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UGN-102 (Mitomycin)

Proposed Indication: Treatment of Adult Patients with Low-Grade Intermediate-Risk Non-Muscle Invasive Bladder Cancer (LG-IR-NMIBC)

Oncologic Drugs Advisory Committee (ODAC) Meeting
FDA Introductory Comments
May 21st, 2025

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Presentation Outline

- Drug Background and Purpose of ODAC
- Disease Setting: NMIBC
- Regulatory Background
- Data submitted by Applicant to support New Drug Application
- Summary and Issues for Committee Discussion

Drug Background and Purpose of ODAC

UGN-102 (Mitomycin)

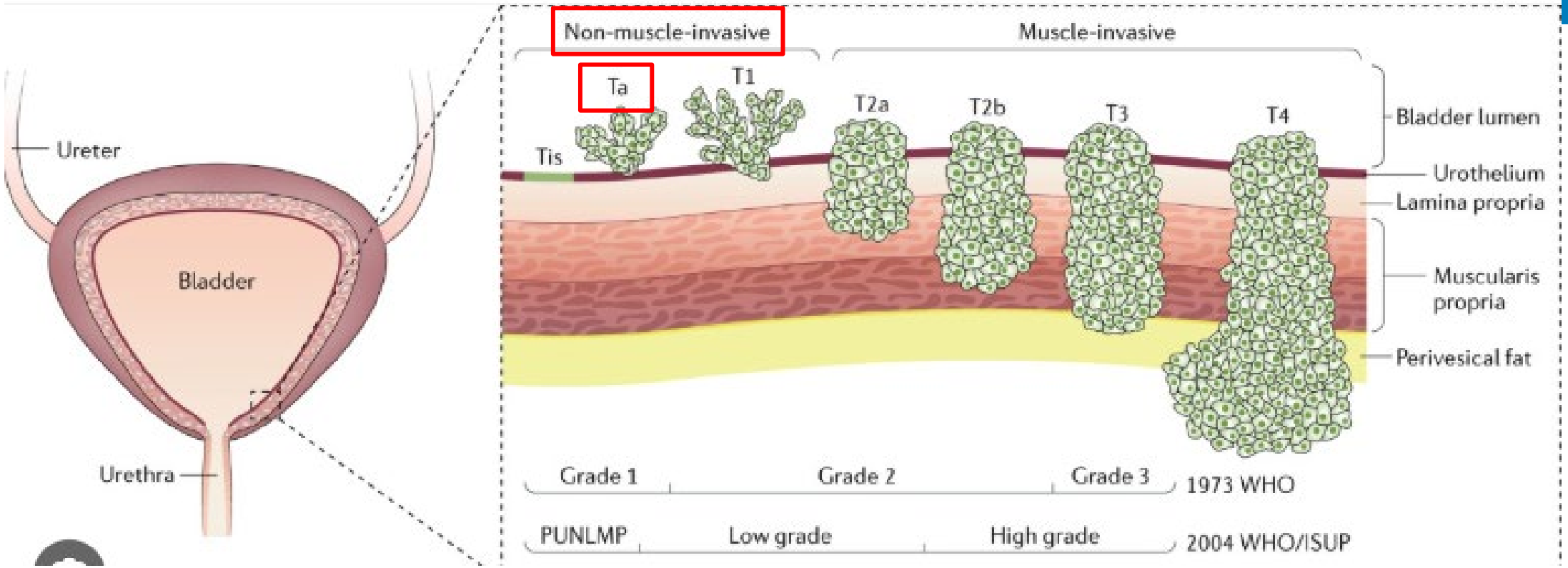
- UGN-102 (mitomycin) is an intravesical solution in a “reverse thermal gel formulation”
- Mitomycin acts as an alkylating agent, inhibiting synthesis of DNA
- Off-label intravesical use in NMIBC to reduce recurrence risk:
  - As single post-operative instillation after TURBT
  - As adjuvant therapy after resection
- Mitomycin hydrogel FDA-approved to treat patients with low-grade Upper Tract Urothelial Cancer (UTUC)

Purpose of ODAC

- Proposed indication: Treatment of Adult Patients with Low-Grade Intermediate-Risk Non-Muscle Invasive Bladder Cancer (LG-IR-NMIBC)
  - No drugs currently FDA-approved for this population
  - Single-arm trial design used in pivotal study to support application
- FDA seeks input from the Committee on the following:
  - Given uncertainty regarding interpretation of duration of response in LG-IR-NMIBC, discuss whether randomized trials should be required in the future to assess the effectiveness of therapies in this disease setting.
  - Is the overall benefit-risk of UGN-102 favorable for patients with recurrent LG-IR-NMIBC?

Disease Setting: NMIBC

Spectrum of Disease in Bladder Cancer



- NMIBC is on earlier end of the bladder cancer disease spectrum
- Ta lesions are non-invasive, papillary tumors

Sanli, O., Dobruch, J., Knowles, M. *et al.* Bladder cancer. *Nat Rev Dis Primers* **3**, 17022 (2017). https://doi.org/10.1038/nrdp.2017.2

Disease Setting: NMIBC

- NMIBC is a heterogenous disease state
- Wide range of recurrence and progression probabilities
- In patients with Ta and T1 tumors:
  - Recurrence risk 15-61% at **1 year** and 31-78% at **5 years**
  - Progression risk 1-17% at **1 year** and 1-45% at **5 years**
- Difficult to quantify specific recurrence and progression rates for individual patients with NMIBC

American Urological Association Guidelines: Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline, 2024
Sylvestor 2006

NMIBC Risk Stratification

Low Risk	Intermediate Risk	High Risk
LG solitary Ta ≤ 3 cm	Recurrence within 1 year, LG Ta	HG T1
PUNLMP	Solitary LG Ta > 3 cm	Any recurrent, HG Ta
	LG Ta, multifocal	HG Ta > 3 cm (or multifocal)
	HG Ta ≤ 3 cm	Any CIS
	LG T1	Any BCG failure in HG patient
		Any variant histology
		Any LVI
		Any HG prostatic urethral involvement

LG=low grade; PUNLMP=papillary urothelial neoplasm of low malignant potential; HG=high grade; CIS=carcinoma in situ; LVI=lymphovascular invasion

- Categories “broadly estimate likelihood of recurrence and progression”

American Urological Association Guidelines: Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline, 2024

