Nové možnosti léčby svalovinu neinvadujících nádorů měchýře (NMIBC) nereagujících na léčbu BCG (BCG unresponsive)

M. Babjuk

Urologická klinika, FN Motol, 2. LFUK, Praha

„BCG unresponsive“ nádory – definice

(= pacienti s recidivujícím NMIBC, u kterých další BCG pravděpodobně nepřinese benefit)

Parametry definice:
- Patologie po BCG (HG nádor)
- „Timing“ perzistence/recidivy po poslední instilaci
- Množství podaného BCG

BCG unresponsive tumour
BCG refractory or T1Ta/HG BCG recurrence within 6 months of completion of adequate BCG exposure** or development of CIS within 12 months of completion of adequate BCG exposure [284] (LE: 4).

** *Adequate BCG is defined as the completion of at least 5 of 6 doses of an initial induction course plus at least 2 out of 6 doses of a second induction course or 2 out of 3 doses of maintenance therapy.*

„BCG refractory“:
- T1G3/HG ve 3 měsících
- TaG3/HG po 3 a/nebo po 6 měsících
- CIS ve 3 a perzistující v 6 měsících

„BCG unresponsive“ nádory - léčba

Category	Treatment options	Strength rating
BCG-unresponsive	1. Radical cystectomy (RC).	Strong
	2. Enrollment in clinical trials assessing new treatment strategies.	Weak
	3. Bladder-preserving strategies in patients unsuitable or refusing RC.	Weak

- Radikální cystektomie je nejúčinnější onkologickou léčbou, ale představuje „overtreatment“ u řady pacientů
- Nové možnosti?

Nové možnosti

- Cytotoxické látky
  - Nové formy chemoterapie (kombinace, nové formy uvolňování látek)
  - Asistované instilace
- Inovativní postupy
  - Genová léčba
  - Imunoterapie (lokální, systémová)
  - Vakcíny
  - Oncolytické adenoviry
  - Recombinantní proteiny

Novinky v chemoterapii

Bladder Cancer 3 (2017) 293–303
DOI 10.3233/BLC-170120
IOS Press

Research Report

Oncological Outcomes of Sequential Intravesical Gemcitabine and Docetaxel in Patients with Non-Muscle Invasive Bladder Cancer

Niv Milbar[a,*], Max Kates[a], Meera R. Chappidi[a], Filippo Pederzoli[b], Takahiro Yoshida[a], Alexander Sankin[c], Phillip M. Pierorazio[a], Mark P. Schoenberg[c] and Trinity J. Bivalacqua[a]
[a]*The James Buchanan Brady Urological Institute, The Johns Hopkins University School of Medicine, Baltimore, MD, USA*
[b]*Universita Vita-Salute San Raffaele, Milan, Italy*
[c]*Department of Urology, Albert Einstein College of Medicine, Bronx, NY, USA*

- Sekvenční aplikace
- 1 g Gem následováno 37.5 mg Doce (6× + maintenance)
- NCT02202772, sekvenční cabazitaxel, gemcitabine, cisplatin (CGC)

• <u>New drug delivery:</u>

- Intravezikální docetaxel-PM (nanoparticle-based formulation to enhance drug delivery) vs mitomycin-C (NCT02982395)
- „Device assisted instilations“ (RITE, Termochemoterapie, EMDA)

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

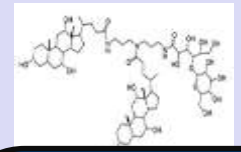
Platinum Priority – Bladder Cancer

Radiofrequency-induced Thermo-chemotherapy Effect Versus a Second Course of Bacillus Calmette-Guérin or Institutional Standard in Patients with Recurrence of Non–muscle-invasive Bladder Cancer Following Induction or Maintenance Bacillus Calmette-Guérin Therapy (HYMN): A Phase III, Open-label, Randomised Controlled Trial

Wei Shen Tan[a,b], Anesh Panchal[c], Laura Buckley[c], Adam J. Devall[c], Laurence S. Loubière[c], Ann M. Pope[c], Mark R. Feneley[b], Jo Cresswell[d], Rami Issa[e], Hugh Mostafid[f], Sanjeev Madaan[g], Rupesh Bhatt[h], John McGrath[i], Vijay Sangar[j], T.R. Leyshon Griffiths[k], Toby Page[l], Dominic Hodgson[m], Shibendra N. Datta[n], Lucinda J. Billingham[c,], John D. Kelly[a,b,c,*]*

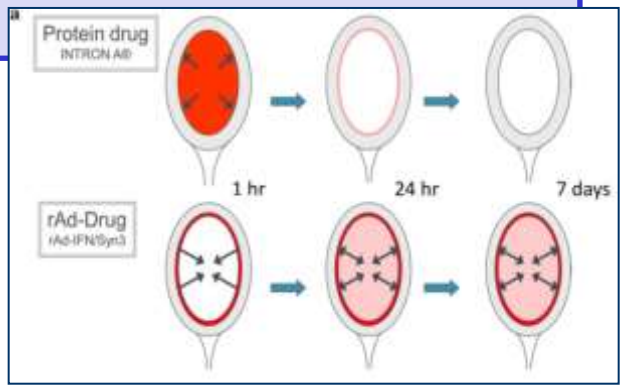
Nadofaragene firadenovec (rAd-IFNα2b/Syn3) Adstiladrin

