 vs 7.3
Avelumab[2]	JAVELIN: Ph Ib	242	16.5% (CR: 4%)	7
Nivolumab[3]	CM275: Ph II	265	21% (CR: 6.7%)	8.6
Atezolizumab[2,5]	IMvigor211: Ph III	931	13% (CR: 3%)	11.1
Durvalumab[6,7]	DANUBE: Ph III	1032	26% (CR: 8%)	13.2

FDA approval for 2nd-line indication for Atezolizumab and Durvalumab were voluntarily withdrawn in 2021.

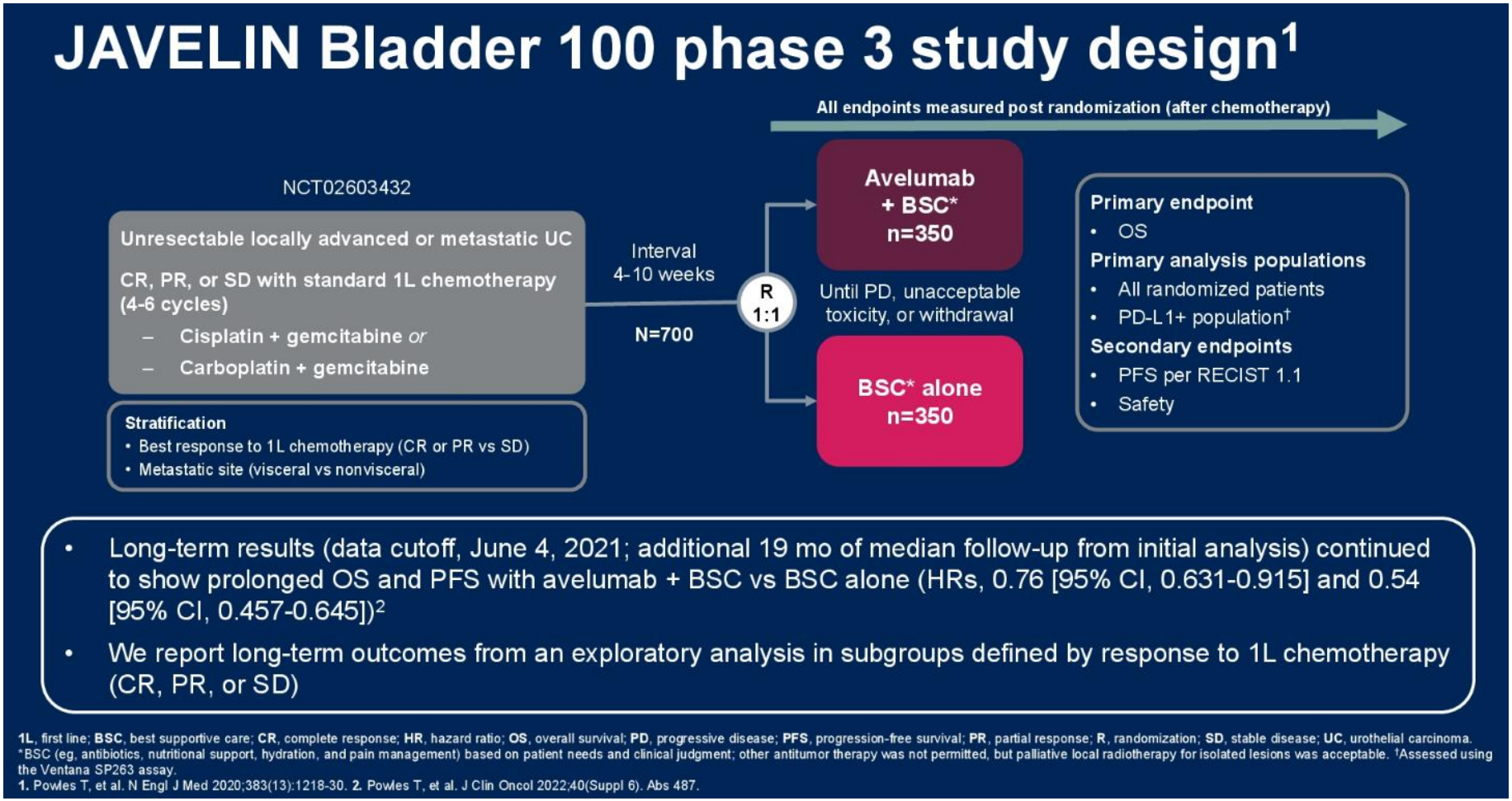
1. Fradet Y. *Annal of Onc* 2019 2. Apolo A. *JITC* 2020 *3. Galsky M. Clin Ca Res 2020* *4.* Van der Heijden M. *Eur Uro* 2021
5. Powles T. *Lancet* 2018 6. Powles T. *JAMA Onc 2017* *7.* Powles T. *Lancet 2020*