Heterogeneity in LG-IR NMIBC

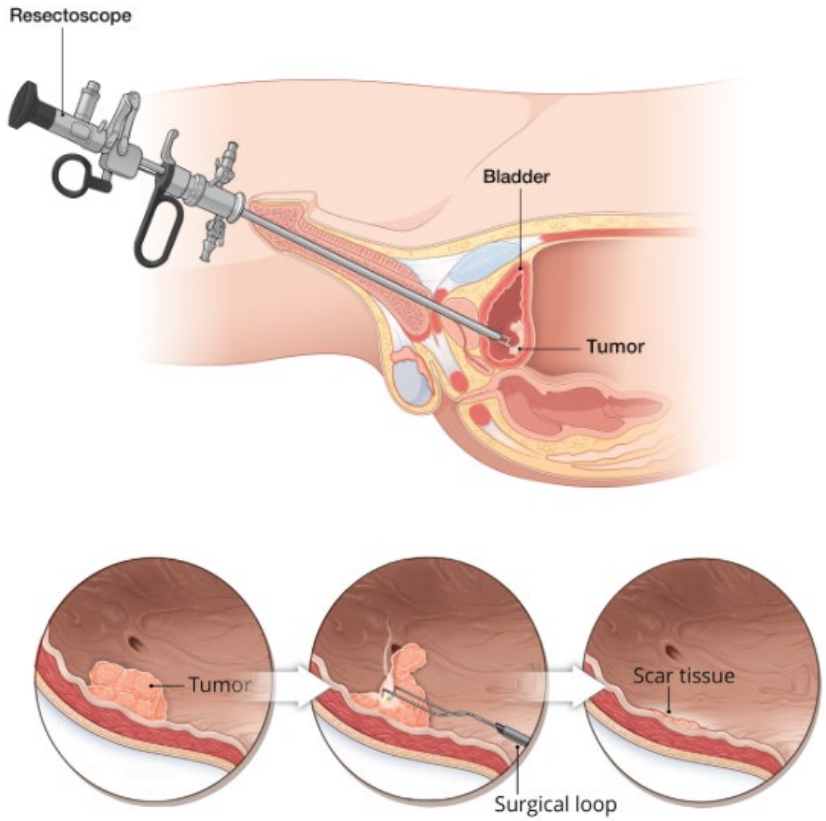
- Natural history of IR disease difficult to predict
- Management varies based on individual characteristics
  - Transurethral resection of bladder tumor (TURBT) alone
  - TURBT with immediate single post-operative chemotherapy instillation
  - TURBT with instillation and maintenance therapies (e.g., BCG, chemotherapy)
  - Some patients may be candidates for active surveillance
- Disease monitoring conducted until recurrence or progression
  - Cystoscopy
  - Urine cytology
  - For-cause biopsy

Zaurito 2024

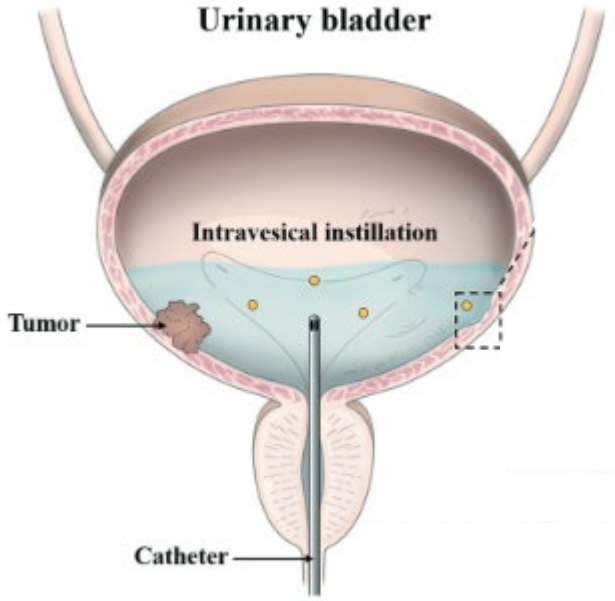
BCG=Bacillus Calmette-Guerin therapy

TURBT vs. UGN-102 Drug Administration

TURBT



Intravesical Drug Delivery via Urinary Catheter



https://www.roswellpark.org/cancer/bladder/treatment/surgery/turbt; Accessed 5/7/25
Yoon et al. 2020; https://doi.org/10.1080/17425247.2020.1810016

Risks Associated with TURBT

- Overall 30-day TURBT complication rate ranges from 5-8%
- Most common complications include UTI and reoperations
- Serious complications include bladder perforation, infection, hematuria
- Mortality rate ~0.8%
- Repeated TURBTs may predispose patients to increased cumulative risk of certain adverse events

UTI=Urinary Tract Infection

Doshi et al. Meeting Abstract: 2025 ASCO Genitourinary Symposium, 2025 American College of Surgeons National Surgical Quality Improvement Program

Applicant's Proposed Rationale for Utility of UGN-102

- TURBT may not resect all tumor
- TURBT procedure may lead to tumor cell reimplantation after resection
- Need for general anesthesia exposes patients to safety risks
- High recurrence rate after TURBT
- Procedural limitations and postoperative complications suggest that a primarily surgical approach is suboptimal

Adapted from Applicant's BL011 Clinical Study Report

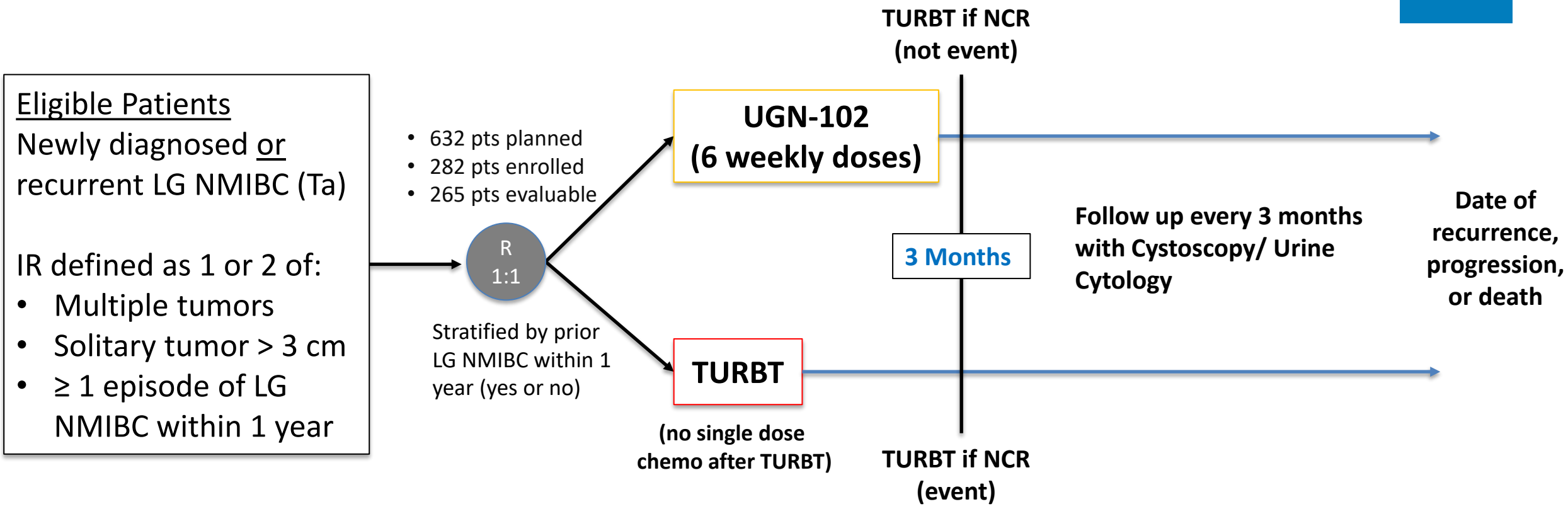
Regulatory Background

Regulatory History

- Multiple interactions between Applicant and FDA dating to 2016
- Applicant has proposed several trial designs to evaluate UGN-102
  - Randomized, non-inferiority designs evaluating DFS endpoint
  - Randomized, superiority designs evaluating DFS endpoint
  - Single arm trial designs assessing CR and DoR
- FDA recommended and encouraged randomized trial design several times

