Oncology Learning Network

Opportunities for Improved Outcomes: The Role of Targeted Therapies in Metastatic Urothelial Carcinoma

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HMP Education

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Faculty Disclosures

- **Rafee Talukder, MD,** and **Val Adams, PharmD, FCCP, FHOPA, BCOP,** have disclosed no relevant financial relationship with any ineligible company (commercial interest)

Program Information

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Learning Objectives

- Evaluate the latest efficacy and safety data for newer and emerging targeted therapies for mUC
- Incorporate current clinical guideline recommendations into clinical practice when caring for patients with mUC
- Employ multidisciplinary, patient-centered strategies to select and sequence optimal treatment, manage AEs, and/or address barriers to optimal outcomes in mUC

mUC = metastatic urothelial carcinoma; AE = adverse event.

Outline

Background

Targeted Therapeutic Options

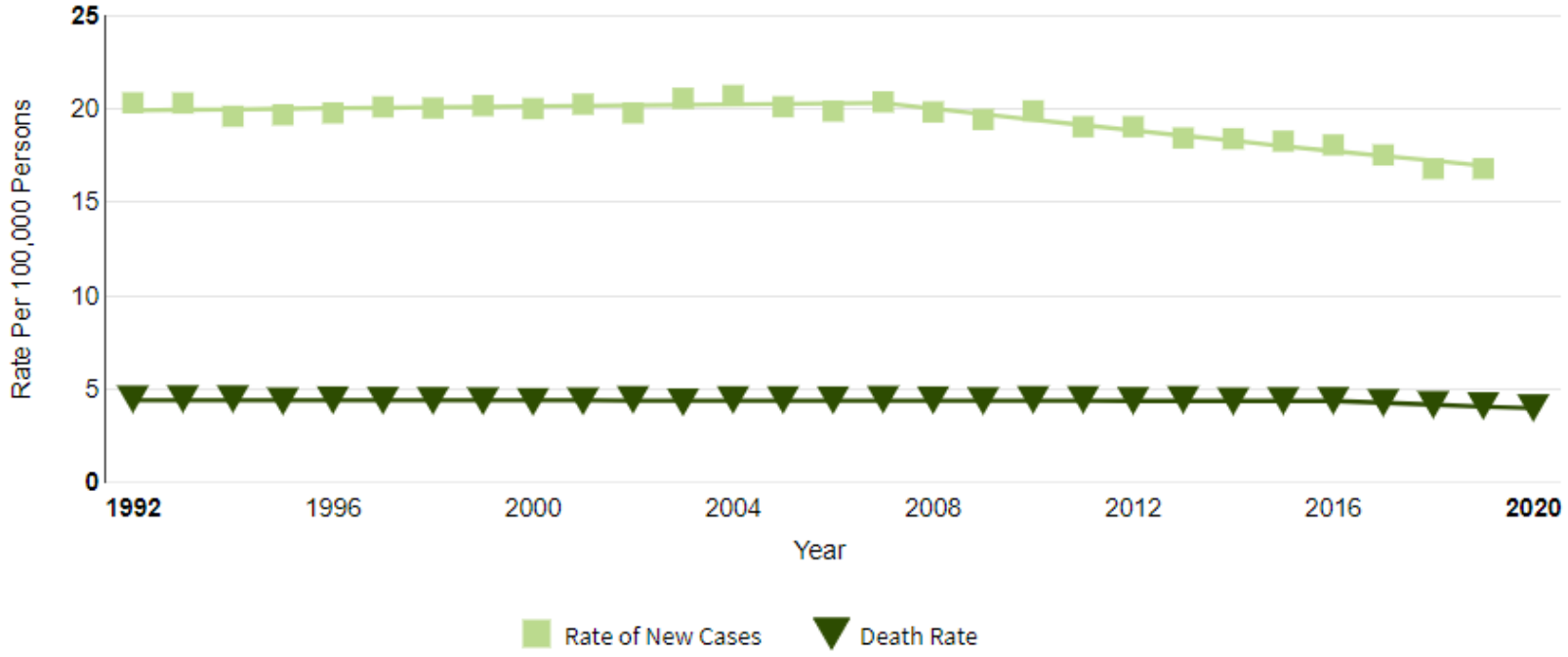
Treatment Strategies

Adverse Event Management

Optimization of Patient-Centered Clinical Care

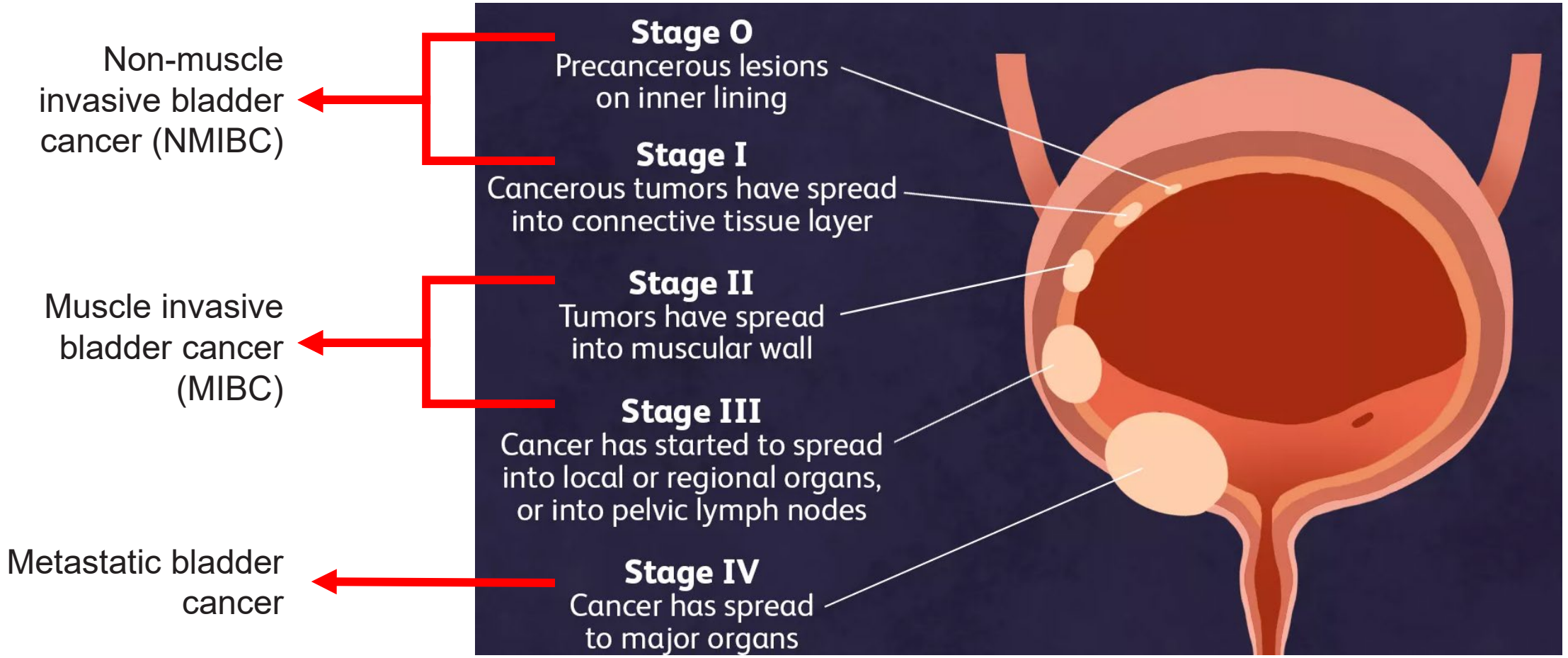
Bladder Cancer

- 83,190 new cases in 2024; 16,840 deaths
- 75% men, 25% women
- Average age of diagnosis: 73



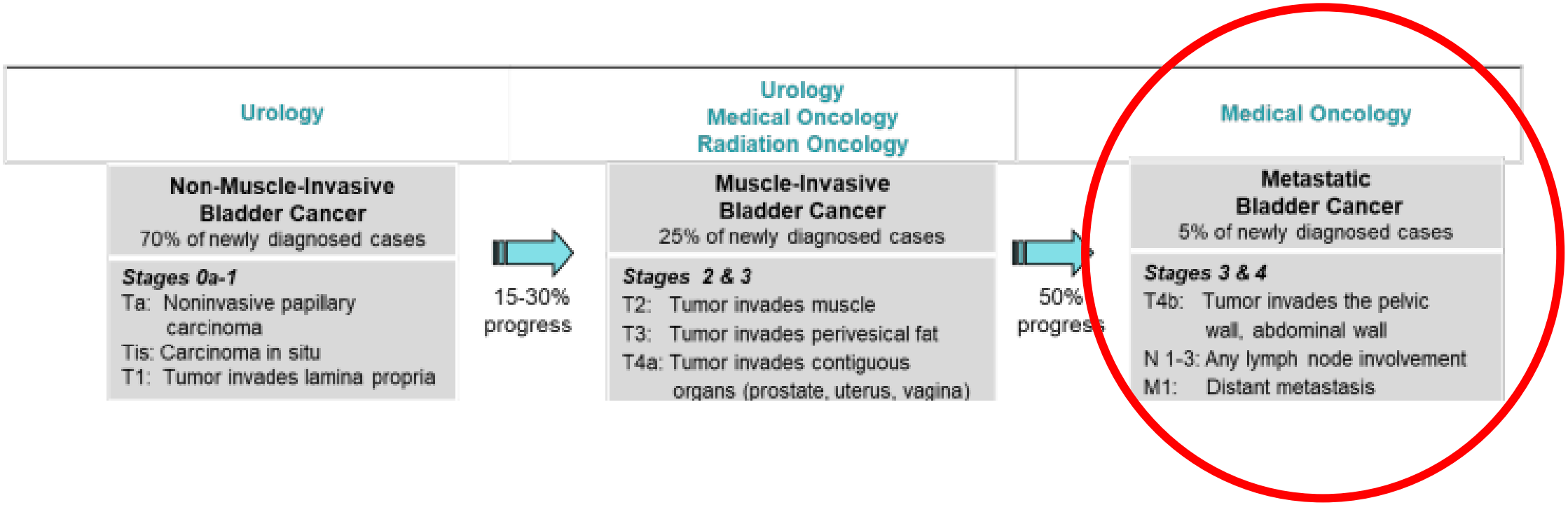
National Cancer Institute SEER Database. Accessed November 1, 2024. https://seer.cancer.gov/statfacts/html/urinb.html.

Stages of Bladder Cancer

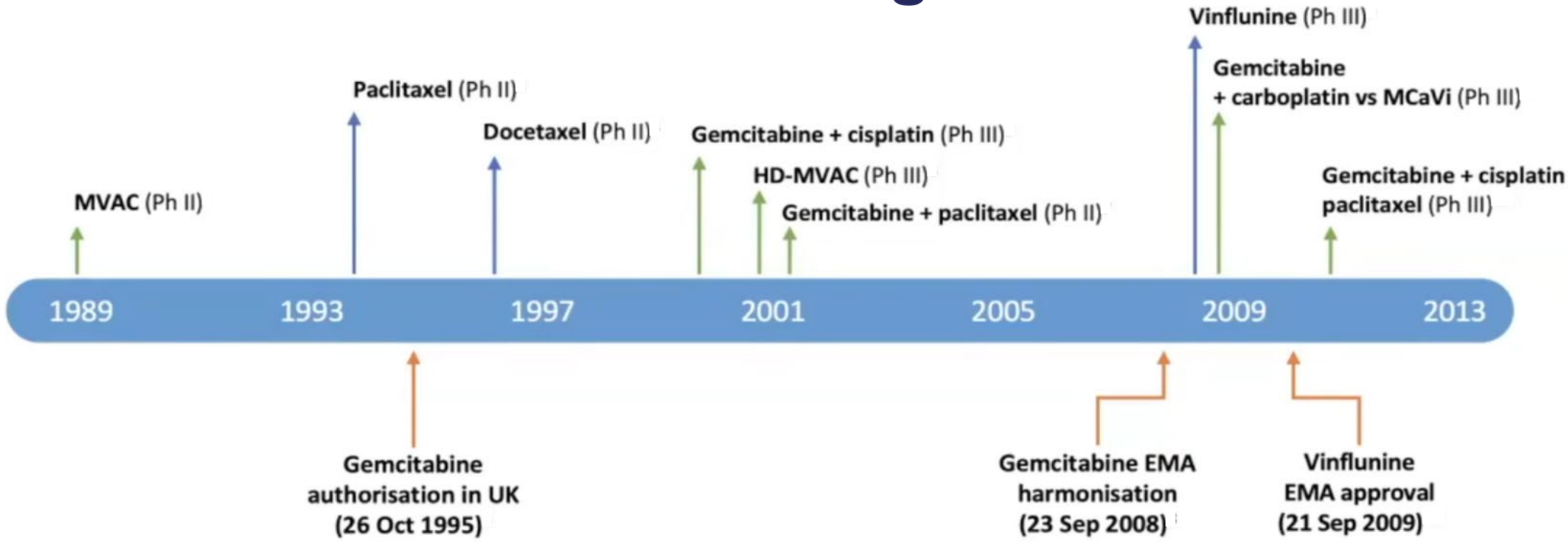


Welsh, J. VeryWell Health. Last updated August 29, 2023. Accessed November 1, 2024. https://www.verywellhealth.com/bladder-cancer-stages-5205019.

Stages 3 and 4 of Metastatic Bladder Cancer



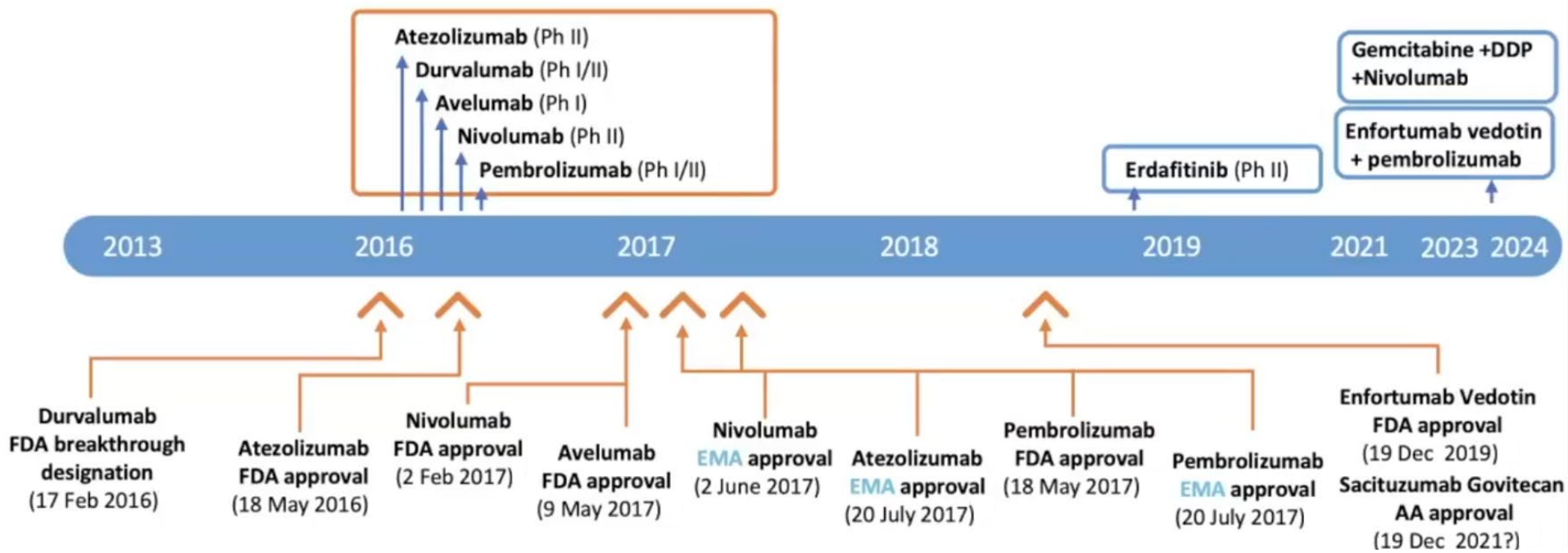
Little Progress in the Past 35 Years with Few New Drugs in UC



MVAC = methotrexate, vinblastine, doxorubicin, and cisplatin; HD-MVAC = high-dose MVAC; MCaVi = carboplatin, methotrexate, and vinblastine; EMA = European Medicines Agency.