Chemo-ICI Combination Trials

- KEYNOTE-361 (NCT02853305) [1]
  - ~~Pembrolizumab~~ vs ~~Pembrolizumab+Gem+Platinum~~ vs Chemo alone
- IMvigor 130 (NCT02807636)[2]
  - ~~Atezolizumab~~ vs ~~Atezolizumab+Gem+Platinum~~ vs Chemo alone
- DANUBE (NCT02516241) [3]
  - ~~Durvalumab~~ vs ~~Durvalumab+Tremelimumab~~ vs Chemo alone
- CheckMate 901 (NCT03036098) [4]
  - ~~Nivo+Ipi~~ vs Nivo+Gem+Cis vs Chemo alone
- NILE (NCT03682068) [5]
  - Durvalumab+Chemo vs Druvalumab+Tremelimumab+Chemo vs Chemo alone

1. Powles T. *Lancet* 2021 2. Galsky M. *Lancet* 2020 3. Powles T. *Lancet* 2020 4. BMS news, press release in May 2022
5. Galsky M. ASCO GU 2021 TPS504

ICI Maintenance: Javelin Bladder 100



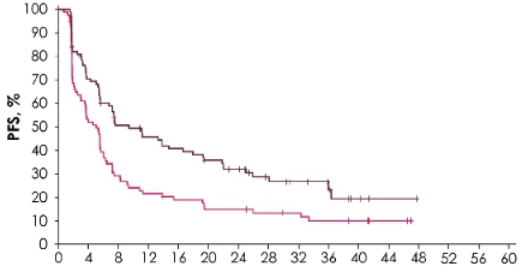
1. Seidhar ASCO GU 2022

Javelin Bladder 100: PFS

Long-term follow-up continues to show prolonged PFS with avelumab + BSC vs BSC alone irrespective of best response to 1L chemotherapy

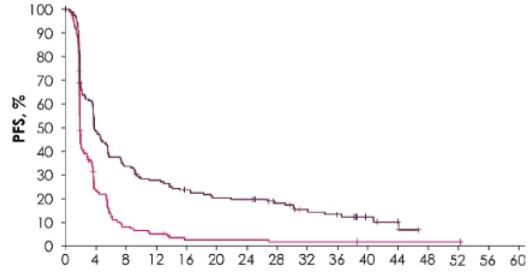
Investigator-assessed progression-free survival

Complete response



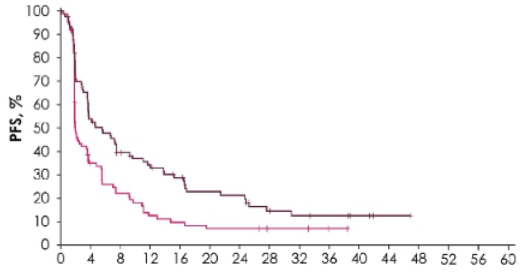
	Avelumab + BSC (n=90)	BSC alone (n=89)
Events, n (%)	63 (70.0)	70 (78.7)
PFS, median (95% CI), mo	9.5 (5.7-16.6)	5.1 (3.0-5.7)
Unstratified HR (95% CI)	0.58 (0.410-0.817)	