DFS=Disease-free survival; CR=Complete response; DoR=Duration of Response

ATLAS (BL006) Trial



Primary Endpoint:

- DFS (noninferiority & superiority)

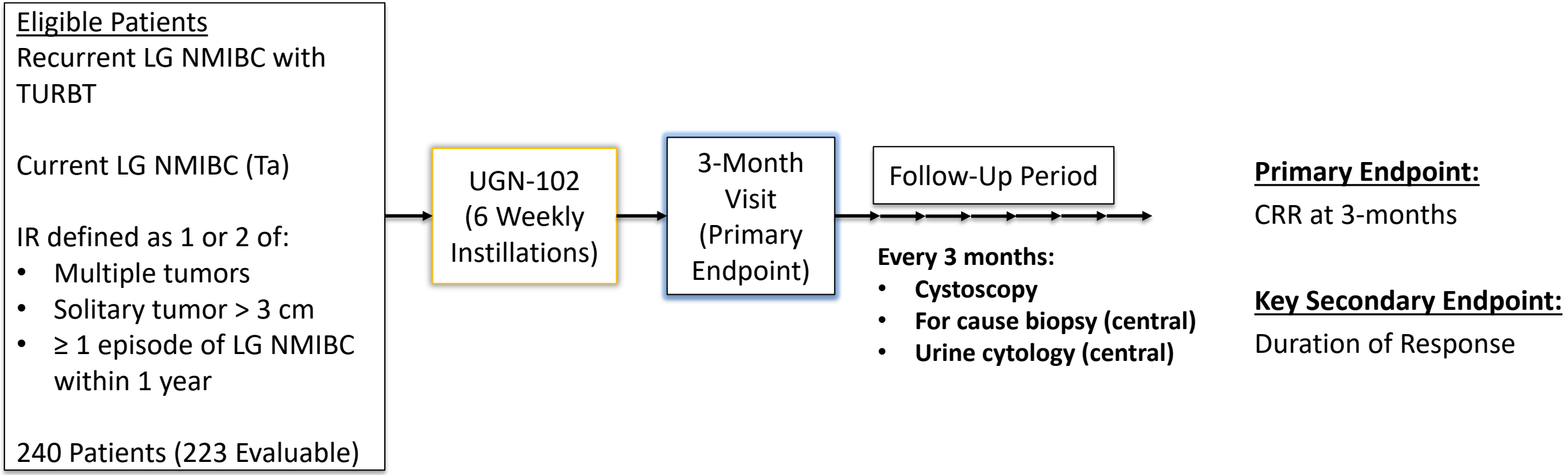
Key Secondary Endpoints:

- CRR
- DoR
- PRO

FDA Input on Single Arm Trial Design

- Single arm design could “possibly serve as a major trial” to support approval if:
  - Enrolls large number of patients
  - Includes sufficient duration of follow up
  - Demonstrates sufficient efficacy and safety that encompasses outcomes with later TURBTs
- Additional FDA input included:
  - Demonstrating treatment effect that is distinct from natural history of disease critical
  - Clinical meaningfulness will depend on population enrolled, complete response and duration of response observed, and safety results
- Would likely need discussion at ODAC
- ATLAS trial subsequently terminated to pursue single arm trial

ENVISION (BL011) Trial



CRR=Complete response rate

Single Arm Vs. Randomized Trial Designs

Challenges for Single Arm Designs

- Potential for selection bias
- Need comparison to historical control to put efficacy in context
- Lack of comparative safety data

Strengths of Randomized Designs

- Accounts for both known and unknown factors
- Concurrent control provides context for efficacy
- Robust comparative safety evaluation

Randomized trial designs should be used to support claims of efficacy unless infeasible or unethical

Durable CR Assessed in Single Arm Trials

- BCG-unresponsive carcinoma-in-situ (CIS) NMIBC
  - Radical cystectomy is morbid procedure, also with risk of mortality
  - Durable CR→ ability to delay or forego radical cystectomy
- Mitomycin hydrogel in Upper Tract Urothelial Cancer
  - Radical nephroureterectomy (RNU) is morbid procedure
  - Durable CR→ ability to delay or forgo RNU
- Risks of TURBT appear to be less than cystectomy and RNU
  - Different benefit-risk considerations

Single Arm Trials and LG-IR-NMIBC

- LG-IR-NMIBC risk is related primarily to recurrence
  - Wide range of recurrence outcomes in this population
  - Some patients may never recur, or may recur infrequently
  - Recurrence may require additional TURBT rather than radical procedure
- Lack of concurrent control presents challenges:
  - Potential selection bias
  - Unclear if DoR is due to drug or natural history of disease
  - Lack of comparative safety data
- Given uncertainty regarding interpretation of duration of response in LG-IR-NMIBC, should randomized trials be required in the future to assess the effectiveness of therapies in this disease setting?

Data Submitted by Applicant to Support NDA

ENVISION (Single Arm Trial) Results

	FDA Analysis Population
# of patients	**223**
CRR at 3-Month Assessment	**77.6% (173/223)** [95% CI: 71.5, 82.9]
Non-Complete Response at 3-Month Assessment:	
Residual disease	14.3% (32/223)
Progression	2.2% (5/223)
Indeterminate	4.0% (9/223)
Missing	1.8% (4/223)
% maintaining CR at 12 months post-3 month CR	**79% (95% CI: 72, 85)**

CRR=Complete response rate

Consistent CRR Across ENVISION and ATLAS Trials

	ENVISION	ATLAS FDA Analysis Population (Defined per ENVISION)
	UGN-102	UGN-102
# of patients	**223**	**51**
CRR at 3-Month Assessment	**77.6% (173/223)** [95% CI: 71.5, 82.9]	**72.5% (37/51)** [95% CI: 58.3, 84.1]

Interpret cross-trial comparisons with caution

CRR=Complete response rate

Safety Assessment of UGN-102

- Most common adverse events were genitourinary toxicities
  - E.g., urinary tract infection, dysuria, hematuria
  - Mostly low-grade events
  - Resolution of most events during or after treatment course
- ATLAS trial comparative safety data:
  - Limited interpretation due to differences in assessments between arms
  - UGN-102 had higher rates of adverse events, Grade 3-4 events
  - Higher rates of dysuria, frequent urination, erectile dysfunction

Summary and Issues for Committee Discussion

Treatment of LG-IR-NMIBC

- Current standard of care is TURBT +/- post-op intravesical chemotherapy
- Some patients may be candidates for active surveillance
- Patients who have frequent recurrences may undergo multiple TURBT procedures
- Risks with general anesthesia, hematuria, bladder perforation

