BLADDER PRESERVATION STRATEGIES SESSION:

Intravesical IO in high risk NMIBC: a HGUCG study.

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Conflicts of interest

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports	Astra Zeneca
Receipt of honoraria or consultation fees	Janssen, IPSEN, Bayer
Stock shareholder	
Other support (please specify):	

BCG Failure

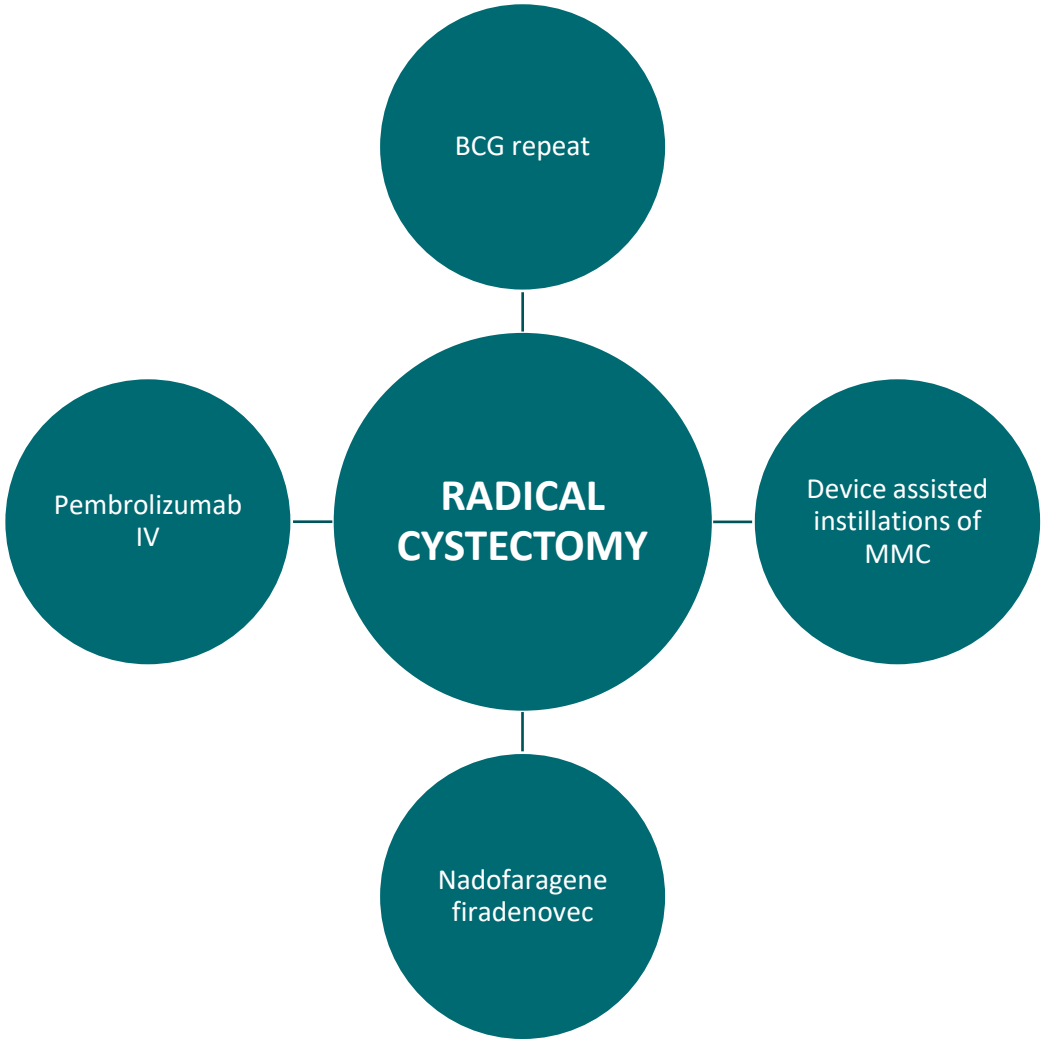
Whenever a MIBC is detected during follow-up.
BCG-refractory tumour
1. If T1G3/HG tumour is present at 3 months [196, 291, 294] (LE: 3). 2. If TaG3/HG tumour is present after 3 months and/or at 6 months, after either re-induction or first course of maintenance [43] (LE: 4). 3. If CIS (without concomitant papillary tumour) is present at 3 months and persists at 6 months after either re-induction or first course of maintenance. If patients with CIS present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases [43, 44, 284] (LE: 1b). 4. If HG tumour appears during BCG maintenance therapy*.
BCG-relapsing tumour
Recurrence of G3/HG (WHO 1973/2004) tumour after completion of BCG maintenance, despite an initial response [288] (LE: 3).
BCG unresponsive tumour
BCG unresponsive tumours include all BCG refractory tumours and those who develop T1Ta/HG recurrence within 6 months of completion of adequate BCG exposure** or develop CIS within 12 months of completion of adequate BCG exposure [292] (LE: 4).
BCG intolerance
Severe side effects that prevent further BCG instillation before completing treatment [266].