Sternberg CN, et al. *Cancer.* 1989;64(12):2448-2458. Roth BJ, et al. *J Clin Oncol*. 1994;12(11):2264-2270. Electronic Medicines Compendium. Last updated July 1, 2014. Accessed November 1, 2024. https://web.archive.org/web/20170710202604/https://www.medicines.org.uk/emc/medicine/596. McCaffrey JA, et al. *J Clin Oncol*. 1997;15(5):1853-1857. Von der Maase H, et al. *J Clin Oncol.* 2000;18(17):3068-3077. Sternberg CN, et al. *J Clin Oncol*. 2001;19(10):2638-2646. Meluch AA, et al. *J Clin Oncol.* 2001;19(12):3018-3024. European Medicines Agency. September 24, 2008. Accessed November 1, 2024. https://www.ema.europa.eu/en/documents/referral/opinion-following-article-30-referral-gemzar-and-associated-names-international-non-proprietary-name-inn-gemcitabine-background-information_en.pdf. Bellmunt J, et al. *J Clin Oncol*. 2009;27(27):4454-4461. European Medicines Agency. August 10, 2009. Accessed November 1, 2024. https://www.ema.europa.eu/en/medicines/human/EPAR/javlor#authorisation-details. De Santis M, et al. *J Clin Oncol*. 2009;27(33):5634-5639. Bellmunt J, et al. *J Clin Oncol*. 2012;30(10):1107-1113. Sternberg C, et al. Presented at: Weill Cornell Medicine; May 23, 2024; New York, New York.

We Now Have 5 Immunotherapeutic Agents for UC plus Other Novel Agents (ADCs)



ADC = antibody-drug conjugate; DDP = cis-diamminedichloroplatinum; FDA = US Food and Drug Administration; AA = accelerated approval.

Rosenberg JE, et al. *Lancet*. 2016;387(10031):1909-1920. Powells T, et al. *JAMA Oncol*. 2017;3(9):e172411. Patel MR, et al. *Lancet Oncol.* 2018;19(1):51-64. Sharma P, et al. *Lancet Oncol.* 2017;18(3):312-322. Woodcock VK, et al. Presented at: American Society of Clinical Oncologists Annual Meeting; June 3-7, 2016; Chicago, Illinois. Abstract 406. Loriot Y, et al. *N Engl J Med*. 2019;381(4):338-348. FDA. Accessed November 1, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761069s000lbl.pdf. FDA. May 18, 2016. Accessed November 1, 2024. https://www.fda.gov/news-events/press-announcements/fda-approves-new-targeted-treatment-bladder-cancer. FDA. Feb 2, 2017. Accessed November 1, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/nivolumab-treatment-urothelial-carcinoma. European Medicines Agency. June 2, 2017. Accessed November 1, 2024. www.ema.europa.eu/en/documents/variation-report/opdivo-h-c-3985-ii-0041-epar-assessment-report-variation_en.pdf. European Medicines Agency. July 20, 2017. Accessed November 1, 2024. https://www.ema.europa.eu/en/documents/assessment-report/tecentriq-epar-public-assessment-report_en.pdf. FDA. May 18, 2017. https://www.fda.gov/drugs/resources-information-approved-drugs/pembrolizumab-keytruda-advanced-or-metastatic-urothelial-carcinoma. European Medicines Agency. July 20, 2017. Accessed November 1, 2024. www.ema.europa.eu/en/documents/smop/chmp-post-authorisation- summary-positive-opinion-keytruda_en.pdf. FDA. Dec 19, 2019. Accessed November 1, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-enfortumab-vedotin-ejfv-locally-advanced-or-metastatic-urothelial-cancer. FDA. December 15, 2023. Accessed November 1, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-enfortumab-vedotin-ejfv-pembrolizumab-locally-advanced-or-metastatic-urothelial-cancer. FDA. March 6, 2024. Accessed November 1, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-combination-cisplatin-and-gemcitabine-unresectable-or-metastatic-urothelial. Sternberg C, et al. Presented at: Weill Cornell Medicine; May 23, 2024; New York, New York.

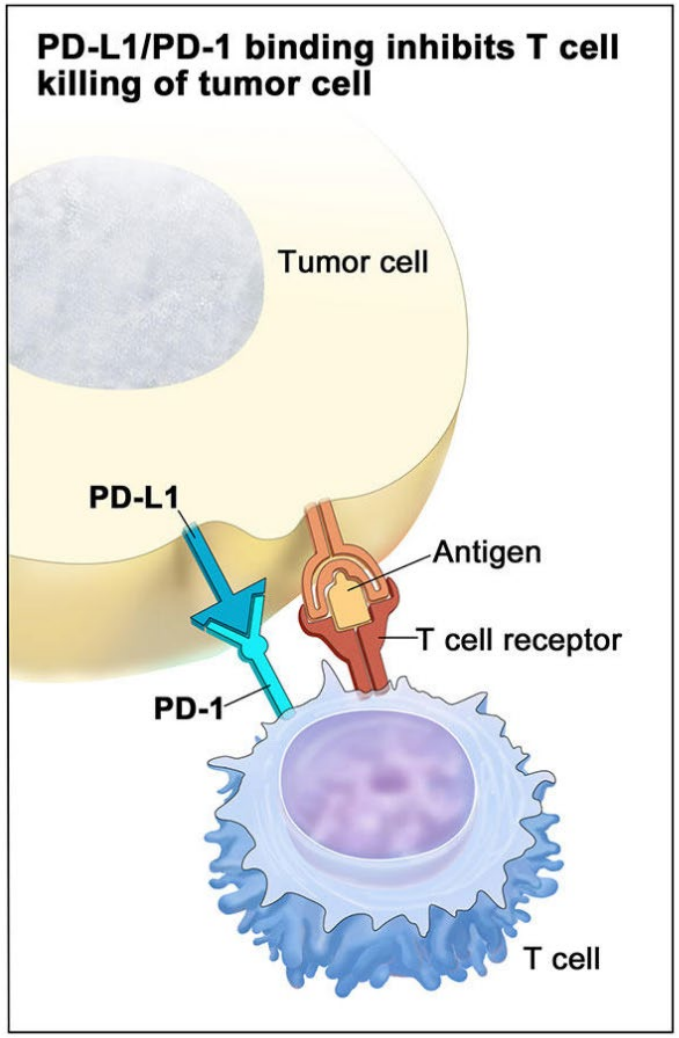
Targeted Therapeutic Options

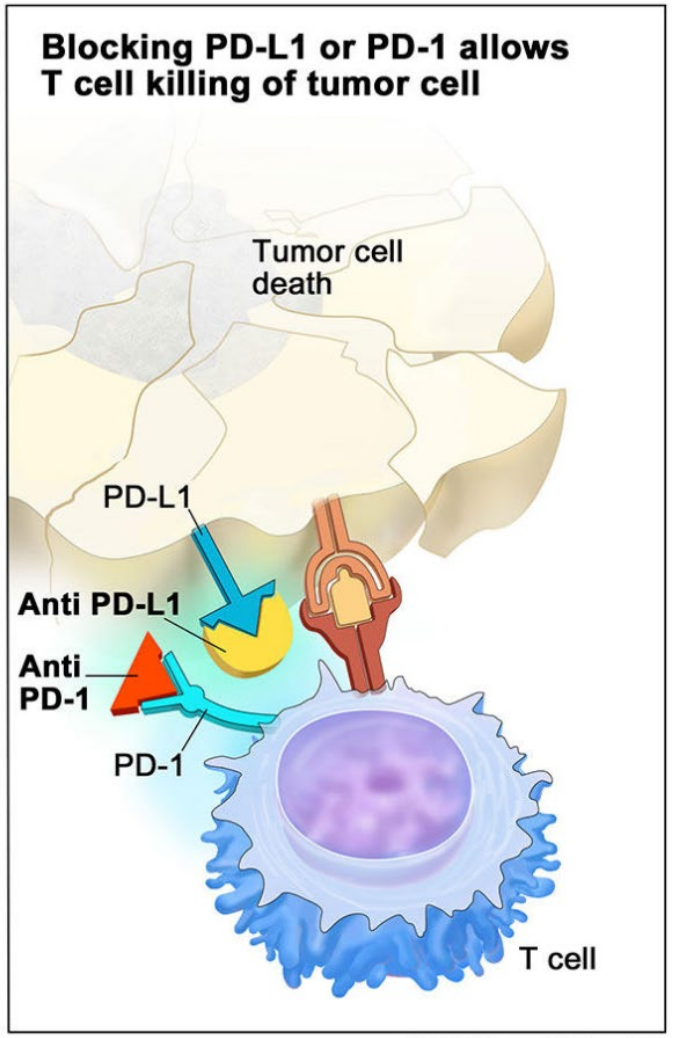
Immune Checkpoint Inhibitors

Antibody Drug Conjugates

Fibroblast Growth Factor Receptor Inhibitors

Immune Checkpoint Inhibitors



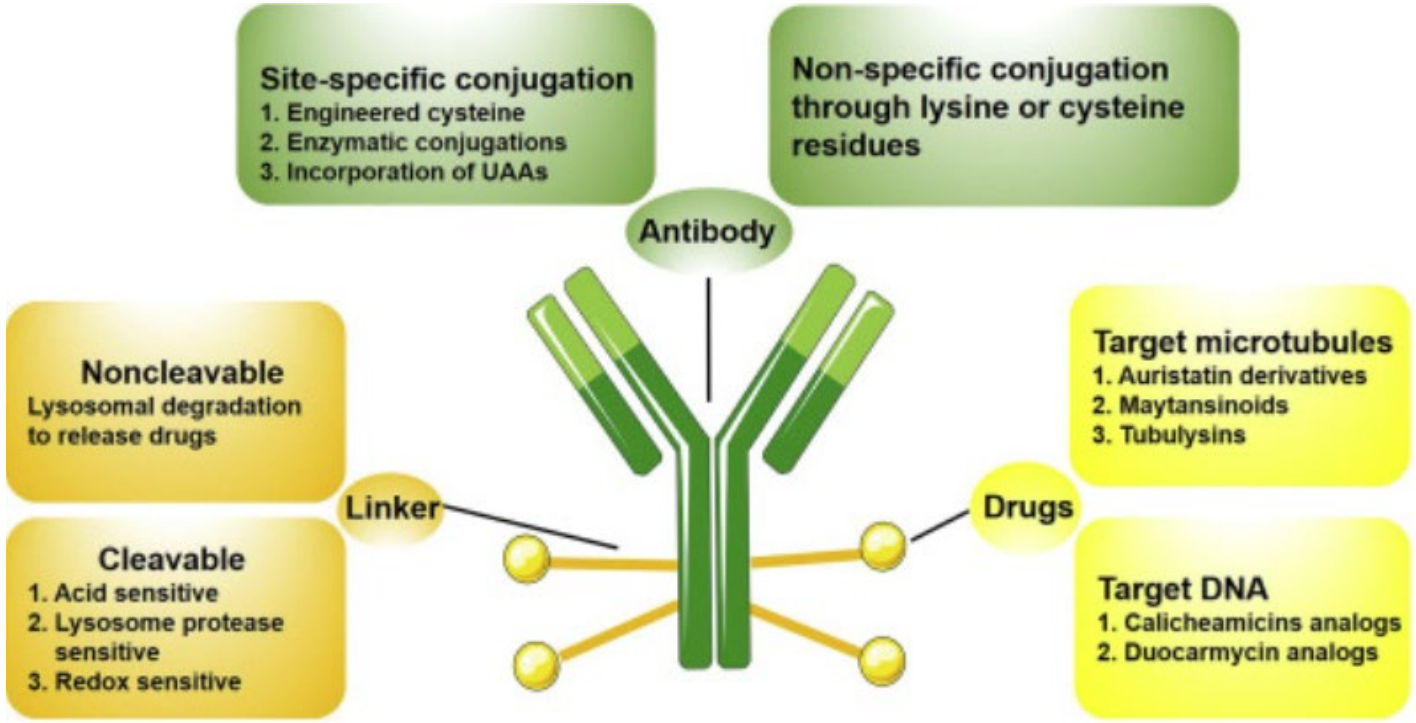


PD-L = programmed death ligand; PD = programmed death protein.

National Cancer Institute. June 7, 2016. Accessed November 1, 2024. https://www.cancer.gov/news-events/cancer-currents-blog/2016/fda-atezolizumab-bladder.

Antibody-Drug Conjugates

- Antibody-drug conjugates are made up of three parts
  - Antibody
  - Pay-load
  - Linker (stable in circulation, but releases cytotoxic agent in the target cell)



UAA = unnatural amino acid.

Xhao P, et al. *Acta Pharm Sin B.* 2020;10(9):1589-1600.

First-Line Treatment Options

Platinum Eligible

- EV + pembrolizumab
- Nivolumab + cis/gem
- ddMVAC
- Cis/gem
- Carbo/gem

→ Avelumab

Platinum Ineligible

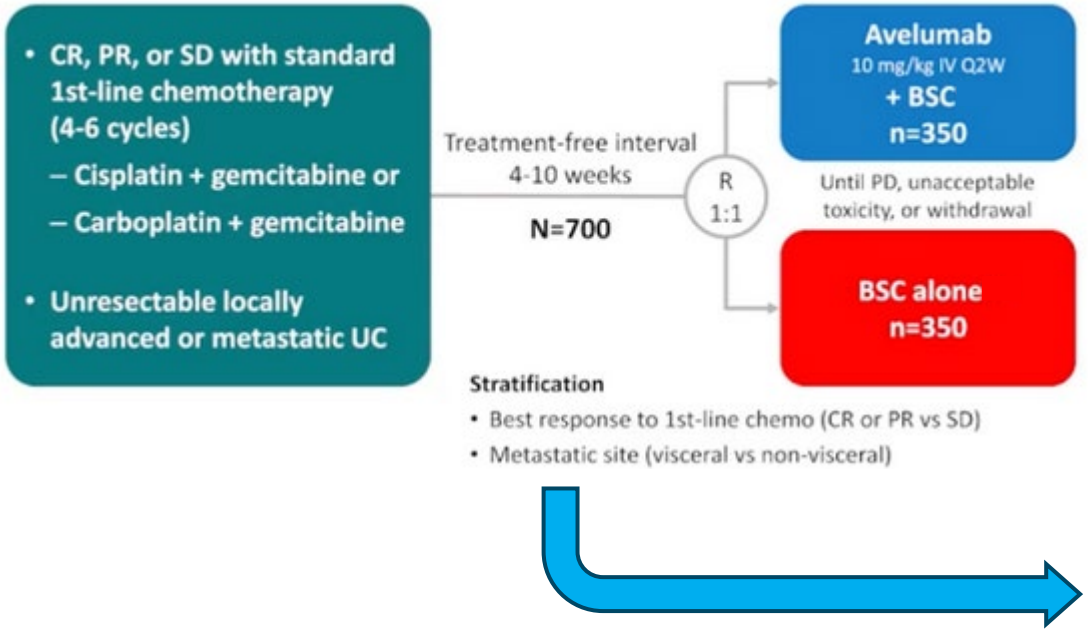
- Pembrolizumab

Second- + (Subsequent) Line Treatment Options

- FGFR 2/3 alt → Erdafitinib
- **Sacituzumab govitecan**
- Pembrolizumab (if not used before)
- EV (if not used before)
- Platinum + gemcitabine (if not used before)
- HER2 positive: trastuzumab deruxetecan

