CO207

The Association Between Event-Free Survival (EFS) and Overall Survival (OS) in High-Risk Non-Muscle Invasive Bladder Cancer (NMIBC) in the Netherlands: An Observational Study of Electronic Health Records

Leo Chen,[1] Joseph Cappelleri,[2] Jane Chang,[3] Julia Brinkmann,[4] Sarah Smith,[5] Louise Lemmens,[6] Sarah Bailey,[6] Jetty Overbeek,[6] Patricia Silva,[7] Meena Venkatachalam,[7] Anthony Eccleston[8]

[1] Pfizer Inc, Bothell, WA, USA; [2] Pfizer Inc, Groton, CT, USA; [3] Pfizer Inc, New York, NY, USA; [4] Pfizer Inc, Berlin, DE; [5] Lumanity, Manchester, UK; [6] PHARMO Institute, Utrecht, NL; [7] Lumanity, London, UK; [8] Pfizer Ltd, Surrey, UK

Objective

To estimate the correlation between EFS and OS in patients with high-risk NMIBC using real-world data from the Netherlands.

Conclusion

A moderate and tangible correlation between EFS and OS was observed. Patients who remained event-free tended to have longer overall survival.

Context

Evaluation of EFS can be used as an informative indicator of OS in high-risk NMIBC and is therefore useful in an HTA context.

Background

- Approximately 70-75% of the patients diagnosed with bladder cancer have non-muscle invasive bladder cancer (NMIBC).[1]
- About 25% of these patients have high-risk NMIBC (HR-NMIBC), as defined by the European Association of Urology (EAU) guidelines.[2]
- 5-year cancer-specific survival in HR-NMIBC is relatively high (71 to 96%),[1] meaning overall survival (OS)-driven trials would require large sample sizes and long follow-up to detect meaningful differences. As a result, recent trials have used event-free survival (EFS) as the primary endpoint to enable more timely assessment of treatment benefit.
- However, the relationship between EFS and OS in HR-NMIBC is not well established, particularly outside the controlled trial setting.

Materials and Methods

- An observational study of patients diagnosed with HR-NMIBC in the Netherlands between 01/01/2016 and 31/12/2022 was performed.
- The PHARMO Data Network was linked to the national cancer registry (NCR) and pathology registry (PALGA). NCR data was used to identify patients with bladder cancer, to identify patients with high-risk status, and to define outcomes of interest. PALGA data was used for CIS identification and outcomes of interest. Hospital data was also used for defining EFS (Table 1).

Key inclusion criteria:

- Histologically confirmed diagnosis of NMI transitional cell carcinoma of the urothelium of the urinary bladder.
- Confirmed HR status, according to the definitions below.
- No recorded bladder cancer prior to 01/01/2016.
- Aged 18 years or older.

Definition of 2 high-risk cohorts:

- Cohort 1: A high-grade tumor with or without concurrent carcinoma in situ (CIS) or CIS alone or fulfilling additional clinical risk criteria (age > 70; multiple papillary tumors; tumor diameter > 3 cm).
- Cohort 2: Treatment with Bacillus Calmette Guérin (BCG); ≥ 7 instillations within 274 days of initiation of treatment (ATC code L03AX03).

Table 1: Definition of events included in EFS

EFS outcome	Definition (events included in the EFS outcome)
Recurrence of NMIBC	Any record of TNM with same stage as the initial diagnosis for the tumor present in TUR sample documented in NCR or based on bladder cancer recurrence code in NCR. In hospital and PALGA data based on codes indicating a recurrence.
Persistence of CIS	If tumor behaviour or morphology code indicate CIS or TNM is pTis or CIS in cutting plane indicates CIS in NCR data. If PALGA records indicate CIS.
Progression	Any record where the TNM staging is more advanced than stage at diagnosis in NCR or a record indicating that the patient started chemotherapy, radiotherapy, or immunotherapy in hospital data or evidence of radical cystectomy from NCR/hospital data.
Death	First date of death from any data source.

