FINAL RESULTS OF THE HIVEC-HR RANDOMISED TRIAL COMPARING HYPERTHERMIC MMC VS BCG IN HIGH-RISK NON-MUSCLE-INVASIVE BLADDER CANCER PATIENTS

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Conflicts of interest

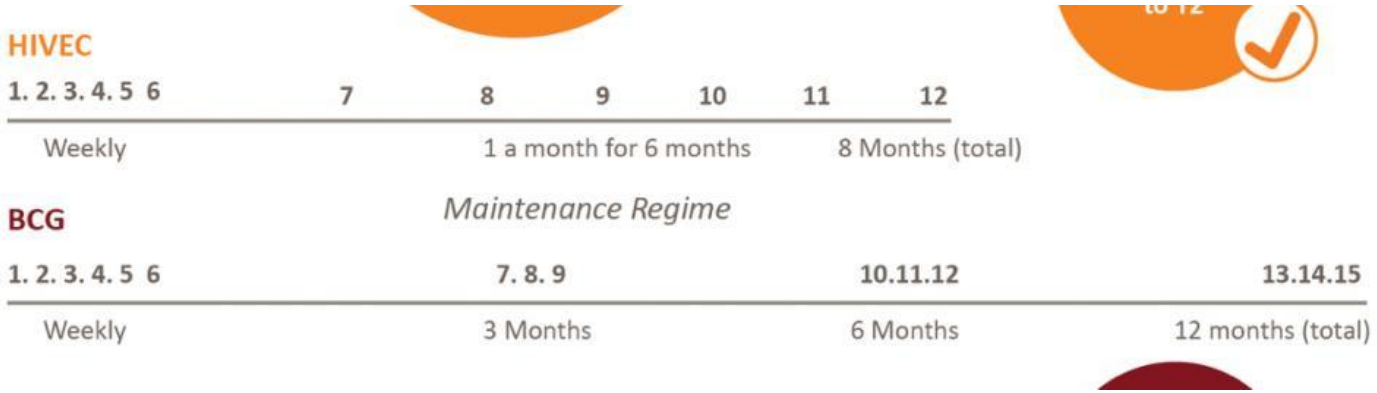
- **Advisory/Consultancy:** Pfizer, BMS, AstraZeneca, Janssen, Taris Bio, Palex Dx, Recordati, Combat Medical
- **Speaker:** Astellas Oncology, Rovi, Recordati, Janssen, Pfizer, AstraZeneca, Combat Medical, Rubió, Palex Dx, Taris Bio, Nucleix
- **Clinical Trials:** Pfizer, Combat Medical, AstraZeneca, BMS, Janssen, Taris Bio, IDL Biotech, UroGen
- **Travel expenses:** Pfizer, Lacer, Combat Medical, Palex Dx, Rovi, Q-Pharma, Recordati, Ipsen, Taris Bio, Kern Pharma

Background and aim

- HR-NMIBC
  - Recurrence 60-80% 5y
  - Progression 20-40% 5y
- Standard of care → BCG
- Issues with BCG
  - Lack of efficacy
  - Toxicity (63% local & 31% systemic)
  - As of 2012: several BCG shortages
- AIM: to compare BCG vs HIVEC-MMC in HR-NMIBC patients

Patients & Methods

- Pilot phase II randomized clinical trial
- HR NMIBC (EAU Guidelines 2016), excluding CIS
- BCG shortage (2014-2016)



