Immune checkpoints inhibitors in NMIBC

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Disclosures – Yohann Loriot

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Consultant	
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Speakers bureau	
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Outline

- Background
- Current use of Immune checkpoints inhibitors
- Immune checkpoints inhibitors in NMIBC

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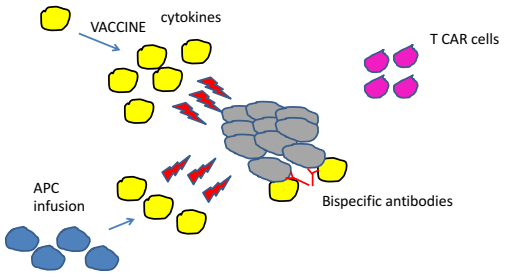
The issues

Metastatic disease= not curable	• mOS≈ 13 months, • 5% alive at 5 years
Non metastatic MIBC = potentially lethal and high impact on QOL	• 50% with relapse • Ostomy
NMIBC= potential to be TVIM	• 30% resistant to BCG • BCG toxicity • BCG shortage

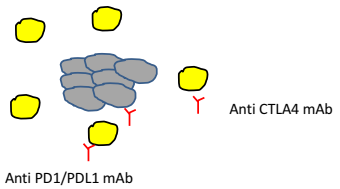
Immunotherapy might tackle the issues

Strategy 1: eliciting tumor-targeting cytolytic lymphocytes

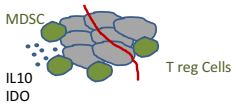


To supply or augment the frequency of T cells in a patient specific for one or more tumor-associated antigens

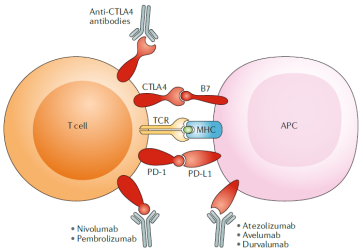
Strategy 2: disrupting immune regulation



Strategy 3: altering the tumor microenvironment



Immune checkpoints inhibitors



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- Current use of Immune checkpoints inhibitors
- Immune checkpoints inhibitors in NMIBC

Current approval : chemotreated patients

FDA

- Pembrolizumab (ph3)
- Atezolizumab (ph3)
- Nivolumab (ph2)
- Durvalumab (ph1/2)
- Avelumab (ph1/2)

EMA

- Pembrolizumab
- Atezolizumab
- Nivolumab

Response rate	Median PFS	Median OS
20%	2 months	10 months

PDL1 status not required

Current approval : chemo-naive patients

FDA

Cisplatin-ineligible patients

- Pembrolizumab (ph2)
- Atezolizumab (ph2)

PDL1-high status required

EMA

Cisplatin-ineligible patients

- Pembrolizumab
- Atezolizumab

PDL1-high status required

Response rate	Median PFS	Median OS
40-45%	2 months	12-16 months

Open questions

- How to identify responders ?
- How to identify superprogressors ?
- When should we treat patients ?
- How long should we treat patients ?
- How should we give ICI for frail patients ?
- How to explain resistance and to overcome resistance ?

Future strategies for immunotherapy

- Targeting several ICI together
- Enhancing neo-antigen expression
- Combination with targeted therapies, chemo or IR
- Targeting T cell metabolism and microenvironnement
- Reprogramming host microbiota
- Use earlier

Future strategies for immunotherapy

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- Reprogramming host microbiota
- Use earlier

Why using earlier ?

- More patients

- Fewer mechanisms of resistance

- Easier to deliver

What are the current data in neoadjuvant setting ?

MIBC → ICI → cystectomy

- PURE-01: pembrolizumab
- ABACUS: atezolizumab
- NABUCO: ipilimumab + nivolumab
- PANDORE: pembrolizumab

MIBC → ICI + chemotherapy → cystectomy

- NEMIO: MVAC + durvalumab

PURE-01 study

Stage III
N=50

pembrolizumab 200 mg × 3 → cystectomy

- Eligible or ineligible to NAC
- cT2-3bN0M0

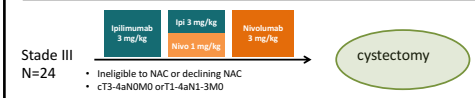
- All patients underwent surgery (96% within the first 12 weeks)
- 94% received 3 cycles
- 30% post surgery complications (sepsis, sub-occlusion)
- Grade ¾: 6%

pCR= 42%
pCR = 54% if PDL1+

PDL1 expression - mutational burden – inflammation signature
Associated with response

