Bladder Cancer: Novel Insights and Recent Approvals

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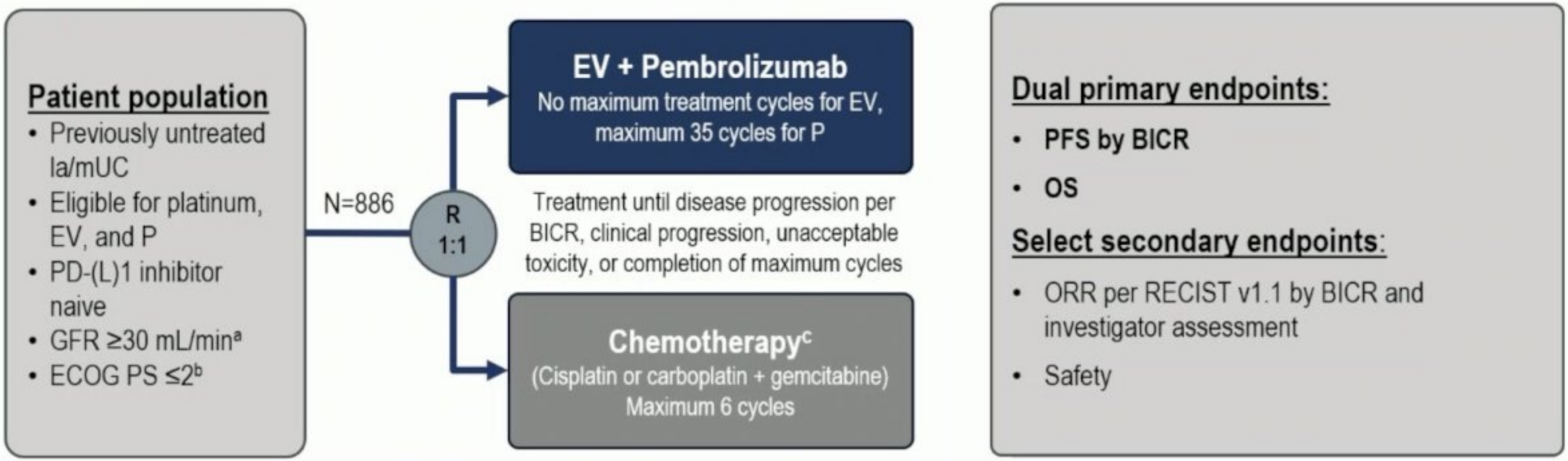
Friday, July 19, 2024
New Orleans Summer Cancer Meeting

Recent Progress in Bladder Cancer

- New SOC in First Line Met Urothelial Cancer (enfortumab vedotin + pembrolizumab)
- FDA Approval of nivolumab + gemcitabine/cisplatin for Met Urothelial Cancer
- FDA Approval of Novel Gene Therapy in NMIBC (nadofaragene firadenovec)
- FDA Approval of Novel Immunotherapy in NMIBC (nogapendekin alfa inbakicept-pmln)
- New data on a Novel Gene Therapy/Immunotherapy Combo in NMIB (cretostimogene grenadenorepvec and pembrolizumab)

EV-302/KEYNOTE-A39 (NCT04223856)

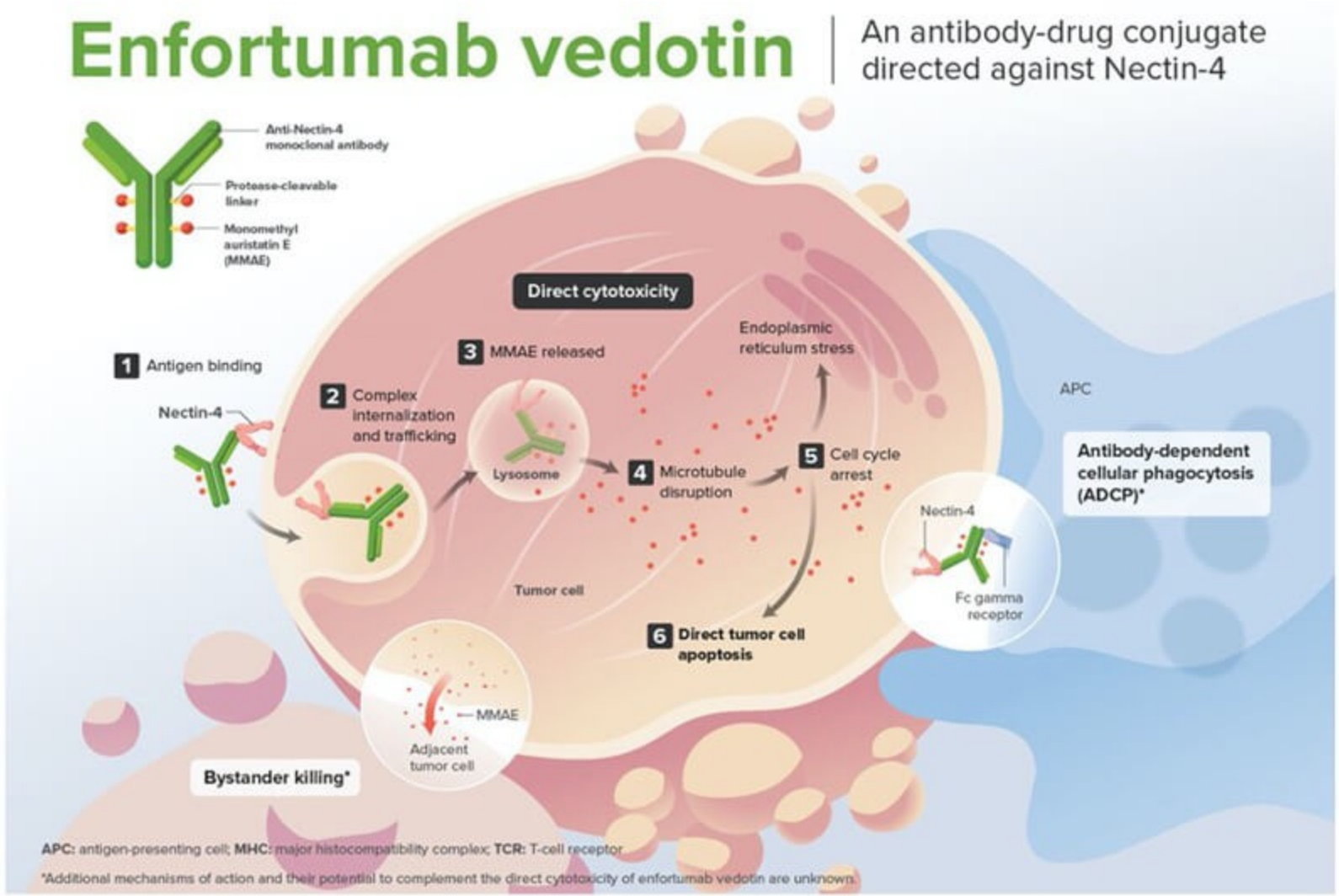


Stratification factors: cisplatin eligibility (eligible/ineligible), PD-L1 expression (high/low), liver metastases (present/absent)