Partial response



	Avelumab + BSC (n=163)	BSC alone (n=163)
Events, n (%)	134 (82.2)	140 (85.9)
PFS, median (95% CI), mo	3.8 (3.7-5.6)	1.9 (1.9-2.1)
Unstratified HR (95% CI)	0.47 (0.367-0.607)	

Stable disease



	Avelumab + BSC (n=97)	BSC alone (n=98)
Events, n (%)	71 (73.2)	77 (78.6)
PFS, median (95% CI), mo	5.6 (3.7-7.5)	2.0 (1.9-3.6)
Unstratified HR (95% CI)	0.59 (0.421-0.816)	

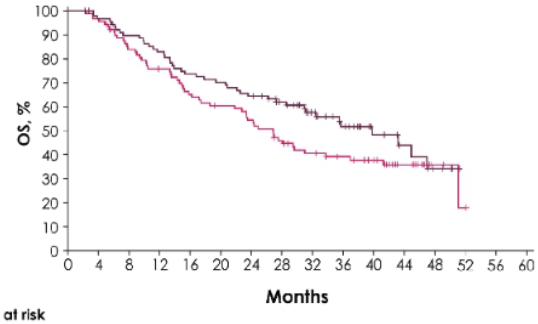
1. Seidhar ASCO GU 2022

Javelin Bladder 100: OS

Long-term follow-up continues to show prolonged OS with avelumab + BSC vs BSC alone irrespective of best response to 1L chemotherapy

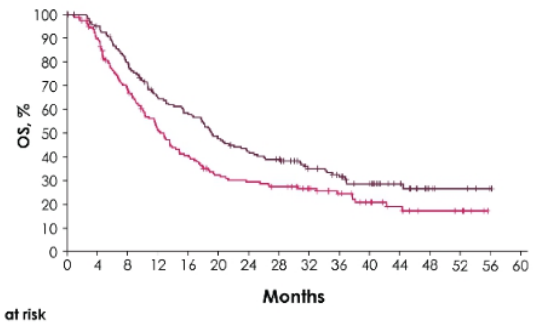
Overall survival

Complete response



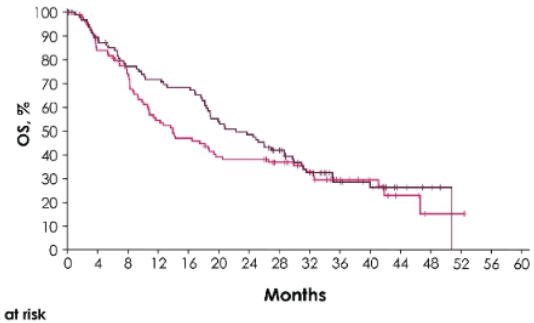
	Avelumab + BSC (n=90)	BSC alone (n=89)
Events, n (%)	43 (47.8)	54 (60.7)
OS, median (95% CI), mo	39.8 (28.5 NE)	26.8 (18.5 33.6)
Unstratified HR (95% CI)	0.72 (0.482-1.076)	

Partial response



	Avelumab + BSC (n=163)	BSC alone (n=163)
Events, n (%)	108 (66.3)	117 (71.8)
OS, median (95% CI), mo	19.2 (16.0-23.8)	12.8 (10.3-14.8)
Unstratified HR (95% CI)	0.70 (0.541-0.914)	

Stable disease



	Avelumab + BSC (n=97)	BSC alone (n=98)
Events, n (%)	64 (66.0)	66 (67.3)
OS, median (95% CI), mo	22.3 (18.2-28.8)	14.0 (10.6-19.6)
Unstratified HR (95% CI)	0.84 (0.596-1.188)	