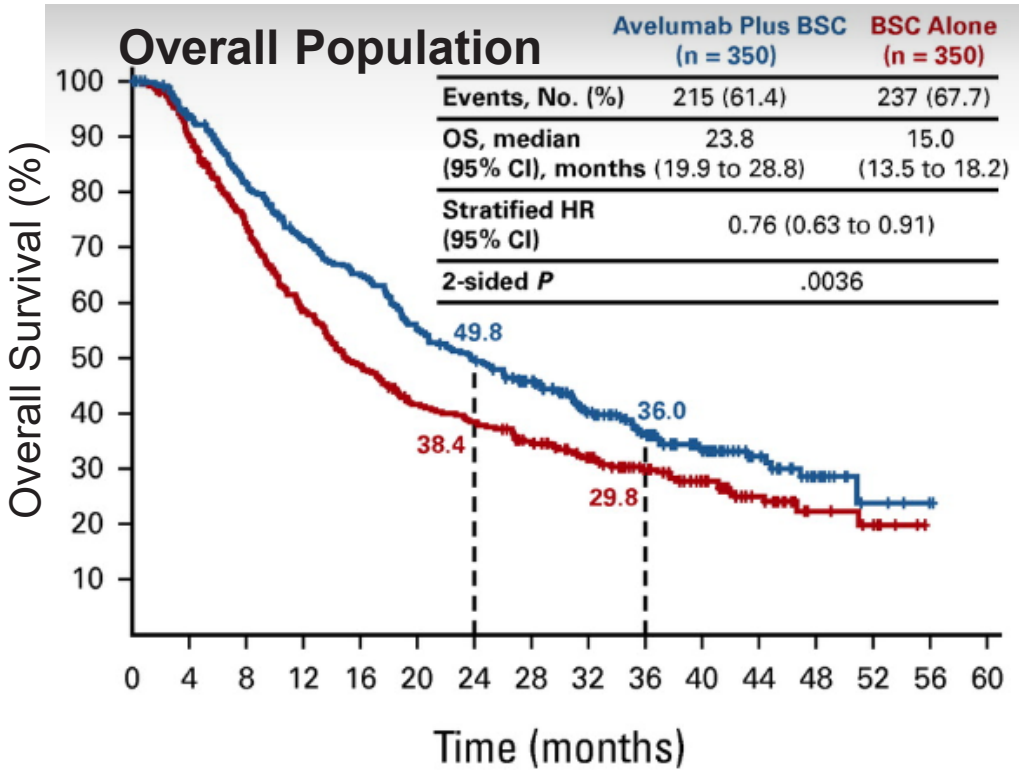
EV = enfortumab vedotin; ddMVAC = dose-dense MVAC; FGFR = fibroblast growth factor receptor; HER = human epidermal growth factor receptor. FDA. Accessed November 13, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-enfortumab-vedotin-ejfv-pembrolizumab-locally-advanced-or-metastatic-urothelial-cancer; fda-approves-nivolumab-combination-cisplatin-and-gemcitabine-unresectable-or-metastatic-urothelial; pembrolizumab-keytruda-advanced-or-metastatic-urothelial-carcinoma; fda-approves-erdafitinib-locally-advanced-or-metastatic-urothelial-carcinoma; fda-grants-accelerated-approval-sacituzumab-govitecan-advanced-urothelial-cancer; fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2; https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-avelumab-urothelial-carcinoma-maintenance-treatment.

JAVELIN BLADDER 100: Maintenance Avelumab after Chemotherapy



Treatment continued until progression or toxicity/withdrawal.

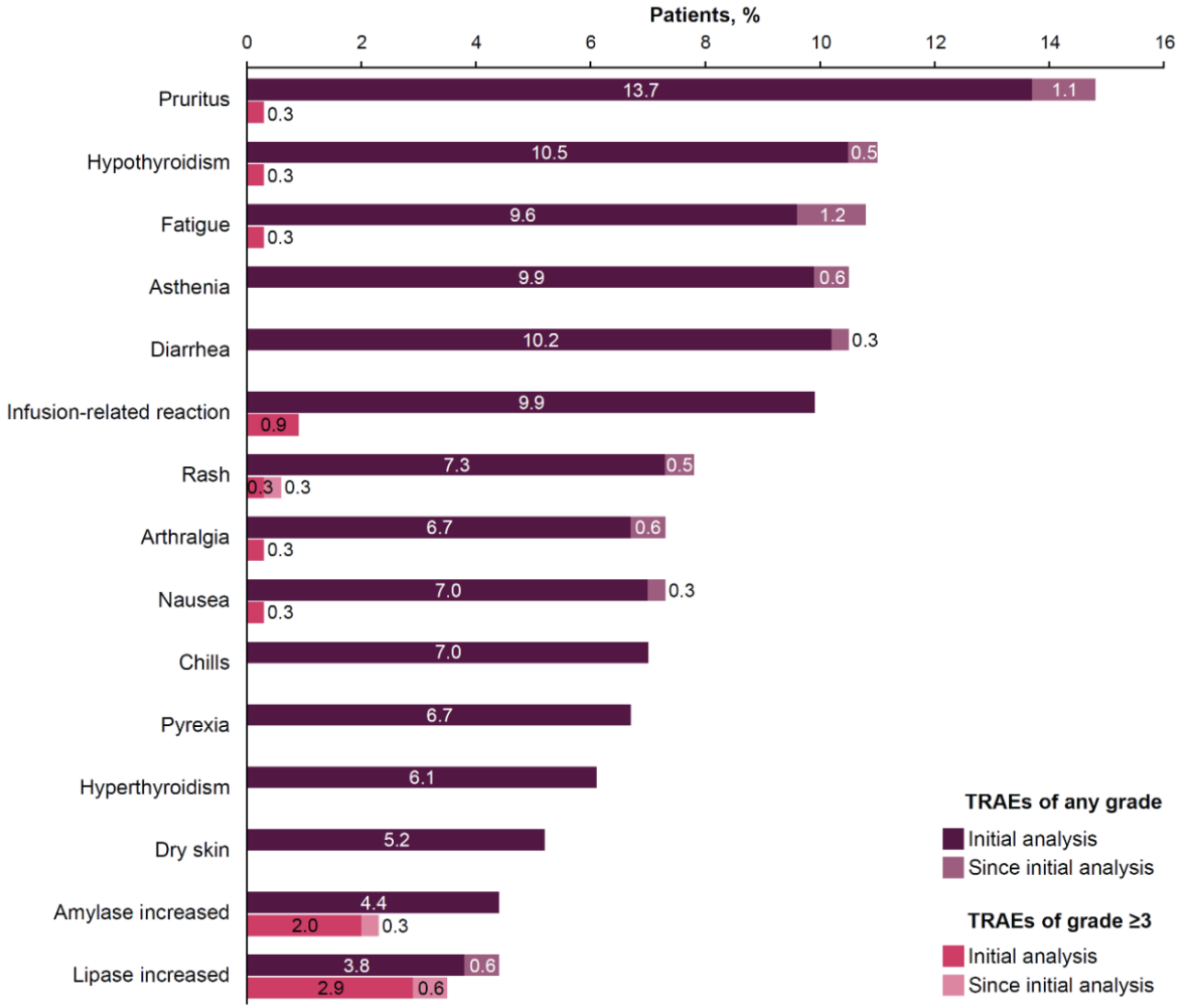
The PD-L1-positive population did significantly better: mOS of 31 months vs 19 months.



CR = complete response; PR = partial response; SD = stable disease; IV = intravenous; BSC = best supportive care; mOS = median overall survival; HR = hazard ratio.

Powles T, et al. *J Clin Oncol.* 2023;41(19):3486-3492. National Institutes of Health (NIH). Accessed November 1, 2024. https://clinicaltrials.gov/study/NCT02603432.

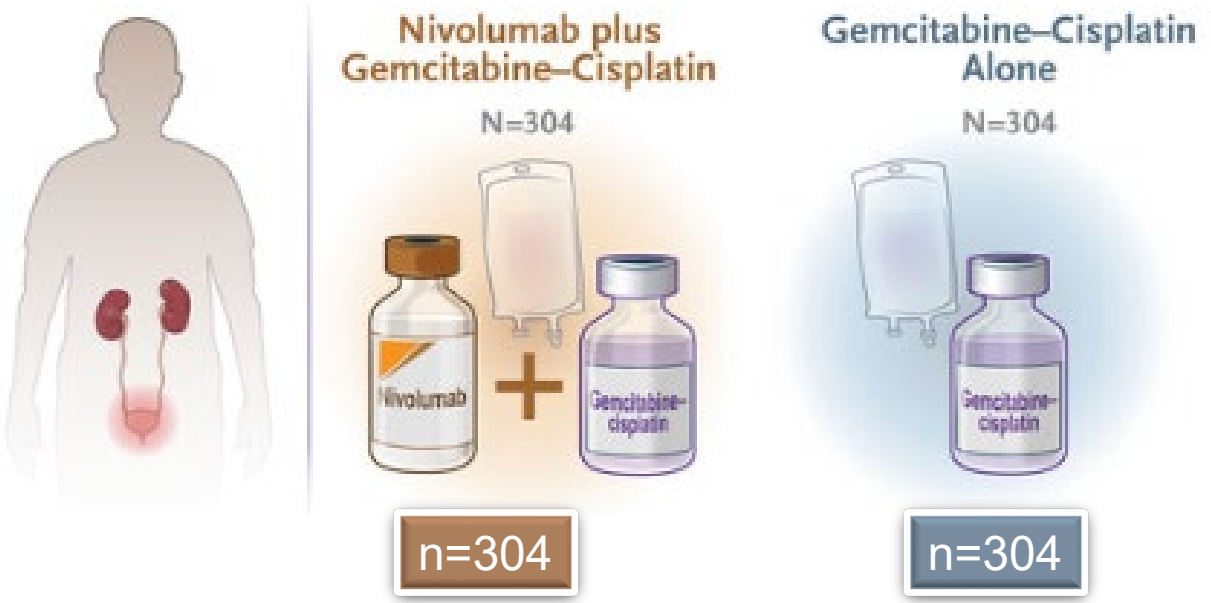
JAVELIN BLADDER 100: Adverse Events



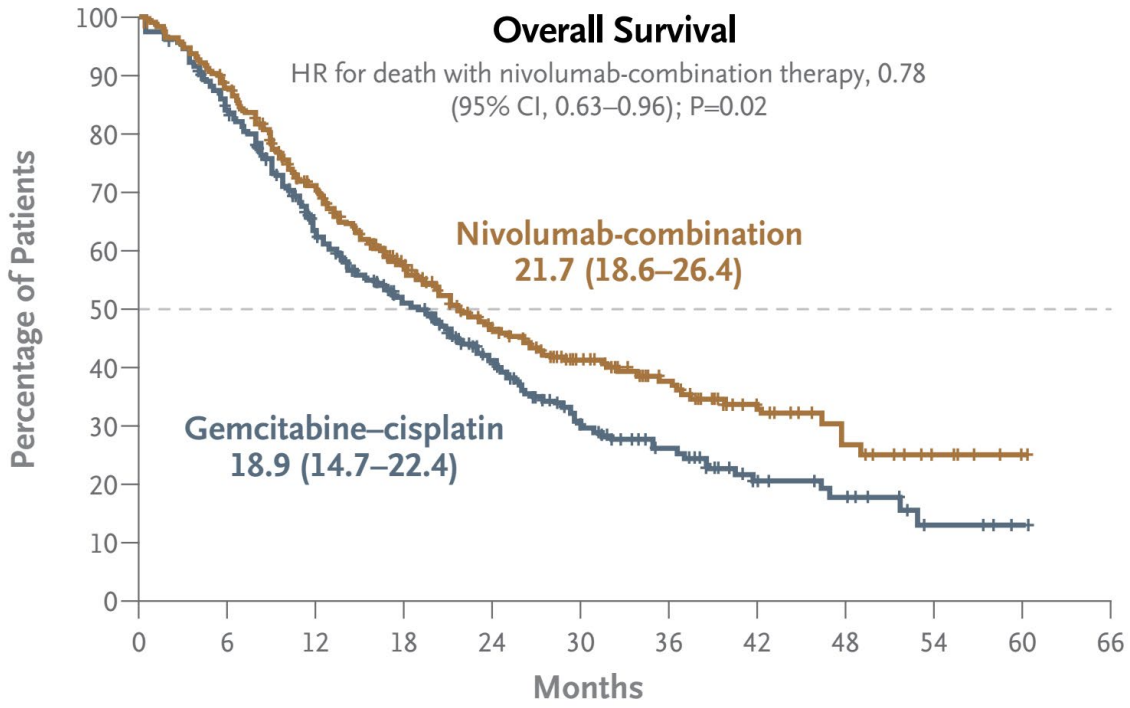
TRAE = treatment-related adverse event.

Powles T, et al. *J Clin Oncol.* 2023;41(19):3486-3492.

CheckMate901: First-Line Advanced/Metastatic UC

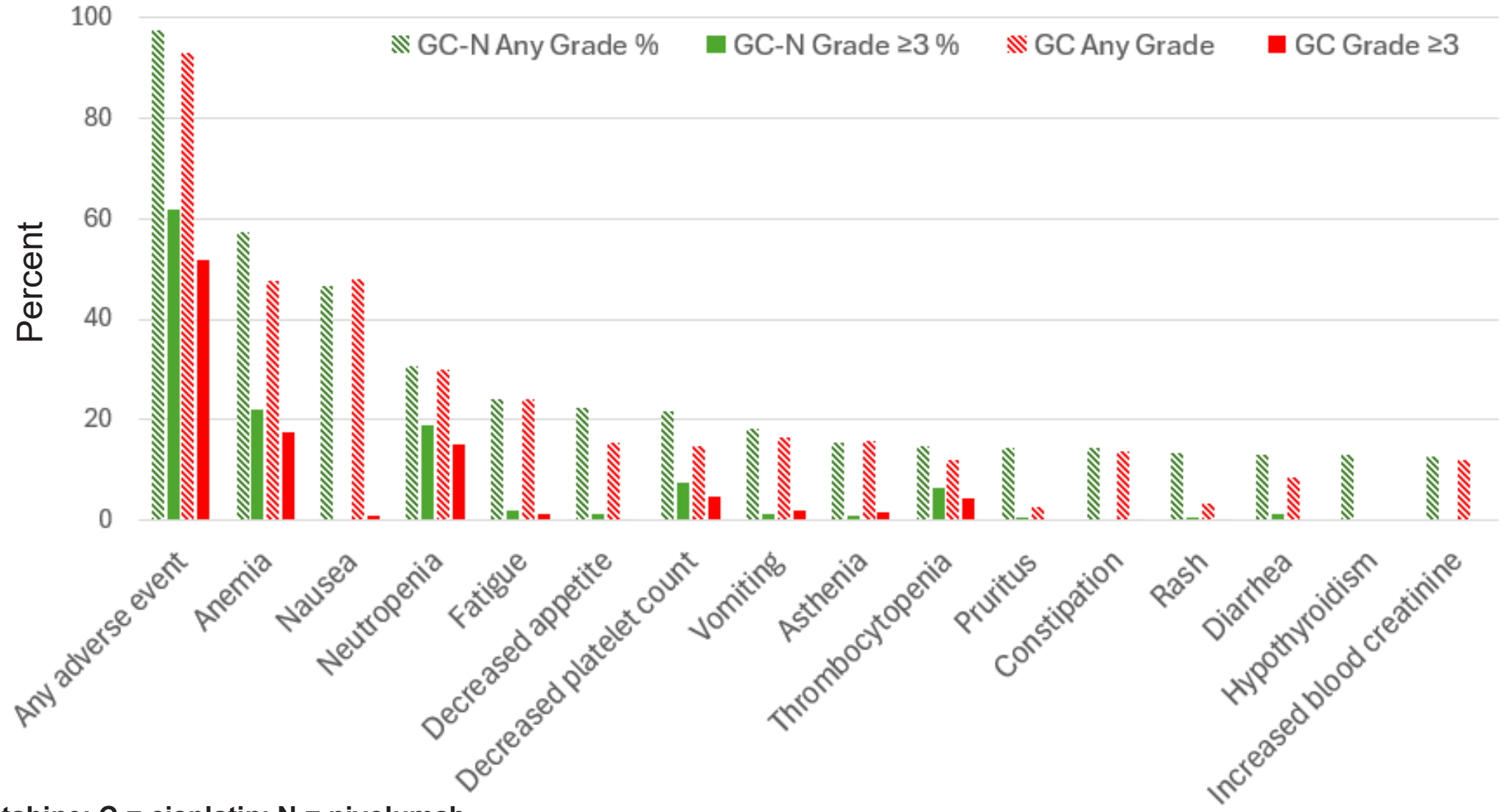


- Stratification for PD-L1 status and liver metastasis
- Platinum for up to 6 cycles
- Nivo q4weeks continued for up to 2 years



Van der Heijden MS, et al. *N Engl J Med*. 2023;389(19):1778-1789. NIH. Accessed November 1, 2024. https://clinicaltrials.gov/study/NCT03036098.