Cisplatin eligibility and assignment/dosing of cisplatin vs carboplatin were protocol-defined; patients received 3-week cycles of EV (1.25 mg/kg; IV) on Days 1 and 8 and P (200 mg; IV) on Day 1

Statistical plan for analysis: the first planned analysis was performed after approximately 526 PFS (final) and 356 OS events (interim); if OS was positive at interim, the OS interim analysis was considered final

https://www.urotoday.com/conference-highlights/esmo-2023/esmo-2023-bladder-cancer/147538-esmo-2023-ev-302-keynote-a39-enfortumab-vedotin-in-combination-with-pembrolizumab-ev-p-vs-chemotherapy-in-previously-untreated-locally-advanced-metastatic-urothelial-carcinoma.html

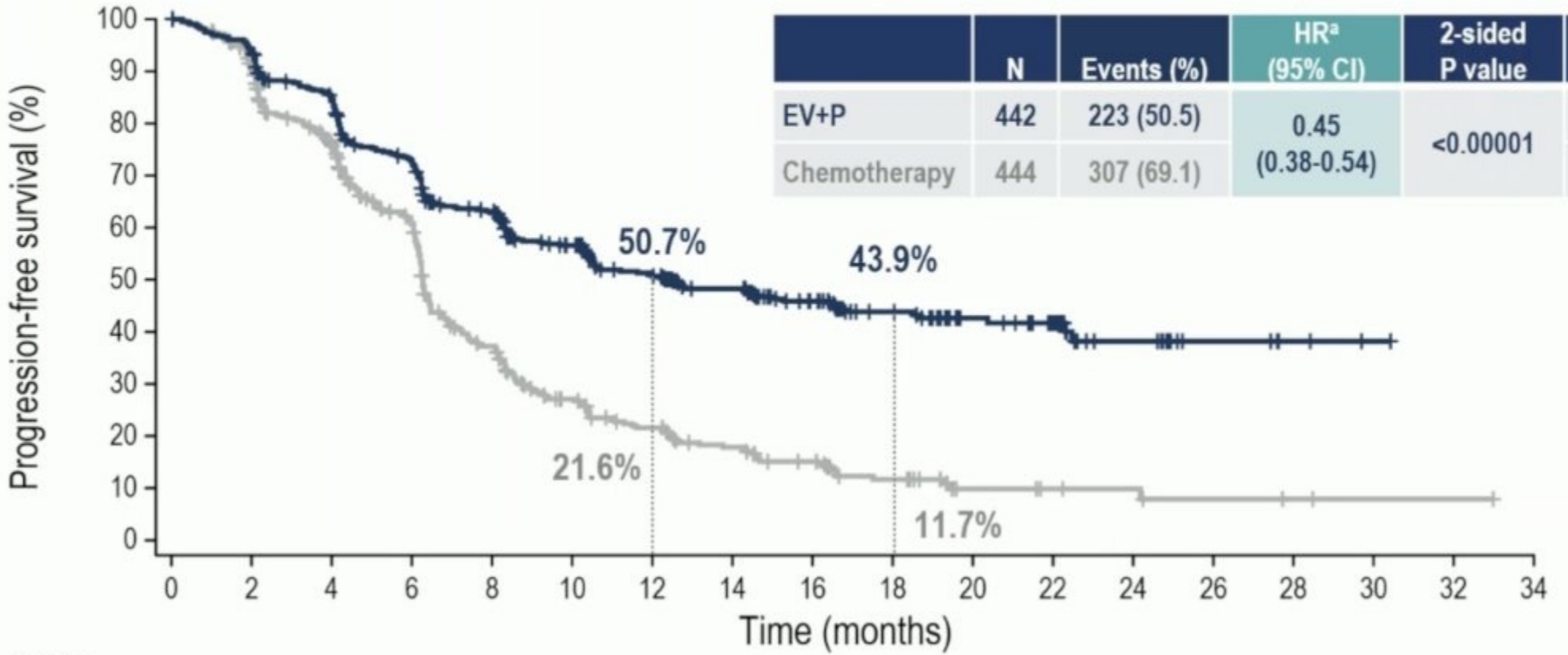


- https://www.biochempeg.com/article/381.html

Progression-Free Survival per BICR

Risk of progression or death was reduced by 55% in patients who received EV+P

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mPFS (95% CI), months
EV+P	442	223 (50.5)	0.45 (0.38-0.54)	<0.00001	12.5 (10.4-16.6)
Chemotherapy	444	307 (69.1)			6.3 (6.2-6.5)



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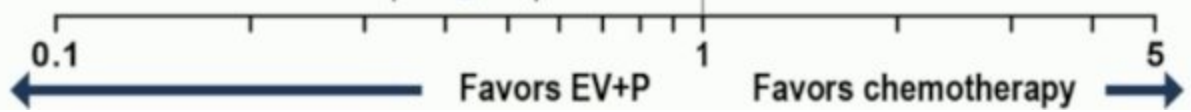
Subgroup Analysis of PFS per BICR

PFS benefit in select pre-specified subgroups was consistent with results in overall population