1. Seidhar ASCO GU 2022

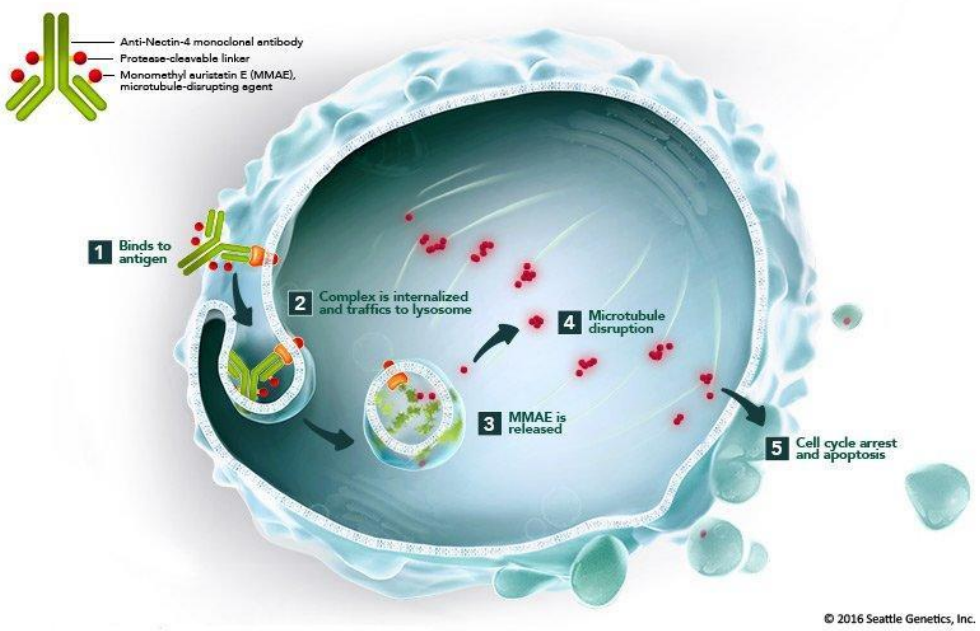
Other Treatment Options

- **Antibody-Drug Conjugates:**
  - Enfortumab Vedotin
  - Sacituzumab Govitecan

- **FGFR inhibitor:**
  - Erdafitinib

Enfortumab Vedotin

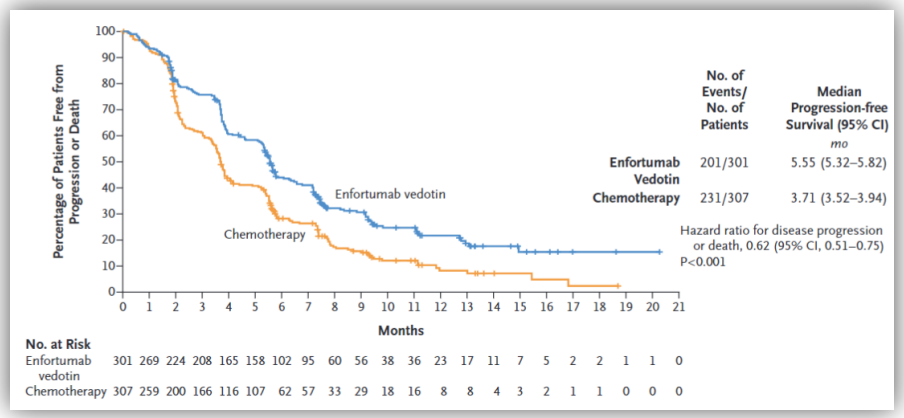
- Initially FDA approved based on the results of EV-201 phase II trial
- Post platinum-based chemo and ICI
- ORR of 44% with CR of 12%
- Med PFS of 5.8 mon
- Med OS of 11.7 mon

