

Overview of the ongoing clinical trials in Bladder Cancer



**SAN RAFFAELE
UROLOGIC ONCOLOGY
RETREAT**

**25 NOVEMBRE 2022 MILANO
AULA SAN RAFFAELE**

1st EDITION 2022

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Disclosures

Role	Sponsor
Consulting or Advisory role	Astellas, Janssen
Travel, Accommodation, Expenses	Gilead, IPSEN

Agenda



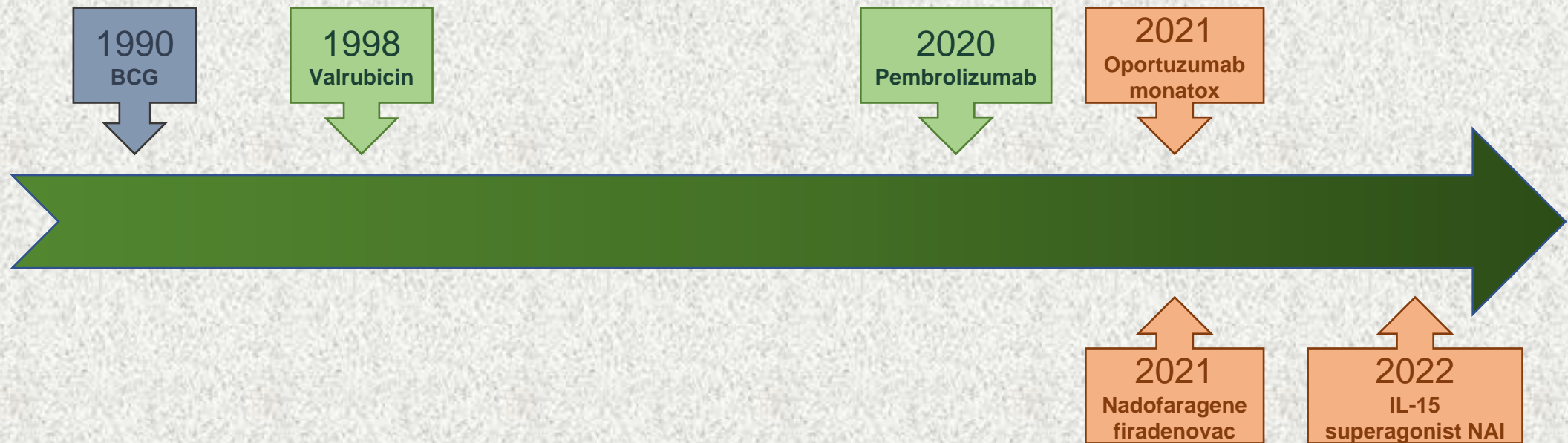
- ❖ Non-muscle invasive Bladder Cancer (NMIBC)
- ❖ Muscle invasive Bladder Cancer (MIBC)
- ❖ Metastatic disease (1st or more advanced lines)

Agenda



- ❖ **Non-muscle invasive Bladder Cancer (NMIBC)**
- ❖ Muscle invasive Bladder Cancer (MIBC)
- ❖ Metastatic disease (1st or more advanced lines)

BCG-unresponsive NMIBC: the story so far..