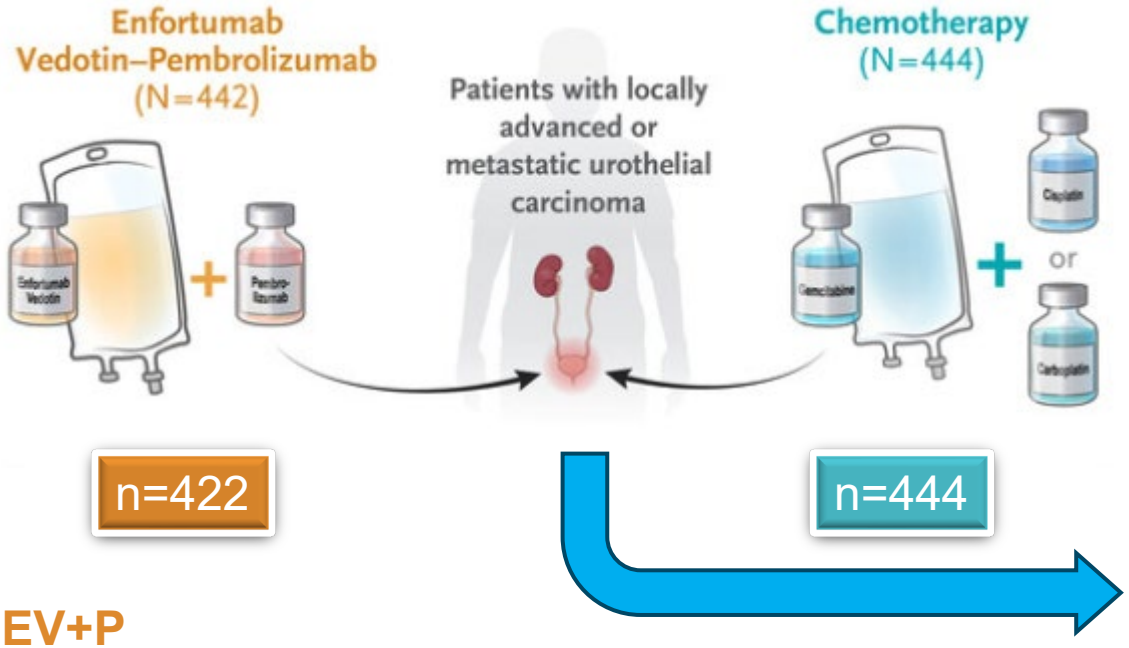
CheckMate901: Adverse Events



G = gemcitabine; C = cisplatin; N = nivolumab.

Van der Heijden MS, et al. *N Engl J Med*. 2023;389(19):1778-1789.

EV-302: EV+P vs Chemotherapy

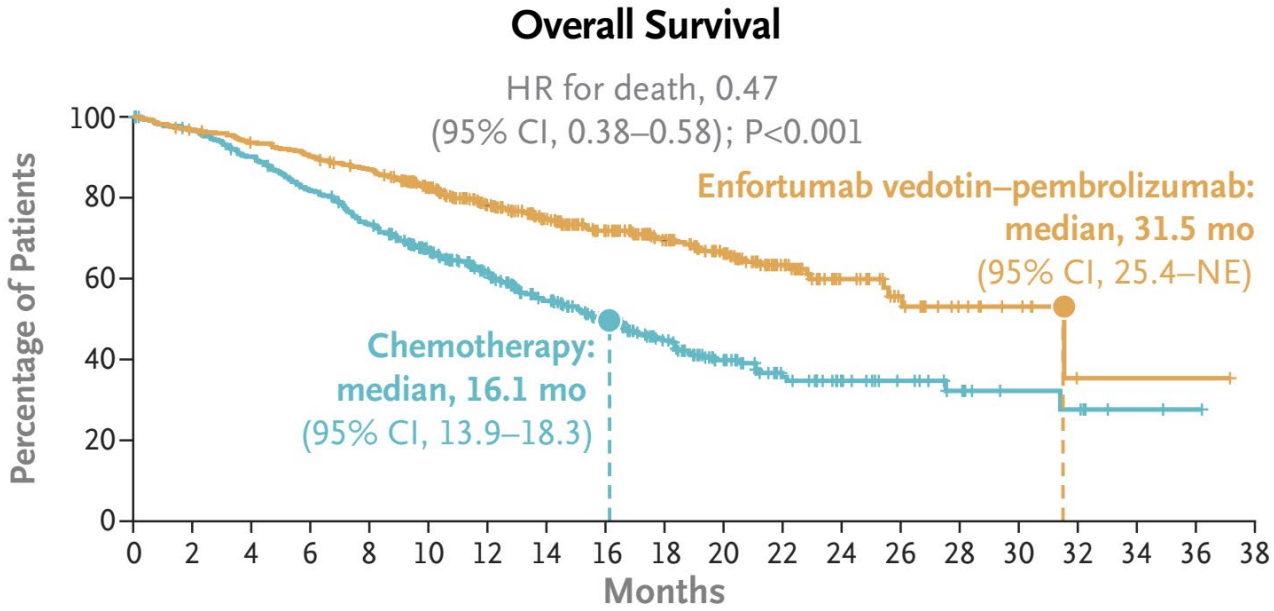


EV+P

Enfortumab vedotin 1.25 mg/kg IV d1&8
AND
Pembrolizumab 200 mg IV d1
Cycle every 3 weeks

Chemotherapy

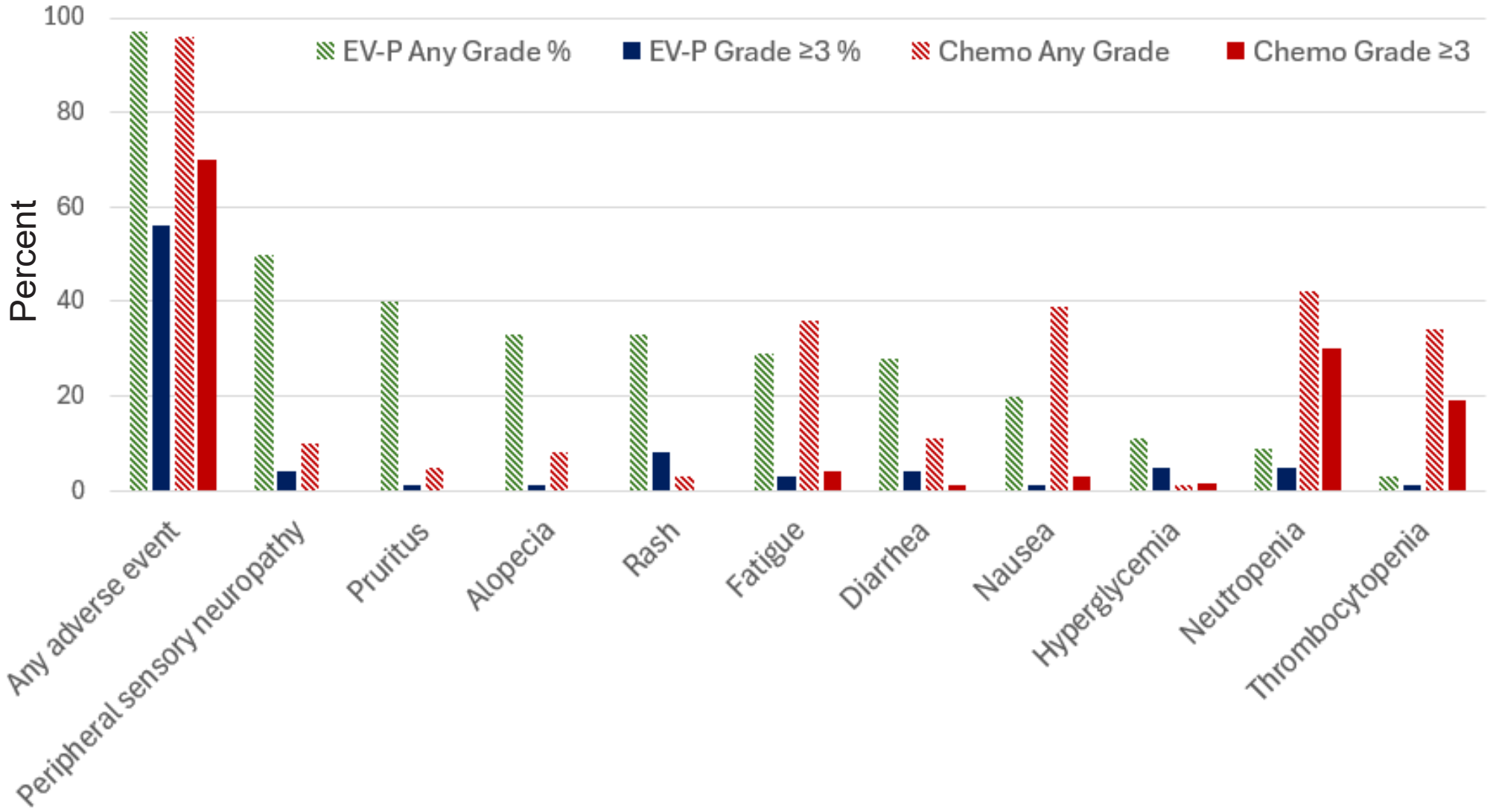
Gemcitabine 1000 mg/m^2 IV d1&8
AND
Cisplatin 70 mg/m^2 IV d1
OR
Carboplatin AUC 4.5-5
Cycle every 3 weeks



P = pembrolizumab; AUC = area under the curve.

Powles T, et al. *N Engl J Med.* 2024;390(10):875-888. NIH. Accessed November 1, 2024. https://clinicaltrials.gov/study/NCT04223856.

EV-302: Adverse Events



Powles T, et al. *N Engl J Med.* 2024;390(10):875-888.

Comparison of ICI + ADC or Chemo

EV-302: EV + Pembro (vs chemo)

mOS: 31.5 mo (vs 16.1 mo)

PFS: 12.5 mo (vs 6.3 mo)

ORR: 67.7% (44.4%)

CR: 29.1% (12.5%)

Grade 3 or above TRAE: 55.9% (69.5%)

Maximum number of treatment cycles
Chemotherapy: 6 cycles
Pembrolizumab: 35 cycles
EV: until progression

CheckMate901: Gem/Cis + Nivo (vs chemo)

mOS: 21.7 mo (vs 18.9 mo)

mPFS: 7.9 mo (vs 7.6 mo)

ORR: 57.6% (43.1%)

CR 21.7% (11.8%)

Grade 3 or above TRAE: 61.8% (51.7%)

Chemo stopped after six cycles—this impacts toxicity measures

JAVELIN BLADDER 100 (maint): Avelumab (vs placebo)

mOS: 23.8 mo (vs 15.0 mo)

mPFS: 5.5 mo (vs 2.1 mo)

ORR: 14.3% (4%)

CR 7.1% (1.1%)

Grade 3 or above TRAE: 19.5% (NR)

Avelumab started 4-10 weeks SD/ORR with chemotherapy—this design impacts the survival and response numbers above

ICI = immune checkpoint inhibitor; PFS = progression-free survival; ORR = overall response rate; NR = not reached.

Powles T, et al. *N Engl J Med.* 2024;390(10):875-888. Van der Heijden MS, et al. *N Engl J Med*. 2023;389(19):1778-1789. Powles T, et al. *J Clin Oncol.* 2023;41(19):3486-3492.

NCCN Guidelines for First Therapy

- Preferred regimen
  - EV-P (category 1)
    - For patients with locally advanced or metastatic UC previously treated with chemotherapy and anti-PD(L)1 therapy
- Other recommended regimens
  - GC followed by avelumab maintenance
  - GC + nivolumab followed by nivolumab maintenance

NOTE: Unless contraindicated, everyone gets immunotherapy +

NCCN = National Comprehensive Cancer Network.

NCCN. Accessed November 1, 2024. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1417.

First-Line Treatment Options

Second- + (Subsequent) Line Treatment Options

Platinum Eligible

- EV + pembrolizumab
- Nivolumab + cis/gem
- ddMVAC
- Cis/gem
- Carbo/gem

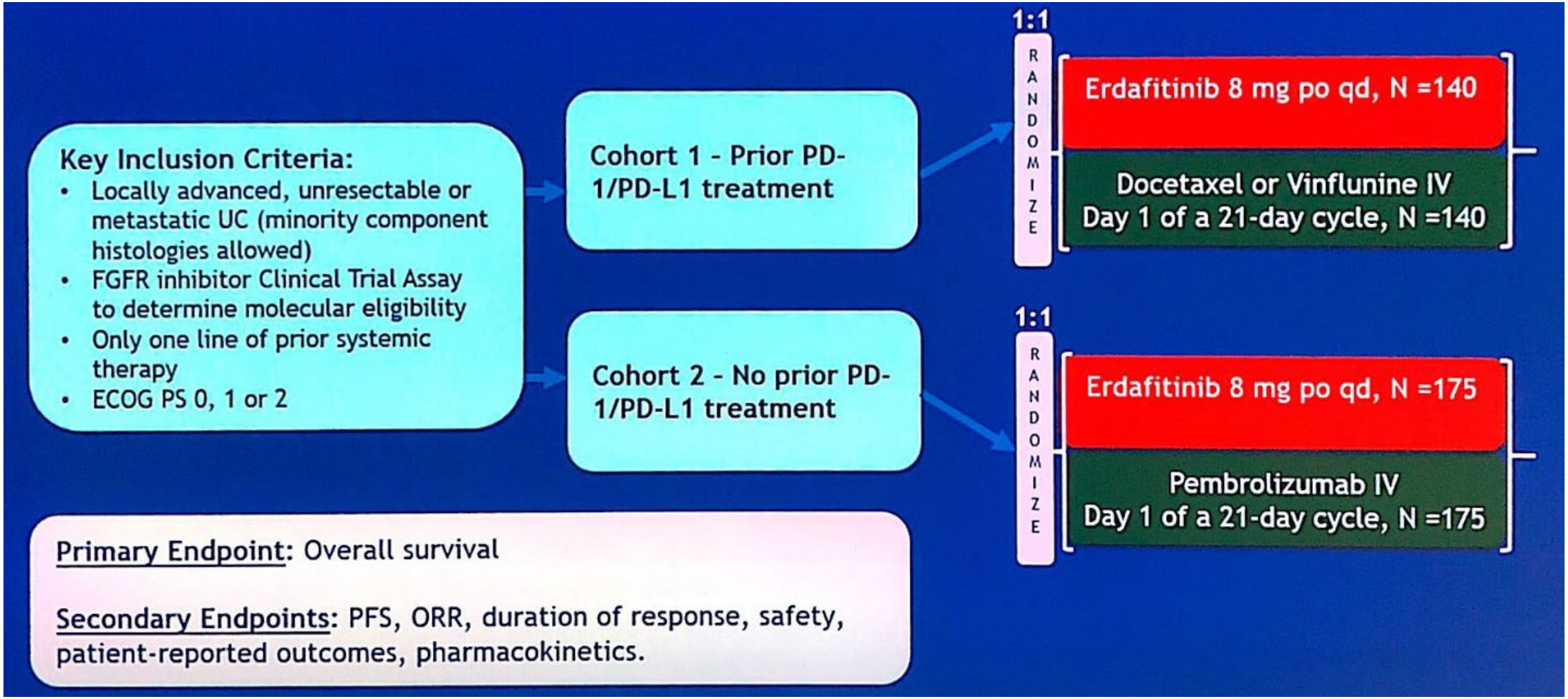
→ Avelumab

Platinum Ineligible

- Pembrolizumab

- FGFR 2/3 alt → Erdafitinib
- **Sacituzumab govitecan**
- Pembrolizumab (if not used before)
- EV (if not used before)
- Platinum + gemcitabine (if not used before)
- HER2 positive: trastuzumab deruxetecan