Necchi et al. JCO 2019

NABUCCO: IPI + nivo



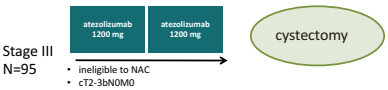
- Ineligible to NAC or declining NAC
- cT3-4aN0M0 orT1-4aN1-3M0

- All patients underwent surgery (96% within 12 weeks)
- 75% received 3 cycles
- Mortality rate at 30 days : 0%
- Mortality rate at 90 days: 4%
- But, 40% grade ¾ toxicities (8% colitis)

pCR= 46%
pCR = 60% if PDL1+

Van der Heidjen et al. ESMO 2019

ABACUS trial



- ineligible to NAC
- cT2-3bN0M0

- 8 have not undergone surgery
- 2 peri-operative deaths
- 17% post surgery complications ¾ (sepsis, sub-occlusion)
- Grade ¾: 11%

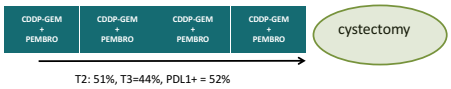
pCR= 31%
DFS at 1 year : 79%

Th1 signature associated with response
Fibroblast and – TGFB signature associated with resistance

Powles et al. Nat Med 2019

ICI and chemotherapy in neoadjuvant setting

- T2-T4a
- eligible to NAC
- N=40



T2: 51%, T3=44%, PDL1+ = 52%

- No DLT
- 39 patients underwent surgery, 1 post surgery death
- Grade ¾: 11%

pT0 + pT1= 60%
pT0=40%
DSF rate at 1 year : 80%

Response regardless of PDL1 status

Hoimes et al. ESMO 2018

What have we learnt so far from ICI in neoadjuvant setting ?

- Feasible
- Antitumour activity at least as single agent
- Data support moving earlier

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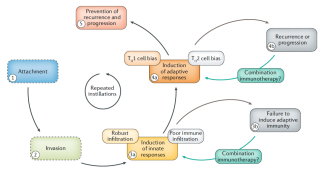
Management of NMIBC

Maximum resection of tumour (TUBRT) followed by		
Risk of progression		
Low	Intermediate	High
Only one Ta tumour, G1, <3 cm, no relapse	Ta G1–2 multifocal or relapsing T1 G1–2	Ta G3 T1 relapsing or G3
		CIS
↓	↓	↓
Surveillance	Chemotherapy or BCG	BCG

BCG therapy



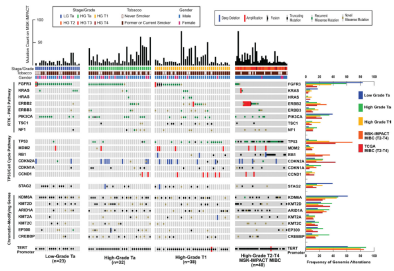
BCG is a live attenuated vaccine derived from Mycobacterium bovis

- BCG attaches to bladder tumour cells as well as urothelial cells by means of specific fibronectin and integrin receptors
- BCG efficacy needs a competent immune system and functional T-cells subtypes amongst other immune cell populations
- BCG induces an inflammatory response within the bladder wall, which is mediated by both local and systemic immune response
- Neutrophils and monocytes are the key mediators of initial response to BCG by producing chemotactic factors

Rationale for NMIBC

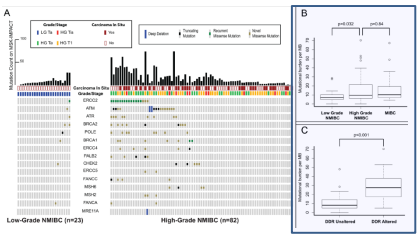
- Increasing tumor cell PD-L1 expression actually predicts localized UC stage progression, independent of tumor grade
- PD-L1 levels are highest in CIS and within granulomata of bladder tissues of patients failing BCG therapy
- Increased expression of T-cell-inhibitory PD-L1 by mononuclear cells that are recruited into bladder tissues in response to BCG therapy may contribute to a decline in the effectiveness of BCG therapy over time.
- Preclinical data suggest high activity of PDL1 inhibitors in orthotopic bladder tumors