Subgroup	Events/N EV+P	Events/N Chemotherapy	Hazard Ratio (95% CI)
Overall	223/442	307/444	0.45 (0.38-0.54)
Age			
<65 years	75/144	88/135	0.45 (0.32-0.62)
≥65 years	148/298	219/309	0.45 (0.36-0.56)
Sex			
Female	55/98	74/108	0.49 (0.34-0.71)
Male	168/344	233/336	0.44 (0.36-0.54)
ECOG PS			
0	93/223	146/215	0.36 (0.28-0.48)
1-2	130/219	161/227	0.53 (0.42-0.68)
Primary disease site of origin			
Upper tract	69/135	70/104	0.50 (0.35-0.71)
Lower tract	152/305	236/339	0.44 (0.35-0.54)
Liver metastases			
Present	66/100	78/99	0.53 (0.38-0.76)
Absent	157/342	229/345	0.43 (0.35-0.52)
PD-L1 expression			
Low (CPS <10)	105/184	127/185	0.50 (0.38-0.65)
High (CPS ≥10)	116/254	176/254	0.42 (0.33-0.53)
Cisplatin eligibility			
Eligible	117/244	149/234	0.48 (0.38-0.62)
Ineligible	106/198	158/210	0.43 (0.33-0.55)



Data cutoff: 08 Aug 2022

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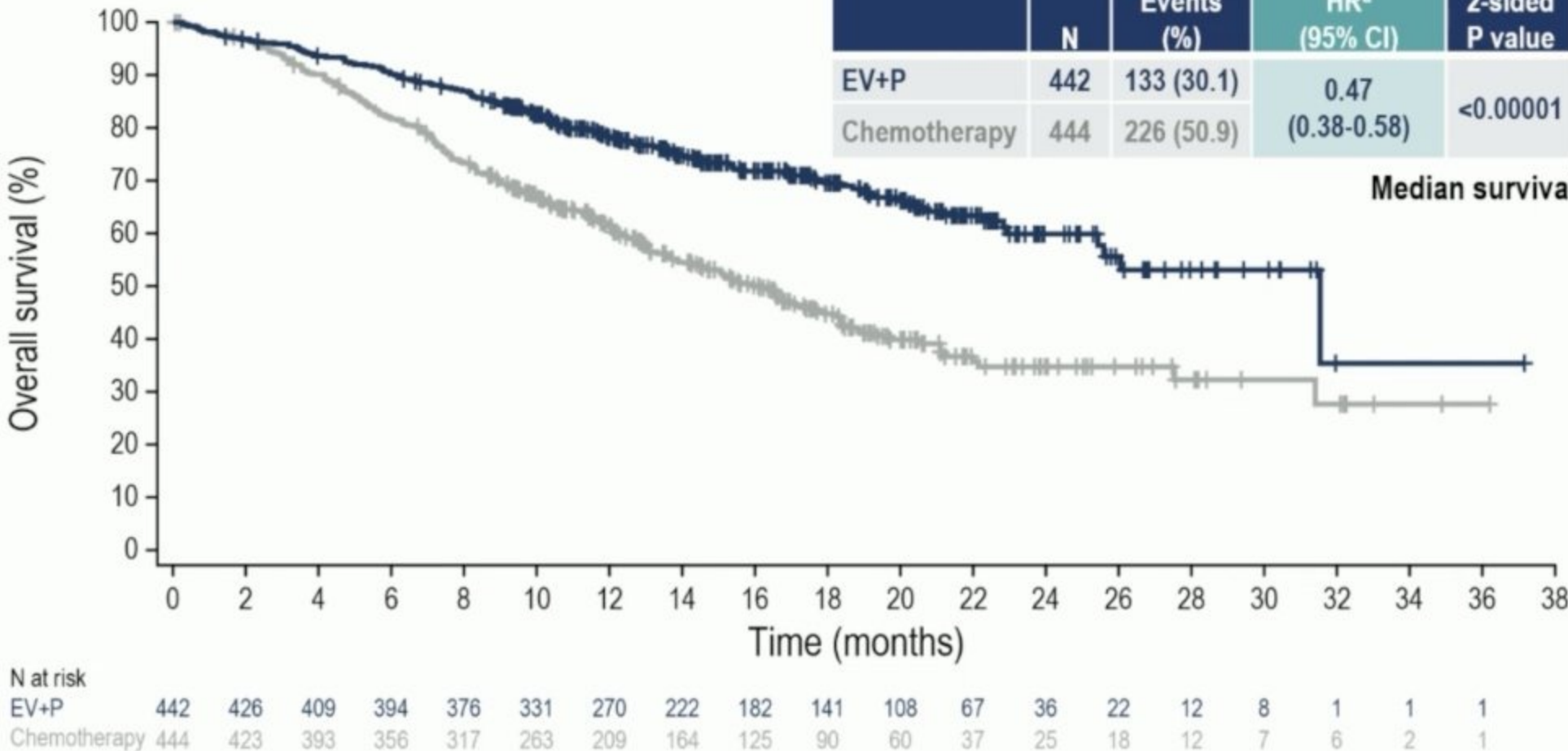
Overall Survival

Risk of death was reduced by 53% in patients who received EV+P

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mOS (95% CI), months
EV+P	442	133 (30.1)	0.47 (0.38-0.58)	<0.00001	31.5 (25.4-NR)
Chemotherapy	444	226 (50.9)			16.1 (13.9-18.3)