Phase III THOR Trial: Erdafitinib



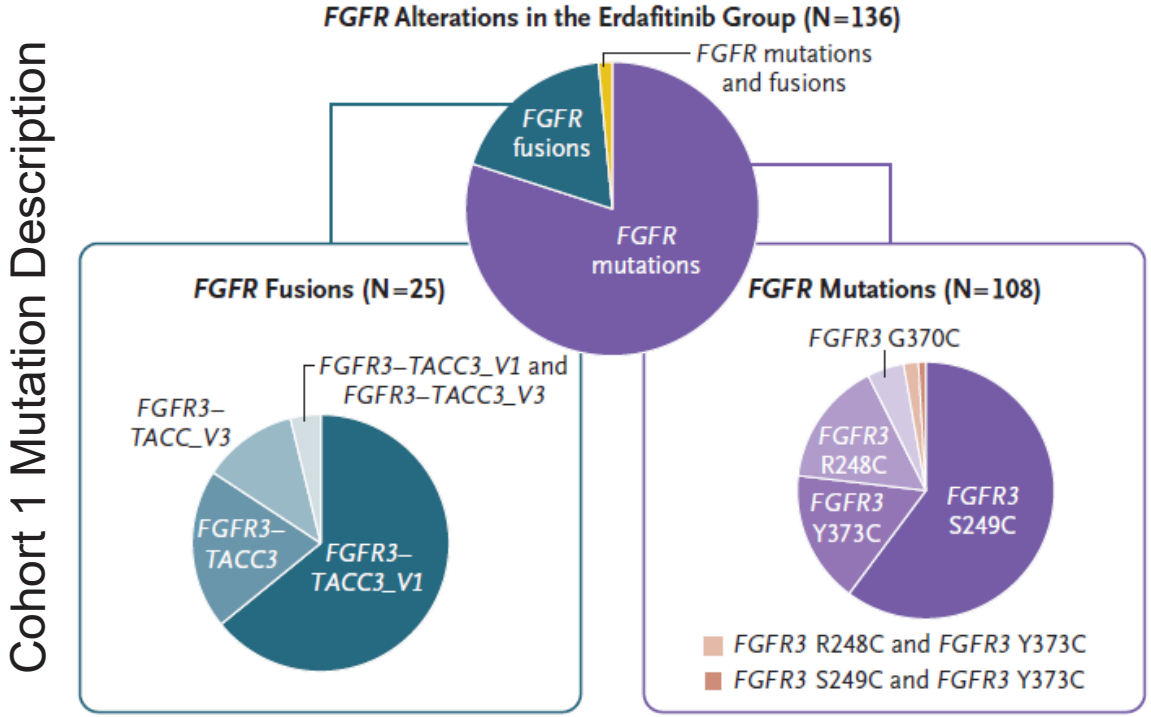
ECOG PS = Eastern Cooperative Oncology Group performance status.

Loriot Y, et al. *N Engl J Med*. 2023;389(21):1961-1971. NIH. Accessed November 1, 2024. https://clinicaltrials.gov/study/NCT03390504.

Phase III THOR Trial: Erdafitinib

Patient selection: 8733 screened for molecular eligibility

- 1212 had an FGFR mutation at a central lab (total tested = 7293)
  - 13.8% of all screened patients were eligible by central lab



Common mutations

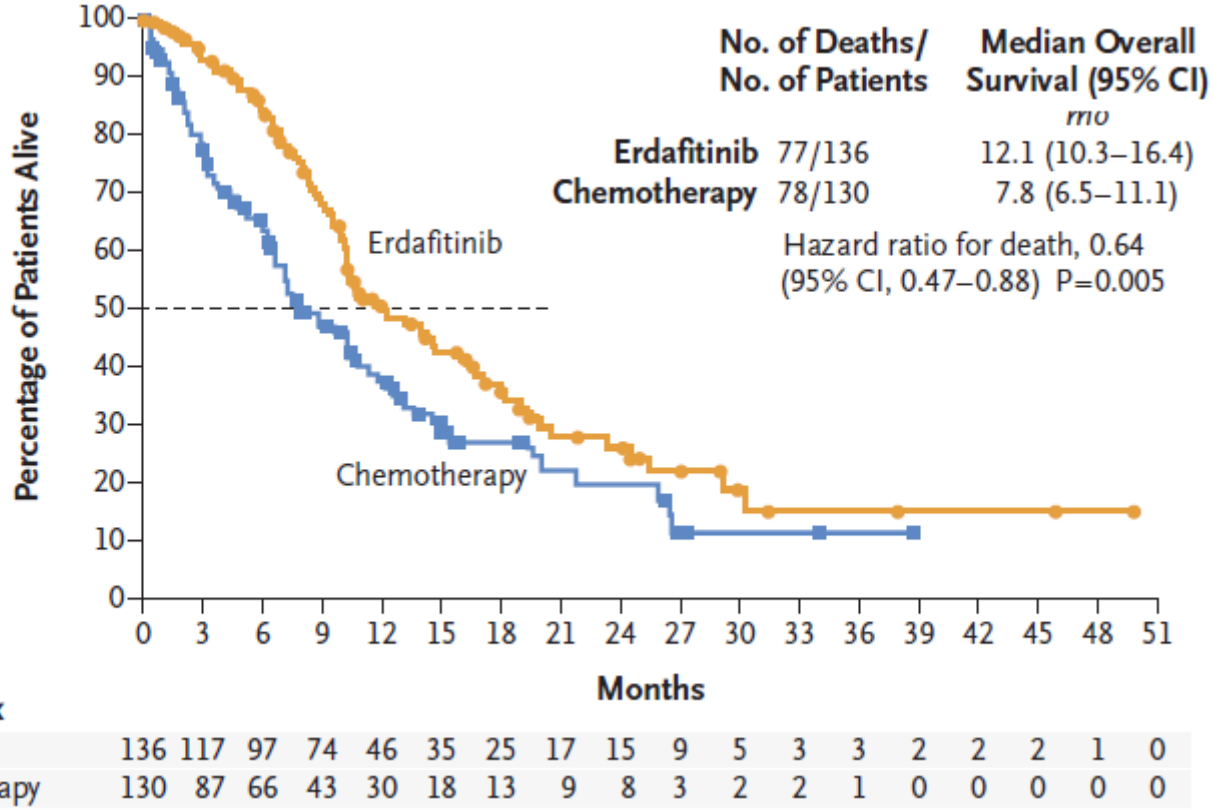
- FGFR3 S249C: 46.6%
- FGFR3 Y373C: 16.9%
- FGFR3-TACC3_V1 fusion: 9.8%

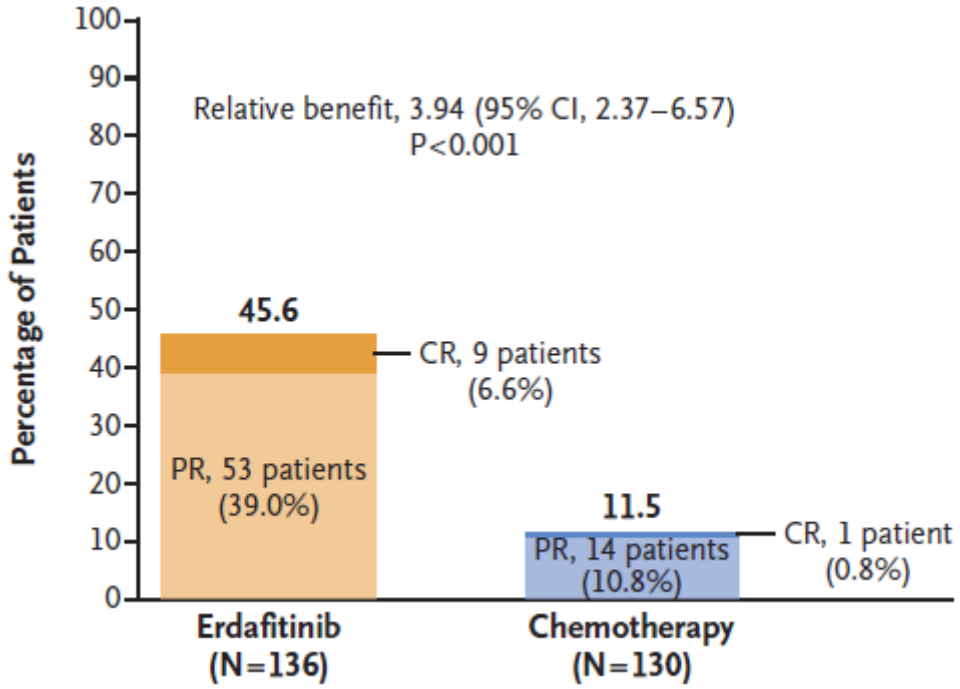
NOTE: No patients had an FGFR alteration

TACC = transforming acidic coiled-coil.

Loriot Y, et al. *N Engl J Med*. 2023;389(21):1961-1971.

THOR (BLC-3001) Trial: Erdafitinib after an ICI (Cohort 1)

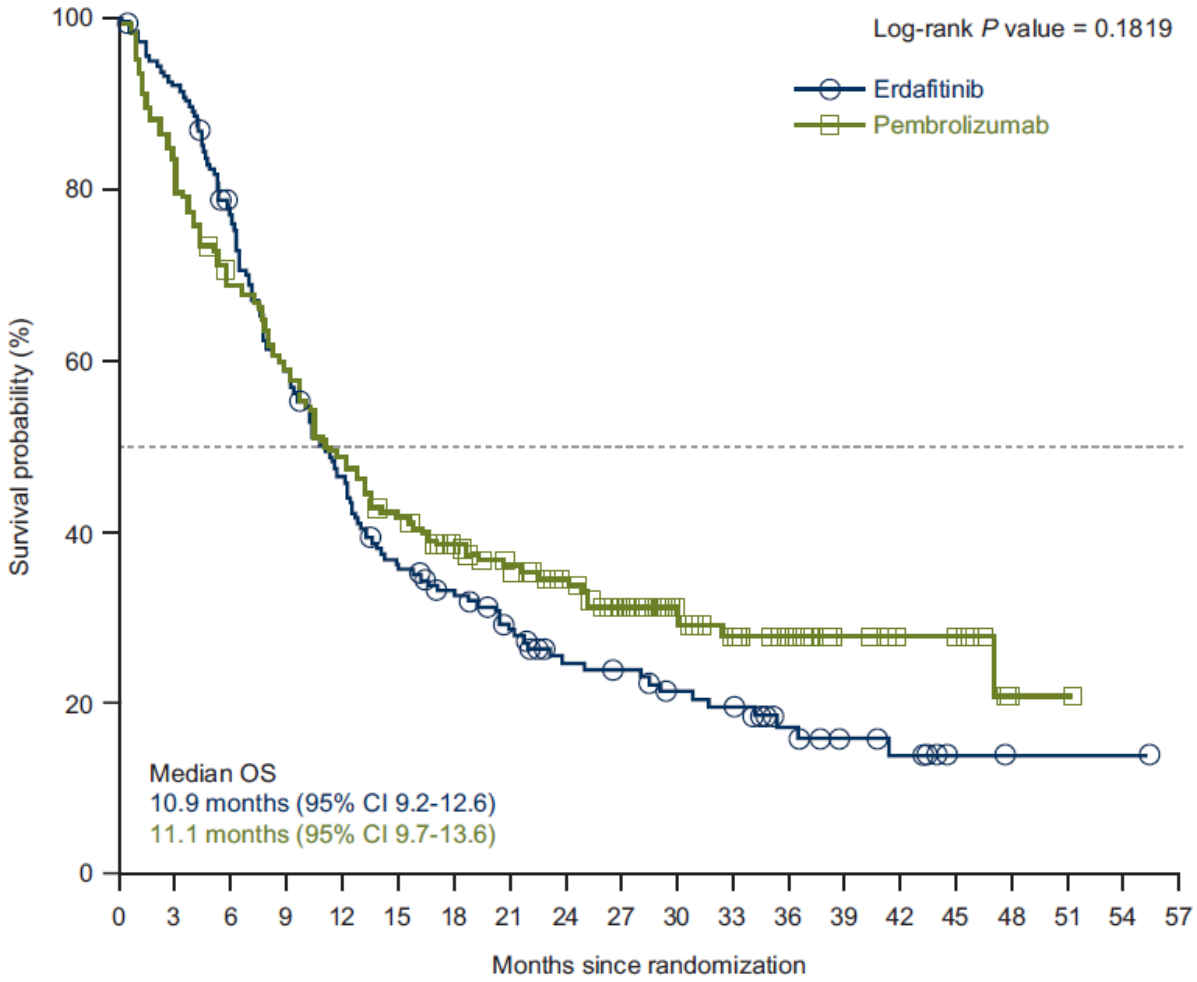


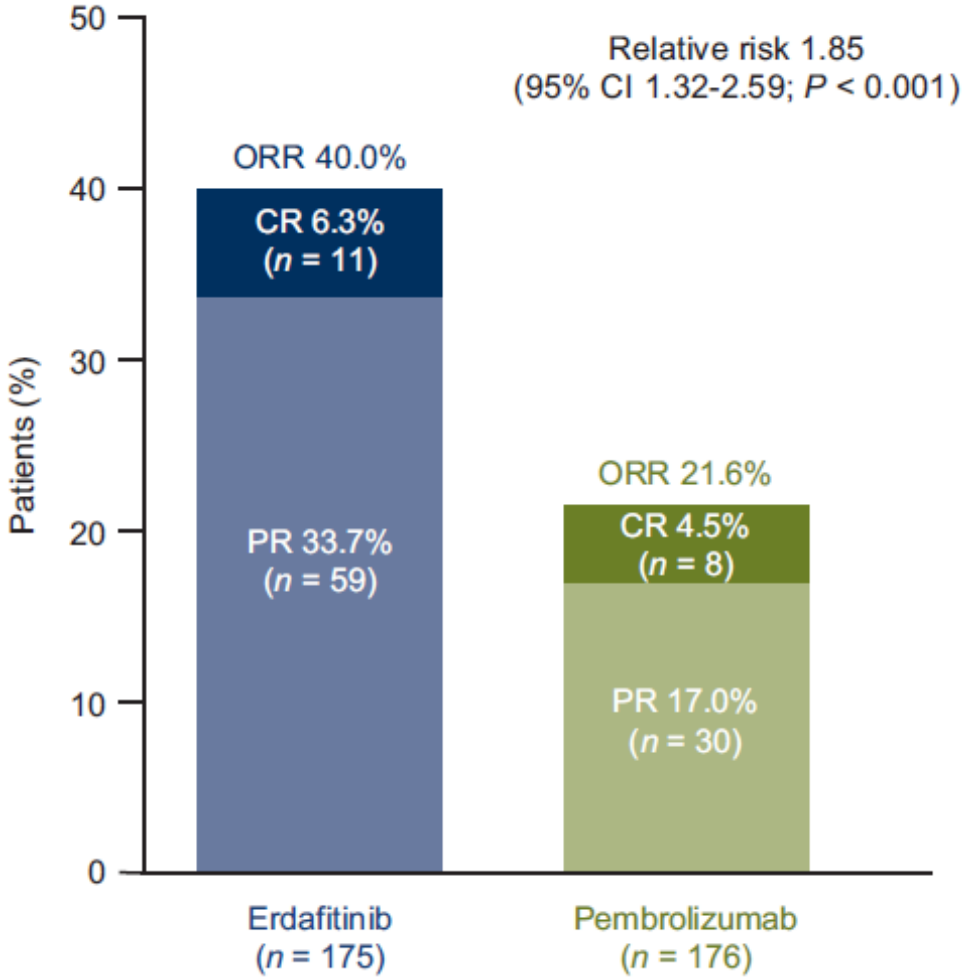


Based on statistically significant improvements in OS, PFS, and ORR, erdafitinib is now approved for patients with locally advanced or metastatic urothelial carcinoma with susceptible *FGFR3* genetic alterations whose disease has progressed on or after at least one line of prior systemic therapy.