Rationale for NMIBC



Pietzak et al. Eur Urol 2017

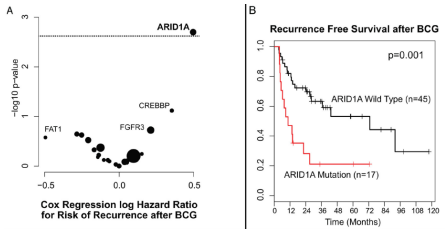
Rationale for NMIBC



High mutational burden in high-risk NMIBC

Pietzak et al. Eur Urol 2017

Rationale for NMIBC

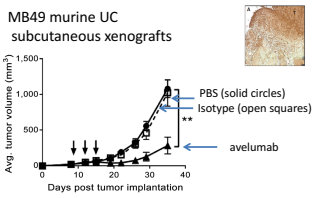


ARID1A : epigenetic genes (interaction between immune system and epigenome)

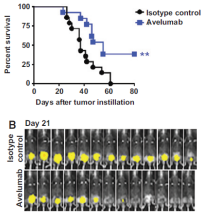
Pietzak et al. Eur Urol 2017

Rationale for NMIBC

MB49 murine UC subcutaneous xenografts



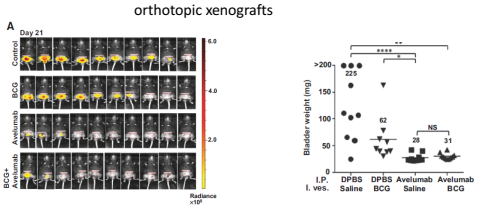
MB49 murine UC orthotopic xenografts



Vandeveer et al, Cancer Immunol Res 2016

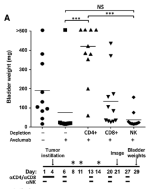
Rationale for NMIBC

MB49 murine UC orthotopic xenografts



Vandeveer et al, Cancer Immunol Res 2016

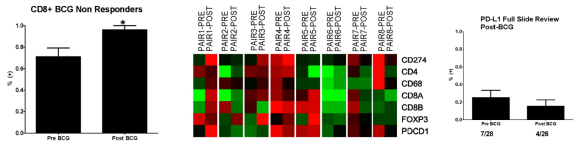
Rationale for NMIBC



These antitumor effects were more dependent on the presence of CD4 than CD8 T cells, as determined by in vivo immune cell depletions.

Vandeveer et al, Cancer Immunol Res 2016

What are the effects of BCG ?



- BCG induces CD8+ T cell influx
- No dramatic changes in PDL1 or immune parameters are observed

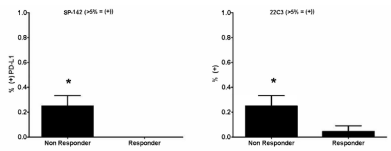
Kates et al. CCR 2019

What are the mechanisms of resistance to BCG ?

	Non-Responder (% (+) Staining))	Responder (% (+) Staining))	P-value
CD8	0.715	0.8	0.4795
CD4	0.48	0.4	0.5302
FOXp3	0.46	0.36	0.4246
CD68	0.75	0.76	0.9306
PD-L1 (SP-142)	0.13	0.04	0.2603
PD-1	0.29	0.32	0.8102

Kates et al. CCR 2019

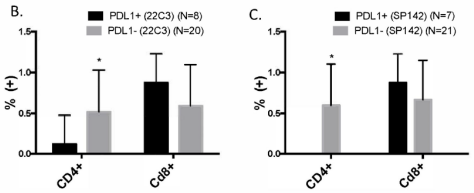
What are the mechanisms of resistance to BCG ?



- PDL1 expression associated with BCG resistance (25% of patients)
- CD8 and PDL1 colocalize : adaptative immune resistance
- No PDL1 staining in pure CIS

Kates et al. CCR 2019

What are the mechanisms of resistance to BCG ?



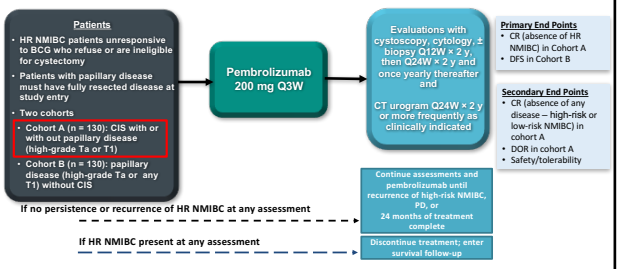
- lack of pre-treatment CD4+ T cells in PD-L1+ nonresponders.
- mechanism of inefficient CD4+ trafficking in BCG nonresponders may be another mechanism of BCG resistance

Kates et al. CCR 2019

Immune checkpoints inhibitors in NMIBC ?