Median survival follow-up: 17.2 months



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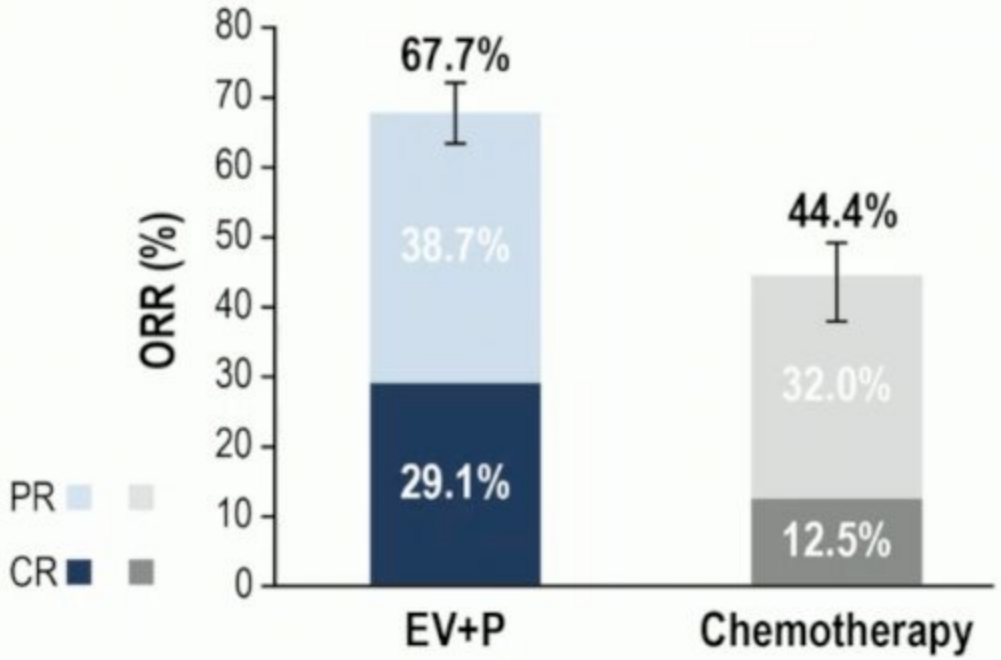
Confirmed Overall Response per BICR

Significant improvement in objective response rate was observed with EV+P



	EV+P (N=437)	Chemotherapy (N=441)
Confirmed ORR, n (%) (95% CI)	**296 (67.7) (63.1-72.1)**	**196 (44.4) (39.7-49.2)**
2-sided P value	<0.00001	
Best overall response[a], n (%)		
Complete response	127 (29.1)	55 (12.5)
Partial response	169 (38.7)	141 (32.0)
Stable disease	82 (18.8)	149 (33.8)
Progressive disease	38 (8.7)	60 (13.6)
Not evaluable/No assessment[b]	21 (4.8)	36 (8.2)

Median DOR (95% CI)	NR (20.2, NR)	7.0 (6.2, 10.2)

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EV Treatment-Related Adverse Events of Special Interest*

Majority of treatment-related AESIs were low grade

	EV+P (N=440) n (%)		Chemotherapy (N=433) n (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Skin reactions	294 (66.8)	68 (15.5)	60 (13.9)	1 (0.2)
Peripheral neuropathy	278 (63.2)	30 (6.8)	53 (12.2)	0 (0.0)
Sensory events	260 (59.1)	19 (4.3)	51 (11.8)	0 (0.0)
Motor events	44 (10.0)	12 (2.7)	5 (1.2)	0 (0.0)
Ocular disorders	94 (21.4)	0 (0.0)	12 (2.8)	0 (0.0)
Dry eye	82 (18.6)	0 (0.0)	8 (1.8)	0 (0.0)
Hyperglycemia	57 (13.0)	27 (6.1)	3 (0.7)	0 (0.0)
Infusion-related reactions	9 (2.0)	0 (0.0)	9 (2.1)	0 (0.0)

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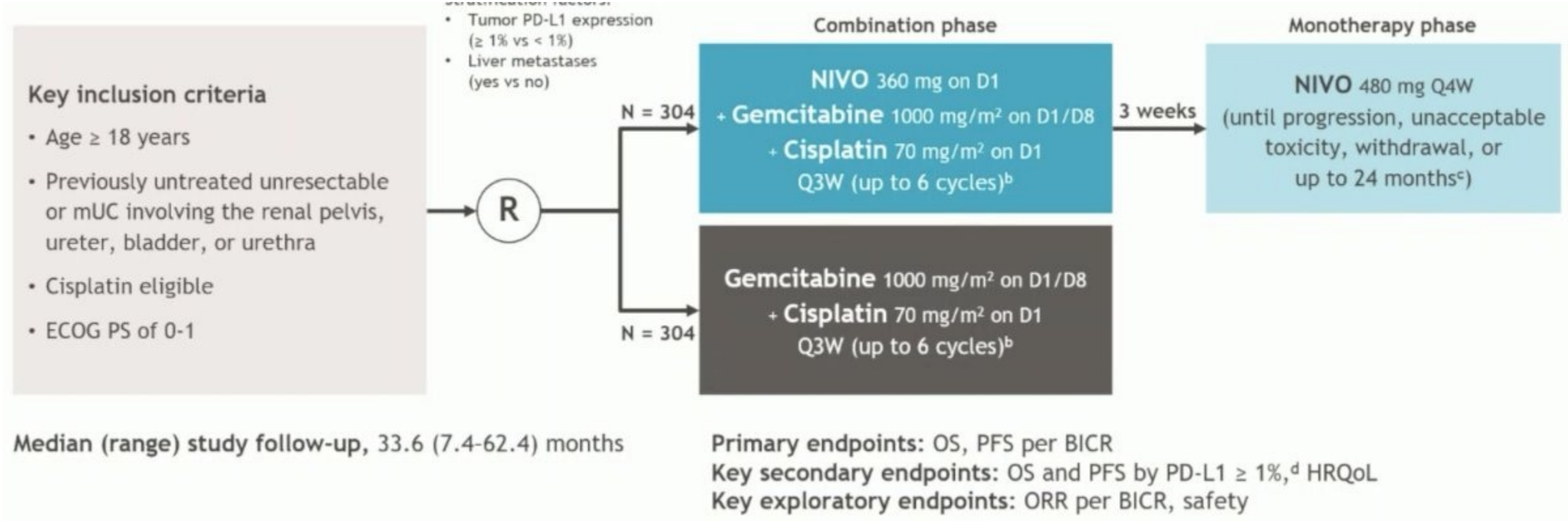
Checkmate 901 Trial