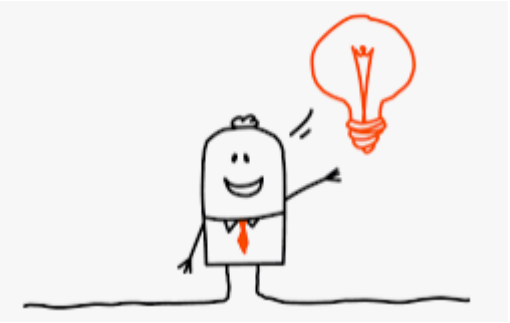
EAU Guidelines on

Non-muscle-invasive Bladder Cancer (TaT1 and CIS)

M. Babjuk (Chair), M. Burger (Vice-chair), E. Compérat, P. Gontero, F. Liedberg, A. Masson-Lecomte, A.H. Mostafid, J. Palou, B.W.G. van Rhijn, M. Rouprêt, S.F. Shariat, R. Sylvester
Guidelines Associates: O. Capoun, D. Cohen, J.L. Dominguez Escrig, T. Seisen, V. Soukup

Treatment Options





- Immunotherapy plays an important role in advanced bladder cancer.
- Intravesical instillations of IO will not lead to side effects similar to systematic administration.
- Urologists are familiar with intravesical instillations.

Intravesical Administration of Durvalumab (MEDI4736) to Patients With High-risk, Non-muscle-invasive Bladder Cancer (NMIBC). A Phase II Study.

Hellenic GenitoUrinary Cancer Group.