- PDL1 expression may be mechanism of resistance to BCG in a subset of NMIBC
- 2 setting to investigate: BCG unresponsive NMIBC and BCG-naive NMIBC
- Later, if positive, ICI may substitute BCG
- Safety is critical to assess
- Duration of response is to most relevant clinical efficacy endpoint
- Translational studies needed in high-risk NMIBC (mutational landscape, TMB, etc)

KEYNOTE-057: Single-Arm, Open-Label Phase 2 Study



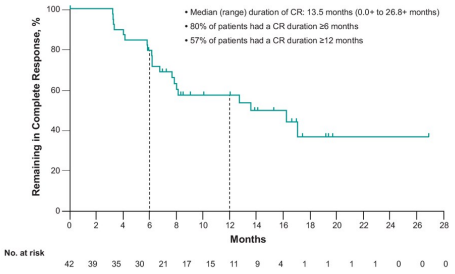
De wit et al. ESMO 2018

KEYNOTE-057: Single-Arm, Open-Label Phase 2 Study

N = 102	n	%	95% CI
CR	42	41.2	31.5-51.4
Non-CR	58	56.9	46.7-66.6
Persistent[b]	41	40.2	30.6-50.4
Recurrent[c]	7	6.9	2.8-13.6
NMIBC stage progression[d]	9	8.8	4.1-16.1
Non–bladder malignancy[e]	1	1.0	0.0-5.3
Progression to T2	0	0	NA-NA
Nonevaluable[f]	2	2.0	0.2-6.9

De wit et al. ASCO 2019

KEYNOTE-057: Single-Arm, Open-Label Phase 2 Study



De wit et al. ASCO 2019

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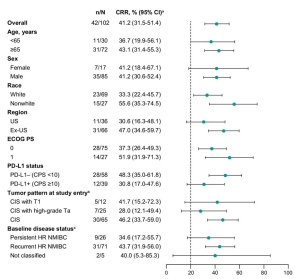


De wit et al. ASCO 2019

KEYNOTE-057: Single-Arm, Open-Label Phase 2 Study

	N = 102
Any-grade treatment-related AEs in ≥3 patients, n (%)	
Any	67 (65.7)
Pruritus	12 (11.8)
Diarrhea	11 (10.8)
Fatigue	11 (10.8)
Hypothyroidism	7 (6.9)
Maculopapular rash	6 (5.9)
Rash	6 (5.9)
Arthralgia	6 (5.9)
Hyperthyroidism	5 (4.9)
Nausea	5 (4.9)
Dry mouth	3 (2.9)
Hyponatremia	3 (2.9)
Malaise	3 (2.9)
Incidence of grade 3/4[a] treatment-related AEs, n (%)	
Any	13 (12.7)
Hyponatremia	3 (2.9)
Arthralgia	2 (2.0)
Adrenal insufficiency	1 (1.0)
Cholestatic hepatitis	1 (1.0)
Hypophosphatemia	1 (1.0)
Adrenocorticotropic hormone deficiency	1 (1.0)
Decreased lymphocyte count	1 (1.0)
Malaise	1 (1.0)
Pruritus	1 (1.0)
Pulmonary embolism	1 (1.0)
Dermatitis	1 (1.0)

De wit et al. ASCO 2019

Phase 2 trial: ADAPT-BLADDER

Objective: to investigate antitumour activity of durvalumab in BCG-refratory NMIBC

Inclusion criteria:

High risk NMIBC defined
- High grade OR
- T1 OR
- In situ carcinoma

Intermediate NMIBC
BCG unresponsive

Primary endpoint
Phase 1 study: RP2D
Phase 2 study: 6-month RFS

Secondary endpoints
- Safety
- 24 month RFS

TURBT → BCG retreatment
Durvalumab i.v every 3 weeks
BCG + Durvalumab i.v every 3 weeks
Radiation + Durvalumab i.v every 3 weeks

NCT03317158 PI: N. Hahn

Phase 2 trial: SWOG 1605

Objective: to investigate antitumour activity of atezolizumab in BCG-refratory NMIBC

Inclusion criteria:

High risk NMIBC defined
- High grade OR
- T1 OR
- In situ carcinoma

BCG unresponsive

Primary endpoint
- pCR in CIS
- EFS

Secondary endpoints
- EFS in pTa/pT1
- PFS
- Cystectomy free survival
- OS
- AEs

TURBT → Registration
N=202 patients
atezolizumab i.v every 3 weeks

NCT02844816 PI: P. Black

Phase 3 trial: KN 676 study

Objective: to investigate whether pembrolizumab improves the outcome of patients treated with BCG for high-risk NMIBC