ANALYSIS

- EFS (Table 1) was assessed twice: once with and once without death included.
- Baseline characteristics (Table 2) were assessed at the date of diagnosis of HR-NMIBC (Cohort1) or date of initiation of BCG treatment (Cohort 2) or the year prior to that date.
- The correlation between EFS and OS at the individual level was assessed using a three-state illness-death model (pre-event, post-event, death) and an inverse probability of censoring weighting (IPCW) to estimate Kendall's Tau.[3]

Electronic Poster

Click or scan this quick response (QR) code to download this poster along with associated material.
To request permission or to ask questions about the poster, please contact Presenting Author: Leo Chen, MPH; Email: Leo.Chen@pfizer.com

References: 1. Intermediate and high-risk non-muscle-invasive bladder cancer: an overview of epidemiology, burden, and unmet needs. Grabe-Heyne, K, Henne, C., Mariappan, P., Geiges, G. Pöhlmann, J., Pollock, J.P. Front Oncol, 2 Jun 2023. 13:1170124. **2.** EAU Guidelines on Non-Muscle-invasive Bladder Cancer (TaT1 and CIS). Babjuk, M., Burger, M., Compérat, E. European Association of Urology, Limited Update March 2023. **3.** Quantifying the association between progression-free survival and overall survival in oncology trials using Kendall's τ. Weber, E. M. & Titman, A. C. Statistics in Medicine vol. 38 Preprint at https://doi.org/10.1002/sim.8001 (2019).

Acknowledgements: This study was sponsored by Pfizer Inc. The authors would like to thank all the healthcare providers contribution information to the PHARMO Data Network.

Copyright ©2026. All rights reserved.

Results

PATIENTS

- A total of 1,753 patients with a clinical definition of HR-NMIBC were included (Cohort 1) (Table 2). Most patients were male (82%), and 72% of patients initiated BCG treatment. Mean follow-up was approximately 3 years (35.6 months; SD 23.6).
- The treatment-based high-risk definition group consisted of 288 patients (Cohort 2). The majority of patients were male (85%), with a mean follow-up time of 38.3 months (SD: 21.6).
- For the Charlson comorbidity score, most patients scored in the severe category (71% in Cohort 1 and 68% in Cohort 2).

Table 2. Patient characteristics at baseline by cohort.

Variable		Cohort 1 N = 1,753 n (%)	Cohort 2 N = 288 n (%)
Age (years), mean, SD		72.5 (9.8)	70.2 (9.6)
Age group			
	18 – 64	351 (20)	80 (28)
	65 – 70	320 (18)	45 (16)
	71 – 75	389 (22)	73 (25)
	76 – 80	310 (18)	54 (19)
	81 – 85	238 (14)	23 (8)
	> 85	145 (8)	13 (5)
Sex		18 (27.7)	16 (26.7)
	Male	1,438 (82)	246 (85)
	Female	315 (18)	42 (15)
Obesity (BMI (kg/m^2) ≥30)			
	Obese	44 (3)	14 (5)
Socio-economic status			
	Low	567 (32)	81 (28)
	Middle	648 (37)	107 (37)
	High	530 (30)	98 (34)
	Unknown	8 (<0.5)	2 (1)
Year of NMIBC diagnosis			
	2016	259 (15)	36 (13)
	2017	249 (14)	35 (12)
	2018	254 (14)	44 (15)
	2019	292 (17)	51 (18)
	2020	235 (13)	46 (16)
	2021	235 (13)	44 (15)
	2022	229 (13)	32 (11)
Comorbidity (Charlson comorbidity score)			
	None	0 (0)	0 (0)
	Mild (1-2)	33 (2)	9 (3)
	Moderate (3-4)	473 (27)	83 (29)
	Severe (>4)	1,247 (71)	196 (68)
Treatments received			
	BCG treatment initiated	1,265 (72)	288 (100)
	7 or more instillations within 274 days	226 (13)	288 (100)
	Radiotherapy	7 (<0.5)	0 (0)
	Immunotherapy	24 (1)	6 (2)
	Chemotherapy	425 (24)	94 (33)
	Surgery	36 (2)	7 (2)
Tumor morphology			
	Transitional cell carcinoma	1,736 (99)	287 (≥99.5)
	Other	17 (1)	1 (<0.5)
	Unknown	0 (0)	0 (0)
Tumor staging, n (%)			
	T1 only	239 (14)	44 (15)
	T1 (and CIS)	111 (6)	15 (5)
	CIS only	217 (12)	47 (16)
	CIS (and Ta)	94 (5)	13 (5)
	Ta only	497 (28)	76 (26)
	Missing	595 (34)	93 (32)
CIS at diagnosis			
	Yes	422 (24)	75 (26)
	No	1,331 (76)	213 (74)
Follow-up (months), mean, SD			
	Mean (SD)	35.6 (23.6)	38.3 (21.6)
	Median (IQR)	33.1 (14.9 - 54.6)	36.0 (19.4 - 55.7)

Key: ASA, American Society of Anaesthesiologists. BMI, body mass index. SD, standard deviation. yrs, years.
Note: Sub-localisation, ASA score, weight, height and BMI not included because these were unavailable from IKNL. Obesity is solely based on hospital data which causes a large underestimation.