Assessment of Effectiveness

- UGN-102 has activity
  - Mitomycin active in other NMIBC settings
  - CR without intervention not expected
- Durability is key component of efficacy evaluation
  - Short DoR unlikely to be clinically meaningful
  - Prolonged DoR may obviate or delay subsequent TURBT
- DOR of UGN-102 difficult to interpret
  - Single arm design: DoR drug effect or natural disease history?
  - Lack of good historical control
  - Wide recurrence probabilities in this population

Overall Benefit-Risk Assessment

- UGN-102 appears to induce complete responses
  - Duration of response challenging to interpret
- Acute genitourinary toxicity with UGN-102
  - Weekly catheterization and treatment x 6 weeks
  - Lack of randomized data to contextualize safety
- Is a single arm trial sufficient to inform benefit-risk?
  - Several weeks of potential toxicity burden
  - Is duration of response observed due to drug or disease?
  - Different benefit-risk considerations than other settings

Discussion

Given uncertainty regarding interpretation of duration of response in LG-IR-NMIBC, discuss whether randomized trials should be required in the future to assess the effectiveness of therapies in this disease setting.

Voting Question

Is the overall benefit-risk of UGN-102 favorable for patients with recurrent LG-IR-NMIBC?

NDA 215793: UGN-102 (mitomycin intravesical solution)

Proposed Indication: Treatment of Adult Patients with Low-Grade Intermediate-Risk Non-Muscle Invasive Bladder Cancer (LG-IR-NMIBC)

Oncologic Drugs Advisory Committee (ODAC) Meeting

May 21st, 2025

Brian Heiss, MD
Clinical Reviewer, Genitourinary Malignancies
Division of Oncology 1, Office of Oncologic Diseases

FDA Review Team

Richard Pazdur, Director, Oncology Center of Excellence (OCE)	Vishal Bhatnagar, Associate Director for Patient Outcomes, OCE
Angelo DeClaro, Acting Deputy Director, Office of Oncologic Diseases	Shenghui Tang, Division Director, Division of Biometrics V (DBV)
Laleh Amiri-Kordestani, Director, Division of Oncology 1 (DO1)	Mallorie Fiero, Supervisory Mathematical Statistician, DBV
Daniel Suzman, Deputy Division Director, DO1	Xin (Cindy) Gao, Statistical Team Lead, DBV
Sundeep Agrawal, Cross Disciplinary Team Leader, DO1	Qingyu (Sophia) Chen, Statistical Reviewer, DBV
Brian Heiss, Clinical Reviewer, DO1	Ting-Yu (Jeff) Chen, Statistical Reviewer, DBV
Sean Clark-Garvey, Clinical Reviewer, DO1	Jared Kabara, Statistical Analyst, Division of Analytics and Informatics

Discussion and Voting Questions

FDA seeks input from the Committee on the following:

Discussion Question:

- Given uncertainty regarding interpretation of duration of response in LG-IR-NMIBC, discuss whether randomized trials should be required in the future to assess the effectiveness of therapies in this disease setting.

Voting Question:

- Is the overall benefit-risk of UGN-102 favorable in patients with recurrent LG-IR-NMIBC?

Presentation Outline

- Background
  - NMIBC setting
  - Key regulatory history
- Summary of efficacy
  - Primary evidence: ENVISION trial
  - Supportive evidence: ATLAS trial
- Summary of safety
  - ENVISION and ATLAS trials
  - Patient reported outcomes
- Considerations for Committee and Voting Question

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- Considerations for Committee and Voting Question

NMIBC Disease Background

- Non-muscle invasive disease:
  - Low progression risk
  - Patients can recur frequently, resulting in repeated interventions

- LG-IR-NMIBC
  - Heterogenous population with wide recurrence and progression probabilities
  - Natural history of disease difficult to predict
  - TURBT +/- single intravesical chemotherapy commonly used in practice

TURBT = transurethral resection of bladder tumor

Key Regulatory History

Interaction Date	Key Regulatory Points
Pre-2021	• Meetings with Applicant about various trial designs • Included randomized ATLAS trial of UGN-102 +/- TURBT vs. TURBT • Non-inferiority design with DFS endpoint not acceptable
August 2021	• FDA stated single arm trial potentially acceptable but would need ODAC
November 2021	• ATLAS enrollment closed early due to business decision • Further discussions regarding single arm trial design (ENVISION)
February 2022	• ENVISION trial first patient consented
September 2023	• Primary results to support application should be from ENVISION • ATLAS data may be considered supportive • FDA reiterated need for ODAC discussion

DFS = disease-free survival

Presentation Outline

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Primary Evidence of Efficacy

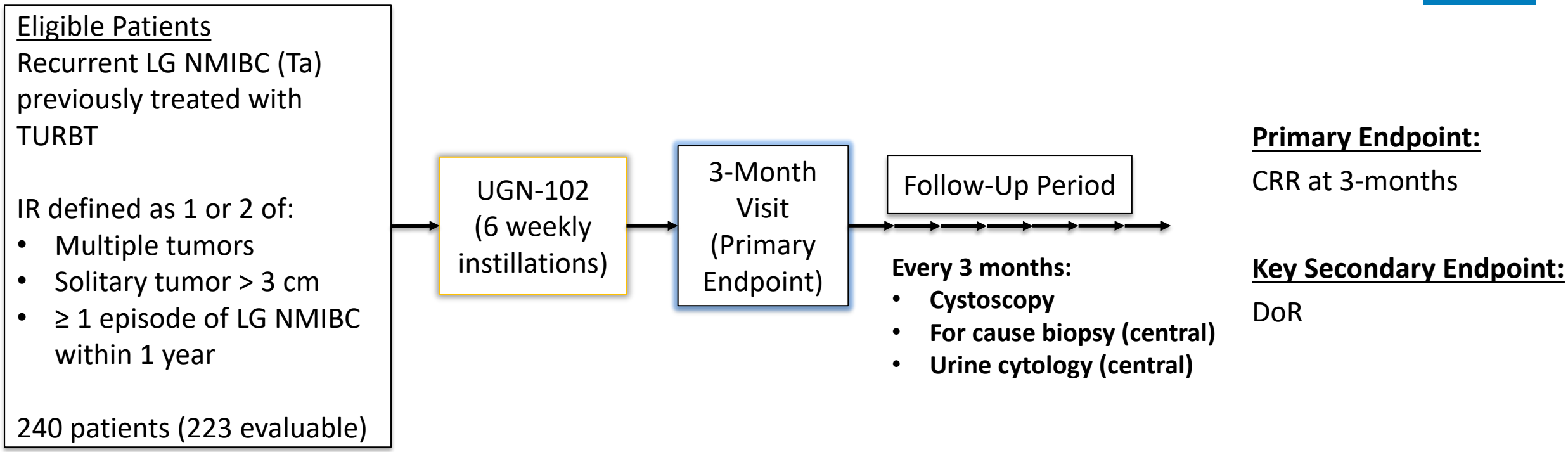
	ENVISION (BL011)	ATLAS (BL006)
Evidence Role	Primary	Supporting
Study Design	Single-arm trial of UGN-102	Randomized trial of UGN-102 +/- TURBT vs. TURBT alone
Patient Population	Recurrent LG NMIBC at Intermediate Risk	Newly Diagnosed and Recurrent LG NMIBC at Intermediate Risk
Patients Enrolled	240 (223 evaluable)	282 (265 evaluable)
Primary Endpoint	CRR at 3 months	DFS (FDA disagreed)
Key Secondary Endpoints	DoR	CRR at 3 months, DoR
Status	18 months follow up	Terminated Early