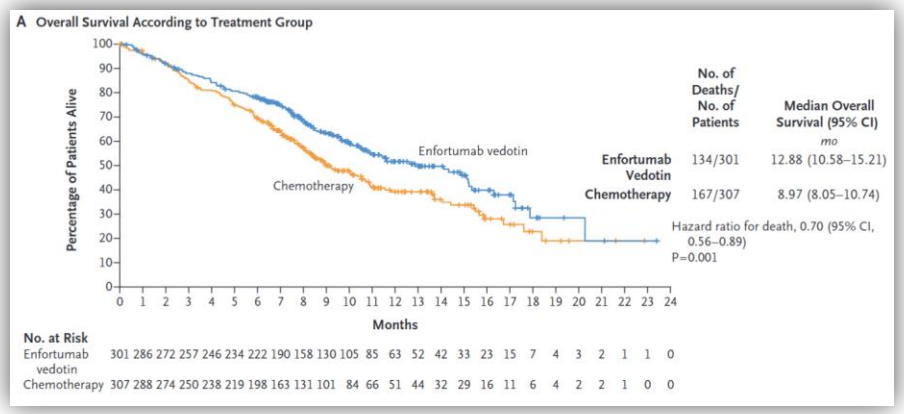


Enfortumab Vedotin: EV-301

- Phase III randomized EV vs chemo
- Post platinum and ICI
- 608 pts randomized

Outcome	Enfortumab Vedotin	Chemotherapy
Median, mos	**n = 301**	**n = 307**
OS (primary endpoint)	12.88	8.97
▪ HR for OS	0.70 (95% CI: 0.56-0.89; *P* = .00142)	
PFS	5.55	3.71
▪ HR for PFS	0.62 (95% CI: 0.51-0.75; *P* < .00001)	
Response, %	**n = 288**	**n = 296**
Confirmed ORR	40.6	17.9
▪ CR	4.9	2.7
▪ PR	35.8	15.2
DCR	71.9	53.4





1. Rosenberg J, ASCO 2022
2. Powles T, NEJM 2021

Enfortumab Vedotin: EV-301

- Treatment related AEs:
  - Peripheral neuropathy
  - Alopecia
  - Fatigue
  - Rash maculopapular
  - Pruritus
  - Cytopenias
  - Diarrhea
  - Nausea

TRAE, %	Enfortumab Vedotin (n = 296)		Chemotherapy (n = 291)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Skin reactions	47	15	16	1
▪ Rash	44	15	10	0*
▪ Severe cutaneous adverse reactions	20	5	8	1
Peripheral neuropathy	46	5	31	2
▪ Sensory	44	4	30	2
▪ Motor	7	2	2	0
Hyperglycemia	6	4	0*	0

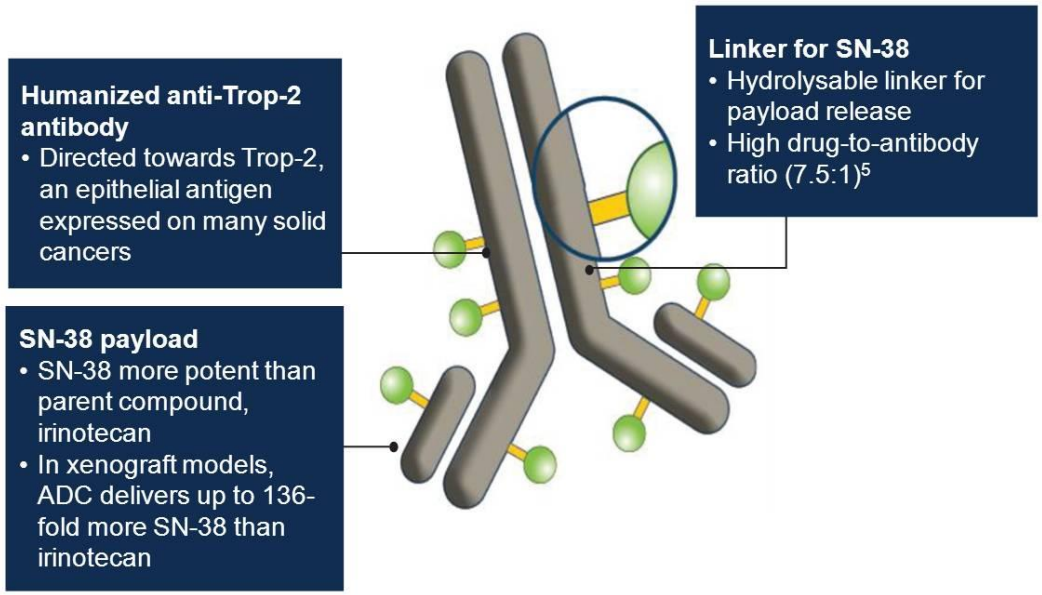
1. Rosenberg J, ASCO 2022
2. Powles T, NEJM 2021