EFS

- During follow-up, 32% of patients in Cohort 1 had an EFS event where death was excluded from the definition; when death was included in the definition, 43% had an EFS event. For Cohort 2, this was 38% and 43%, respectively.
- The Kaplan-Meier (KM) curve estimated a median EFS of 48.4 months (95% confidence interval: 39.6-58.2) in Cohort 1, when death was included as an event. Median EFS time was not reached, when death was excluded as an event. For Cohort 2, this was 49.6 months, when death was included. Again, when death was excluded, median EFS time was not reached.

Table 3. Events occurring at any time during follow up for Cohort 1 and Cohort 2

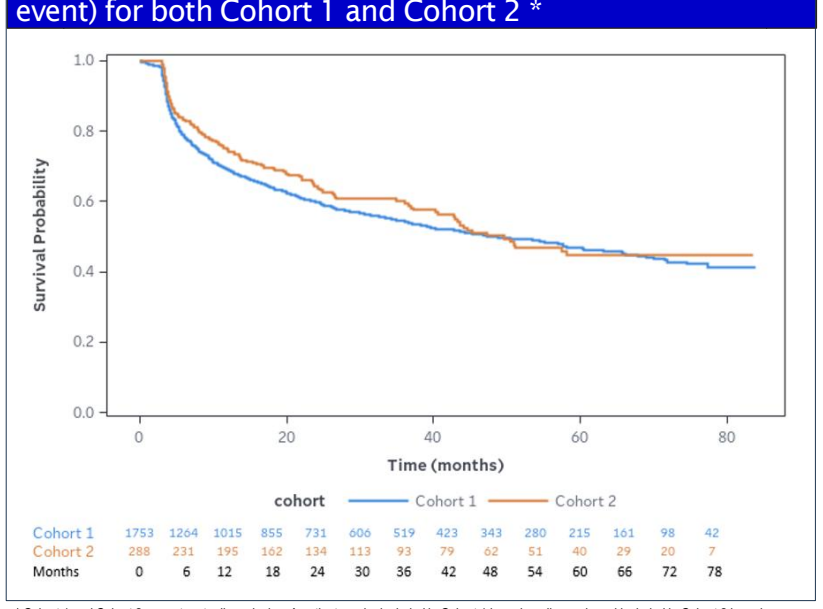
Event	Cohort 1 N = 1,753 n (%)	Cohort 2 N = 288 n (%)
EFS (including death)	756 (43)	123 (43)
EFS (excluding death)	567 (32)	110 (38)
High-grade recurrence	120 (7)	25 (9)
Progression [a]	430 (25)	81 (28)
Persistence of CIS	106 (6)	15 (5)
CIS at baseline	*422 (24)*	*75 (26)*
Death after 90 days	293 (17)	35 (12)
Death during total follow-up period	322 (18)	35 (12)

Key: EFS, event-free survival. CIS, carcinoma in situ.

INDIVIDUAL-LEVEL CORRELATION ESTIMATES

- Overall, results suggest moderate correlation between EFS and OS, but results require confirmation with more mature data.
- For the three-state generalized illness-death model (Cohort 1), Kendall's tau was 0.50 (SE 0.04). For the IPCW model the Tau was 0.56 (SE 0.02).
- For Cohort 2, Kendall's tau for the generalized approach was 0.41 (SE 0.12) for the generalized approach and 0.52 (SE 0.06) for the IPCW model.
- The individual-level surrogacy analyses concluded there was moderate correlation between EFS and OS.
- Patients who remain event-free tend to live longer, but the relationship is only moderate.

Figure 1. Kaplan-Meier plot of EFS (death included as an event) for both Cohort 1 and Cohort 2 *



* Cohort 1 and Cohort 2 are not mutually exclusive. A patient can be included in Cohort 1 based on diagnosis and included in Cohort 2 based on medication

LIMITATIONS

- To assess some of the EFS outcomes, we used data from three data sources (NCR, PALGA and hospital data), with inconsistent registration of events among them.
- The number of patients included in Cohort 2 was only 288, resulting in larger standard errors (e.g. 0.12 for the generalized approach).
- The mean follow-up time ranged from 35 to 38 months, resulting in a lower power for OS outcomes.