FDA-approved

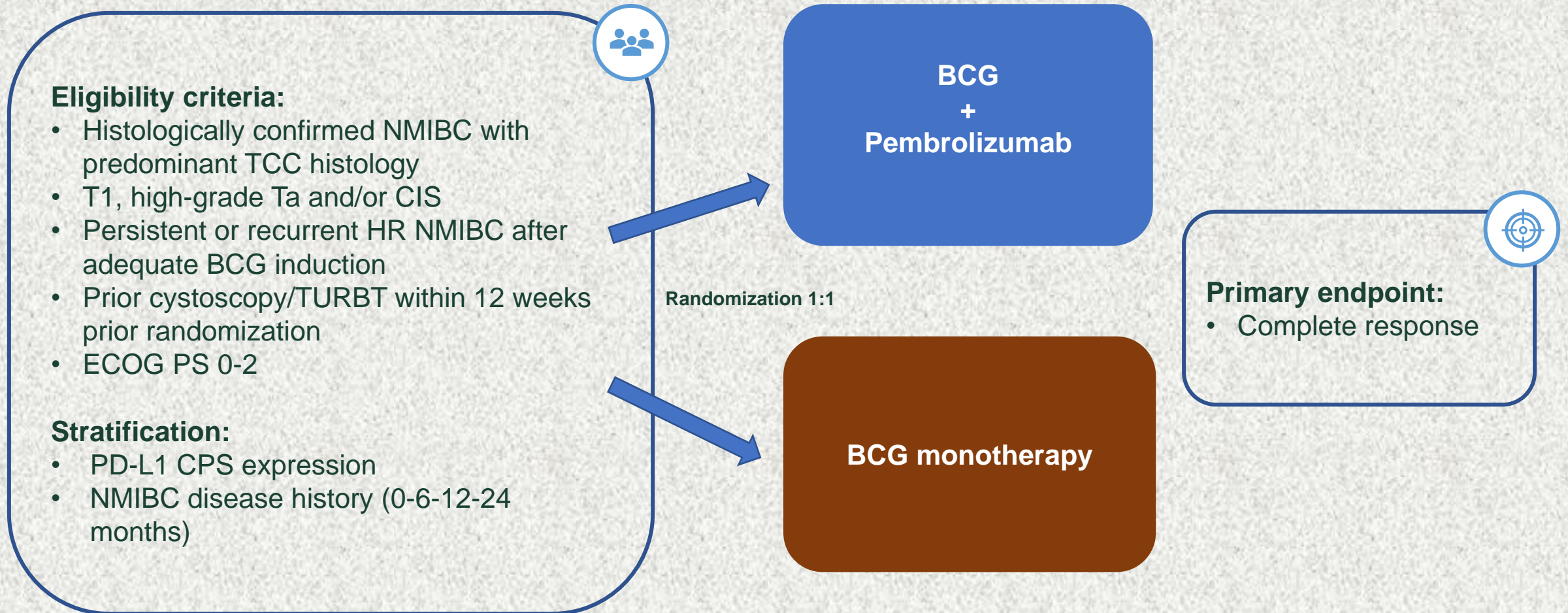
FDA-granted

NAI, nogapendekin alpha-inbakicept

BCG-unresponsive organ-sparing landscape in 2022

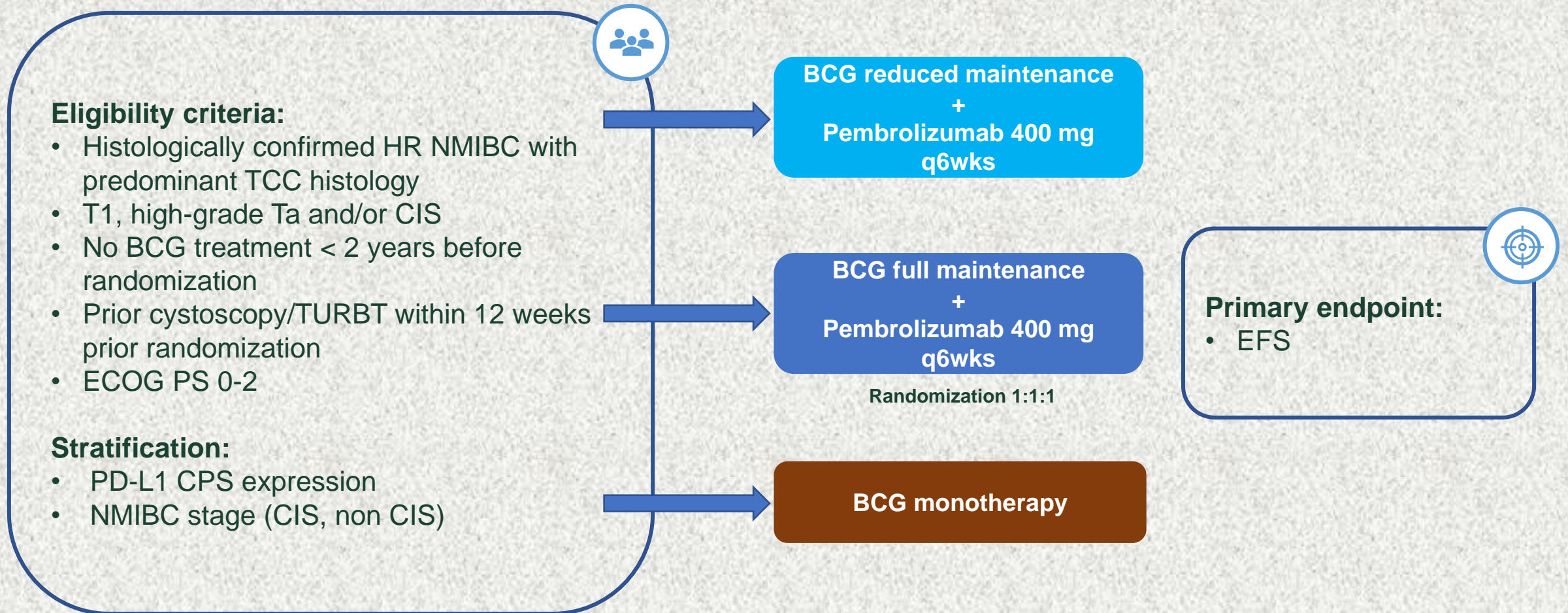
Author	Journal	Year	Intervention	Response	Timing of 1 st eval.
McKiernan	JCO	2006	Docetaxel	56% CR, 11% PR, 33% NR	10 weeks
McKiernan	J Urol	2014	Nab-paclitaxel	35.7% CR	12 weeks
Skinner	J Urol	2013	Gemcitabine	47% CR	3 mo
Steinberg	J Urol	2000	Valrubicin (FDA-approved only)	21% CR 15% Ta residual	3 mo
Balar	Lancet Oncol	2021	Pembrolizumab (FDA-approved only)	40.2% CR (CIS)	3 mo
Black	JCO	2020	Atezolizumab	27% CR (CIS)	3 mo
Dickstein	GU-ASCO	2021	Oportuzumab monatox	40% (CIS) 71.1% (Ta/T1)	3 mo
Boorjian	Lancet Oncol	2020	Nadofaragene firadenovac	53.4% CR (CIS)	3 mo
Chang	(GU)-ASCO	2022	ALT-803 + BCG	71% (Cohort A – CIS) DFS 19.3 mo (Cohort B)	3 or 6 mo (Cohort A) 12-mo DFS (Cohort B)