Loriot Y, et al. *N Engl J Med*. 2023;389(21):1961-1971.

THOR (BLC-3001) Trial: Erdafitinib with 1+ Prior Therapies (PD1/L1-Naive)





Siefker-Radtke AO, et al. *Ann Oncol*. 2024;35(1):107-117.

THOR (BLC-3001) Trial: Erdafitinib with 1+ Prior Therapies Safety

Table 2. Overall safety summary

Patients with events, *n* (%)	Erdafitinib (*N* = 173)	Pembrolizumab (*N* = 173)
AEs	173 (100)	167 (96.5)
Treatment-related	169 (97.7)	105 (60.7)
Grade 3-4 AEs	112 (64.7)	88 (50.9)
Treatment-related	75 (43.4)	21 (12.1)
Serious AEs	69 (39.9)	80 (46.2)
Treatment-related	23 (13.3)	18 (10.4)
AEs leading to death	5 (2.9)	12 (6.9)
Treatment-related	0	3 (1.7)
AEs leading to treatment discontinuation	33 (19.1)	19 (11.0)
Treatment-related	26 (15.0)	8 (4.6)

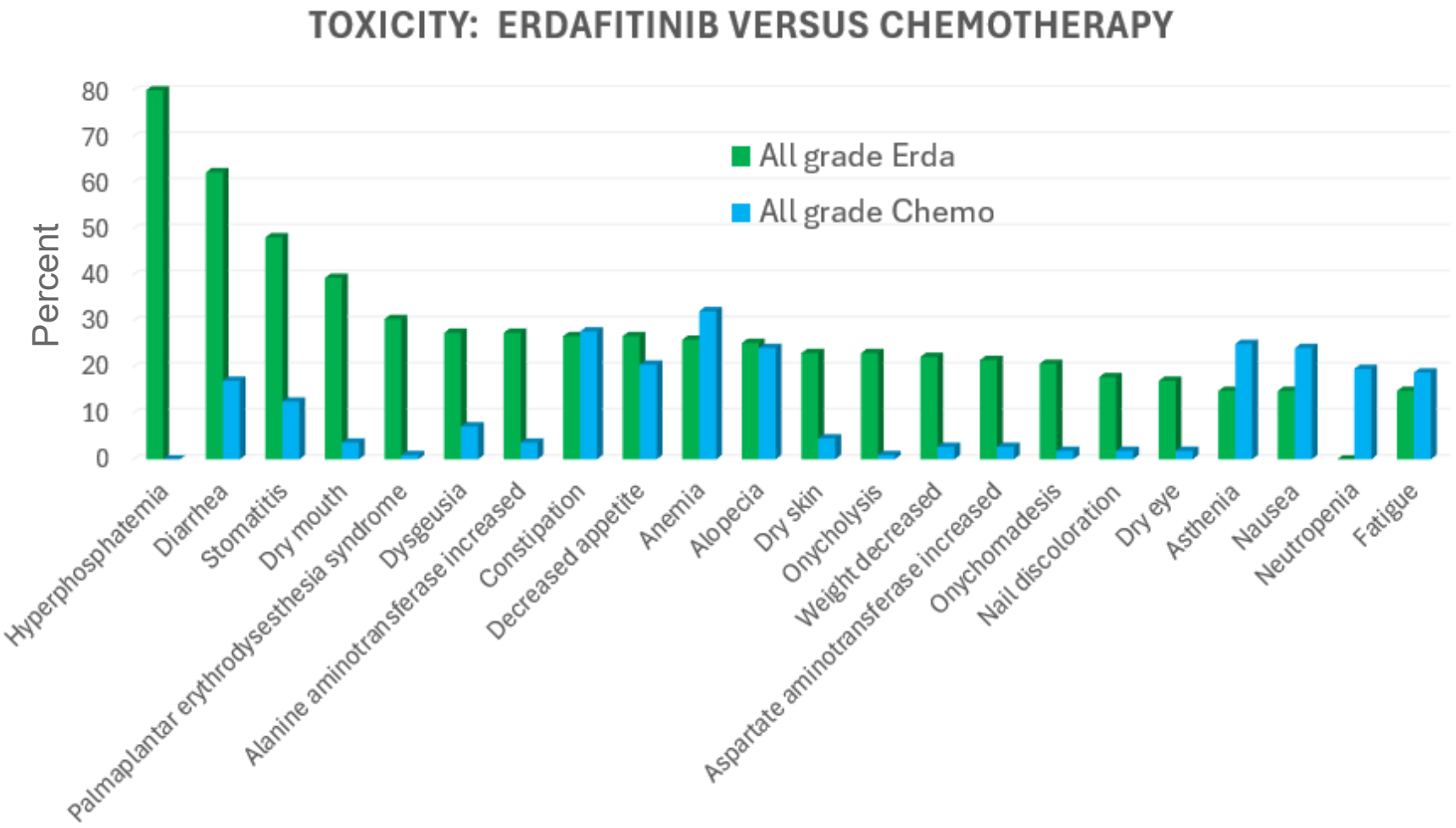
Treatment-related toxicity lower with pembrolizumab

Grade 3-4 AEs significantly lower with pembrolizumab

Fewer patients stopped treatment with pembrolizumab

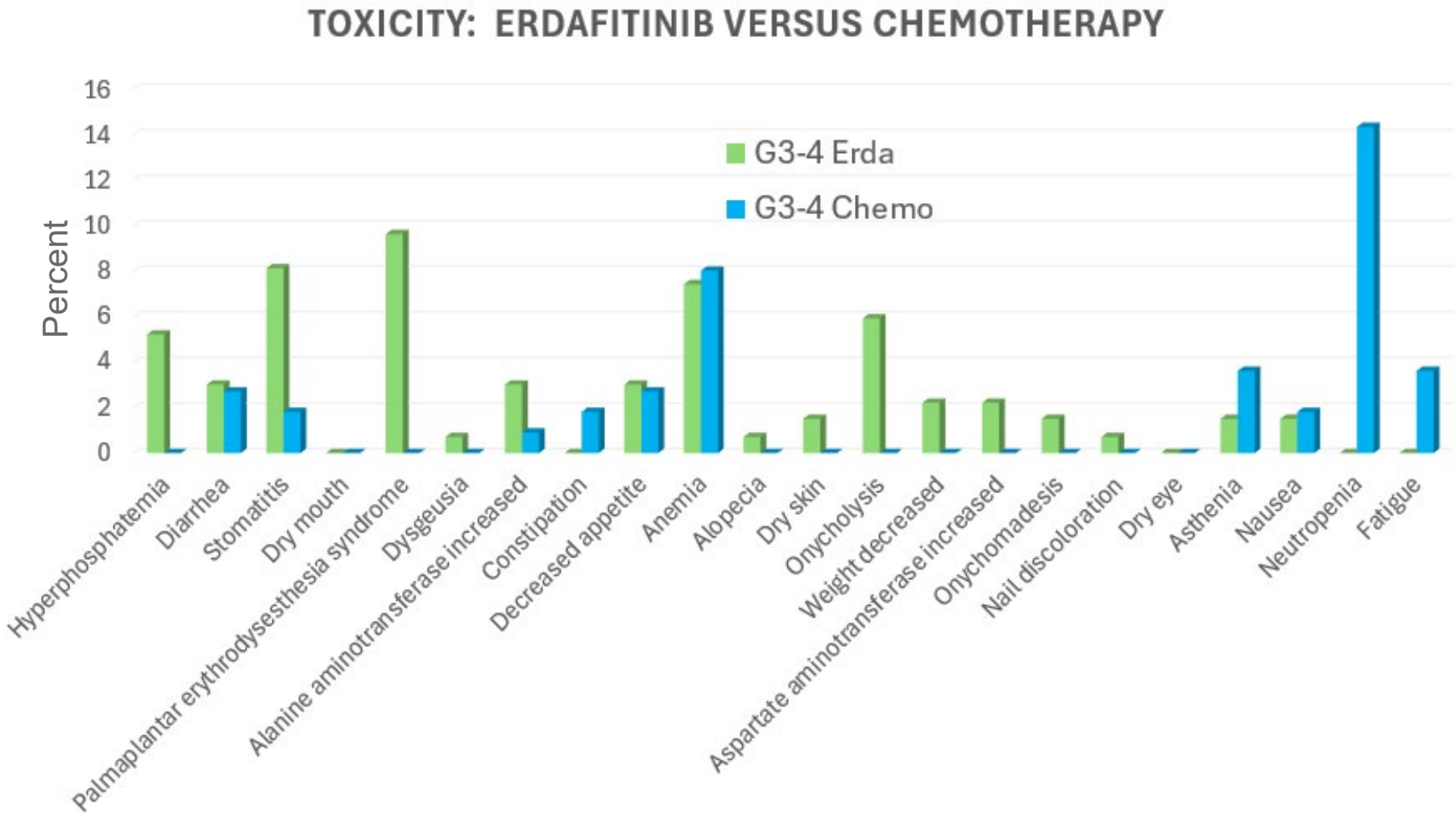
Siefker-Radtke AO, et al. *Ann Oncol*. 2024;35(1):107-117.

THOR (BLC-3001) Trial: Erdafitinib after ICI Treatment Safety



Loriot Y, et al. *N Engl J Med*. 2023;389(21):1961-1971.

THOR (BLC-3001) Trial: Erdafitinib after ICI Treatment Safety



Loriot Y, et al. *N Engl J Med*. 2023;389(21):1961-1971.

Erdafitinib AEs and Dosing

Patients with AEs, n (%)	Erdafitinib (n=135)	
	Any grade	Grade 3-4
≥1 treatment-related AE	131 (97.0)	62 (45.9)
Hyperphosphatemia	106 (78.5)	7 (5.2)
Diarrhea	74 (54.8)	4 (3.0)
Stomatitis	62 (45.9)	11 (8.1)
Dry mouth	52 (38.5)	0
PPE syndrome	41 (30.4)	13 (9.6)
Onycholysis	31 (23.0)	8 (5.9)
Patients who discontinued study treatment, n (%)		
Discontinuation due to treatment-related AEs	11 (8.1%)	

- **Starting dose:** 8 mg orally once daily
  - Dose increase to 9 mg (three 3 mg tablets) once daily based on tolerability at 14 to 21 days if serum phosphate level is < 9.0 mg/dL and there are no ocular disorders or grade 2 or greater adverse reactions
  - Dose decrease if the phosphate level is 9.0 mg/dL or higher at 14 to 21 days based on table below

Dose	1st dose reduction	2nd dose reduction	3rd dose reduction	4th dose reduction	5th dose reduction
9 mg → (three 3 mg tablets)	8 mg (two 4 mg tablets)	6 mg (two 3 mg tablets)	5 mg (one 5 mg tablet)	4 mg (one 4 mg tablet)	Stop
8 mg → (two 4 mg tablets)	6 mg (two 3 mg tablets)	5 mg (one 5 mg tablet)	4 mg (one 4 mg tablet)	Stop	

- Monitor phosphate levels monthly for hyperphosphatemia

Loriot Y. Presented at: American Society of Clinical Oncology Annual Meeting; June 2-6, 2023; Chicago, Illinois. Abstract LBA4619.
Drugs@FDA: FDA-Approved Drugs. Accessed November 5, 2024.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/212018s010lbl.pdf.

Sacituzumab Govitecan: Where Do We Stand?

- TROPHY U-01 phase 2 study in mUC after progression on platinum chemo and ICI
  - ORR 27%, PFS 5.4 mo, OS 10.9 mo
  - Received FDA accelerated approval in 2021 based on this
- However, confirmatory phase 3 TROPiCS-04 DID NOT meet primary endpoints; data presented at ASCO 2024 Annual Meeting
  - ORR of 11%, PFS 2 mo, OS data immature
  - **Gilead WITHDREW US indication for metastatic UC for SG on October 18, 2024**

ASCO = American Society of Clinical Oncology; SG = sacituzumab govitecan.

NIH. Accessed November 1, 2024. https://clinicaltrials.gov/study/NCT03547973; NCT04527991.

First-Line Treatment Options

Platinum Eligible

EV + pembrolizumab

Nivolumab + cis/gem

- ddMVAC
- Cis/gem
- Carbo/gem

→ Avelumab

Platinum Ineligible

Pembrolizumab

Second- + (Subsequent) Line Treatment Options

FGFR 2/3 alt → Erdafitinib

~~Sacituzumab govitecan~~

Pembrolizumab (if not used before)

EV (if not used before)

Platinum + gemcitabine (if not used before)

