Emerging therapies in high-risk NMIBC

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Conflicts of interest

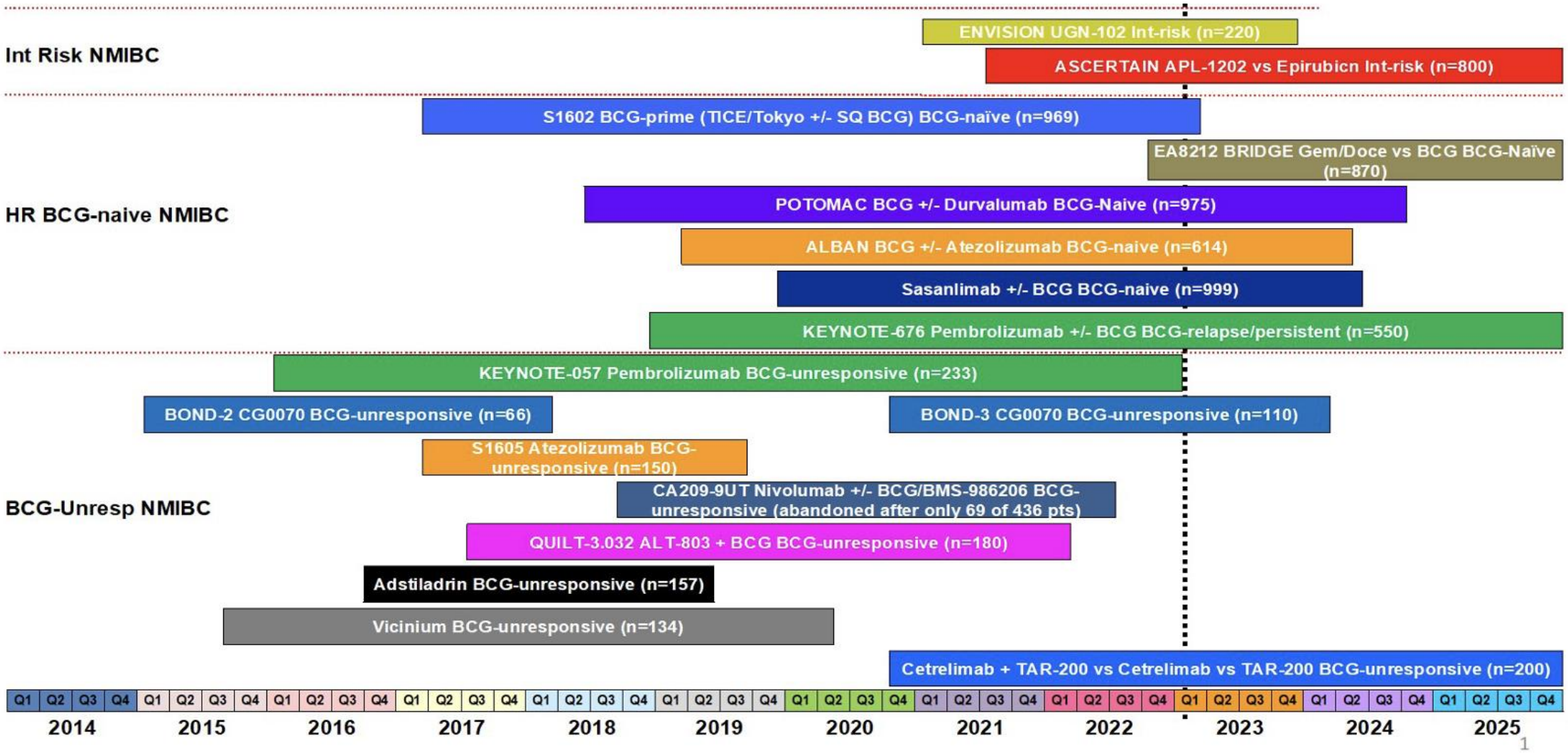
- Advisory board : Ipsen Pharma, Janssen, Ferring, Astellas, MSD, BMS.
- Speaker : Ipsen Pharma, Janssen-Oncology, Ferring, BMS, MSD.
- Investigator and steering committee member : Astrazeneca, Bayer, Ferring, Ipsen, Janssen-Oncology, MSD, Pfizer, QED.

- Panel member French Guidelines in Bladder Cancer (CC-AFU).
- Panel member European Guidelines NMIBC (EAU).
- Editor in chief Educationnal Platform Uro-Onco of the EAU.
- Board member European School of Urology (ESU-EAU).
- Head of Education Office French School of Urology (AFU)

Emerging therapies in HR-NMIBC

- **Background**
- BCG-unresponsive CIS NMIBC

Ongoing practice changing trials in NMIBC



BCG unresponsive NMIBC a true daily practice dilemma

- Term coined in context of clinical trial development, but equally important in routine clinical practice
- Defines a group of patients with high-grade Ta/T1/CIS who have exhausted BCG as a treatment option
- Radical cystectomy is recommended by guidelines as standard of care for these patients due to lack of established alternative effective bladder-preserving options
  - Morbid surgery:
    - ✓ complication rates during primary hospitalization is around 35%,
    - ✓ with rates increasing post-surgery to 39% at 30 days
    - ✓ and 60% at 90 days.
    - ✓ average in-hospital mortality rate is around 2.4%,
    - ✓ and a 90-day mortality rate of 4.7%.
  - Impacts QoL negatively
  - Many patients are not fit for or accepting of cystectomy

Maibom et al. BMJ 2021; Hladun et al. Cent Eur Urol 2022

Why focus on CIS?

- AUA-SUO-FDA panel 2013-16:
  - It is not possible to conduct a randomized trial because there is **no established comparator other than radical cystectomy**
  - Ta/T1 tumors are **completely resected**, so that any bladder-preserving therapy is adjuvant and the effect of the experimental treatment will be uncertain without a comparator
  - CIS **cannot be completely resected**, therefore the experimental therapy must eradicate it, and the **complete response rate** in patients with CIS is the best measure of treatment efficacy

Emerging therapies in HR-NMIBC

- Background
- **BCG-unresponsive CIS NMIBC**
  - ✓ IO monotherapies
  - ✓ Gene therapies
  - ✓ Other intravesical options

Emerging therapies in HR-NMIBC

- Background
- **BCG-unresponsive CIS NMIBC**
  - ✓ **IO monotherapies**
  - ✓ Gene therapies
  - ✓ Other intravesical options

IO monotherapy in BCG-unresponsive KEYNOTE-057

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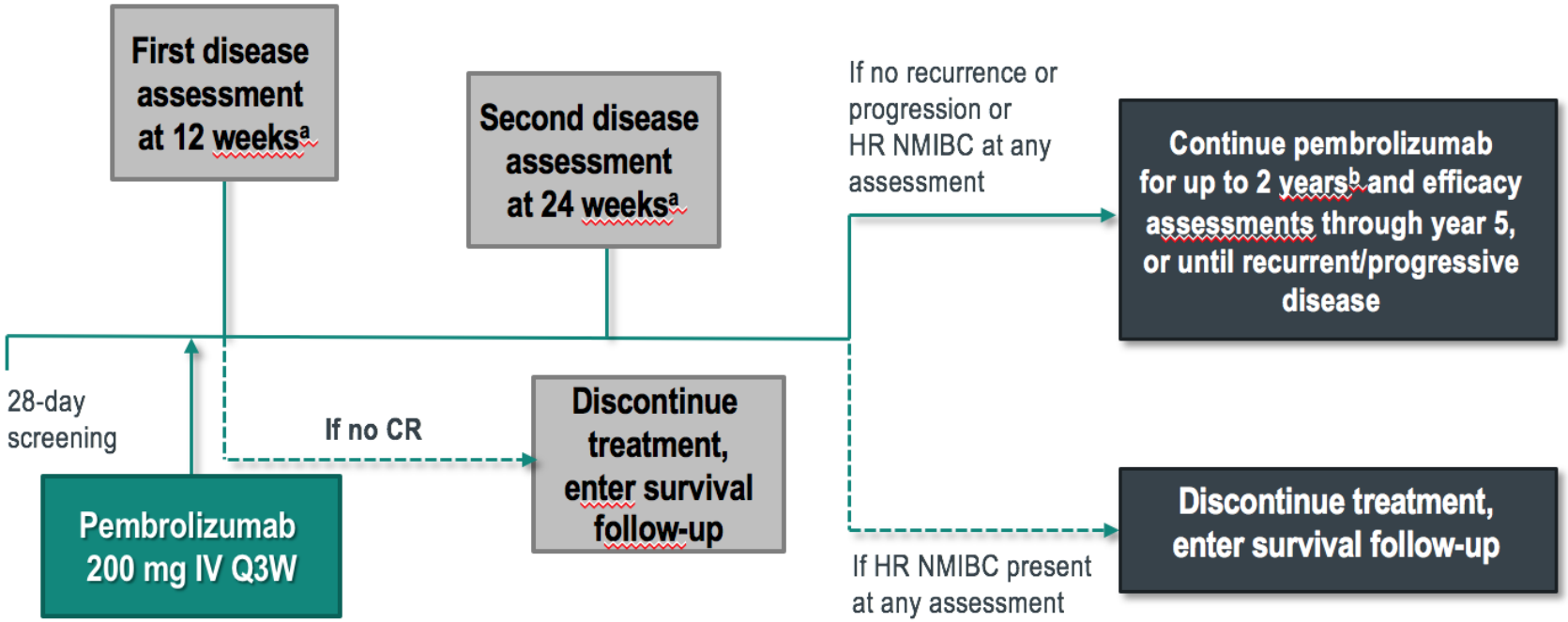
Key Inclusion Criteria