Inclusion criteria:
High risk NMIBC defined
- High grade
- T1
- In situ carcinoma
- Multiple and recurrent and large tumors

Persistent or recurrent after induction

Primary endpoint
- CR

Secondary endpoints
- EFS
- RFS
- OS
- DSS

BCG (adequate induction) → Randomization
N=975 patients
Control: BCG : I + M (2 y)
Experimental: BCG : I + M + pembrolizumab i.v (2 y)

NCT03711032

Selection of ongoing trials

Trial	Type	ICI	Location	Criteria	Sample size
SINGLE AGENT					
NCT02808143	Phase 1 Single-arm	Pembrolizumab intravesically	Northwestern University	High risk or BCG refractory	27
NCT03950362	Phase 2 Single-arm	Radiotherapy + avelumab IV	France	Bcg-unresponsive	67
NCT03519256	Phase 2 Three-arm	Nivolumab IV Nivo + IDOi Nivo + IDOi + BCG	US, EUROPE	BCG unresponsive	436
NCT03106610	Phase 2	Gemcitabine intravesically + Pembo i,v	NCI	BCG unresponsive	72
NCT02901548	Phase 2	Durvalumab i,v	Lee Moffitt Cancer Center	BCG unresponsive CIS	34

Phase 3 trial: ALBAN study

Objective: to investigate whether atezolizumab improves the outcome of patients treated with BCG for high-risk NMIBC

Inclusion criteria:

High risk NMIBC defined
- High grade OR
- T1 OR
- In situ carcinoma

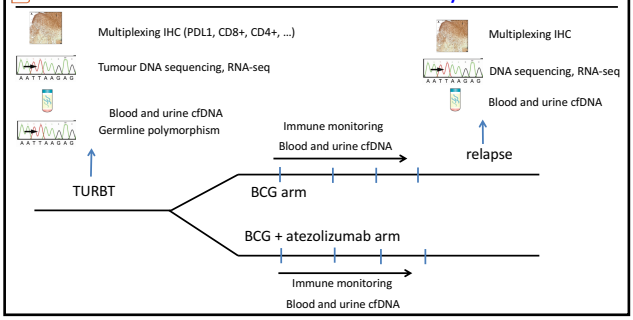
Primary endpoint
- Recurrence free-survival

Secondary endpoints
- Progression-free survival
- Overall survival
- Cancer specific survival
- Disease worsening

TURBT → Randomization
N=614 patients
Control: BCG : 6 + 3 (1y)
Experimental: BCG : 6 + 3 (1y) + atezolizumab i.v (1 y)

Eudract N°: 2017-004512-19 PI: M.Rouprêt & Y.Loriot

Phase 3 trial: ALBAN study



Phase 3 trial: POTOMAC study

Objective: to investigate whether durvalumab improves the outcome of patients treated with BCG for high-risk NMIBC

Inclusion criteria:

High risk NMIBC defined
- High grade
- T1
- In situ carcinoma
- Multiple and recurrent and large tumors

Primary endpoint
- Recurrence free-survival

Secondary endpoints
- Progression-free survival
- Overall survival
- Cancer specific survival
- Disease worsening

TURBT → Randomization (N=975 patients)

Control: BCG : I + M (2 y)

BCG : I + durvalumab i.v (1 y)

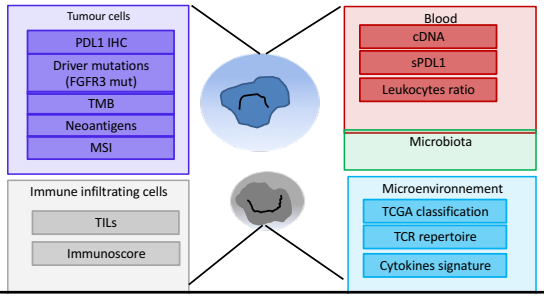
Experimental: BCG : I + M + durvalumab i.v (1 y)

Immune checkpoints inhibitors in NMIBC : the need of biomarkers

Luminal		Basal	
I	II	III	IV
Immune desert	Inflamed tumor	Inflamed but immune suppressed	

- Tumor cell
- Immune cells (Tumor-infiltrating lymphocytes)
- MDSc, fibroblast, stroma cells

biomarkers



Conclusion

- Current data support the investigation of ICI in NMIBC
- Large phase 3 trials ongoing
- Safety is key
- Ultimate goal: bladder preservation and maybe BCG substitution
- ALBAN is ongoing: feel free to participate

Thank you

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