TURBT
Optional postop MMC instillation

High risk*
No CIS

RANDOMIZATION* *According to EAU Guidelines*

BCG
6W + 3W at 3, 6 y 12M
N = 25

CHT + MMC 40mg
6W + 6M
N = 25

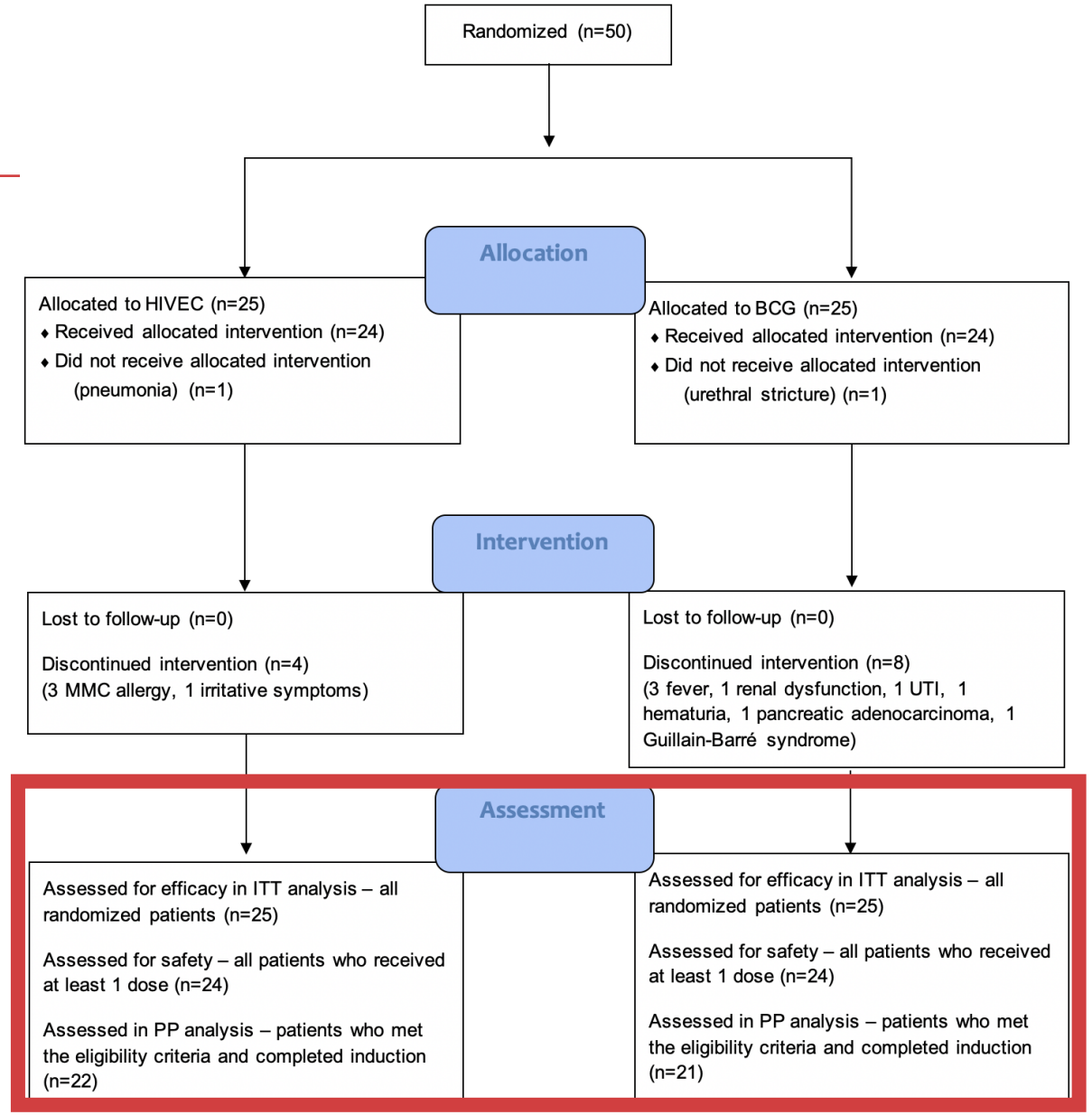
24 MONTHS
RECURRENCE
Progression
Cancer-specific survival
Safety
Quality of life

Patients & Methods

- BCG OncoTICE® 50 mg
- MMC 40 mg/40 mL distilled water
  - Recirculation time 60 min (200 mL/min)
  - Target temperature: 43 ± 0.5ºC
- Follow-up according to HR (EAU Guidelines)
  - Cystoscopy + cytology every 3 months
  - CT-urography at screening & yearly
  - TURBT if suspected recurrence

Patients & Methods

Treatment arm	Number of instillations received	Cause of discontinuation	Status / recurrence / progression
BCG	0	Uretheral stenosis	Exitus due to gastric neoplastic disease
HIVEC	0	Hospitalization due to pneumonia	Exitus due to acute myocardial infarction
HIVEC	4	MMC allergy	Progression to T2G3; neo + cystectomy T0N0M0
BCG	6+3	Concomitant CIS	Progression to T2G3; cystectomy T4N2M0. Exitus due to bone metastases
HIVEC	5	MMC allergy (continued with BCG × 6)	Recurrence TURBT – TaG3 treated with BCG
BCG	4	Fever	Exitus due to lung cancer
BCG	5	Guillain-Barré syndrome	Exitus due to Guillain-Barré syndrome