- HR NMIBC patients unresponsive to BCG who decline to undergo or are ineligible for radical cystectomy
- Patients with papillary disease must have fully resected disease at study entry
- CIS with or without papillary disease (high-grade Ta or T1)



Primary End Point

- CR rate of HR NMIBC (defined as the absence of HR NMIBC or PD by central review)

Key Secondary End Points

- DOR, PFS, OS, safety

Pembrolizumab IV 24mo
CR evaluation Biopsy at 3mo mandatory

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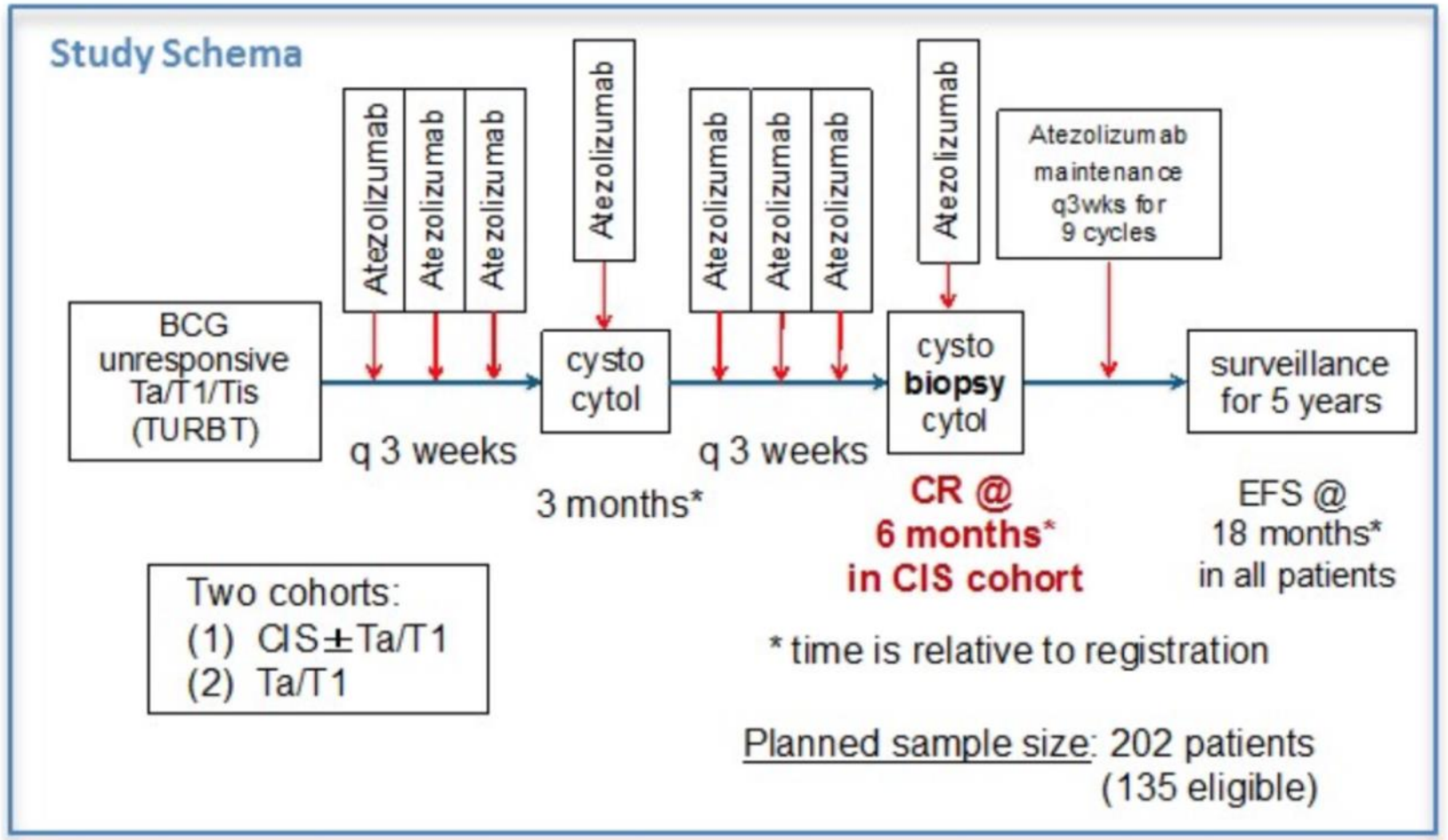
Balar AV et al. Lancet Oncol 2021

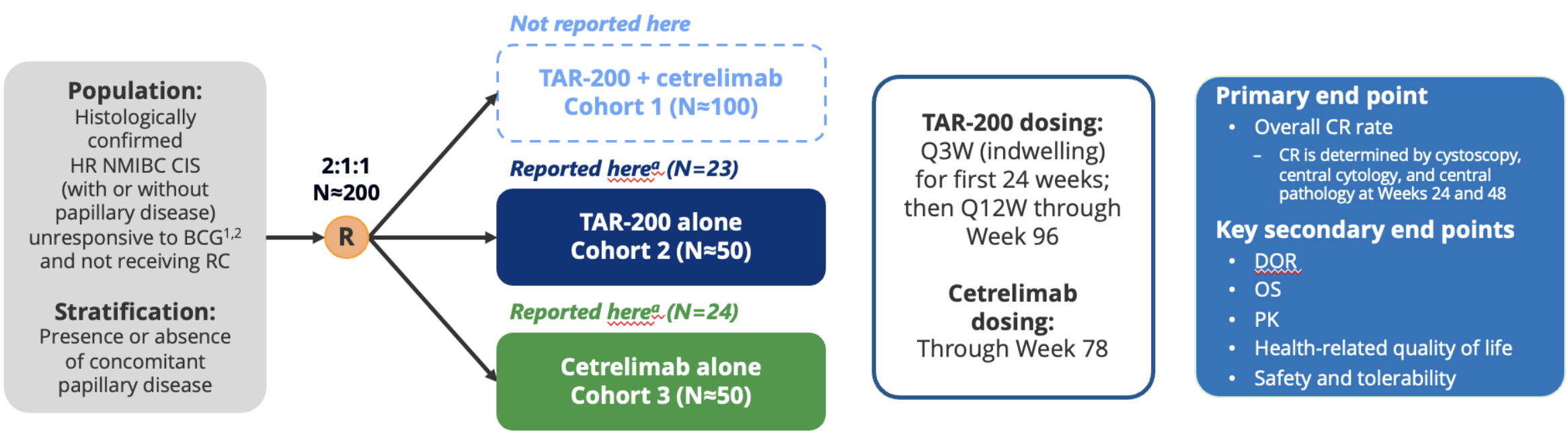
IO monotherapy in BCG-unresponsive SWOG S1605



Atezolizumav IV 12mo
CR evaluation Biopsy at 6mo mandatory

Black PC et al. Eur Urol 2023

IO monotherapy in Cis BCG-unresponsive
SUNRISE 1



Cetrelimab IV 18mo
CR evaluation Biopsy at 6mo mandatory

Daneshmand S et al. AUA 2023

Complete response rates in Cis BCG-unresponsive

Characteristic, n (%)	Keynote-057 Pembrolizumab Cohort A n=102	SWOG S1605 Atezolizumab Cohort Cis n= 74	SUNRISE 1 Cetrelimab monotherapy n=21
Complete response	**42 (41.2%)**	**20 (27%)**	**8 (38.1%)**
No complete response	58 (56.9%)	54 (73%)	13 (61.9%)
Evaluation	At 3mo Biopsy	At 6mo Biopsy	At 6mo Biopsy

Biopsy-based complete response rates between 27 and 41% depending on follow-up (3mo vs 6mo)

Balar AV et al. Lancet Oncol 2021; Black PC et al. Eur Urol 2023, Daneshmand S et al. AUA 2023