Sacituzumab Govitecan

mUC results in IMMU-132-01 Study

Sacituzumab Govitecan is a Trop-2-Directed Antibody-Drug Conjugate (ADC)

- Trop-2 is an epithelial cell surface antigen highly expressed in UC[1].
- Sacituzumab govitecan is distinct from other ADCs:[2-6]
  - High drug-to-antibody ratio[5]
  - Hydrolysis of the linker releases the SN-38 cytotoxic intracellularly and in the tumor microenvironment. Thus, Sacituzumab govitecan-bound tumor cells are killed by intracellular uptake of SN-38, and adjacent tumor cells are killed by SN-38 released extracellularly[6]
- Sacituzumab govitecan has shown preclinical and clinical activity.[3,7,8]

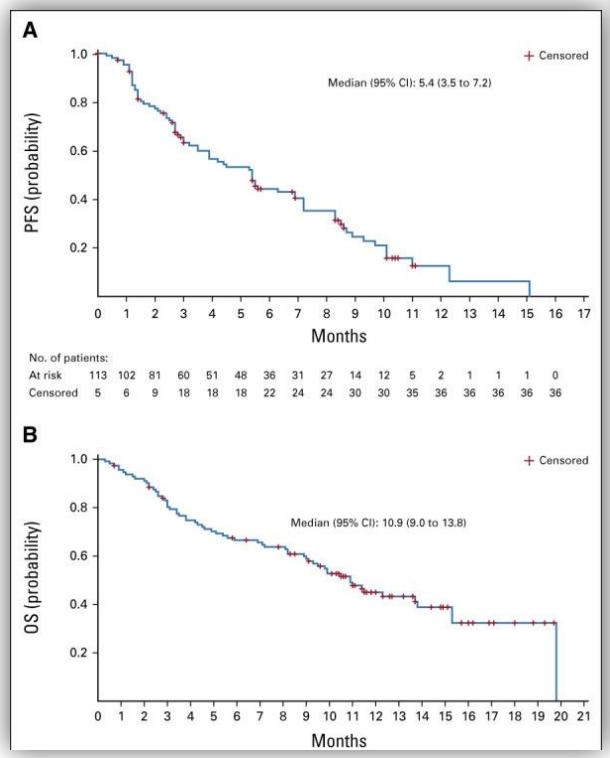


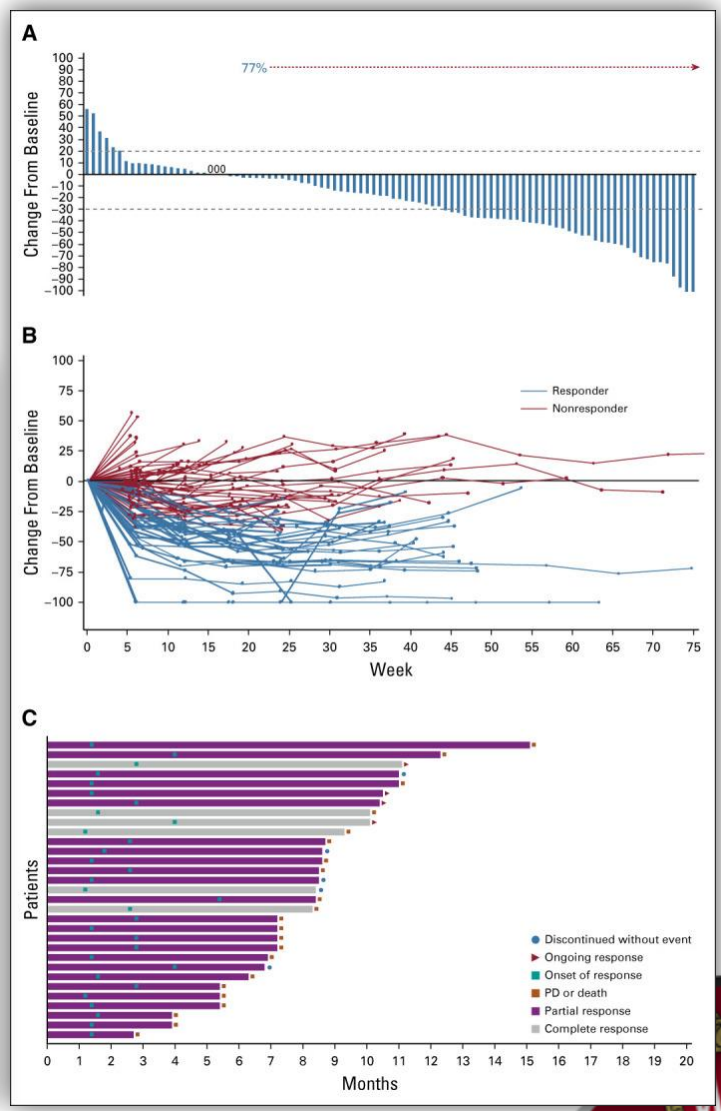
Trop-2: trophoblast cell surface antigen 2; 1. Avellini et al. Oncotarget 2017;8:58642.. 2. Starodub et al. Clin Cancer Res 2015;21:3870. 3. Cardillo et al. Clin Cancer Res. 2011;17:3157-3169. 4. Sharkey et al. Clin Cancer Res. 2015;21:5131-5138. 5. Cardillo et al. Bioconjugate Chem. 2015;26:919-931. 6.Govindan et al. Mol Cancer Ther. 2013;12:968-978. 7. Faltas et al. *Clin Genitourin Cancer*. 2016;14 e75-79. 8. Bardia et al. J Clin Oncol. 2017;35:2141-2148

1. Tagawa S, ASCO GU Feb 2019

Sacituzumab Govitecan: TROPHY-U01

- Multicohort, phase II, registrational study
- Cohort 1: post platinum and ICI,
- 113 patients with med follow up of 9.1 mon
- ORR: 27%
- PFS: 5.4 mon
- OS: 10.9 mon
- DOR: 7.2 mon