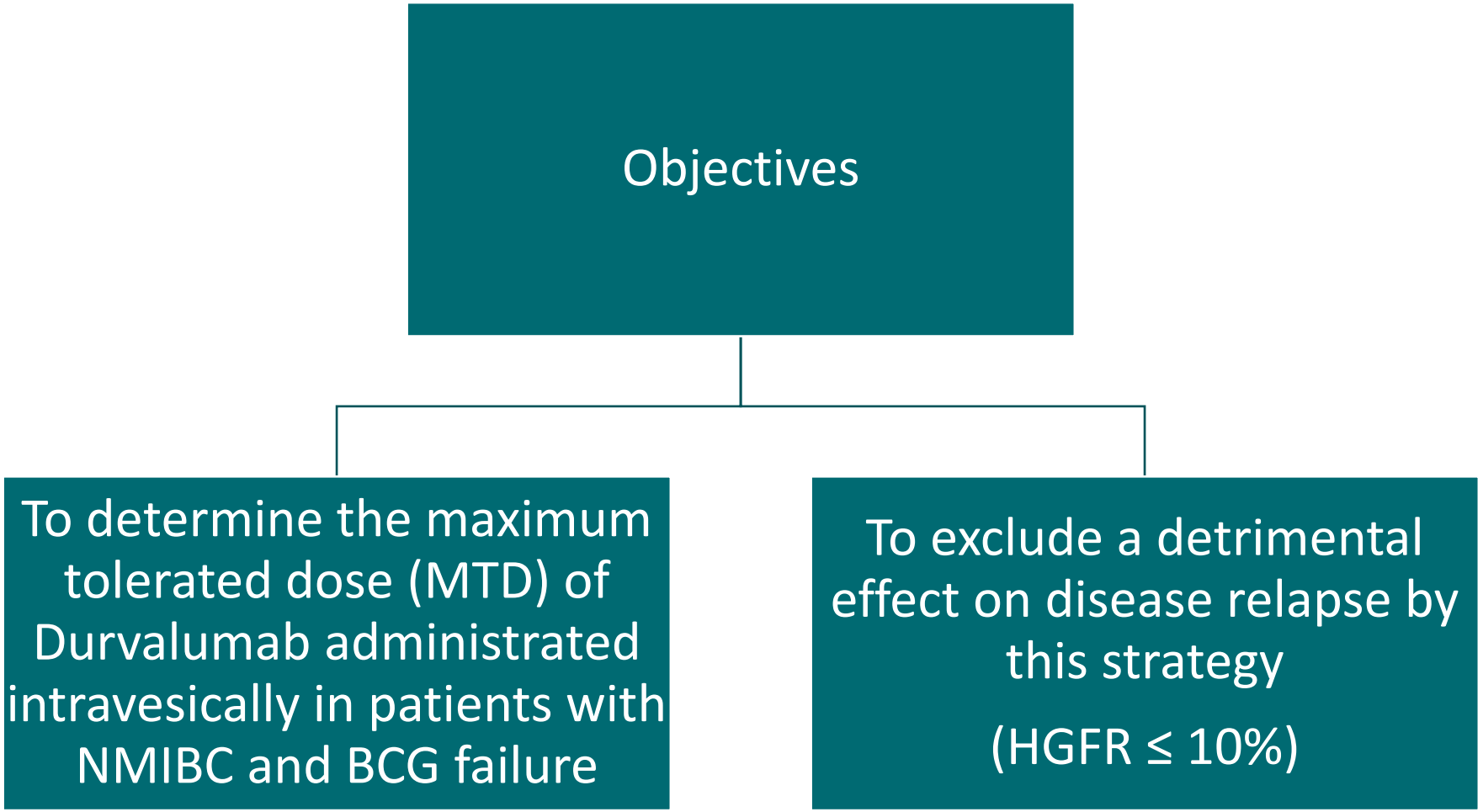
ESR-16-12611.

NCT03759496.