Duration of response in Cis BCG-unresponsive

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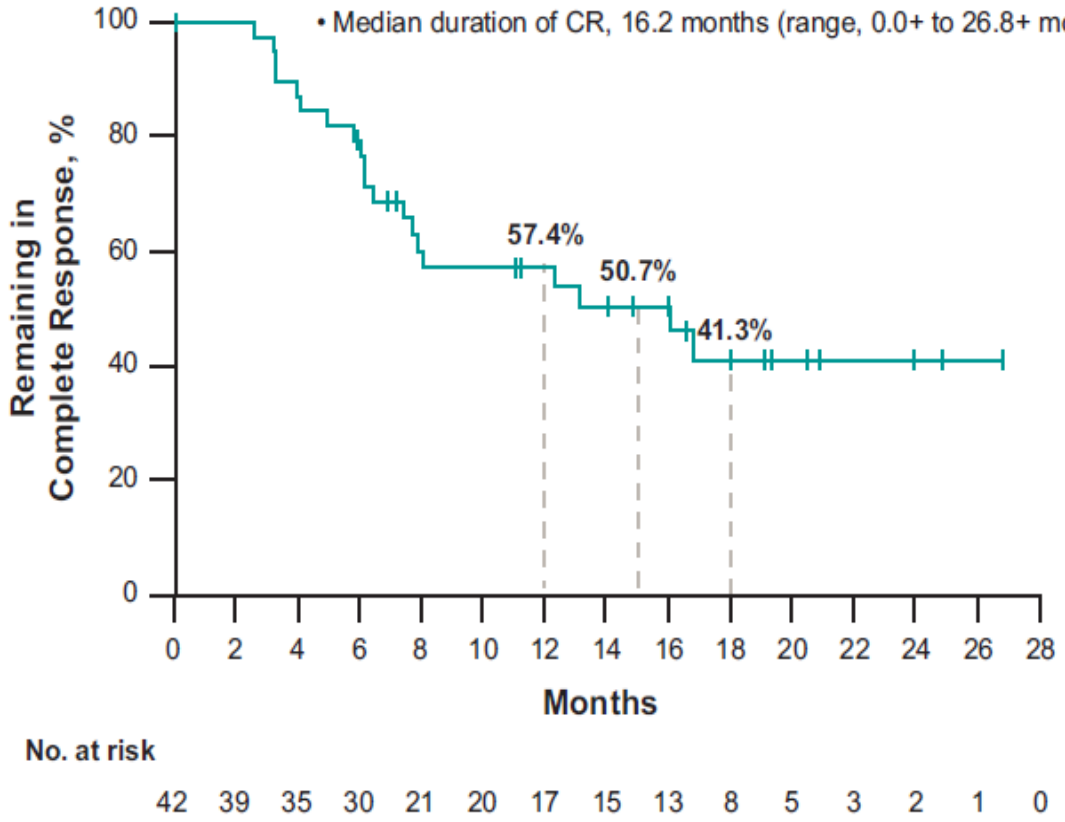
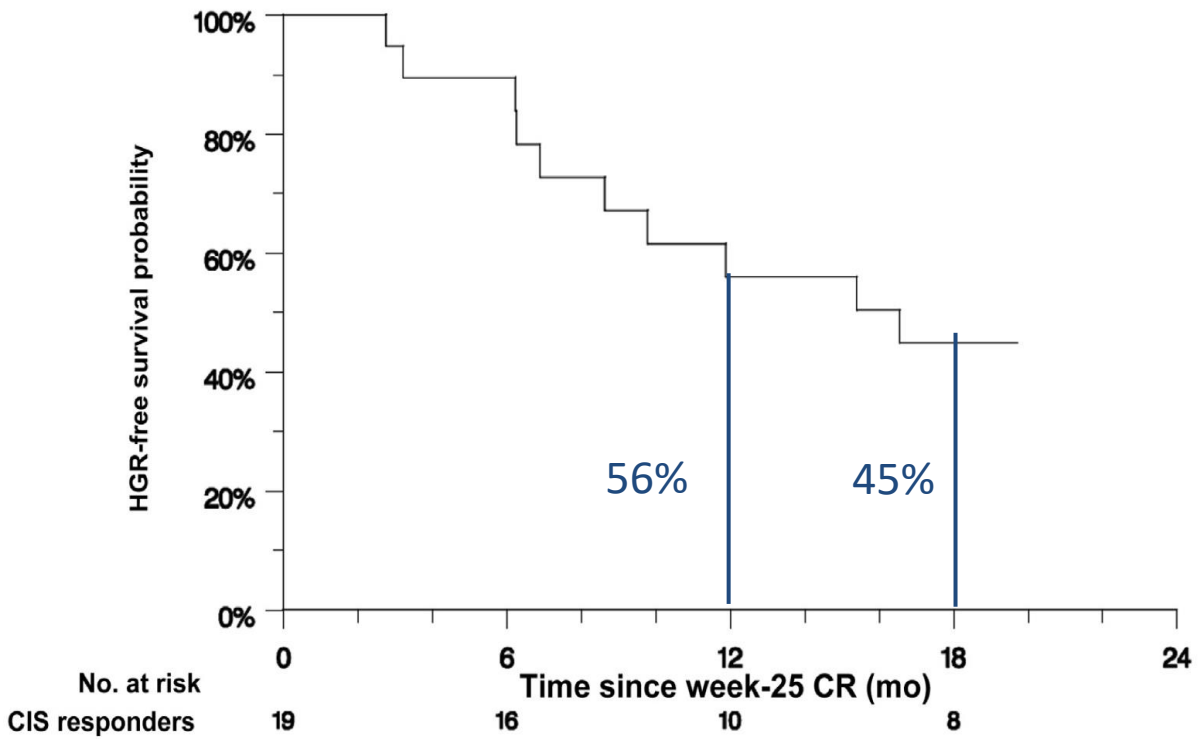
Median follow-up : 24.3 mo



SWOG S1605

Median follow-up : 17 mo



Approximately half of the CR patients will retain the response at 12mo
Independently of the systemic IO

Balar AV et al. Lancet Oncol 2021; Black PC et al. Eur Urol 2023

Safety profile of immune checkpoint inhibitors in Cis BCG-unresponsive

n (%)	Keynote-057 Pembrolizumab Cohort A n=104	SWOG S1605 Atezolizumab Cohort Cis n= 96	SUNRISE 1 Cetrelimab monotherapy n=21
Any all-grade treatment-related AEs	67 (65.7%)	81 (97%)	19 (79.2%)
Grade 3/4 treatment-related AE	**13 (12.7%)**	**13 (14%)**	**2 (8.3%)**
Serious treatment-related AE	8 (7.8%)	9 (9%)	1 (4.2%)
Discontinuation because of treatment-related AE	9 (8.8%)	9 (9%)	1 (4.2%)
Death because of treatment-related AE	0 (0%)	2 (2%)	0 (0%)

Grade 3-4 IO-related 8-14% and SAE IO-related 4-9%

Balar AV et al. Lancet Oncol 2021; Black PC et al. Eur Urol 2023, Daneshmand S et al. AUA 2023

IO monotherapy in Cis BCG-unresponsive

- IO monotherapy demonstrated clinical activity leading to FDA approval
- Systemic immunotherapy does not seem the answer to Cis NMIBC unresponsive to intravesical immunotherapy explaining the low adoption from the Uro-Onco community
- « Loss of chance » may be a concern as well as life-time immune–induced toxicity

Emerging therapies in HR-NMIBC

- Background
- **BCG-unresponsive CIS NMIBC**
  - ✓ IO monotherapies
  - ✓ **Gene therapies**
  - ✓ Other intravesical options
- BCG-naive HR-NMIBC

Gene therapies in BCG-unresponsive NMIBC

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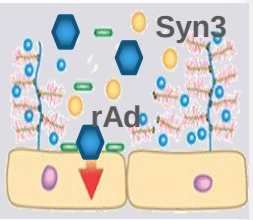
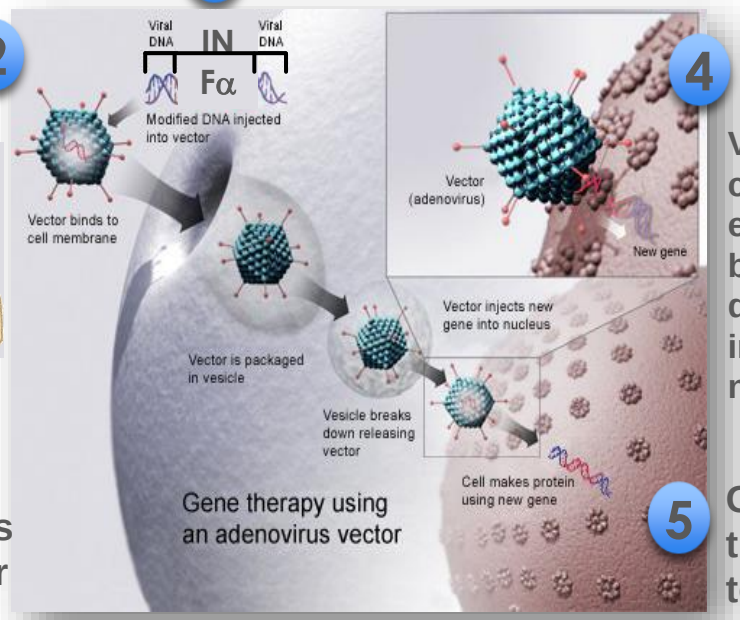
Nadofaragene Firadenovec