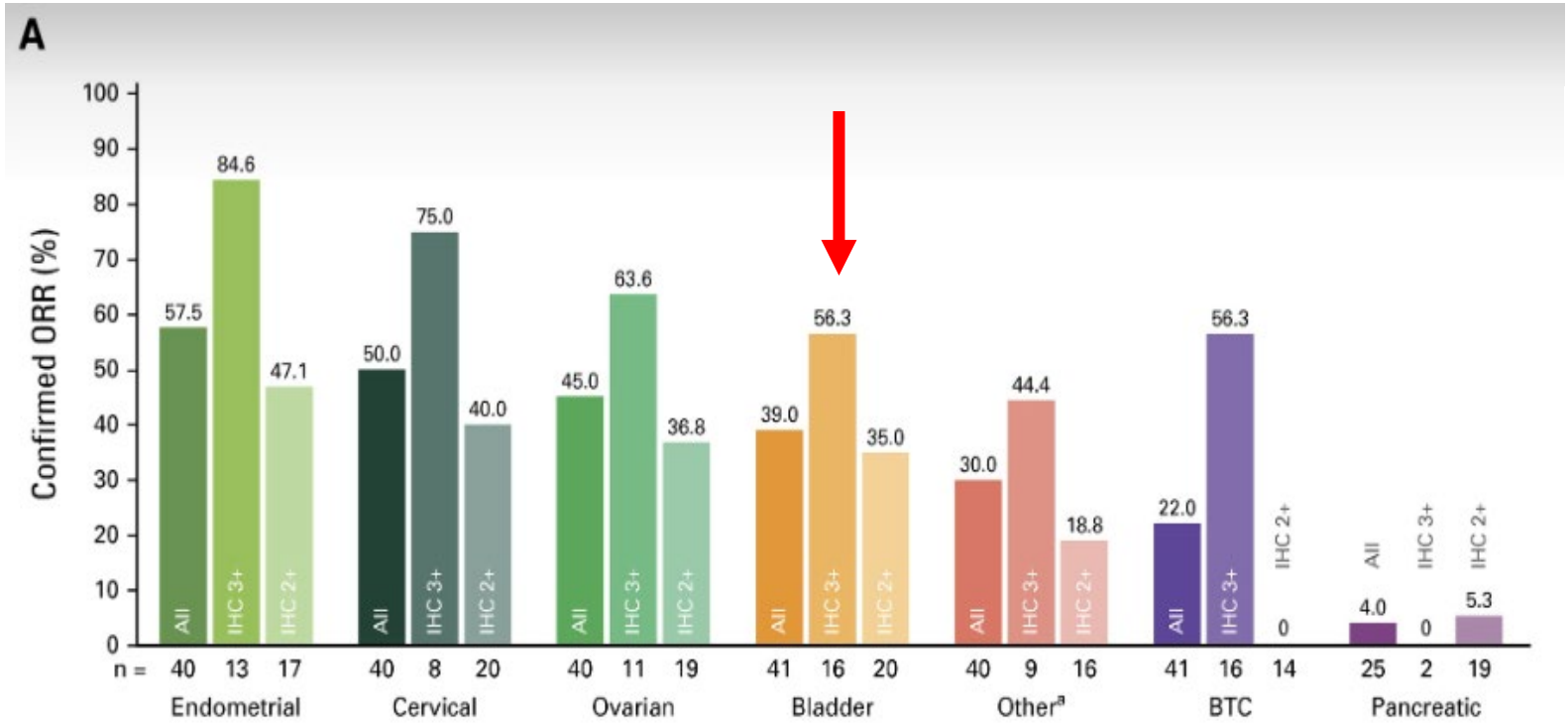
HER2 positive: trastuzumab deruxetecan

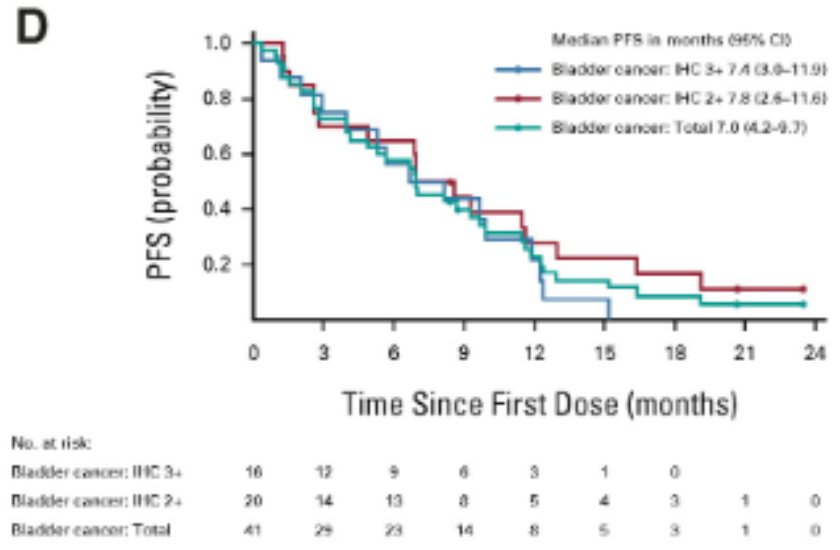
Immunotherapy as Second-Line Therapy

	Atez[illegible]ab	N[illegible]ab	Pembrolizumab	Av[illegible]b	Du[illegible]ab
Phase	Phase III Randomized vs chemotherapy	Phase II Single Arm	Phase III Randomized vs Chemotherpay	Phase Ib	Phase I/II
Number of Patients	931	265	542	249 (161 pts ≥ 6 mos f/u)	191
Dosing	1200mg every 3 weeks	3mg/kg every 2 weeks	200mg every 3 weeks	10mg/kg every 2 weeks	10mg/kg every 2 weeks
ORR	13.4%	19.6%	21.1%	17%	17.8%
Duration of Response	63% of responses ongoing at median f/u of 21.7 mos	77% of responses ongoing at median f/u of 7 mos	72% of responses ongoing at median f/u of 14.1 mos	96% of responses ongoing at 6 mos f/u	50% of responses lasting ≥ 6 mos
Median OS	8.6 mos	8.7 mos	10.3 mos	6.5 mos	18.2 mos
Median PFS	2.1 mos	2.0 mos	2.1 mos	1.5 mos	1.5 mos
Rate of Grade 3/4 Treatment-related AEs	20%	18%	15%	8%	6.8%

Powles T, et al. *Lancet.* 2018;391(10122):748-757. Sharma P, et al. *Lancet Oncol.* 2017;18(3):312-322. Bellmunt J, et al. *N Engl J Med.* 2017;376(11):1015-1026. Patel MR, et al. *Lancel Oncol.* 2018;19(1):51-64. Powles T, et al. *JAMA Oncol.* 2017;3(9):e172411. NIH. Accessed November 1, 2024. https://clinicaltrials.gov/study/NCT03547973; NCT04527991.

DESTINY-PanTumor02: Trastuzumab Deruxtecan in HER2+ mUC



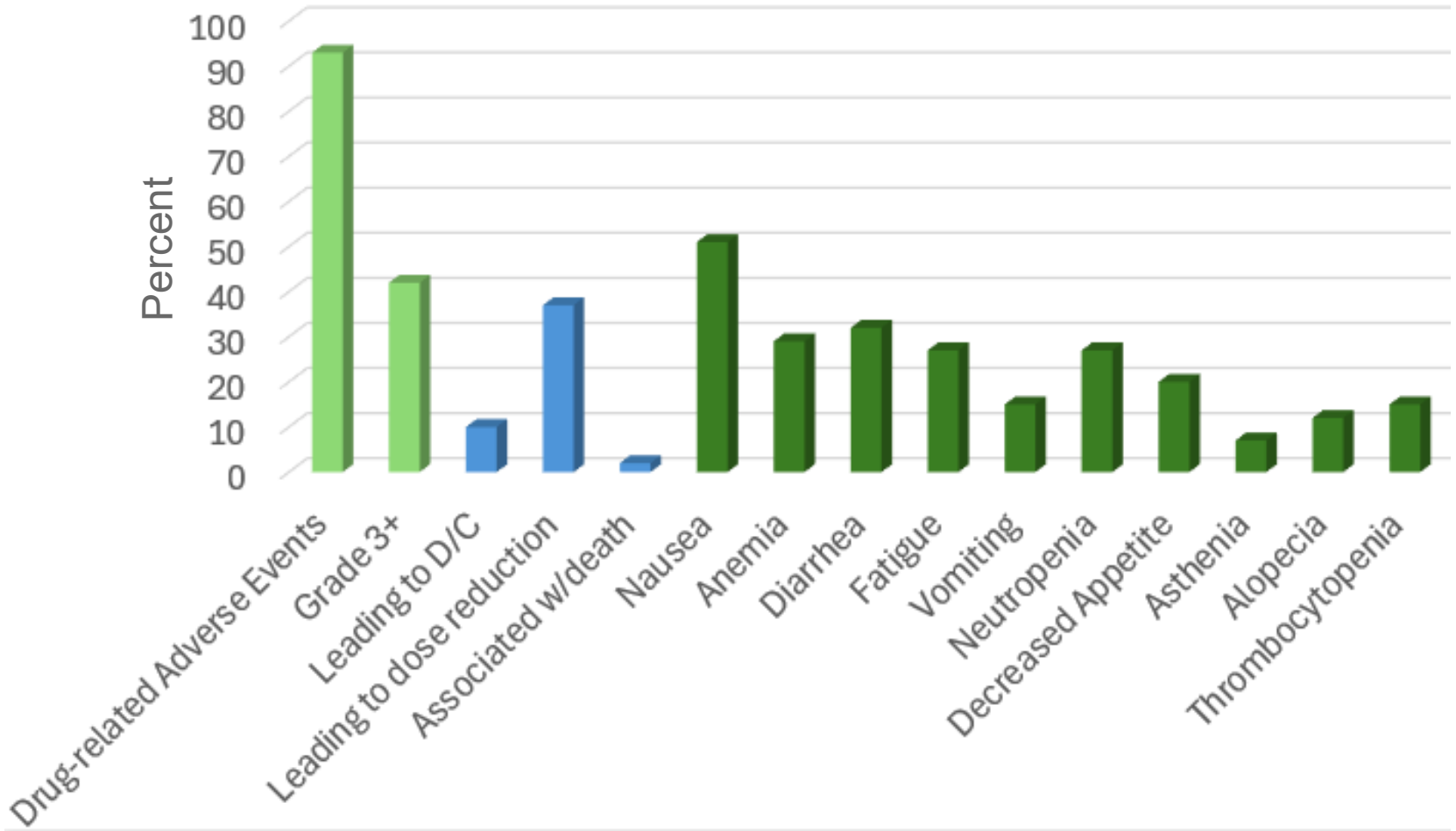


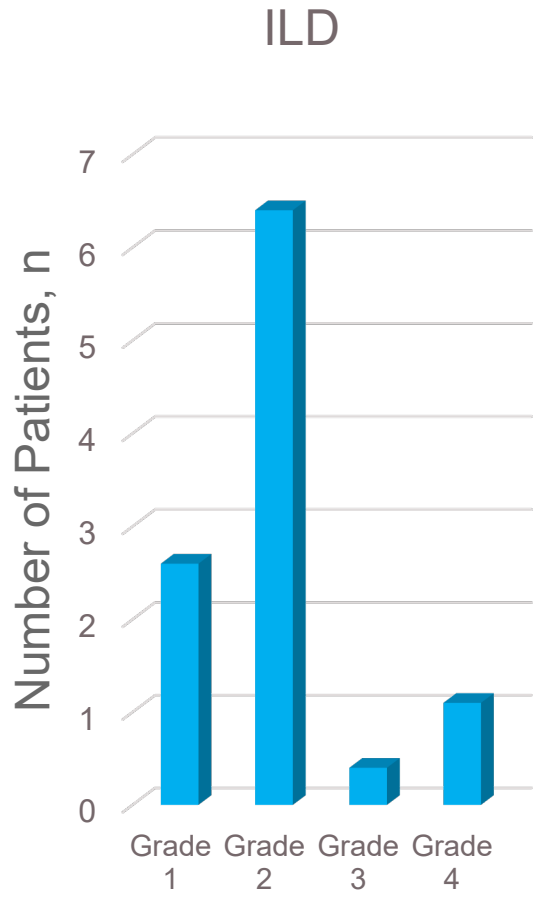
- In bladder cohort (41 patients): ORR 39% (56% if HER2 3+) with mPFS of 7 months
- This phase 2 trial led to FDA approval for trastuzumab deruxtecan (T-DXd) in refractory metastatic urothelial cancer if HER2+ by IHC

mPFS = median progression-free survival; IHC = immunohistochemistry.

Meric-Bernstam F, et al. *J Clin Oncol.* 2023;42(1):47-58. NIH, Accessed November 1, 2024. https://clinicaltrials.gov/study/NCT04482309.

DESTINY-PanTumor02: Trastuzumab Deruxtecan Toxicity in Bladder CA Patients





D/C = discontinuation; CA = cancer; ILD = interstitial lung disease.

Meric-Bernstam F, et al. *J Clin Oncol.* 2023;42(1):47-58.

First-Line Treatment Options

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EV + pembrolizumab

Nivolumab + cis/gem

- ddMVAC
- Cis/gem
- Carbo/gem

→ Avelumab

Platinum Ineligible

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Second- + (Subsequent) Line Treatment Options

FGFR 2/3 alt → Erdafitinib

~~Sacituzumab govitecan~~

Pembrolizumab (if not used before)

EV (if not used before)

Platinum + gemcitabine (if not used before)

HER2 positive: trastuzumab deruxetecan

Exciting Agents or Combination Therapies for Patients with Advanced Bladder Cancer

First-line

- BAYOU: Olaparib plus durvalumab (in cisplatin- or platinum-ineligible patients with DDR mutations)
- NORSE: Erdafitinib plus cetrelimab in FGF3-altered tumors
- ATLANTIS: Rucaparib maintenance post-response platinum therapy
- JAVELIN Bladder Medley: Avelumab maintenance therapy in combination with other agents, including Sacituzumab govitecan, for patients with metastatic urothelial carcinoma (NCT05327530)

Second-line

- Disitimab vedotin (HER2 ADC)
  - RC48-C005 and RC48-C009: ORR 50% (CR 2%), DOR: 7.3mo, PFS: 6 mo
- TROPHY U-01 Cohort 3: Sacituzumab govitecan plus pembrolizumab
- Pembrolizumab in combination with sEphB4-HSA
- MORPHEUS-UC: Combination atezolizumab with multiple agents targeting different mechanisms (via nectin-4, PARP, CD47, CD38, DPP-4, IL-6R)
- Sitravatinib (spectrum-selective TKI) plus nivolumab
- JAVELIN DDRiver Bladder: Tuversetib (ATR inhibitor) plus avelumab

DDR = DNA damage response; TKI = tyrosine kinase inhibitor.

Fulton B, et al. *Trials.* 2020;21(1):344. NIH. Accessed November 1, 2024. https://clinicaltrials.gov/study/NCT03459846; NCT03473743; NCT05327530; NCT03507166; NCT03809013; NCT03547973; NCT02717156; NCT03869190; NCT03606174; NCT06424717.

Treatment Strategies

Platinum and Cisplatin Eligibility Criteria

Cisplatin vs Platinum Ineligibility		
	Cisplatin Ineligibility (Galsky criteria)	Platinum Ineligibility (Gupta criteria)
Performance status (ECOG)	≥2	≥3
Renal function (Cr Cl)	<60 ml/min	<30 ml/min
Hearing	Grade ≥2 hearing loss	Grade ≥2 hearing loss
Neuropathy	Grade ≥2 peripheral neuropathy	Grade ≥ 2 peripheral neuropathy
Heart Failure	NYHA Class III	NYHA Class III
		* In patient with ECOG PS ≥ AND CrCl<30, they are considered platinum ineligible

CrCl = creatinine clearance; NYHA = New York Heart Association.

Galsky MD, et al. *J Clin Oncol*. 2011;29(17):2432-2438. Gupta S, et al. *J Natl Cancer Inst.* 2024;116(4):547-554.