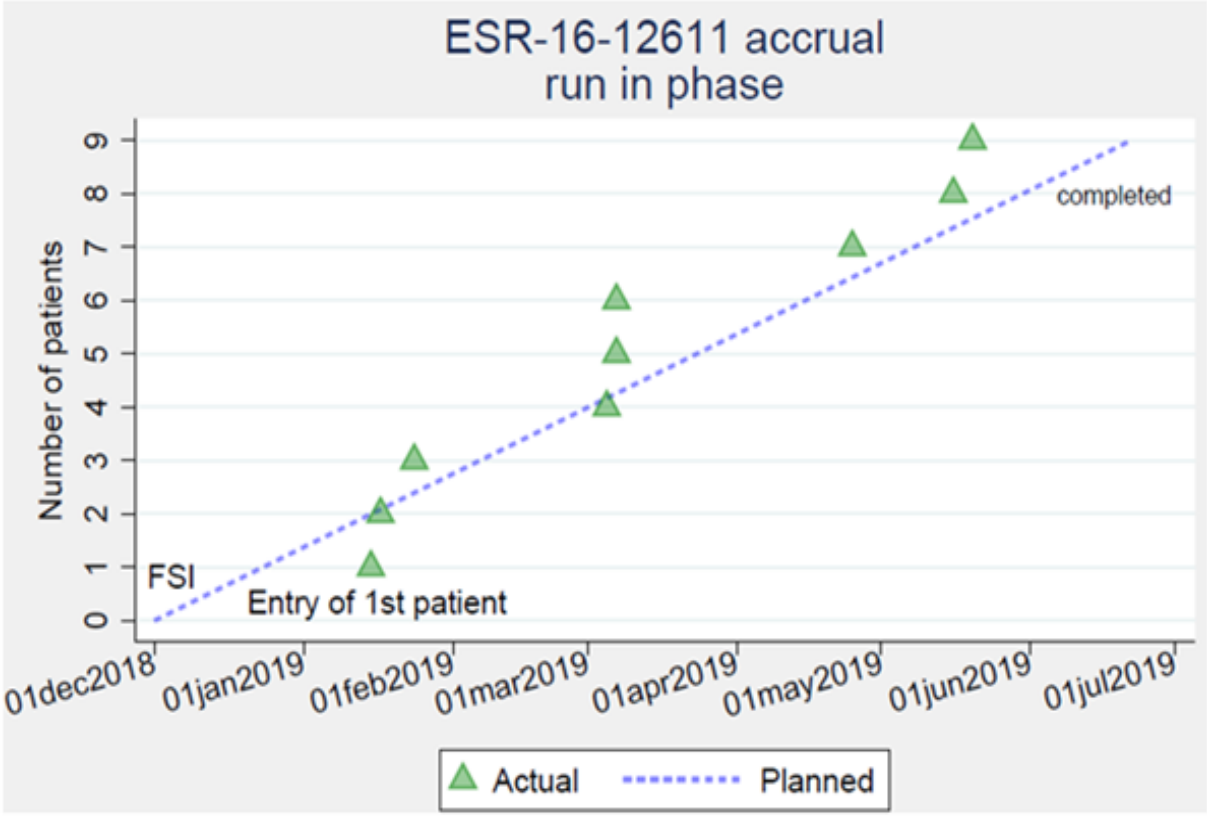
Inclusion Criteria

- Written informed consent.
- Age > 18 years at time of study entry.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Diagnosis of high grade NMIBC:
  - BCG refractory disease
  - High grade recurrence after an initial response to BCG therapy.
  - Patients intolerant to adequate BCG exposure
- Subjects are not candidates for immediate cystectomy or have elected not to undergo the procedure.
- Adequate normal organ and marrow function.

Run-in Phase


Objectives
To determine the maximum tolerated dose (MTD) of Durvalumab administrated intravesically in patients with NMIBC and BCG failure
To exclude a detrimental effect on disease relapse by this strategy
(HGFR ≤ 10%)

Patient Accrual



- Durvalumab intravesical instillations were performed weekly with a total of 6 instillations per patient.
- The starting dose was 500mg and the absence of dose-limiting toxicities (DLTs) up to 1 week after the last durvalumab administration in this group permitted the escalation to the next dose level.

Dose Escalation – Maximum Tolerated Dose

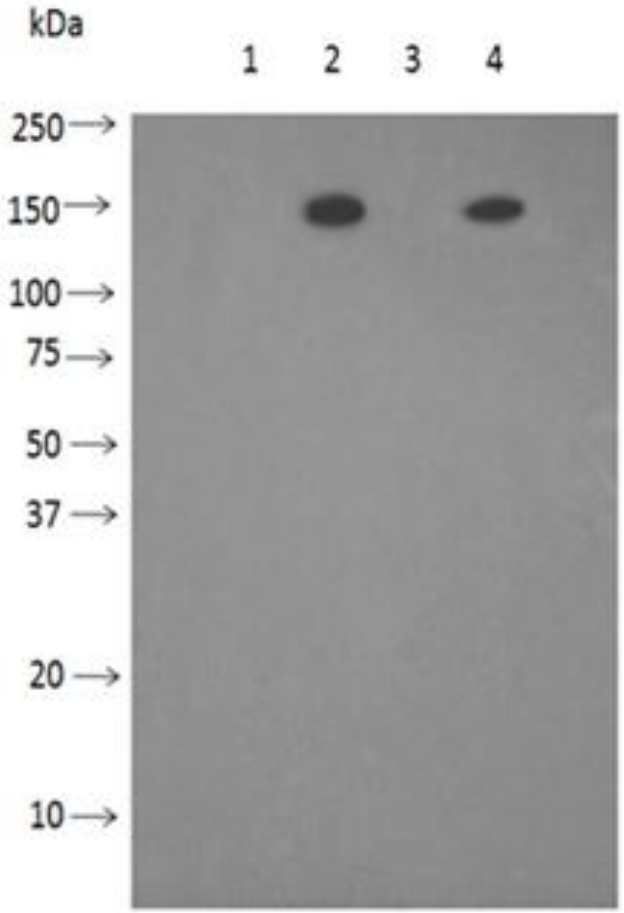
Durvalumab Dose	Number of Patients	DLTs
500 mg	3	0
750 mg	3	0
1000 mg	3	0