IFN α2b gene inserted into Ad5

Adenovirus binds to cell surface



1 Syn3 excipient modulates GAG layer to enable viral access

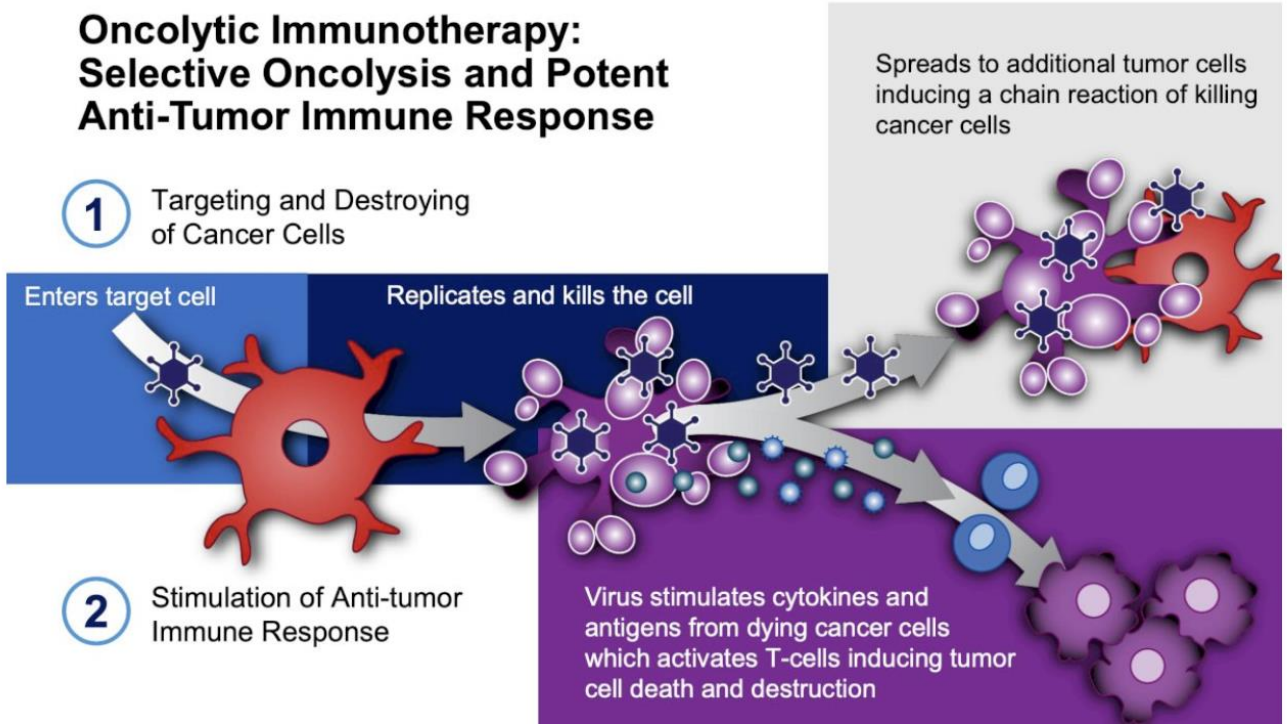


4 Virus enters cell by endocytosis, broken down, gene injected into nucleus

5 Gene read by transcriptase to produce endogenous IFN α2b protein

6 Protein works inside cell and on adjacent cell

Cretostimogene grenadenorepvec



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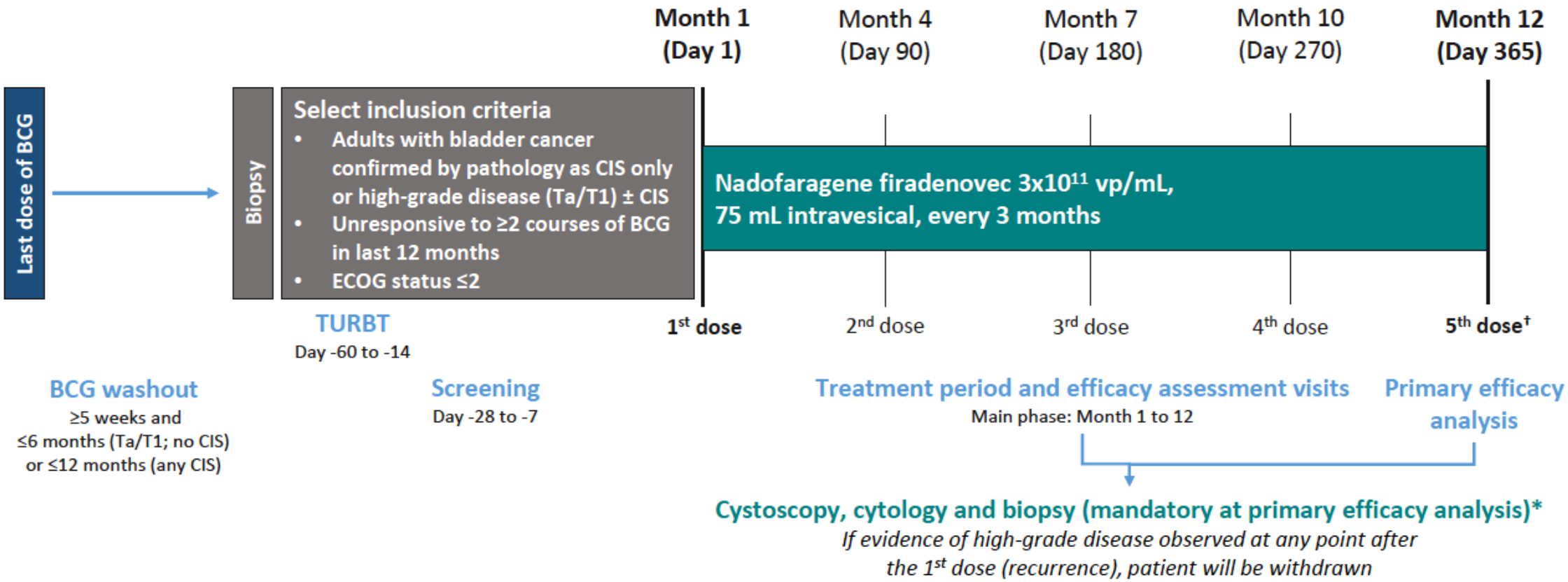
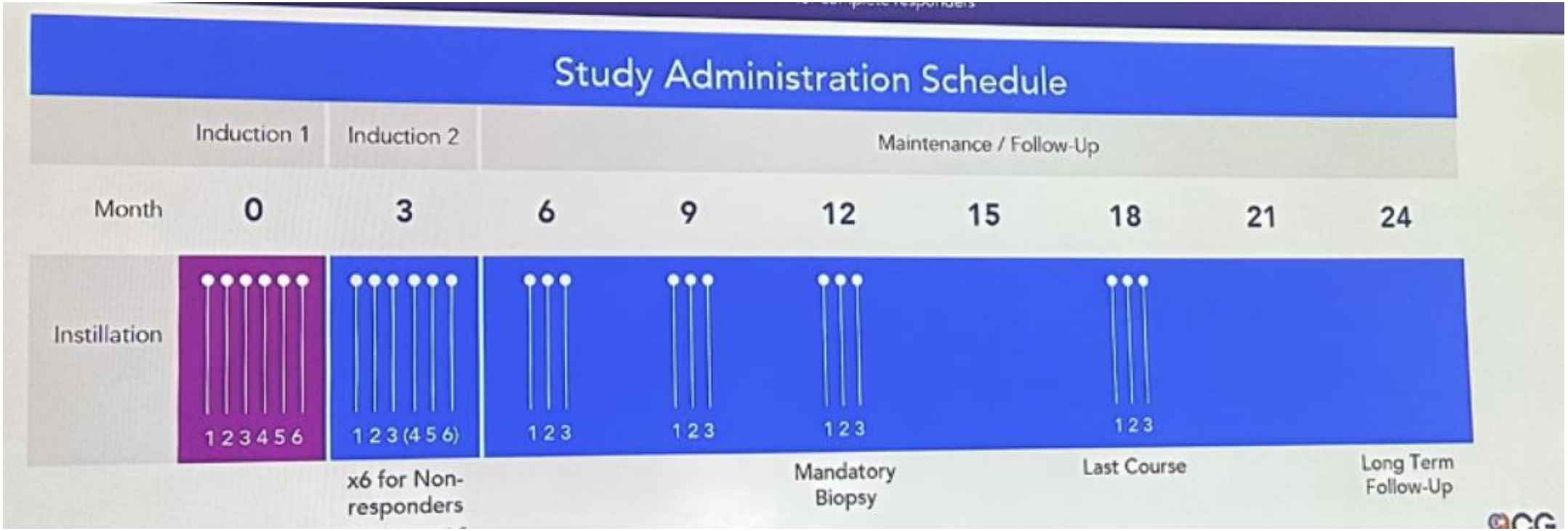
Nadofaragene firadenovec monotherapy
Study design

Study design: Phase III multi-centre, open-label, repeat-dose study (main phase)