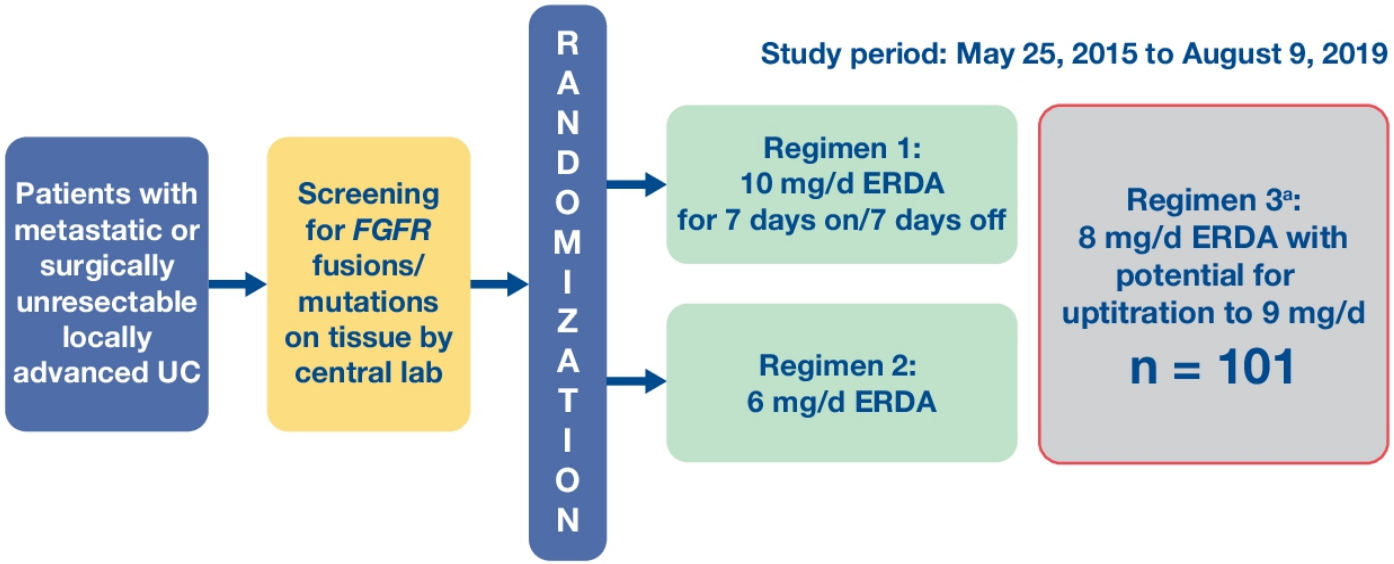




1. Tagawa S, ASCO GU 2021

Erdafitinib: BLC2001

BLC2001: Open label Phase II trial



[a]Dose uptitration if ≥ 5.5 mg/dL target serum phosphate not reached by Day 14 and if no TRAEs.

1. Loriot Y, *NEJM* 2019

Erdafitinib: Treatment Response

Table 2. Antitumor Activity of Erdafitinib in the 99 Patients in the Selected-Regimen 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	2	2
Median time to response — mo	1.4	
Median duration of response (95% CI) — mo	5.6 (4.2–7.2)	
Response per independent radiologic assessment — no. of patients†		
Objective response	34	34 (25–44)
Complete response	3	3
Partial response	31	31
Response according to previous treatment — no./total no.		
No chemotherapy	5/12	42
Progression or relapse after chemotherapy	35/87	40
Immunotherapy	13/22	59

1. Loriot Y, *NEJM* 2019
2. Siefker-Radtke A. *Lancet* 2022

Erdafitinib: Adverse Events

TRAEs in > 20% of Patients, n (%)	Erdafitinib 8 mg QD (N = 99)	
	Any Grade	Grade 3
Hyperphosphatemia	72 (73)	2 (2)
Stomatitis	54 (55)	9 (9)
Dry mouth	43 (43)	0
Diarrhea	37 (37)	4 (4)
Dysgeusia	35 (35)	1 (1)
Dry skin	32 (32)	0
Alopecia	27 (27)	0
Decreased appetite	25 (25)	0
Hand–foot syndrome	22 (22)	5 (5)
Fatigue	21 (21)	2 (2)

TRAEs of Special Interest or Clinical Importance, n (%)	Erdafitinib 8 mg QD (n = 99)	
	Any Grade	Grade ≥ 3
Hyperphosphatemia	72 (73)	2 (2)