- Nine patient with median age 63.5 years were enrolled.
  - 8 males
  - 1 female
- All patients concluded the 6 weeks course of intavesical instillations of durvalumab.
- No DLTs occurred at any of the tested group.
- The MTD of durvalumab was determined at 1000mg.

Run-in Phase Results

- Durvalumab was well tolerated and no serious adverse events were recorded.
- One month after the last instillation of durvalumab, tumor evaluation was performed for all patients according to local standards.
- Three patients (33.3%) were tumor free, therefore, the null hypothesis was rejected by the futility analysis.
- In vitro testing showed that durvalumab was stable in urine up to 2h.

Durvalumab Functional Assay



1. Patient 1 pro administration
2. Patient 1 after administration
3. Patient 2 pro administration
4. Patient 2 after administration

Durvalumab is isolated in patients' urine 1 hour post administration.

Phase II

- Primary endpoint:
  - Efficacy of intravesical administration of Durvalumab at MTD in patients with BCG-refractory NMIBC assessed by 1-year high-grade-relapse-free (HGRF)-rate.

- Secondary endpoints:
  - Toxicity of the MTD of intravesical Durvalumab administration.
  - Efficacy assessed by the high-grade progression-free rate at 30 days after the last durvalumab instillation and 6 months following durvalumab therapy.
  - PD-L1 and VEGF expression assessed in tumor tissue obtained before and after durvalumab instillation Immunohistochemistry will be used for the evaluation of PD-L1 and VEGF expression levels
  - Assessment of PD-L1 and VEGF protein levels in urine samples obtained before and after durvalumab instillation

Current Status

	Number of Patients
Patients Enrolled	21
Completed treatment	20
Withdrawn from trial	1
Completed follow-up	20

- A total of 21 additional patients were enrolled in order to receive 1000mg of intravesical durvalumab for a total of 6 weekly doses.
- Together with the 9 patients of the run-in phase, they were followed for efficacy and adverse events for a year after the end of treatment.

Patient Characteristics

Patient Characteristics	
Mean Age	66.5 yrs
Gender	26 males 4 females
Smoking history (%)	92
TNM CIS TaHG T1HG TaHG + CIS T1HG + CIS	 2 4 18 1 4

Results

- One patient died from Covid-19, 3 months after the last durvalumab administration.
- After 1 year of follow-up DFS was 34.6%.
- DFS at 1, 3 and 6 months was 73%, 65.3% and 50% respectively.
- Five patients experienced a ≥T2 disease relapse.
- Five out of the six patients who received 500mg or 750mg of durvalumab relapsed within 1 year.
- Interestingly, 2 out of 2 patients with only CIS disease at baseline experienced a tumor complete response, which was durable and was maintained for a year.

Adverse Events

Adverse Event	Number of Patients	Grade
Hematuria	5	1
Anemia	1	1
Thrombopenia	1	1
Leucopenia	1	1
Lymphopenia	2	1

Are the results promising?

Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study

Arjun V Balar, Ashish M Kamat, Girish S Kulkarni, Edward M Uchio, Joost L Boormans, Mathieu Roumiguié, Laurence E M Krieger, Eric A Singer, Dean F Bajorin, Petros Grivas, Ho Kyung Seo, Hiroyuki Nishiyama, Badrinath R Konety, Haojie Li, Kijoeng Nam, Ekta Kapadia, Tara Frenkl, Ronald de Wit

Tumour stage	
Carcinoma in situ with T1	12 (12%)
Carcinoma in situ with high-grade Ta	25 (25%)
Carcinoma in situ alone	64 (63%)

- Patients who received pembrolizumab had a complete response rate of 41%, with a median duration of complete response of 16·2 months.
- 46% of initial responders had a complete response that lasted for 12 months or longer at the time of data cutoff.
- The safety profile of pembrolizumab was consistent with previous reports of pembrolizumab monotherapy.

	Cohort A efficacy population (n=96)*
Complete response	39 (41%, 30·7–51·1)
Non-complete response	56 (58%, 47·8–68·3)
Persistent disease†‡	40 (42%, 31·7–52·2)
Recurrent disease	6 (6%, 2·3–13·1)
Non-muscle-invasive bladder cancer stage progression§	9 (9%, 4·4–17·1)
Non-bladder malignancy¶	1 (1%, 0·0–5·7)
Progression to muscle-invasive disease (T2)	0 (NA–NA)
Non-evaluable‖	1 (1%, 0·0–5·7)

Data are n (%, 95% CI). NA=not applicable. *Patients with high-risk non-muscle-invasive bladder cancer who received at least one dose of the study drug, had baseline evaluations, and had at least one post-baseline disease assessment. †Defined as patients with carcinoma in situ at baseline who also had carcinoma in situ with or without papillary tumour at month 3. ‡Defined as pathologically confirmed appearance of papillary tumour (high-grade Ta or T1) without carcinoma in situ at month 3. §Defined as an increase in stage from carcinoma in situ or high-grade Ta at baseline to T1 disease. ¶For this patient, new liver lesions were found on imaging; later, a second primary malignancy of pancreatic cancer was found. Subsequent review of the baseline scan showed subtle findings that, in retrospect, could be attributed to pancreatic cancer, and later scans showed metastases that were most likely from the pancreatic cancer. Clinical course and laboratory values further supported the diagnosis of metastatic pancreatic cancer. ‖Patients whose protocol-specified efficacy assessments were missing or who discontinued from the trial for reasons other than progressive disease were not evaluable for efficacy and considered non-responders.

***Table 2:* Best overall response at month 3 by central review in patients with BCG-unresponsive carcinoma in situ**

Are the results promising?

Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial

Complete response and freedom from high-grade recurrence in the efficacy population

	Carcinoma in situ cohort (n=103)	High-grade Ta or T1 cohort (n=48)	All patients (n=151)
Patients with complete response at month 3 *	55 (53·4%; 43·3–63·3)	35 (72·9%; 58·2–84·7)	90 (59·6%; 51·3–67·5)
Duration of complete response † or high-grade recurrence-free survival ‡, months	9·69 (9·17-NE)	12·35 (6·67-NE)	7·31 (5·68–11·93)
Patients who were free from high-grade recurrence			
Month 6	42 (40·8%; 31·2–50·9)	30 (62·5%; 47·4–76·0)	72 (47·7%; 39·5–56·0)
Month 9	36 (35·0%; 25·8–45·0)	28 (58·3%; 43·2–72·4)	64 (42·4%; 34·4–50·7)
Month 12	25 (24·3%; 16·4–33·7)	21 (43·8%; 29·5–58·8)	46 (30·5%; 23·2–38·5)

- Complete response rate 3 months after treatment initiation among patients with carcinoma in situ was 53.4% (55 patients from a total of 103). 25 patients remained in a complete response status at 12 months.
- Progression to muscle invasive disease was documented only in 5 patients.
- The study also included a cohort involving 48 high grade Ta or T1 patients with 72.9% of them being high grade tumor free 3 months after treatment initiation.

Conclusion

- Intravesical immunotherapy using Durvalumab is feasible.
- Excellent safety profile.
- Promising oncological results.
- Although only 2 patients with CIS without papillary tumor were recruited, they both presented complete response.