Applicant submitted data from separate single-arm trial (OPTIMA II) and cohort in 8 patients (BL010)

- Cannot draw conclusions from these cohorts
- Different populations, local assessments only, limited follow up

LG = low grade; CRR = complete response rate; DoR = duration of response

ENVISION (BL011) Trial



Complete Response (CR) Definition:

- (-) cystoscopy **AND** (-) or atypical urine cytology
- (+) cystoscopy with (-) biopsy **AND** (-) or atypical urine cytology
- (-) cystoscopy **AND** (+) repeated urine cytology with UTUC eval either (+) **OR** (-) with (-) bladder biopsy

UTUC = upper tract urothelial cancer

ENVISION: 3-Month CRR and DoR Results

	FDA Analysis Population
# of patients	**223**
CRR at 3-Month Assessment	**77.6% (173/223)** [95% CI: 71.5, 82.9]
Non-Complete Response at 3-Month Assessment:	
Residual disease	14.3% (32/223)
Progression	2.2% (5/223)
Indeterminate	4.0% (9/223)
Missing	1.8% (4/223)
Response at 12 months from 3-month CR:	
% of Responding Patients	**79.2% (137/173)** [95% CI: 72.3, 85.0]
% of All Treated Patients	**61.4% (137/223)** [95% CI: 54.7, 67.9]

ENVISION Subgroup Analysis by IR Criteria Consistent with Overall CRR Primary Endpoint

Intermediate Risk (IR) - recurrent LG NMIBC (Ta) with 1 or 2 of the following:

- Multiple tumors
- Solitary tumor size >3 cm
- Early or frequent recurrence (≥ 1 occurrence within 1 year)

	CRR at 3 Months (95% CI)
Baseline Tumor Count*	
Single (n = 34)	79.4% (62.1, 91.3)
Multiple (n = 188)	77.7% (71.0, 83.4)
Baseline Tumor Diameter*	
≤ 3 cm (n = 204)	78.0% (71.6, 83.4)
> 3 cm (n = 14)	85.7% (57.2, 98.2)
Prior LG NMIBC within 1 Year	
Yes (n = 122)	76.2% (67.7, 83.5)
No (n = 101)	79.2% (70.0, 86.6)

*Baseline tumor count and diameter measurements were missing for 1 and 5 patients, respectively.

CI = confidence interval

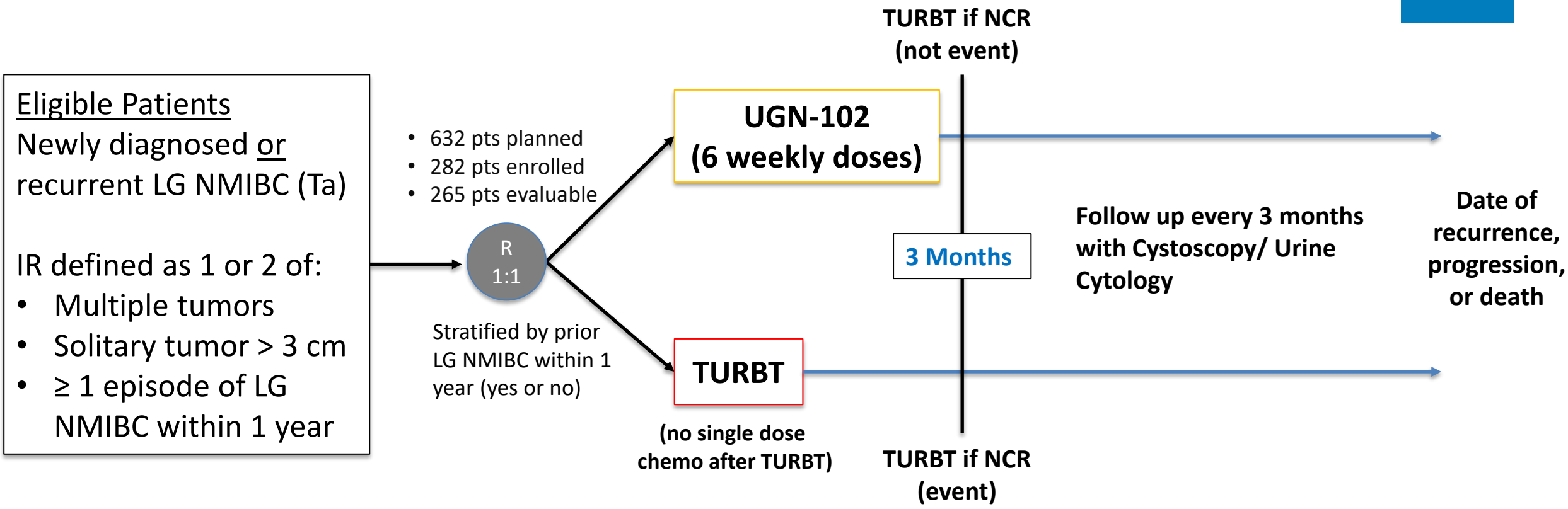
Interpretation Challenges of ENVISION Results

- CRR can be affected by:
  - Intra- and inter-operator variability at cystoscopy
  - Inter-reader variability of pathology

- Interpreting CRR in absence of concurrent control can be challenging
  - Potential for selection bias
  - Extrapolating data to broader LG-IR-NMIBC population difficult

- FDA review included exploratory analyses of ATLAS trial
  - Terminated early
  - CRR and DoR were secondary endpoints

ATLAS (BL006) Trial



Primary Endpoint:

- DFS (noninferiority & superiority)

Key Secondary Endpoints:

- CRR
- DoR
- PRO

NCR = non-complete response; PRO = patient reported outcomes

ATLAS Trial Limitations

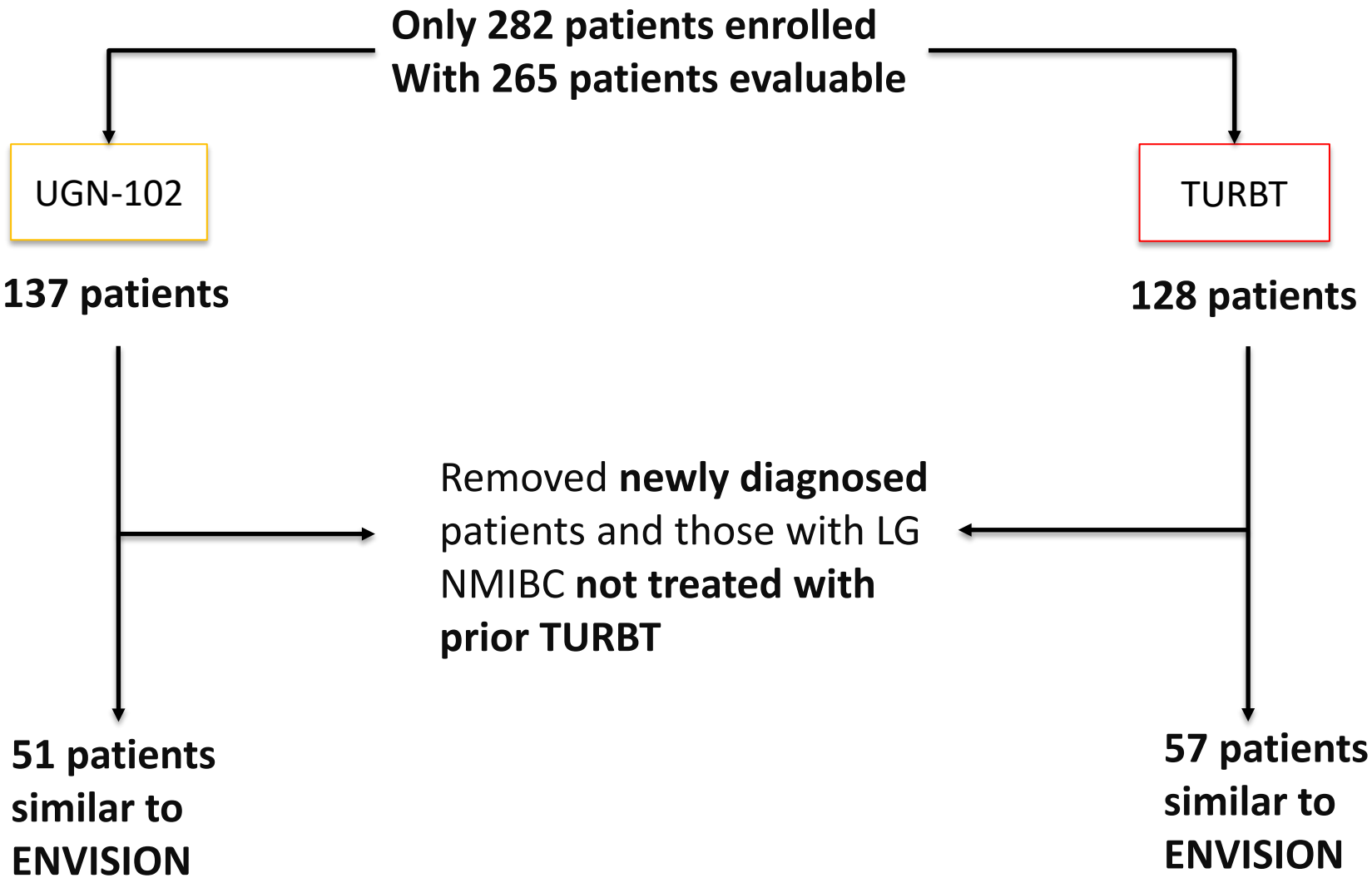
Design Issues:

- **Primary endpoint:** DFS had different definitions of “disease-free” per arm
- **Analysis plan:** Uninterpretable non-inferiority design
- **Treatment:** Lack of post-TURBT intravesical chemotherapy
  - May underestimate TURBT CRR in clinical practice
- CRR at 3 months and DoR descriptive only
- Differing PRO assessment frequency

Conduct Issues:

- Terminated early
  - Not fully enrolled
  - Limited follow up

Selection of ATLAS Patients Matching ENVISION Patients



Baseline Disease Characteristics in Recurrent Patients

	ENVISION	ATLAS (Recurrent Only)
	UGN-102 (N = 223)	UGN-102 (N = 51)
Tumor Count		
Multiple	188 (84.3%)	34 (66.7%)
Longest Tumor Diameter (cm)		
≤ 3	204 (91.5%)	44 (86.3%)
Previous LG NMIBC episodes within 1 year		
Yes	122 (54.7%)	33 (64.7%)
# of previous LG NMIBC episodes		
1	142 (63.7%)	27 (52.9%)
2	38 (17.0%)	11 (21.6%)
> 2	43 (19.3%)	13 (25.5%)
# of prior TURBT to treat LG NMIBC		
1	149 (66.8%)	27 (52.9%)
2	36 (16.1%)	13 (25.5%)
> 2	38 (17.0%)	11 (21.6%)

ENVISION Results and FDA Exploratory Analysis of ATLAS

	ENVISION	ATLAS FDA Analysis (Defined per ENVISION)
	UGN-102	**UGN-102**
# of patients	**223**	**51**
CRR at 3-Month Assessment	**77.6% (173/223)** [95% CI: 71.5, 82.9]	**72.5% (37/51)** [95% CI: 58.3, 84.1]
% responders who maintained CR at 12 months post 3-month CR	**79.2%** (137/173) [95% CI: 72.3, 85.0]	**40.5%** (15/37) [95% CI: 24.8, 57.9]

- 3-Month CRR in ATLAS appears supportive of ENVISION
- DoR in ATLAS difficult to compare to ENVISION due to limited follow up

Comparison of UGN-102 to TURBT in ATLAS is Exploratory Only

	ATLAS FDA Analysis Population (Defined per ENVISION)
	TURBT Alone
# of patients	**57**
CRR at 3-Month Assessment	**56.1% (32/57)** [95% CI: 42.4, 69.3]
% responders who maintained CR at 12 months post 3-month CR	**21.9%** (7/32) [95% CI: 9.3, 40.0]

- Post hoc subgroup analysis
- TURBT arm not per most active standard of care (no peri-op chemotherapy)

Efficacy Summary

- ENVISION: 3-Month CRR of 77.6% (95% CI: 71.5, 82.9)
  - Consistent with subgroup analyses and exploratory ATLAS results
- ENVISION: 79.2% of responders maintain CR at 12 months post-CR
  - Unclear if observed DoR is due to effect of UGN-102 or natural disease history
- Comparison of UGN-102 to TURBT in ATLAS is exploratory only

Clinical Meaningfulness of 3-Month CRR and DoR

- Obtaining CR at 3 months can delay or potentially allow forgoing of additional therapy
- Length of time patients maintain CR key to clinical meaningfulness
- Lack of comparator arm in ENVISION limits interpretability, particularly for DoR
- Recurrence results in subsequent intervention, however:
  - Recurrence risk in this population not well characterized
  - Unclear how many patients will require further TURBTs
  - Uncertain durability with UGN-102 → unclear recurrence-free interval
- With UGN-102, one TURBT avoided upfront, but is this worth associated toxicity?