Baseline characteristics

- Mean age: 73.5 years
- 88% male

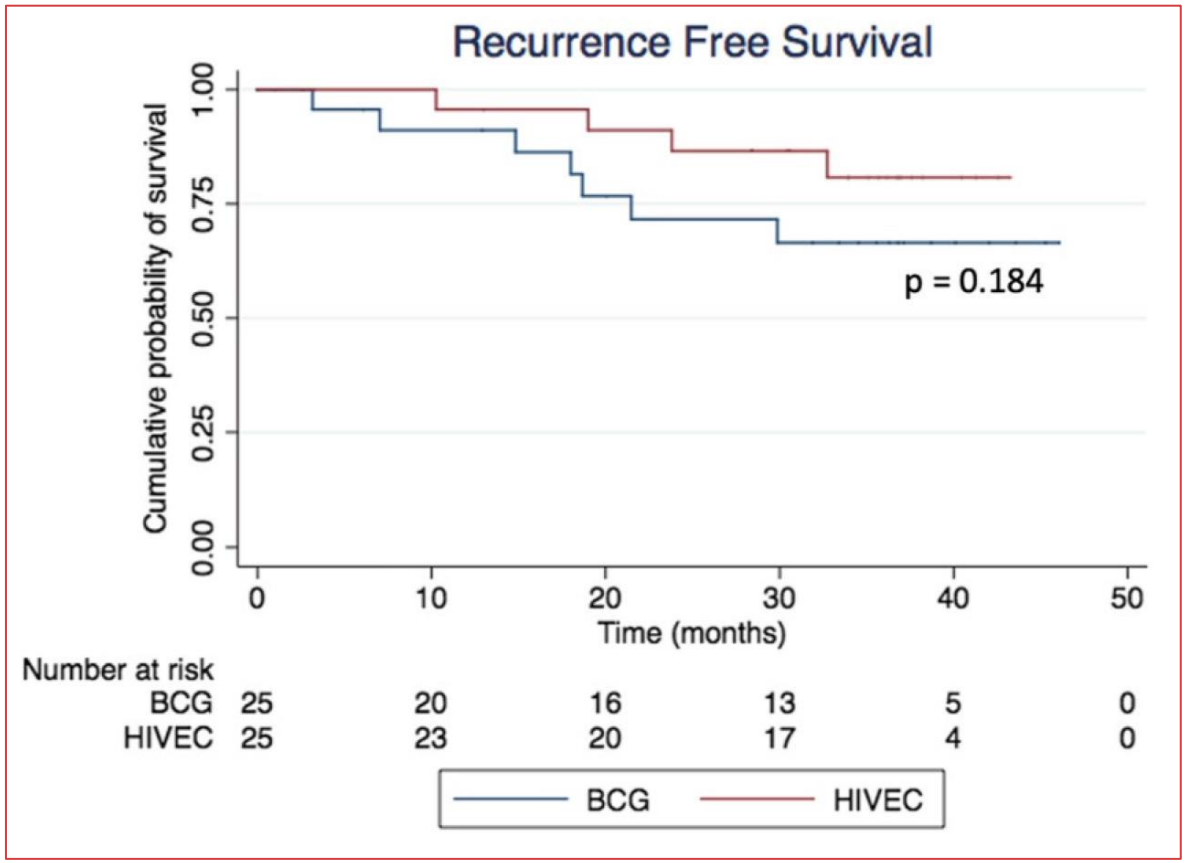
- Median follow-up 33.7 months (IQR 18.6-37.1)
- 11 recurrences (BCG 7, HIVEC 4)
- 7 progressions (BCG 6, HIVEC 1)
- 11 deaths (only 2 due to bladder cancer)