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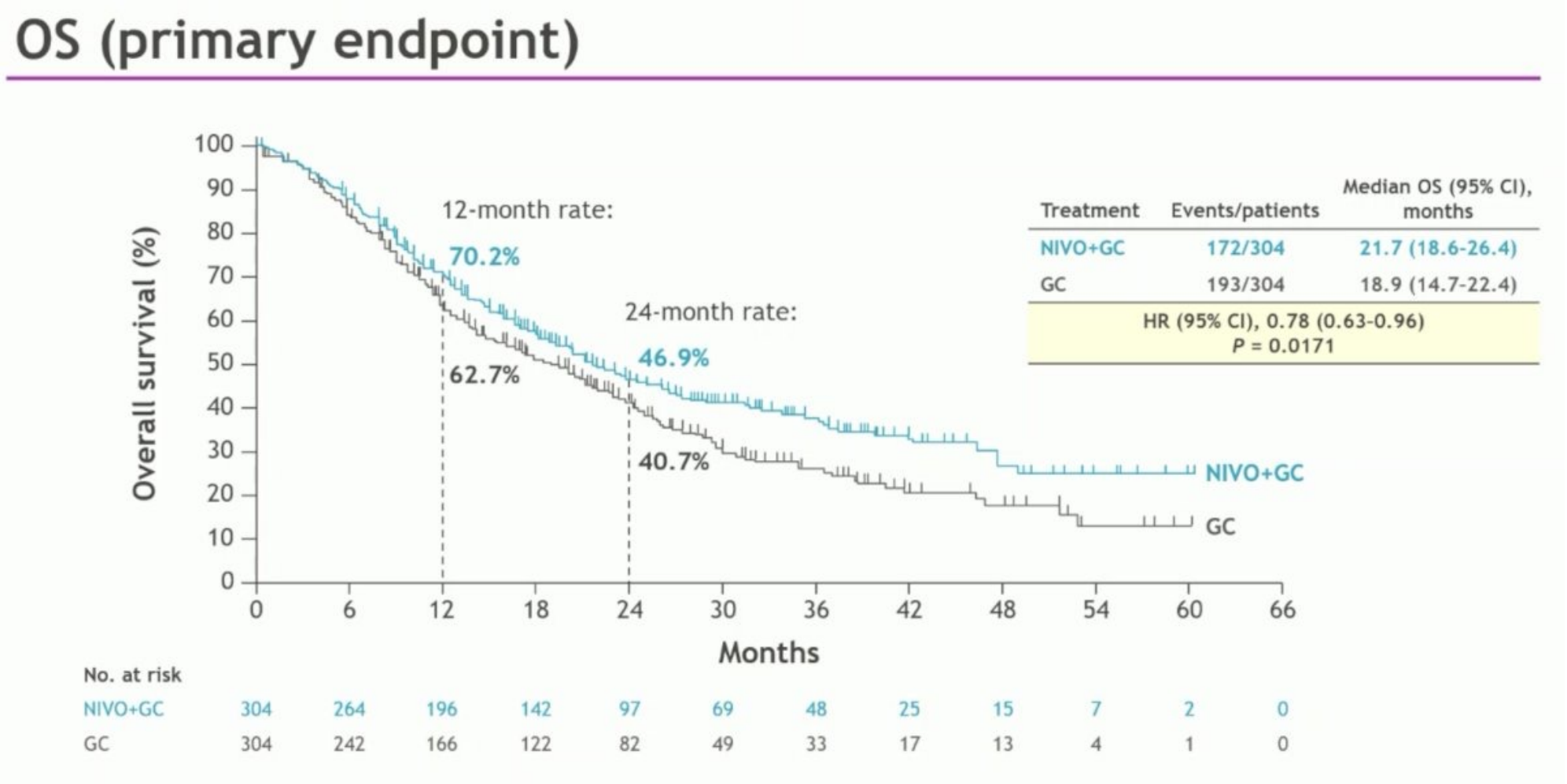

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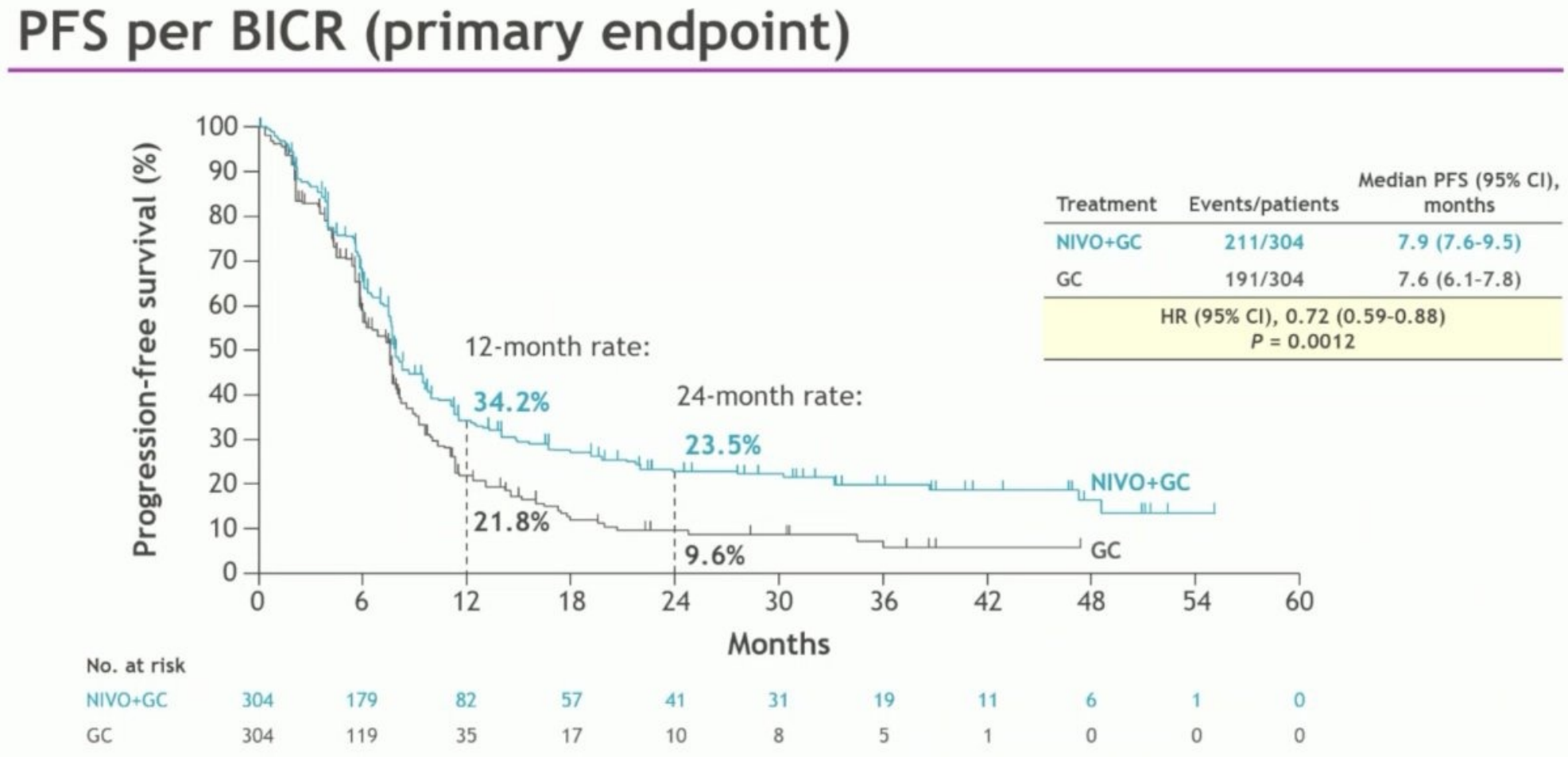