Skin events	48 (49)	6 (6)
▪ Dry skin	32 (32)	0
▪ Hand–foot syndrome	22 (22)	5 (5)
Nail events	51 (52)	14 (14)
▪ Onycholysis	16 (16)	2 (2)
▪ Paronychia	14 (14)	3 (3)
▪ Nail dystrophy	16 (16)	6 (6)
Ocular events		
▪ CSR	21 (21)	3 (3)
▪ Non-CSR events*	51 (52)	5 (5)

CSR: central serous retinopathy

1. Loriot Y, *NEJM* 2019
2. Siefker-Radtke A. *Lancet* 2022

Bladder Cancer Take Home Points

- Neoadjuvant cisplatin-based chemotherapy should be considered for eligible patients with MIBC undergoing radical cystectomy.
- Adjuvant nivolumab is FDA approved for high-risk patients with MIBC after radical cystectomy +/- neoadjuvant chemotherapy.
- Platinum based combination chemotherapy remains the most effective regimen for the first line setting in mUC.
- Maintenance avelumab post 4-6 cycles of platinum chemo improved PFS and OS.
- ICIs are approved in platinum refractory setting or for patients who are unfit for platinum chemotherapy.
- Antibody Drug Conjugates (ADCs) including enfortumab vedotin and sacituzumab govitecan are approved for post platinum and ICI treatment setting.
- Erdafitinib is approved for patients with FGFR alteration.
- Multiple combination regimens are being evaluated in different lines of treatment from peri-operative to treatment refractory settings.

Thank you for your attention!

Questions?

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