Boorjian et al. Lancet Oncol 2021

Cretostimogene grenadenorepvec monotherapy
BOND-003 study design



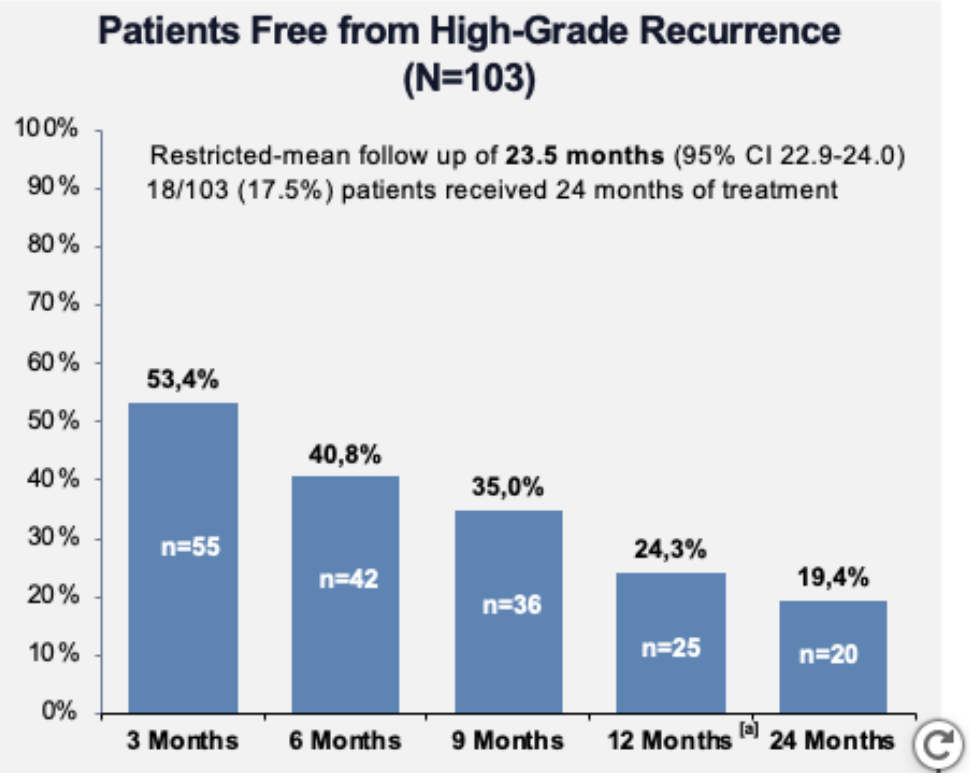
Gene therapies in Cis-BCG unresponsive
Complete response and duration of response

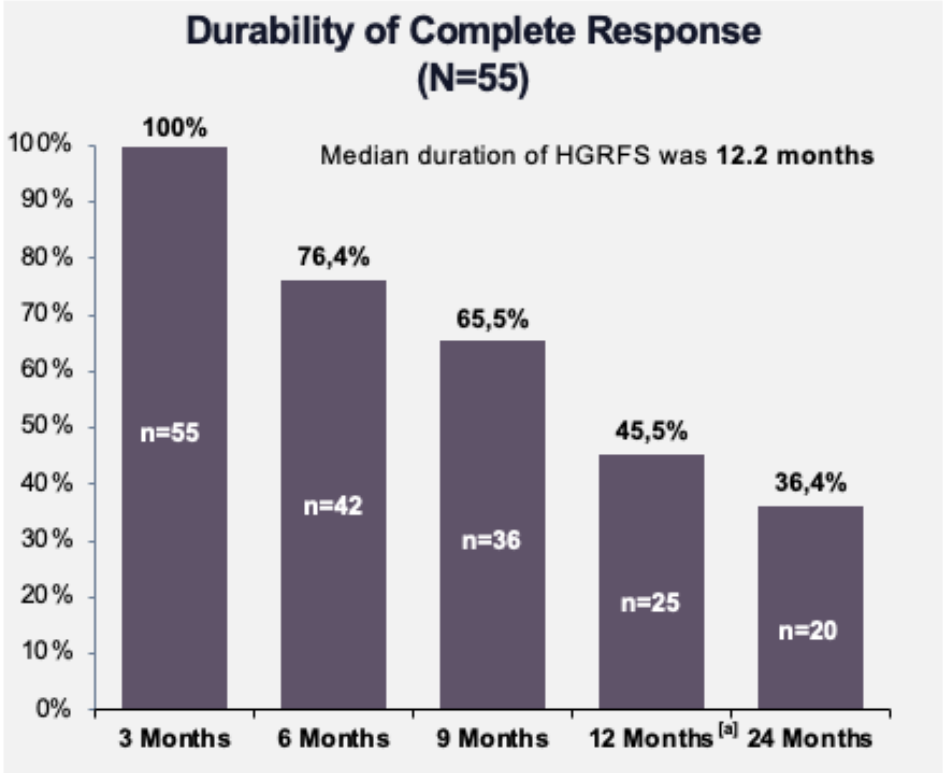
		Nadofaragene firadenovec (n=103)	Cretostimogene grenadenorepvec BOND-003 (n=66)
Complete response rates at 3mo		**53.4% (43.3-63.3%)**	**68.2% (55-79%)**
Duration of response		9.69 (9-17) mo	-
	6 months	**40.8% (31.2-50.9%)**	**63.6% (51-75%)**
	9 months	35.0% (25.8-45.0%)	-
	12 months	24.3% (16.4-33.7%)	-

Biopsy-based complete response rates between 53.4 and 68.2% at 3mo

Boorjian et al. Lancet Oncol 2021; Tyson M et al. SUO 2023

Duration of response in Cis BCG-unresponsive treated with Nadofaragene firadenovec





Half of the patients with 3mo-CR will remain free of disease at 12mo

Dinney et al. SUO 2019; Boorjian et al. Lancet Oncol 2021

Safety profile of intravesical gene therapies

n (%)	Nadofaragene firadenovec n=153	BOND-003 Cretostimogene grenadenorepvec n= 112
Any all-grade treatment-related AEs	109 (70%)	63 (56.33%)
Grade 3/4 treatment-related AE	**6 (4%)**	**0 (0%)**
Serious treatment-related AE	0 (0%)	0 (0%)
Discontinuation because of treatment-related AE	9 (8.8%)	9 (9%)
Death because of treatment-related AE	0 (0%)	0 (0%)

Few major Aes
All Bladder related

Boorjian et al. Lancet Oncol 2021; Tyson M et al. SUO 2023

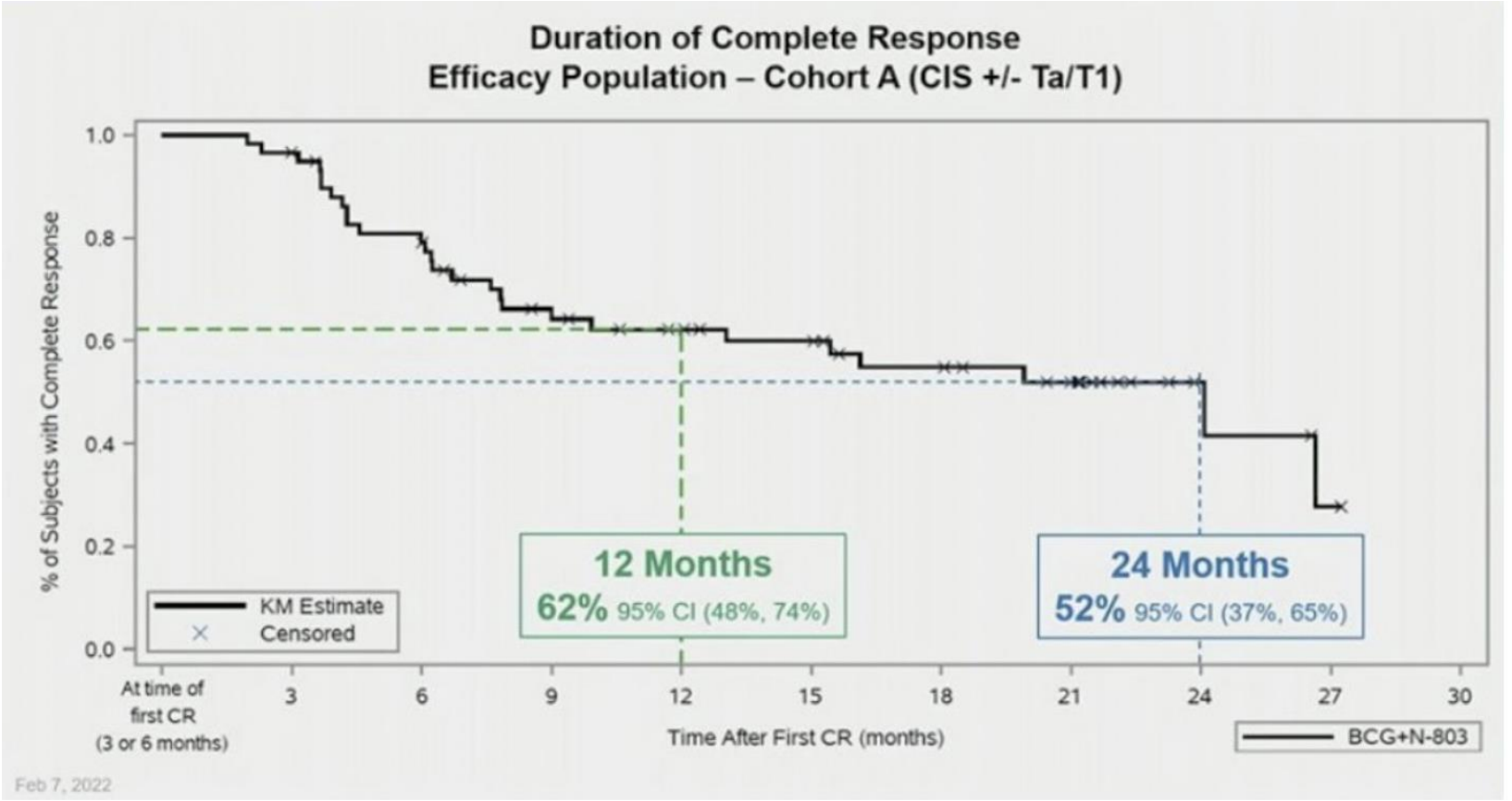
Intravesical gene therapies in Cis BCG-unresponsive