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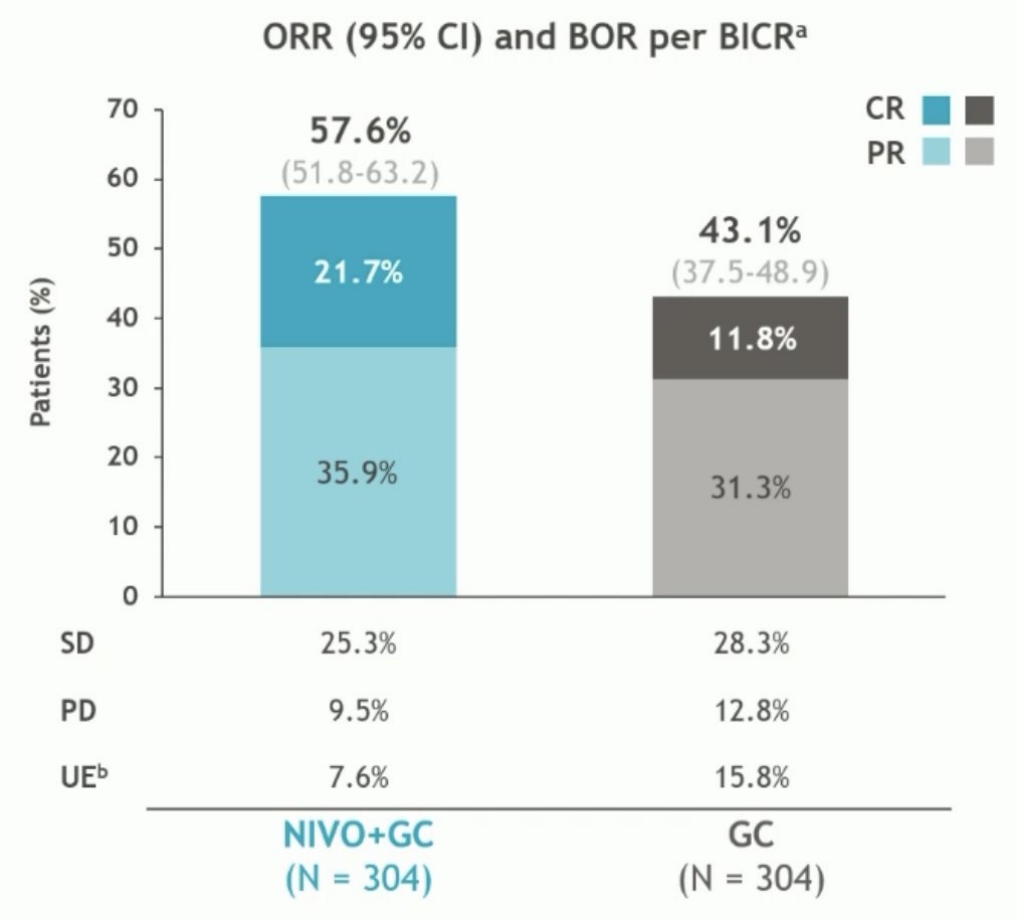