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Summary of Toxicity Observed in ENVISION and Pooled Safety Database*

Treatment-Emergent Adverse Events (TEAEs)	ENVISION N = 240 %	Pooled* N = 449 %
Any TEAE	57	68
Grade 3-4 TEAEs	13	11
Serious TEAEs	12	11
Treatment Interruption due to TEAE	10	10
Treatment Discontinuation due to TEAE	2.9	4.2
Death within 30 days	0.4	0.2

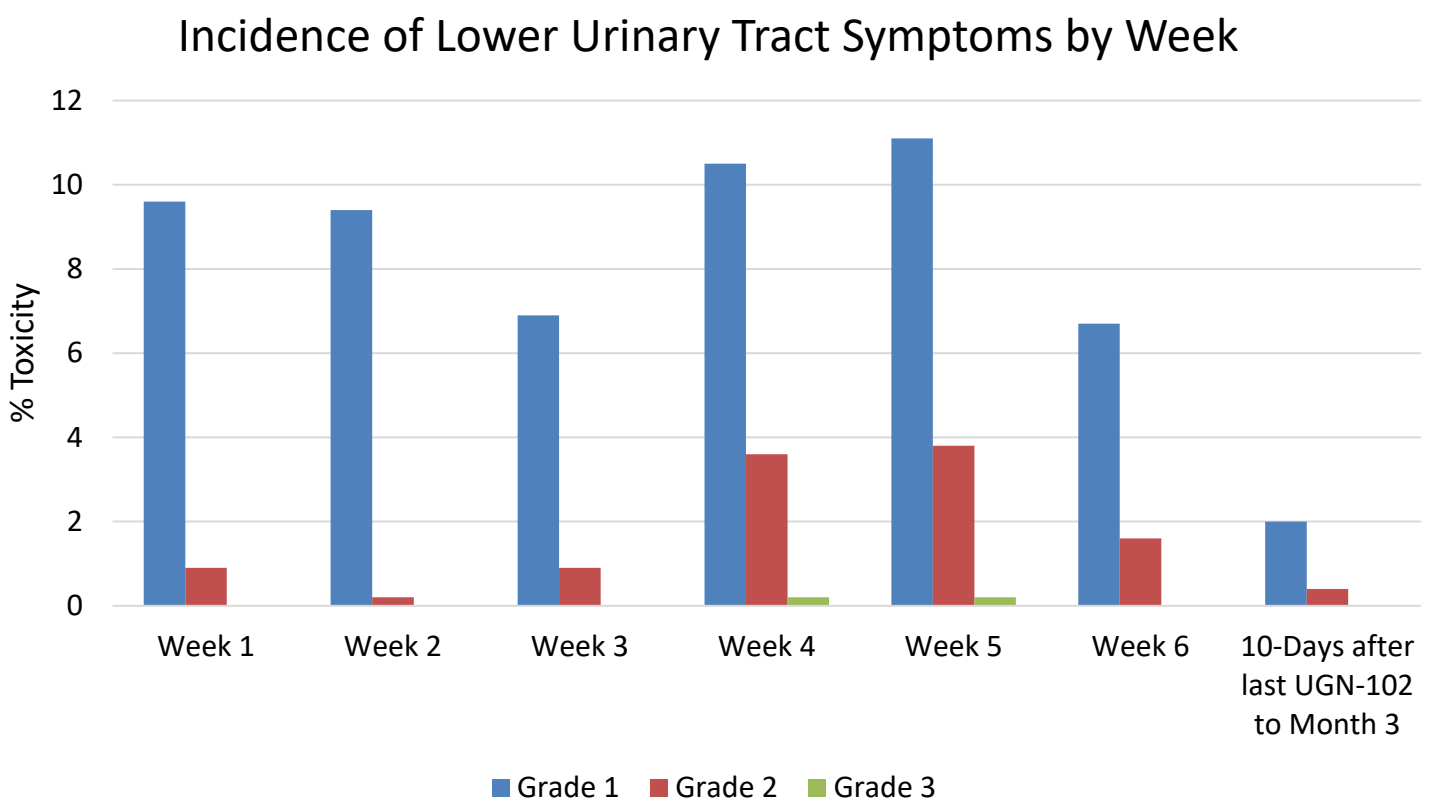
* Pooled database includes ENVISION (BL011), ATLAS (BL006), OPTIMA II (BL005), and BL010 trials

Toxicity Observed in ENVISION

Adverse Events	ENVISION N = 240	
	All Grades %	Grade 3-4 %
Any Adverse Events	57	13
Dysuria	23	0.4
Urinary Tract Infection	12	0.8
Hematuria	10	0
Frequent Urination	7	0
Incontinence	5	0
Urinary Retention	5	0.8
Urethral Stenosis	4.6	0.4

Pooled Incidence of Lower Urinary Tract Symptoms (LUTS)

Lower Urinary Tract Symptoms	Pooled N = 449 %
Overall Incidence through month 3	37
Grade 1	34
Grade 2	9
Grade 3	0.4
Median Duration (days)	16
% Lasting > 3 weeks	19



LUTS group term includes dysuria, pollakiuria, micturition urgency, nocturia, urinary incontinence, bladder spasm, genital discomfort, lower urinary tract symptoms, urge incontinence, urinary tract pain, hypertonic bladder, urethral pain, bladder pain, incontinence, bladder discomfort, urethral polyp, urinary tract discomfort.

ATLAS: Safety in Context of TURBT

Genitourinary Adverse Events (≥ 5%)	UGN-102 +/- TURBT N = 138	TURBT Alone N = 132
	All Grades %	All Grades %
Dysuria	30	4.5
Micturition Urgency	19	8
Nocturia	18	7
Frequent Urination	16	6
Urinary Tract Infection	7	7
Hematuria	7	4.5
Erectile dysfunction	7	3

- Grade 3-4 TEAEs: 6.5% in UGN-102 +/- TURBT and 3.8% in TURBT alone
- Comparison likely confounded by unequal collection of TEAEs between arms