- Gene therapies monotherapy demonstrated strong initial clinical activity leading to FDA approval
- Adoption is ongoing in the countries where approval was granted
- Production and ability to deliver worldwide these therapies may be a challenge
- Long-term response may be a concern
- Financial toxicity

Emerging therapies in HR-NMIBC

- Background
- **BCG-unresponsive CIS NMIBC**
  - ✓ IO monotherapies
  - ✓ Gene therapies
  - ✓ **Other intravesical options**

New intravesical Immunotherapy
IL-15RαFc Superagoniste N-803 in combination with BCG



Among Cohort A (CIS), there were 83 patients enrolled. With a 23.9 month median follow-up, the complete response rate was 71% (95% CI 60.1%, 80.5%), with median duration for 3-month responders of 24.1 months and a 55% probability of maintaining this complete response for ≥ 18-months (95% CI 40.1%, 67.3%). The cystectomy free rate in responders was 93%, with a 100% cancer specific survival at 24-months. The 12 month (62%) and 24 month (52%) durable complete

Chang et al. ASCO GU 2022

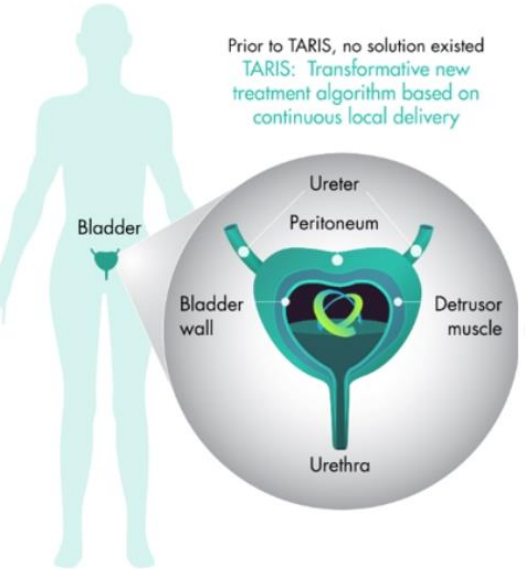
Safety profile of N-803 + BCG

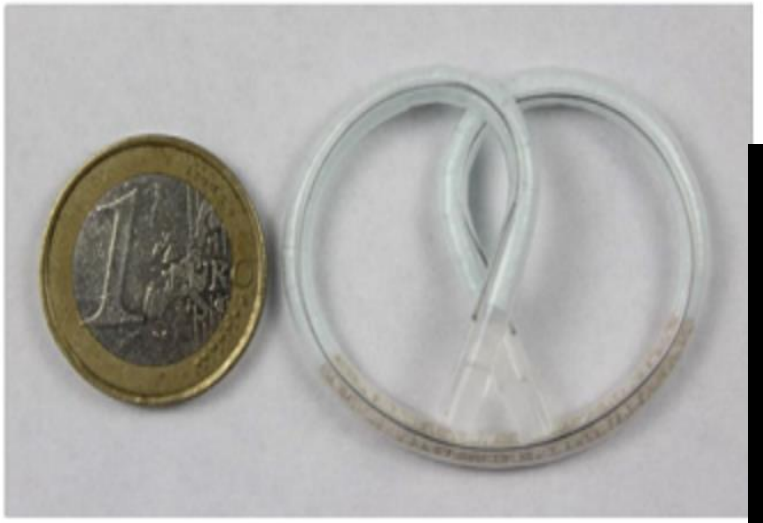
Summary	Cohorts A and B Combined (N = 161) — no. (%)
Patients with at least 1 TEAE grade 1 or 2	139 (86)
Patients with at least 1 TEAE grade 3	32 (20)
Patients with at least 1 TEAE grade 4; or grade 5	3 (2); 1 (1)
Patients with at least 1 TEAE with outcome of death	1 (1)
Patients with at least 1 immune-related grade 3 TEAE	3 (2)