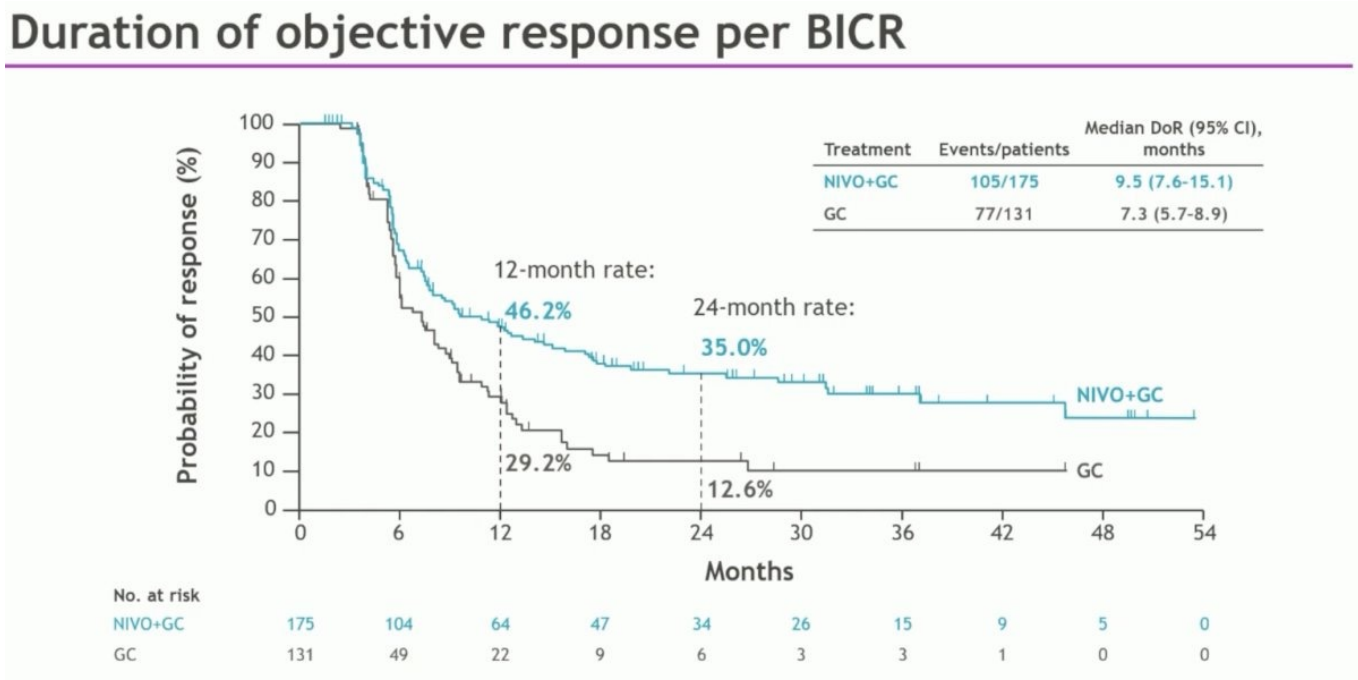

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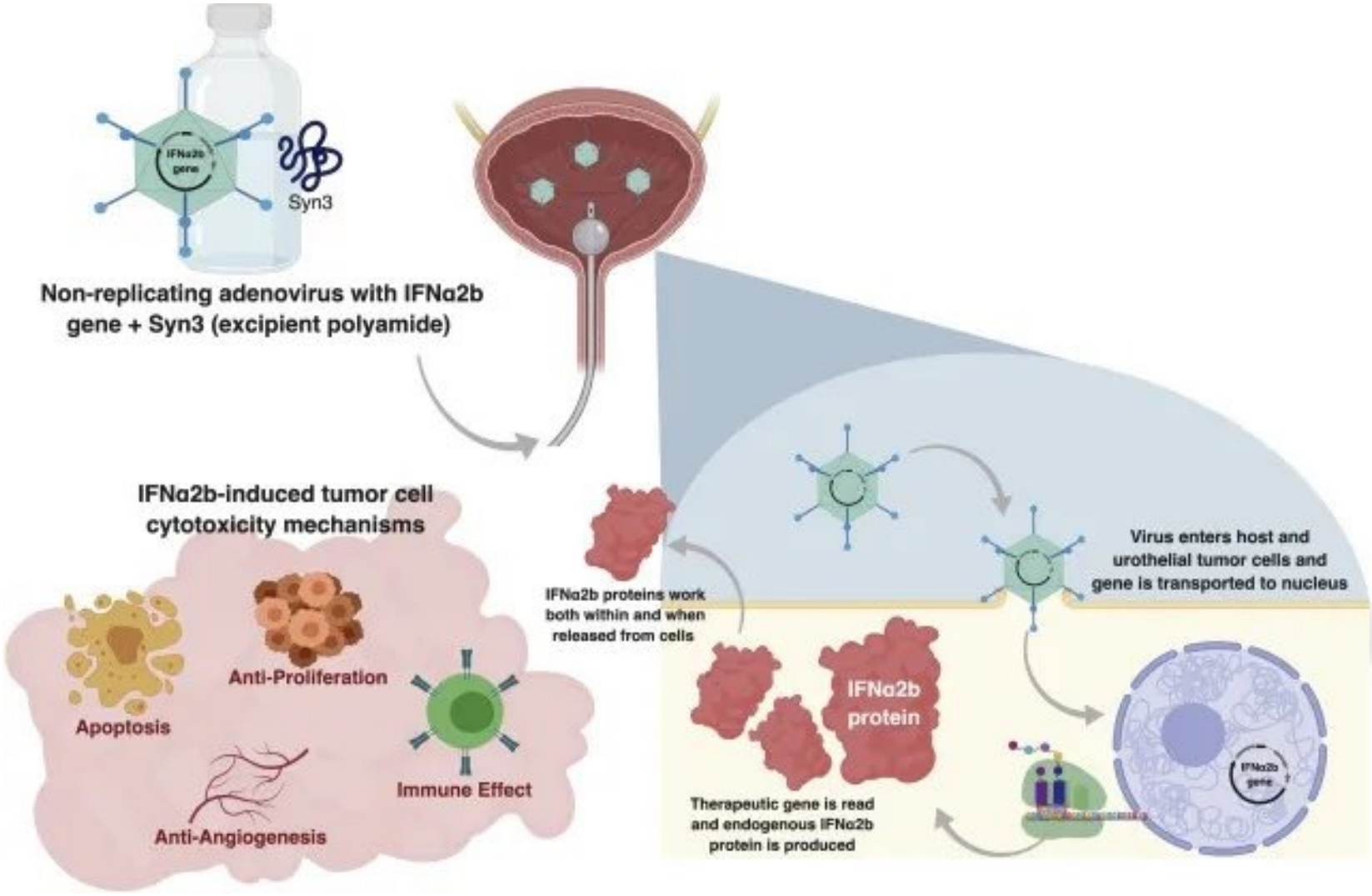
Nadofaragene firadenovec-vncg

- The FDA has approved nadofaragene firadenovec-vncg as the first gene therapy for the treatment of adult patients with high-risk Bacillus Calmette-Guérin (BCG)–unresponsive non–muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors.

- Approval was based on CS-003 trial.
  - CR = 51% (n = 50/98; 95% CI, 41%-61%) by 3 months in those with CIS with or without concomitant high-grade Ta or T1 disease.
  - Median DOR was 9.7 months (range, 3-52+)
  - Of those who achieved CR, 46% (n = 23) continued to be free of high-grade recurrence at 12 months.

https://pubmed.ncbi.nlm.nih.gov/33253641/

Nadofaragene Firadenovec



https://www.urotoday.com/conference-highlights/aua-2024/aua-2024-bladder-cancer/151852-aua-2024-efficacy-of-nadofaragene-firadenovec-vncg-for-patients-with-bacillus-calmette-guerin-unresponsive-non-muscle-invasive-bladder-cancer-final-results-from-a-phase-3-trial.html

Nogapendekin alfa inbakicept-pmln

- Nogapendekin alfa inbakicept-pmln is a first-in-class interleukin (IL)-15 receptor super agonist.
- It is now approved in combination with BCG for adults with BCG-unresponsive NMIBC with carcinoma in situ with or without papillary tumors.