Safety Summary

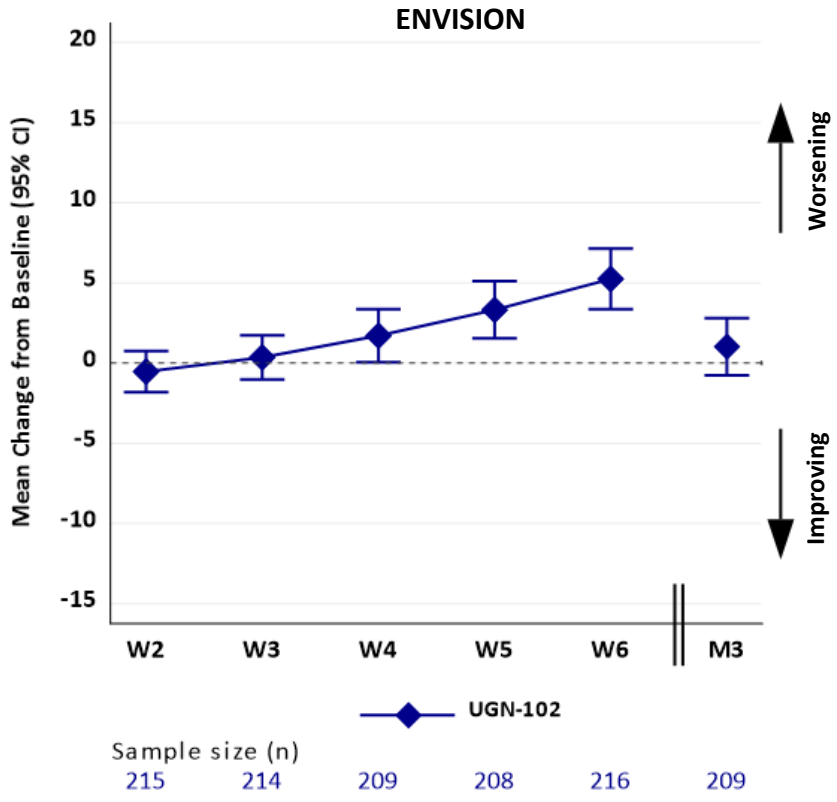
- UGN-102 safety data from ENVISION:
  - Most common TEAEs: Grade 1-2 acute genitourinary toxicities
  - Toxicity burden from 6 weekly intravesical UGN-102 instillations may be greater than with a single TURBT procedure
  - Longer-term toxicities not collected

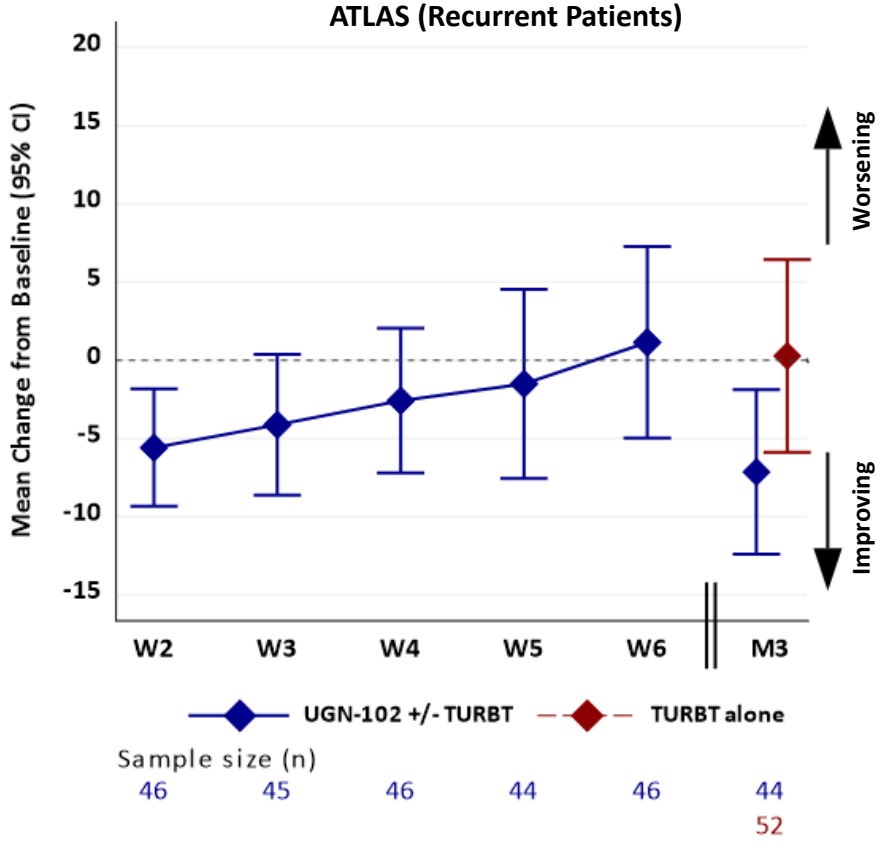
- UGN-102 and TURBT in ATLAS:
  - Higher incidence of Grade 1-2 genitourinary toxicities in the UGN-102 arm
  - Not designed to:
    - Capture surgical or long-term TURBT toxicity
    - Robustly compare safety between UGN-102 and TURBT

- UGN-102 was not demonstrated to be a safer option compared to TURBT.

PRO: Change from Baseline in Urinary Symptoms (EORTC QLQ-NMIBC24)

- PRO completion rates were above 90% while on treatment and at Month 3
- Worsening Urinary Symptoms during UGN-102 treatment, however peak symptoms and resolution of symptoms were not adequately captured by PRO assessments





EORTC = European Organization for Research and Treatment of Cancer; QLQ = Quality of Life Questionnaire

Presentation Outline

- Background
  - NMIBC setting
  - Key regulatory history
- Summary of efficacy
  - Primary evidence: ENVISION trial
  - Supportive evidence: ATLAS trial
- Summary of safety
  - ENVISION and ATLAS trials
  - Patient reported outcomes
- Considerations for Committee and Voting Question

Summary of Submitted Data

- Single arm ENVISION trial considered primary source of evidence
  - CRR at 3 months in 77.6% of patients
  - DoR: 79.2% of responders maintained CR at 12 months (after 3-month CR)

- Randomized ATLAS trial exploratory analyses
  - CRR at 3 months of 72.5% consistent with ENVISION results
  - Comparison to TURBT arm exploratory only

- Toxicity primarily genitourinary events
  - GU toxicity occurred throughout the 6 week treatment course
  - In ATLAS:
    - Toxicity burden with UGN-102 appears greater compared to TURBT alone
    - Not well designed to compare safety or tolerability

Considerations for the Committee

- Can durable CR assessed in a single arm trial establish efficacy?
  - CR may obviate need for 1 TURBT but not necessarily future procedures
  - Prevention/delay of 1 TURBT different than prevention/delay of radical procedures
  - Length of time patients maintain CR is key to establishing clinical meaningfulness
  - Single arm trial → Can't distinguish between treatment effect vs. natural history of disease
  - Lack of well-established historical control

- Additional uncertainties:
  - Long-term risks of recurrence/progression after UGN-102 unknown
  - Outcomes for TURBT after UGN-102 not well captured
  - Potential for resistance to therapies at progression unknown

Is the Overall Benefit-Risk Favorable?

- Toxicity appears more frequent with UGN-102 compared to TURBT
  - Genitourinary symptoms can persist or recur throughout and beyond 6 weeks
  - Toxicity expected to be of shorter duration after one TURBT

- Repeat TURBT may be difficult for some patients:
  - General anesthesia and cardiac risk
  - Bladder perforation or other persistent GU toxicities from procedure
  - However, insufficient follow up and data capture in Applicant's trials

- Does obtaining a durable complete response at the expense of potentially increased genitourinary toxicities constitute favorable benefit-risk?

Discussion Question

Given uncertainty regarding interpretation of duration of response in LG-IR-NMIBC, discuss whether randomized trials should be required in the future to assess the effectiveness of therapies in this disease setting.

Voting Question

Is the overall benefit-risk of UGN-102 favorable in patients with recurrent LG-IR-NMIBC?