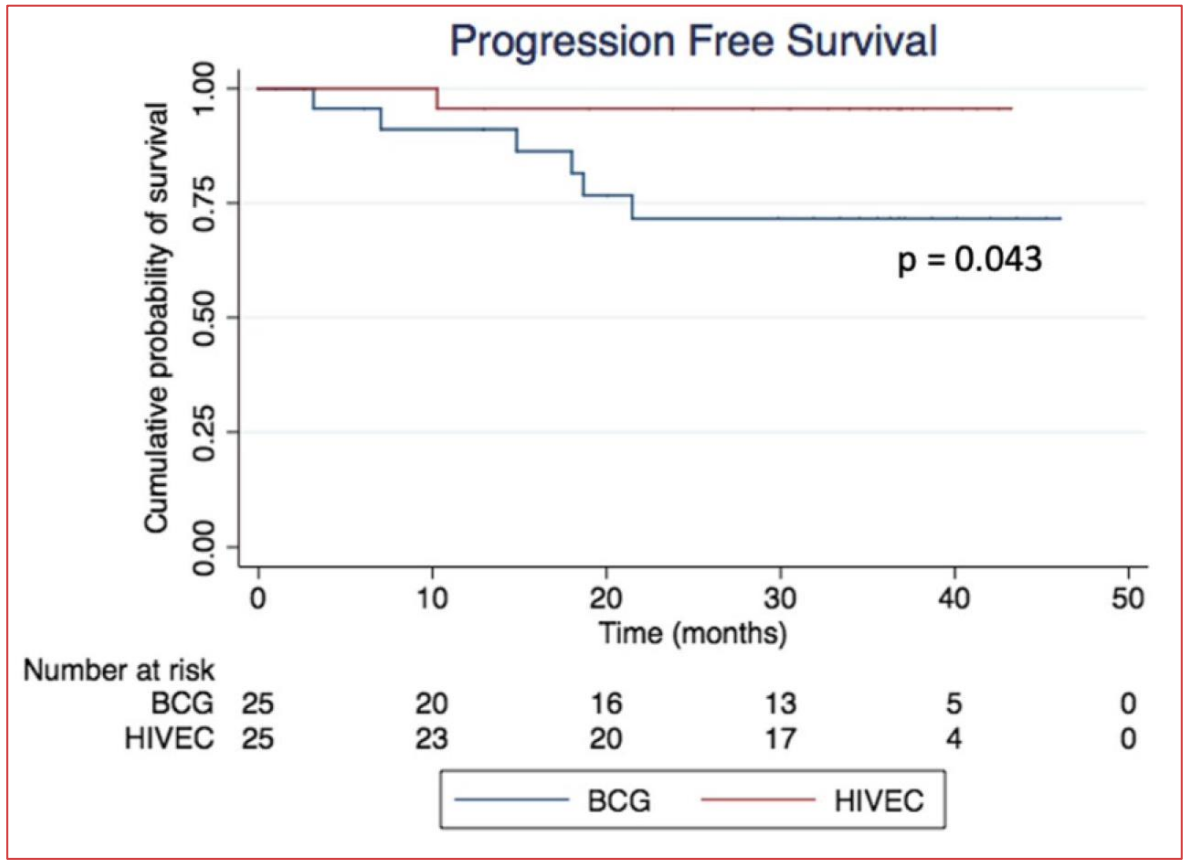
		BCG		HIVEC	
		n	%	n	%
Gender	Men	22	88	21	84
	Women	3	12	4	16
Age	Mean (±SD)	73.0 ± 8.65		74.1 ± 10.4	
Primary vs recurrent	Primary	18	72	22	88
	Recurrent <1/year	3	12	3	12
	Recurrent >1/year	4	16	0	0
Stage	Ta	11	44	14	56
	T1	14	56	11	44
Grade	G2	0	0	1	4
	G3	25	100	24	96
Number of tumors	1	19	76	19	76
	2–7	5	20	6	24
	≥8	1	4	0	0
Tumor size	<3 cm	17	68	15	60
	≥3 cm	8	32	10	40
Postoperative MMC	No	18	72	20	80
	Yes	7	28	5	20
Prior intravesical therapy	No	20	80	23	92
	Yes	5*	20	0	0
	Unknown	0	0	2	8
Repeat second-look TURBT	No	19	76	19	76
	Yes	6	24	6	24

Efficacy outcomes

	INTENTION TO TREAT			PER PROTOCOL		
	HIVEC (n=25)	BCG (n=25)		HIVEC (n=24)	BCG (n=21)	
RFS (24m)	86.5%	71.8%	HR 0.41 (95% CI 0.10-1.66) p=0.215	95.0%	75.1%	HR 0.48 (95% CI 0.11-2.03) p=0.315
PFS (24m)	95.7%	71.8%	HR 0.14 (95% CI 0.02-1.29) p=0.071	100%	75.1%	HR 0.16 (95% CI 0.02-1.4) p=0.102
CSS (24m)	100%	100%	N/A			
OS (24m)	91.5%	81.8%	p=0.498			
Cystectomy	4%	20%	N/A			
Time to recurrence	21.5m	16.1m	p=0.315			

RFS & PFS (ITT population)





Adverse events

- 31 patients (64.6%) reported at least one AE
- 23 patients (47.9%) reported at least one THERAPY-RELATED AE
- Grade 4-5: only 2 patients (both receiving BCG)

	Grade 1- 2		Grade 3		Grade 4 - 5	
	HIVEC	BCG	HIVEC	BCG	HIVEC	BCG
Hematuria	1 (4.2%)	1 (4.2%)		1 (4.2%)		
Irritative		1 (4.2%)	1 (4.2%)			
Spasms	7 (29.2%)					
Fever				3 (12.5%)		
UTI		2 (8.3%)				
Allergy			3 (12.5%)			
Dysuria		1 (4.2%)				
Other						2
Total	8 (33.3%)	5 (20.8%)	4 (16.7%)	4 (16.7%)	0	2 (8.3%)

Limitations

- Phase II pilot trial
- RFS as primary outcome due to urgent need for alternatives to BCG
- Small sample size
- 5 patients failing previous treatment in the BCG arm vs 2 patients in the HIVEC arm (however, chemotherapy failure)

Conclusion

HIVEC-HR compared HIVEC and BCG in patients with high-risk papillary NMIBC. This pilot trial suggests that HIVEC with MMC provides **comparable safety and efficacy to BCG** and represents a **reasonable alternative** that should be considered during **BCG shortages**. A larger trial will be required to determine whether HIVEC is superior to BCG in this population.

Thank you very much!

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