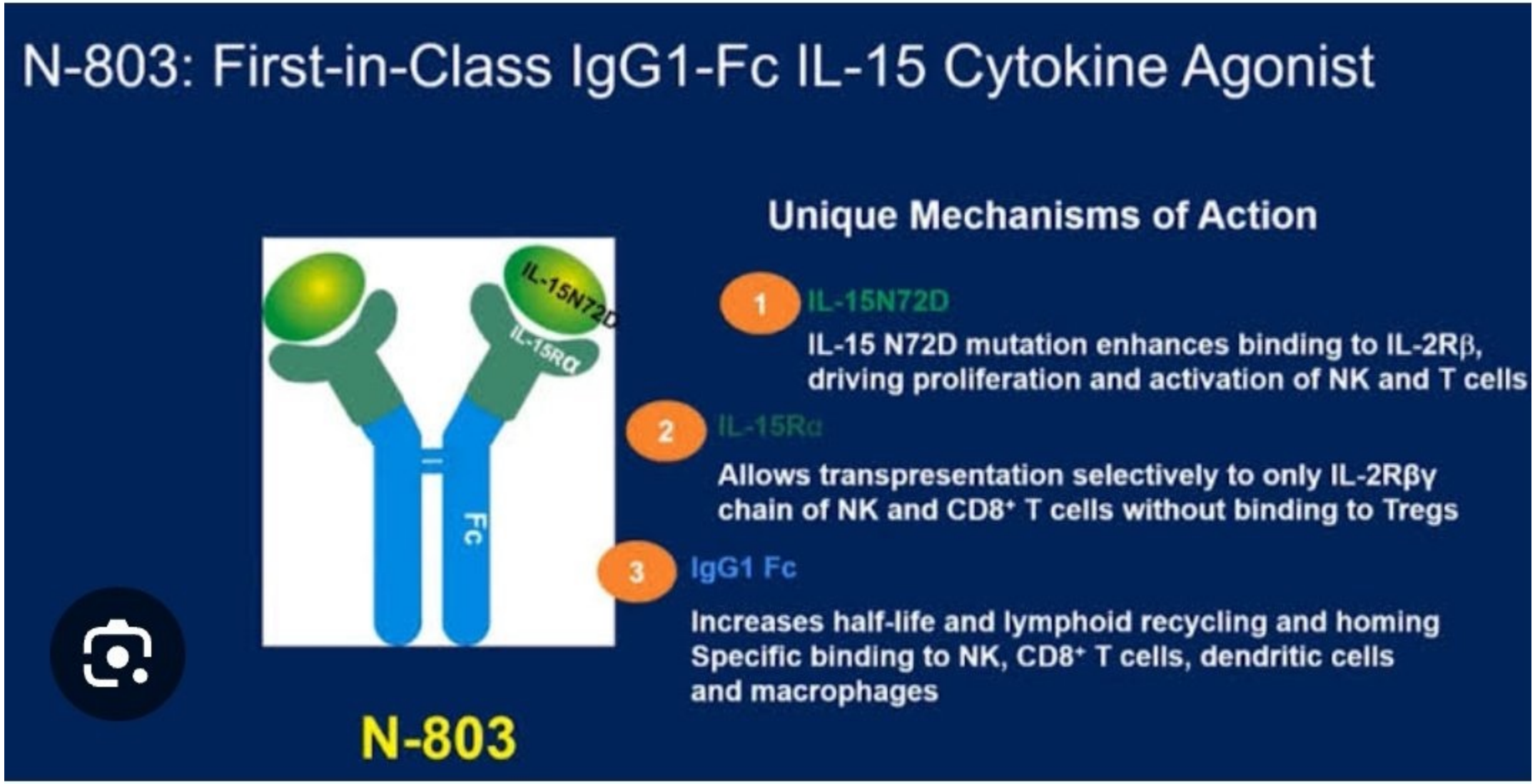
https://pubmed.ncbi.nlm.nih.gov/33253641/

Nogapendekin alfa inbakicept-pmln

- Approval was based on data from the single-arm, multicenter QUILT-3.032 trial.
- Trial included 77 evaluable patients who received the novel immunotherapy along with BCG maintenance therapy for up to 37 months.
- CR = 62% (95% CI 51-73)
- 58% of responders had DOR >/= 1 year
- 40% of responders had DOR >/= 2 years

https://pubmed.ncbi.nlm.nih.gov/33253641/

Nogapendekin alfa inbakicept-pmln



https://x.com/SuyogCancer/status/1782584475135930707/photo/4

Cretostimogene grenadenorepvec + pembrolizumab

- Direct cell killing
  - The virus selectively infects and replicates in tumor cells, which can cause them to lyse.
- Immune-mediated cell killing
  - The virus also expresses granulocyte-macrophage colony stimulating factor (GM-CSF), which can stimulate a cytotoxic T cell response against the tumor cells. When cancer cells rupture, they release tumor antigens and GM-CSF, which can trigger a systemic immune response.

https://www.urologytimes.com/view/cretostimogene-grenadenorepvec-plus-pembrolizumab-sustains-high-cr-rate-in-nmibc

Cretostimogene grenadenorepvec + pembrolizumab

- 2 CORE-001 trial presented at the 2024 ASCO
- 35-patient intention-to-treat (ITT) population; BCG–unresponsive non–muscle-invasive bladder cancer (NMIBC)
- CR rate was 83%
- Over half of CRs maintained their response at 24 months
- PFS was 100%.

https://www.urologytimes.com/view/cretostimogene-grenadenorepvec-plus-pembrolizumab-sustains-high-cr-rate-in-nmibc

Ongoing Trials of Interest

- Olaparib in Patients With Metastatic/Advanced Urothelial Carcinoma With DNA-Repair Defects

- MEDI4736 (Durvalumab) and Chemotherapy for Patients With High Grade Upper Tract Urothelial Cancer Prior to Nephroureterectomy

- Multiple ctDNA studies

- ClinicalTrials.gov

Conclusions

- New treatment modalities (ADCs, novel immunotherapies, and gene therapies) now offer new hope to patients with bladder cancer.

- Defining novel molecular targets and new biomarkers of response will allow us to better personalize innovative treatments options for patients with bladder cancer.