Treatment Landscape in Advanced Urothelial Cancer from First to Sixth Line

Treatment	Treatment line, No. (%) of patients (n = 7260)					
	First	Second	Third	Fourth	Fifth	Sixth
All	7260 (100)	2714 (37.4)	857 (11.8)	282 (3.9)	81 (1.1)	27 (0.4)
Carboplatin-based regimen	2241 (30.9)	403 (14.8)	106 (12.4)	28 (9.9)	7 (8.6)	2 (7.4)
Cisplatin-based regimen	2008 (27.7)	157 (5.8)	48 (5.6)	10 (3.5)	0	2 (7.4)
PD-1/PD-L1 inhibitors	2174 (29.9)	1412 (52.0)	258 (30.1)	75 (26.6)	13 (16.0)	5 (18.5)
Single-agent nonplatinum chemotherapy	565 (7.8)	342 (12.6)	169 (19.7)	47 (16.7)	23 (28.4)	7 (25.9)
Enfortumab vedotin	57 (0.8)	219 (8.1)	159 (18.6)	62 (22.0)	13 (16.0)	2 (7.4)
Erdafitinib	14 (0.2)	39 (1.4)	28 (3.3)	8 (2.8)	4 (4.9)	3 (11.1)
Sacituzumab govitecan	6 (0.1)	14 (0.5)	34 (4.0)	27 (9.6)	15 (18.5)	1 (3.7)
Other	195 (2.7)	128 (4.7)	55 (6.4)	25 (8.9)	6 (7.4)	5 (18.5)

- Only 1/3 of patients with metastatic bladder cancer will make it to second-line therapy, and only about 11% of patients will make it to third-line therapy
- We need to make the treatments count!
- Once a patient progresses on first-line treatment, need to have extensive discussion regarding next best line of therapy for patient; every patient is different

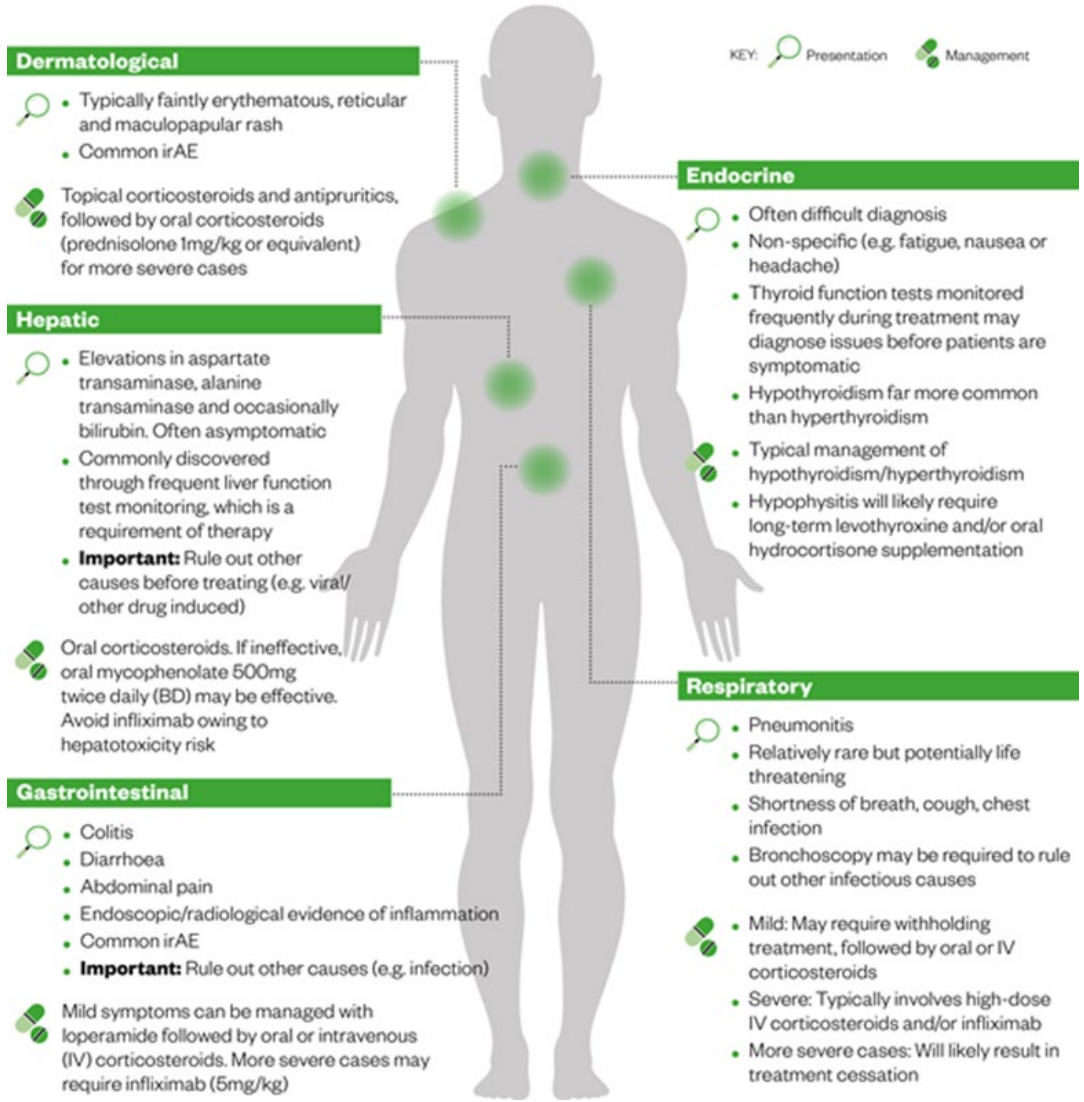
Thomas VM, et al. *JAMA Netw Open.* 2024;7(5):e249417.

Treatment Considerations Based on Side Effect Profile

- If severe neuropathy → avoid cisplatin and EV
- If uncontrolled diabetes → avoid EV
- If active autoimmune disease (on immunosuppressive medication) → avoid pembrolizumab
- If severe heart failure → avoid cisplatin and trastuzumab
- If ILD → avoid trastuzumab
- If liver cirrhosis/liver disease → avoid EV

Adverse Event Management

Immune-Related Adverse Events (irAEs)



Spain L, et al. *Cancer Treat Rev.* 2016;44:51-60.

General Management of irAEs

Grade 1: minor symptoms; no impact on ADLs	Symptomatic treatment Monitor closely
Grade 2: moderate symptoms; impact on ADLs	Withhold immunotherapy until grade 1 Symptoms last > 1 week or worsening: Systemic corticosteroids
Grade 3/4: severe symptoms; consider hospitalization; life-threatening	Consider permanently discontinuing immunotherapy Systemic corticosteroids
Steroid-Refractory	Infliximab Calcineurin inhibitors Mycophenolate

ADL = activity of daily living.

Spain L, et al. *Cancer Treat Rev.* 2016;44:51-60.

Dermatologic Toxicity from EV-P

Risk factors	Prevention
• Prior history of a dermatologic condition (including immune-related skin disorders such as psoriasis or lupus) • Rash/pruritus • Allergies • Dry skin • Immunosuppression • High sun exposure • Prior cutaneous reactions to previous lines of anticancer therapies • Skin damage due to therapeutic radiation	Recommendations for the prevention of skin reactions follow best practice prophylaxis protocols for general treatment-associated dermatologic events: • Barrier protectants (e.g., zinc-containing moisturizers) • Sunscreen • Emollients • Proper hydration • Avoid hot showers • Mild skin cleaners • Avoid OTC acne medications

MONITORING AND MANAGEMENT

- Routine skin assessments should begin with cycle 1
- Counsel patients and caregivers to immediately report new or worsening skin reactions

Grade 1	Closely monitor and continue at same dose level with supportive care as clinically indicated (topical emollients, topical corticosteroids, anti-infectives, and topical and oral antihistamines)
Grade 2	• Closely monitor and continue at same dose level with supportive care as clinically indicated (topical emollients, topical corticosteroids, anti-infectives, and topical and oral antihistamines) • For worsening rash or skin reactions with concomitant fever, hold both agents until grade ≤1 or has returned to baseline, then resume EV treatment at same dose level or reduced by one level, and resume Pembro. Consider specialist referral • For persistent or recurrent grade 2, hold both agents until grade ≤1, then consider reintroduction of EV at same or reduced dose, and resume Pembro. Consider specialist referral

Grade 3	• Hold both agents if rapid onset or worsening symptoms
	• Oral or systemic corticosteroids while holding both drugs until complete or partial resolution (grade ≤1)
	  • May supplement with the supportive care recommendations described for Grades 1 and 2 above
	• Specialist referral
	• Consider skin biopsy to assist with diagnosis
	• After improvement to grade ≤1, and either on prednisone ≤10 mg (or equivalent) per day or off corticosteroids
	  • Consider reintroduction of EV at same dose level or reduced by one level
	  • Consider reintroduction of Pembro depending upon the severity and presentation of the skin reaction

Signs and symptoms of potential SJS/TEN include malaise, fever ≥100.4°F or ≥38°C, mucosal involvement (ocular, oral, genital), and dermatodynia

Biopsy of any desquamating or blistering rash recommended

Suspected SJS/TEN	• Hold both agents. Perform skin biopsy. Discontinue permanently if confirmed SJS/TEN. Otherwise see grade 2–4 skin reactions • Consider inpatient and specialist management
Grade 4; recurrent grade 3	• Permanently discontinue both agents • Consider inpatient and specialist management • Skin biopsy may assist with diagnosis

SJS/TEN = Stevens-Johnson syndrome/toxic epidermal necrolysis; OTC = over-the-counter.

Brower B, et al. *Front Oncol.* 2024;14:1326715.

Neuropathy from EV-P

Risk factors	Prevention
• Certain anticancer therapies, including MMAE-containing ADCs • Comorbidities (e.g., diabetes mellitus) • Older age • Spinal involvement of mUC • Nonmalignant spinal disease	• Provide patient education on signs and symptoms • Monitor closely with early, conservative intervention to prevent peripheral neuropathy from becoming severe

MONITORING AND MANAGEMENT

- Evaluate for signs and symptoms of peripheral neuropathy and assess impact on activities of daily living regularly
- Simple tests (e.g., picking up a coin, buttoning their shirt, or handwriting) can be helpful in assessing the extent of their symptoms
- Patients should be informed about how peripheral neuropathy can manifest and that any numbness and tingling of the hands or feet, muscle weakness (especially in legs, or issues with balance) should be reported immediately

Grade 1
- Consider proactive dose reduction or dose hold of EV
- Consider holding Pembro (low threshold to hold), monitor symptoms closely for a week
- Consider adjunct treatment with medications for nerve pain (e.g., duloxetine, pregabalin, and gabapentin)

Grade 2
- Withhold EV until grade ≤1 or return to baseline
  - For first occurrence, resume treatment at the same dose level
  - For recurrent grade 2, resume treatment reduced by one dose level
- Consider workup for immune-mediated etiology
- Consider adjunct treatment with medications for nerve pain (e.g., duloxetine, pregabalin,and gabapentin)
- Consider physical or occupational therapy

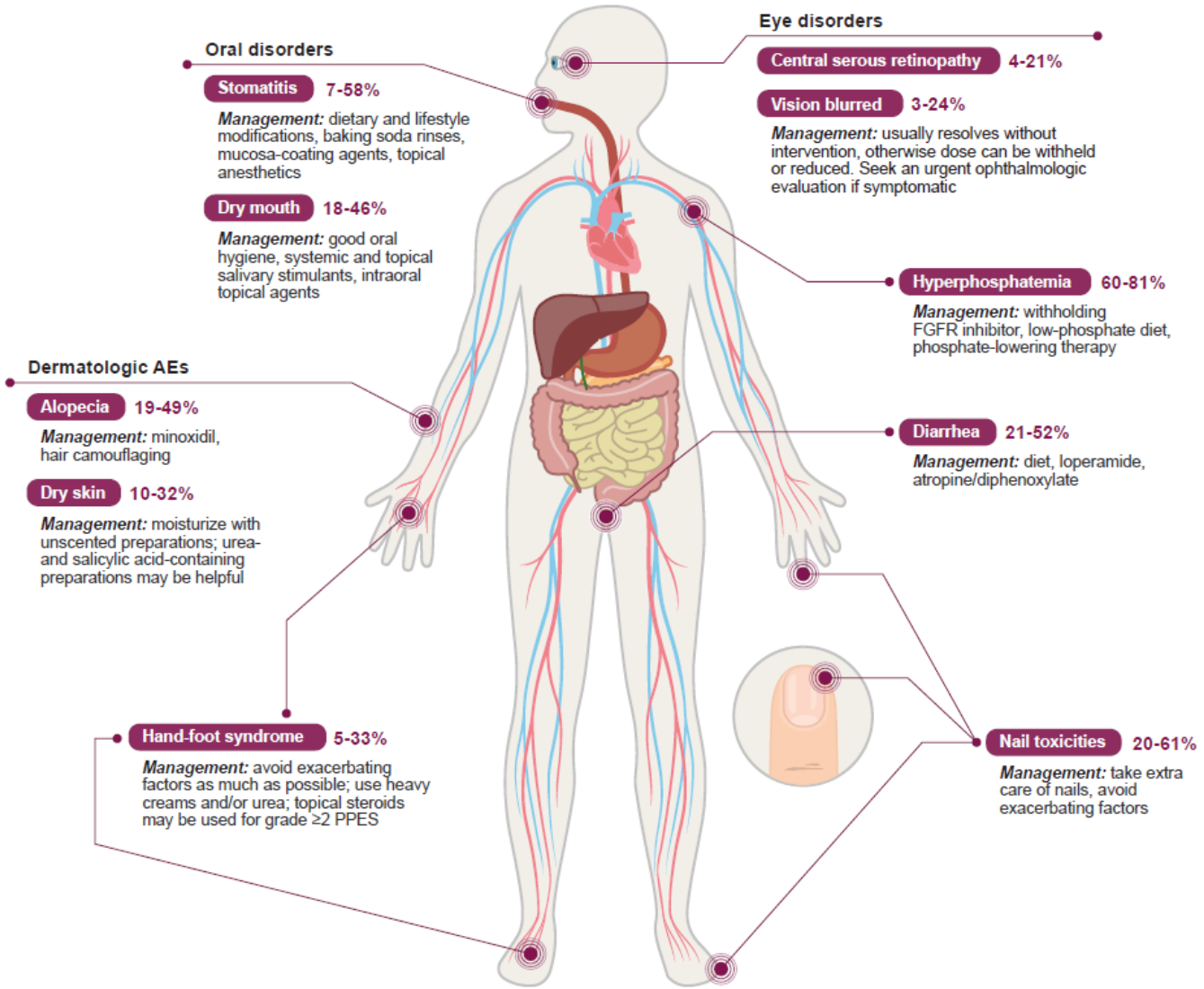
Urgent neurologist referral if the following are suspected
- Myasthenia gravis (muscle weakness, dysphagia, ptosis, vision changes
- Guillain-Barré syndrome (muscle weakness with absent or reduced tendon reflexes)
- Encephalitis (confusion, altered behavior, headaches, seizures)

Grade ≥3
- Permanently discontinue both agents
- Specialist referral

Possible immune-related nervous system AE (e.g., symptoms not consistency with peripheral sensory neuropathy)
- Hold Pembro
- Specialist referral and neurologic workup

Brower B, et al. *Front Oncol.* 2024;14:1326715.

Toxicity Management with FGFRi



PPES = palmar-plantar erythrodysesthesia syndrome; FGFRi = FGFR inhibitor.

Subbiah V, et al. *Cell Rep Med*. 2023;4(10):101204.

Toxicity Management with Trastuzumab Deruxtecan

Toxicity	Management
Nausea and vomiting	• Pretreatment with a 5-HT3 receptor antagonist and dexamethasone with or without a neurokinin-1 receptor antagonist • Delayed nausea prophylaxis: give dexamethasone on days 2-3
Neutropenia	• Grade 3: hold until resolved to grade 2, then maintain dose • Grade 4/NF: hold until resolved to grade 2, then reduce dose 1 level
Thrombocytopenia	• Grade 3: hold until resolved to grade 2, then maintain dose • Grade 4: hold until resolved to grade 2, then reduce dose 1 level
Infusion-related reactions	• First infusion: administer over 90 min; subsequent infusions may be given over 30 min if prior infusions reactions • The infusion rate may be reduced to 50% or temporarily stopped if a patient experiences an infusion-related reaction (grade 1 or grade 2, respectively); the infusion should be permanently stopped if the reaction is severe (grade 3 or 4)
ILD/pneumonitis	• Asymptomatic/grade 1: hold until resolved to grade 0, then - If resolved in 28 days, maintain dose - If resolved in >28 days, reduce dose 1 level - Consider corticosteroid treatment at onset • Symptomatic/grade 2: permanently discontinue T-DXd and begin corticosteroid

NF = neutropenic fever.

Rugo HS, et al. *ESMO Open*. 2022;7(4):100553.

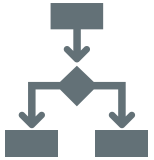
Optimization of Patient-Centered Clinical Care

Understanding patient factors and barriers

Multidisciplinary care

- Engage palliative/ supportive care early!!
- Consider alternative palliative modalities (interventional pain for nerve block, radiation oncology for symptom control)
- Work closely with urology if need stenting, debulking, etc.

Utilization of nurse navigators



Shared decision-making

Key Learning Points

- Based on statistically significant improvements in OS, PFS, and ORR demonstrated in the BLC-3001 (THOR) trial, **erdafitinib** is now approved for patients with locally advanced or metastatic urothelial carcinoma with susceptible *FGFR3* genetic alterations whose disease has progressed on or after at least one line of prior systemic therapy
- **Enfortumab vedotin** is a category 1 preferred systemic therapy option in the current NCCN guidelines for locally advanced or metastatic UC previously treated with chemotherapy and anti-PD(L)1 therapy
- **Regular monitoring of phosphate levels to manage hyperphosphatemia** is recommended for mitigating potential AEs associated with FGFR kinase inhibitor therapy

Questions?