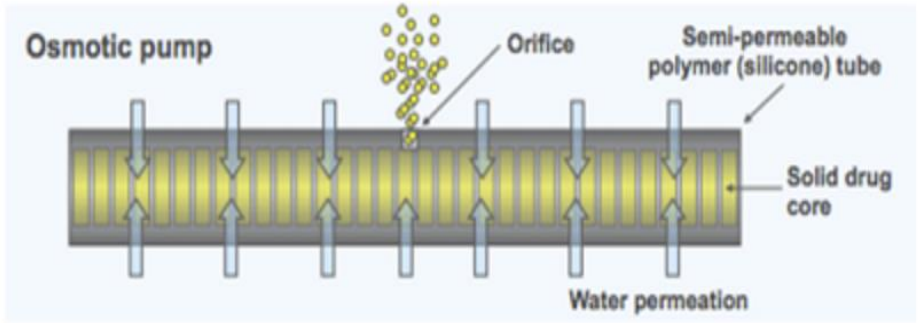
Few major AEs
All Bladder related

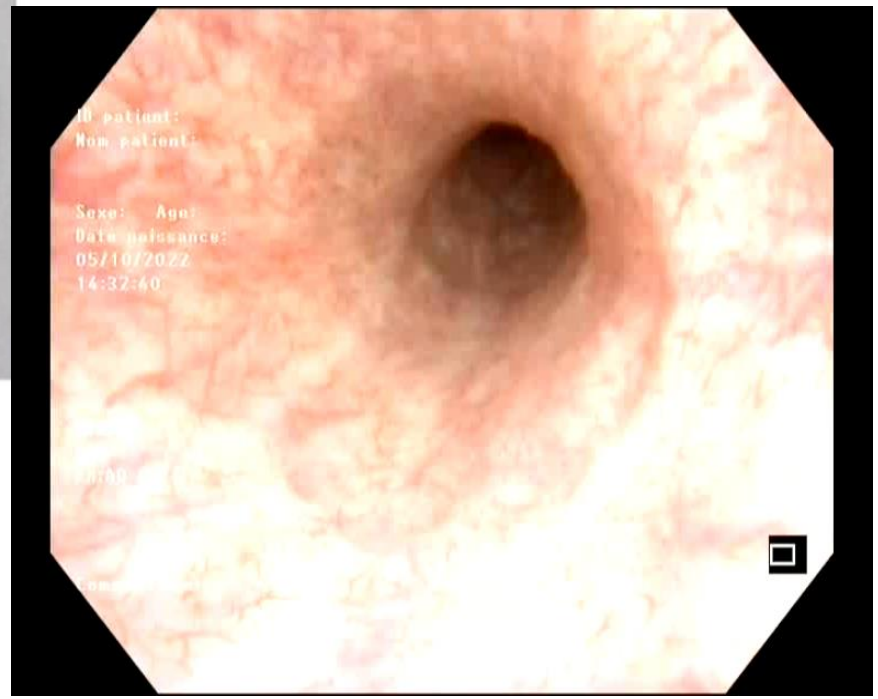
TAR-200

TARIS

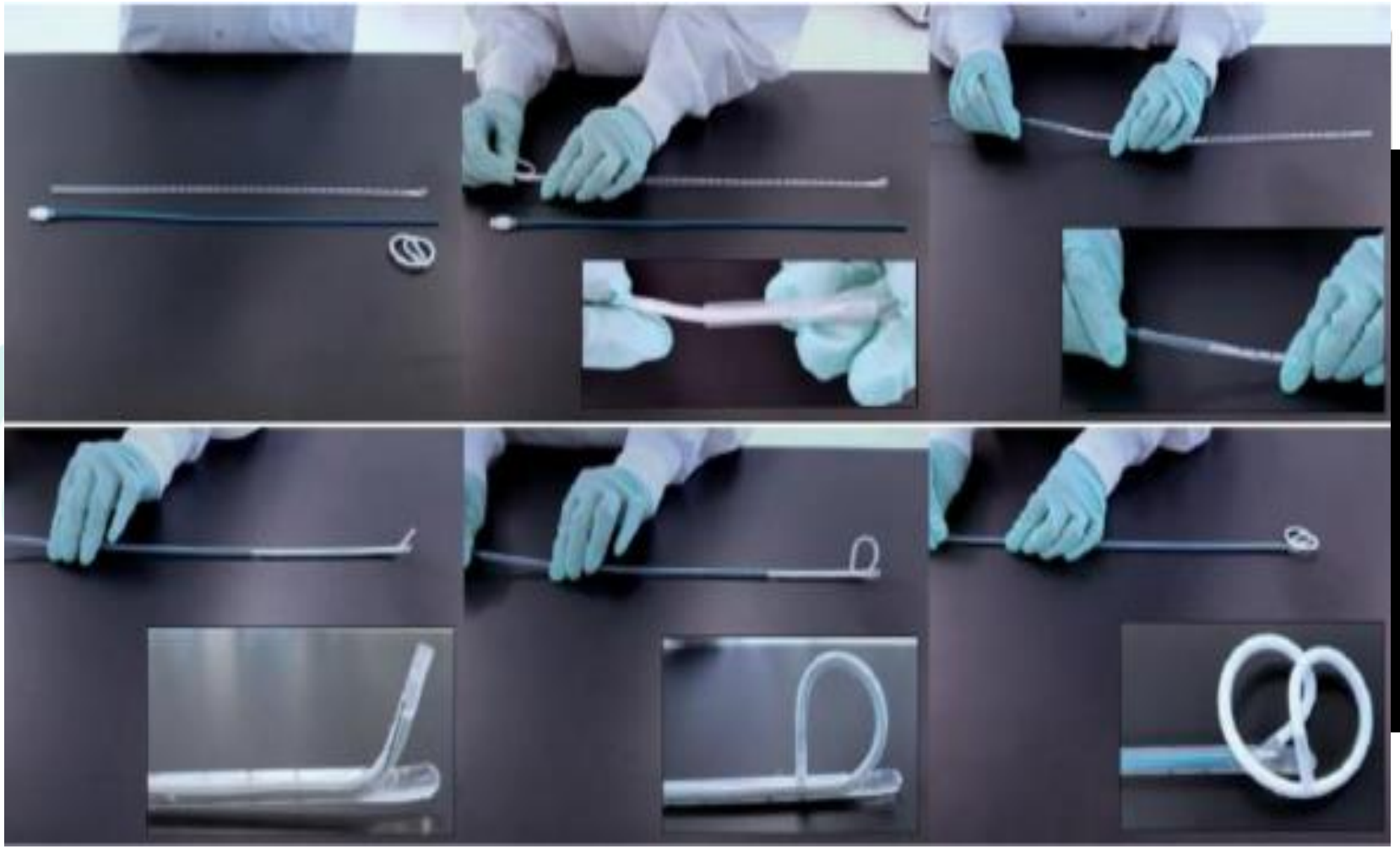


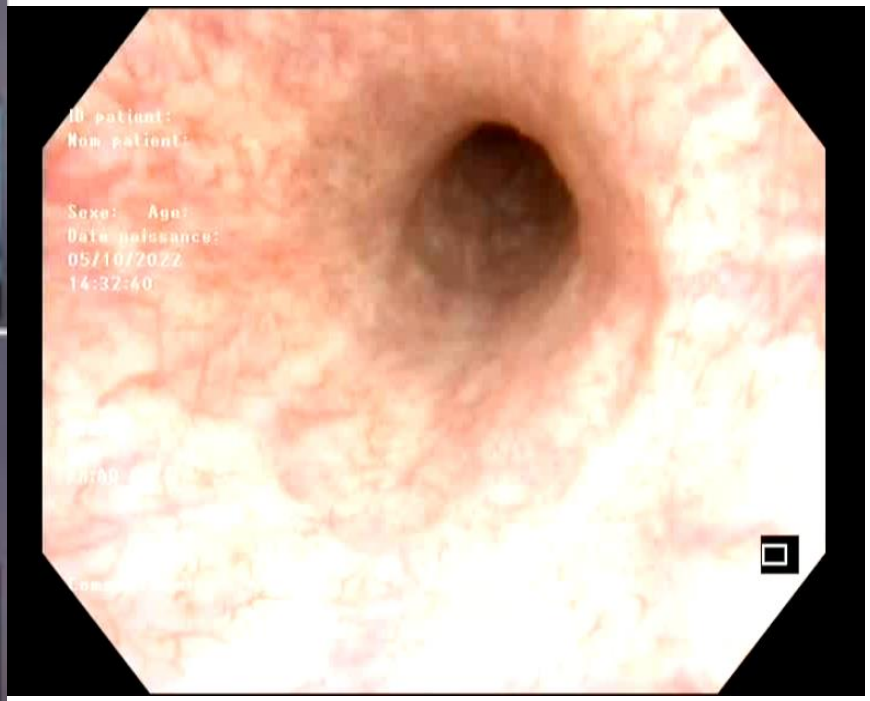






TAR-200

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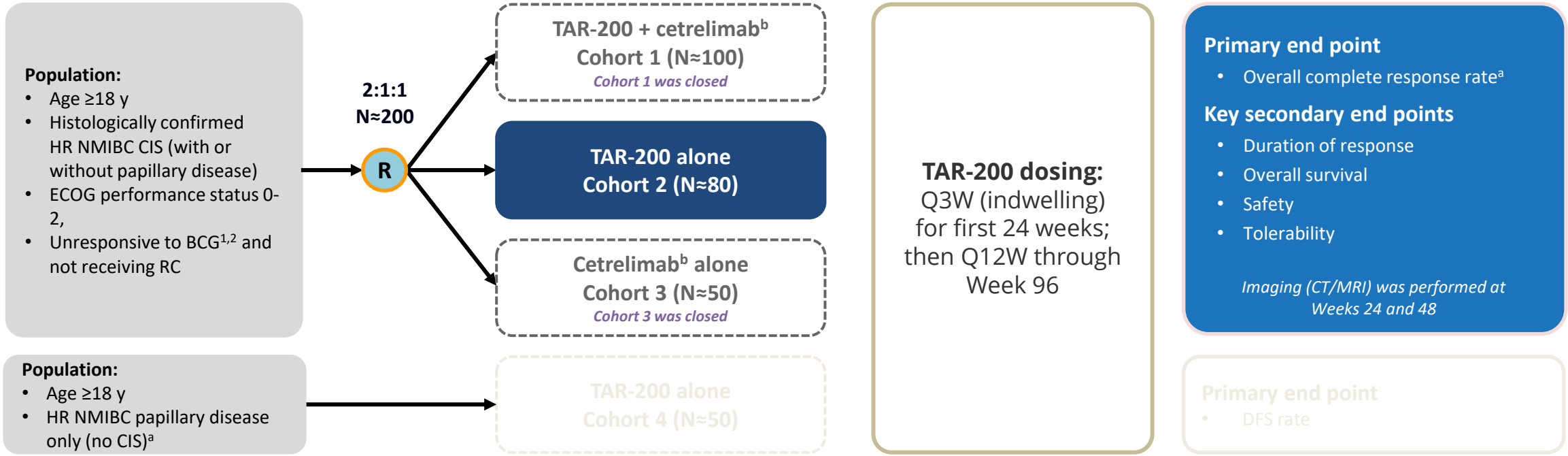
SunRISe-1 is an Ongoing Phase 2b Randomized, Open-label Study



NCT04640623

Cohort 2
TAR-200 Monotherapy

TAR-200 monotherapy in Cis BCG-unresponsive Complete response

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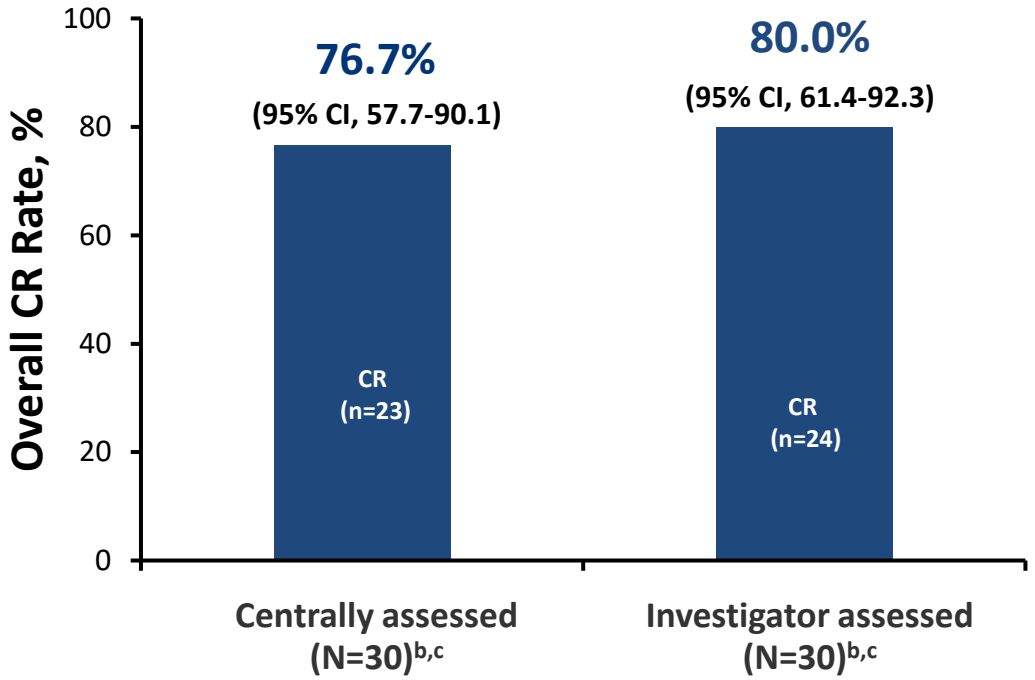
CR Rate in Patients With HR NMIBC CIS (Cohort 2)