- rAd-IFNα2b je ne-replikující rekombinantní adenovirus nesoucí gen pro IFNα2b



- Syn3 je syntetický analog, který porušuje uroteliální GAG vrstvu a zvyšuje průnik do urotelu a NMIBC

- rAd-IFNα2b přenáší gen IFNα2b do hostitelova jádra k zahájení transkripce, aniž by gen inkorporoval do hostitelovy DNA
- Po instilaci produkují po určitou dobu buňky urotelu a NMIBC IFNα2b protein (až 10 dní dle studií Fáze I)
- IFNα má protitumorozní účinek



Patients (n [%]) Who Achieved HGRF Survival at:	CIS, n = 55	Papillary Disease, n = 35
3 months	55 (100.0)	35 (100.0)
6 months	42 (76.4)	30 (85.7)
9 months	36 (65.5)	28 (80.0)
12 months	25 (45.5)	21 (60.0)

Boormans (EAU 2020 #772) KEYNOTE-057: A Single-Arm Phase 2 Trial, pembrolizumab (200mg a 3 týdny) u „BCG unresponsive“ nádorů

Disposition

- Median time from enrollment to database cutoff date: 28.4 months (range 18.2-40.5)
- No progression to muscle-invasive or metastatic bladder cancer at time of treatment discontinuation based on study-specified disease assessments

HR NMIBC with CIS
N = 102

Treated
(safety population)
N = 102

Excluded, n = 6
Did not meet FDA definition of BCG-unresponsive NMIBC, n = 5
Participant without CIS at baseline (vendor transcription error), n =1

Efficacy population
n = 96

Discontinued, n = 86
Persistent disease,[a] n = 38
Recurrent disease/stage progression, n = 33
All AEs, n = 9
TRAEs, n = 8
Physician decision, n = 1
Patient withdrawal, n = 2
Electively discontinued after 18 months with continued CR,[b] n = 3

Completed
n = 3

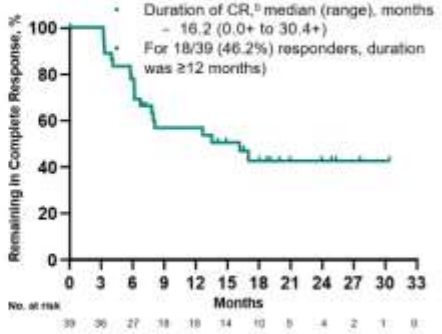
Ongoing
n = 7

[a]Includes patients who had CIS (± papillary tumors) at baseline and discontinued the study treatment because of [illegible] allowed per protocol to discontinue study treatment after 18 months. Data cutoff date: May 24, 2019.

Complete Response and Duration of Response

Best Response	N = 96 n (%)	95% CI
CR	39 (40.6)	30.7-51.1
Non-CR	56 (58.3)	47.8-68.3
Persistent	40 (41.7)	31.7-52.2
Recurrent	6 (6.3)	2.3-13.1
NMIBC stage progression	9 (9.4)	4.4-17.1
Non–bladder malignancy[a]	1 (1.0)	0.0-5.7
Progression to T2	0	NA-NA
Nonevaluable	1 (1.0)	0.0-5.7

- Duration of CR,[b] median (range), months – 16.2 (0.0+ to 30.4+)
- For 18/39 (46.2%) responders, duration was ≥12 months)



[a]Patient developed new liver lesions (substantiated by imaging) and was later found to have a second primary malignancy of pancreatic cancer. Subsequent review of the baseline imaging showed subtle findings that, in retrospect, could be attributed to pancreatic cancer. Clinical course and laboratory values further supported the diagnosis of metastatic pancreatic cancer. [b]Month 0 = time point when initial CR was achieved. The onset of response was 3 months for most patients. Data cutoff: May 24, 2019. Duration of follow-up data cutoff date: September 24, 2019.

15:15

The FDA's Oncologic Drugs Advisory Committee (ODAC) voted 9 to 4 supporting the approval of a new drug application (NDA) for pembrolizumab (Keytruda) for the treatment of patients with Bacillus Calmette-Guerin (BCG)–unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in-situ (CIS) with or without papillary tumors who are ineligible for or chose to not undergo cystectomy.

The NDA is based on findings from the phase II KEYNOTE-057 trial (NCT02625961). An FDA analysis of 97 patients from the trial found that pembrolizumab elicited a 41.2% (95% CI, 31.5-51.4) complete response (CR) rate and a median duration of CR of 16.2 months (range, 0.0+ to 26.8+) in this patient population. Nineteen (48%) of the 40 responding patients maintained their response for 1 year or more.

Rentsch (EAU 2020 #777) Rekombinantní BCG u „BCG unresponsive“ nádorů