The Highest rate of complete response at any time
Caveat small sample size and different stages of follow-up

Necchi A et al. ESMO 2023

Sustained Durable Responses with TAR-200 Monotherapy

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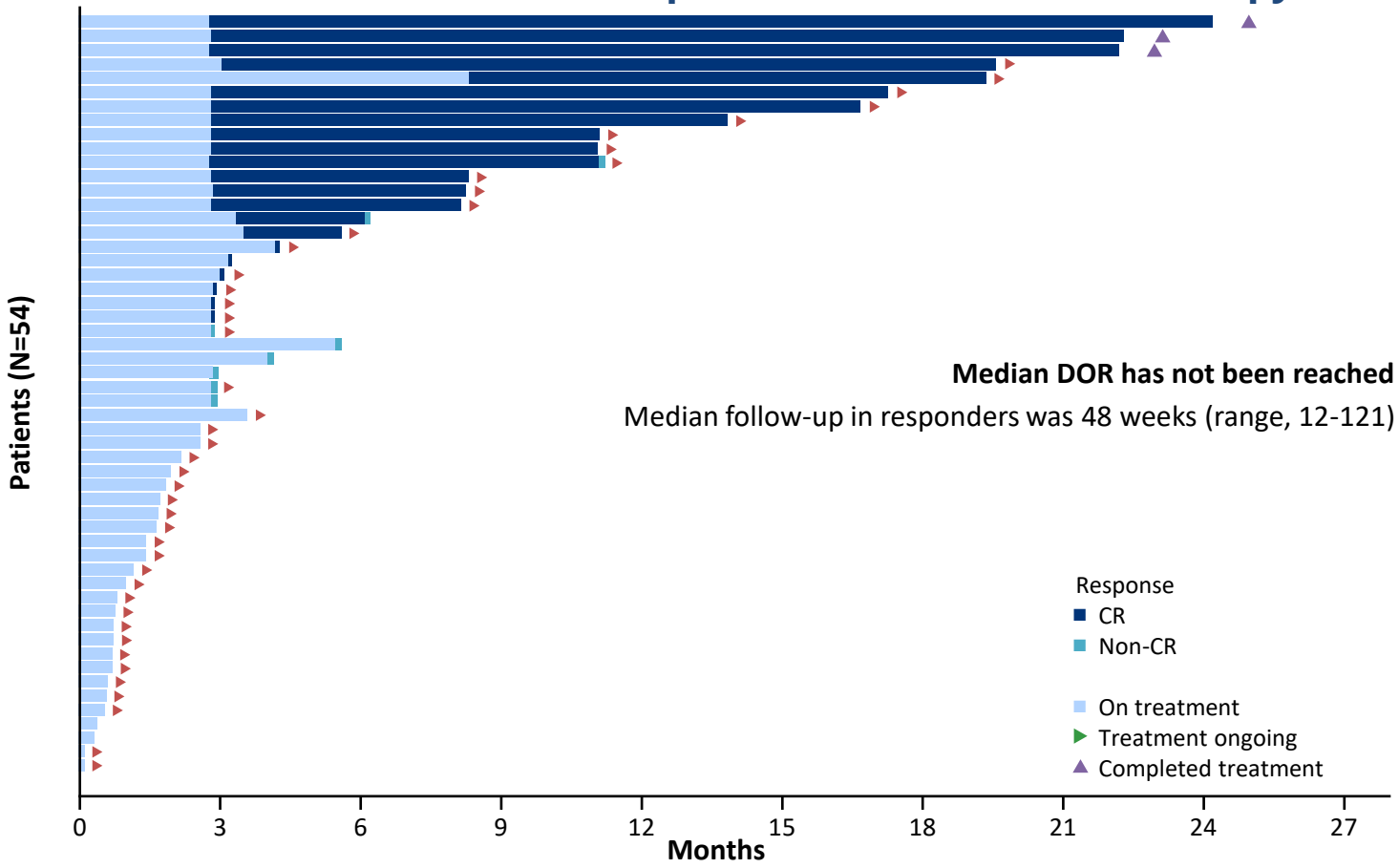
Treatment Duration and Response to TAR-200 Monotherapy



- **21 of 23 responses are ongoing**
  - At 3 months after initial CR, 14 of 23 patients had ongoing response
  - At 6 months after initial CR, 11 of 23 patients had ongoing response
  - At 12 months after initial CR, 6 of 23 patients had ongoing response
- **None of the patients with CR have undergone cystectomy**

Promising duration of response
No cystectomy data yet reported

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Necchi A et al. ESMO 2023

TAR-200 monotherapy in Cis BCG-unresponsive
Safety profile

- Overall, most AEs in the TAR-200 cohort were Grade 1 or 2
- 29 patients (53.7%) had ≥1 treatment-related AE
- 1 patient (1.9%) had ≥1 serious treatment-related AE
- **4 patients (7.4%) had grade ≥3 treatment-related AEs**
- Low rate of treatment discontinuation due to adverse events:

2 patients (3.7%)

- No deaths were reported

Patients with events, n (%)	TAR-200 (N=54)	
	Any grade	Grade ≥3
≥1 AE	37 (68.5)	9 (16.7)
≥1 treatment-related AE	29 (53.7)	4 (7.4)
Pollakiuria	12 (22.2)	1 (1.9)
Dysuria	11 (20.4)	0
Micturition urgency	10 (18.5)	0
Hematuria	6 (11.1)	0
Noninfective cystitis	4 (7.4)	0
Urinary tract pain	3 (5.6)	1 (1.9)
Urinary retention	2 (3.7)	1 (1.9)
Renal impairment	1 (1.9)	1 (1.9)
Urosepsis	1 (1.9)	1 (1.9)

Few major Aes
All Bladder related

Necchi A et al. ESMO 2023

Provocative perspective with emerging therapies for NMIBC

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	Pembrolizumab	Atezolizumab	Cetrelimab	Nadofaragene Firadenovec	Cretostimogene	N-803 + BCG	TAR-200	?
Mechanism	PD-1	PD-L1	PD-1	Adenovirus immunotherapy	Oncolytic immunothérapy	IL-15 superagonist	Chemotherapy	
3 month CR	41%	27% (6mo)	38.1% (6mo)	53%	68.2%	71%	76.7%	
12 month CR	19%	13%	-	24%		61.6%	-	
Duration of CR Responders (mo)	24.1	15.4	-	9.7		26.6	-	
Ttt schedule	Q3wk x 2y	Q3w x 1y	Q3w x 18mo	Q3mo x 1y		Qwk x 6, maintenance x 3	Q3w 24w Q12w 2y	
Total potential physician visits over 2y	34	15	26	5		26	14	
G3-5 AEs	12.7%	16%	8.3%	3.8%	0%	5%	16.7%	
Cystectomy-free	63%	73.6%	-	68%	-	84%	-	

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Provocative perspective with emerging therapies for NMIBC

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	Pembrolizumab	Atezolizumab	Cetrelimab	Nadofaragene Firadenovec	Cretostimogene	N-803 + BCG	TAR-200	Gem/Doce
Mechanism	PD-1	PD-L1	PD-1	Adenovirus immunotherapy	Oncolytic immunothérapy	IL-15 superagonist	Chemotherapy	**Direct cytotoxicity**
3 month CR	41%	27% (6mo)	38.1% (6mo)	53%	68.2%	71%		**-**
12 month CR	19%	13%	-	24%		61.6%		**60%**
Duration of CR Responders (mo)	24.1	15.4	-	9.7		26.6		**13.9**
Ttt schedule	Q3wk x 2y	Q3w x 1y	Q3w x 18mo	Q3mo x 1y		Qwk x 6, maintenance x 3	Q3w 24w Q12w 2y	**Qwk x 6, then monthly maintenance**
Total potential physician visits over 2y	34	15	26	5		26	14	**26**
G3-5 AEs	12.7%	16%	8.3%	3.8%	0%	5%		**3.3%**
Cystectomy-free	63%	73.6%	-	68%	-	84%		**84.4%**

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Conclusion

- IO FDA approved (No EMA approval) but not so exciting based on CR/Safety profile
- Gene therapy (FDA approved, awaiting for EMA) good option but caveats duration of response and production
- New intravesical therapies evidence and approval on the making (with TAR-200 having the best CR rates ever seen in this setting)
- **Inclusion in clinical trials is key (combinations?)**

Emerging therapies in high-risk NMIBC

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