KEYNOTE-676: A Phase 3, Randomized, Clinical Trial of Pembrolizumab in Combination with BCG in Participants with HR NMIBC that is either Persistent or Recurrent Following BCG Induction or that is Naïve to BCG Treatment (**COHORT A**)



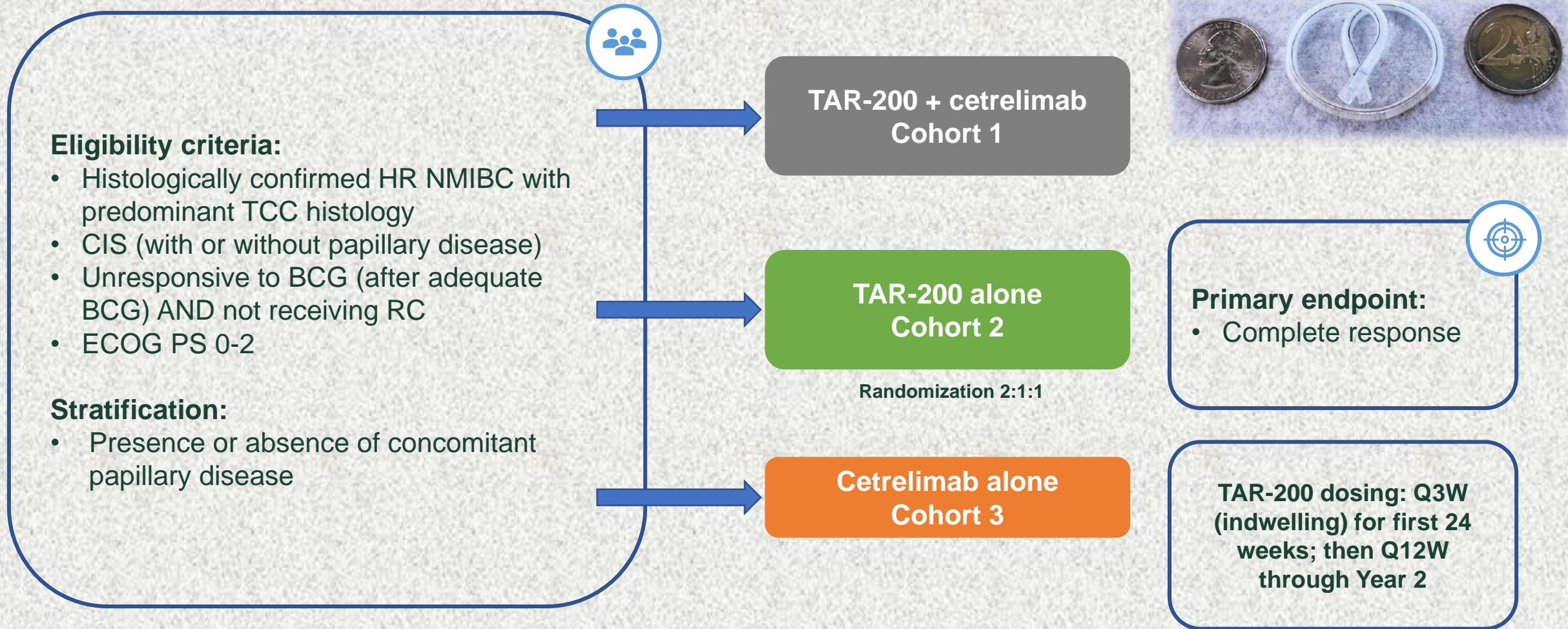
ECOG PS, Eastern Cooperative Oncology Group performance status; NMIBC non muscle-invasive bladder cancer: HR high risk
LA/mUC, locally advanced/metastatic urothelial carcinoma; ORR, overall response rate; OS, overall survival; QoL, quality of life; CPI checkpoint inhibitor
PFS, progression-free survival; Q21D, every 21 days.
EudraCT Number: 2018-001967-22

KEYNOTE-676: A Phase 3, Randomized, Clinical Trial of Pembrolizumab in Combination with BCG in Participants with HR NMIBC that is either Persistent or Recurrent Following BCG Induction or that is Naïve to BCG Treatment (**COHORT B**)



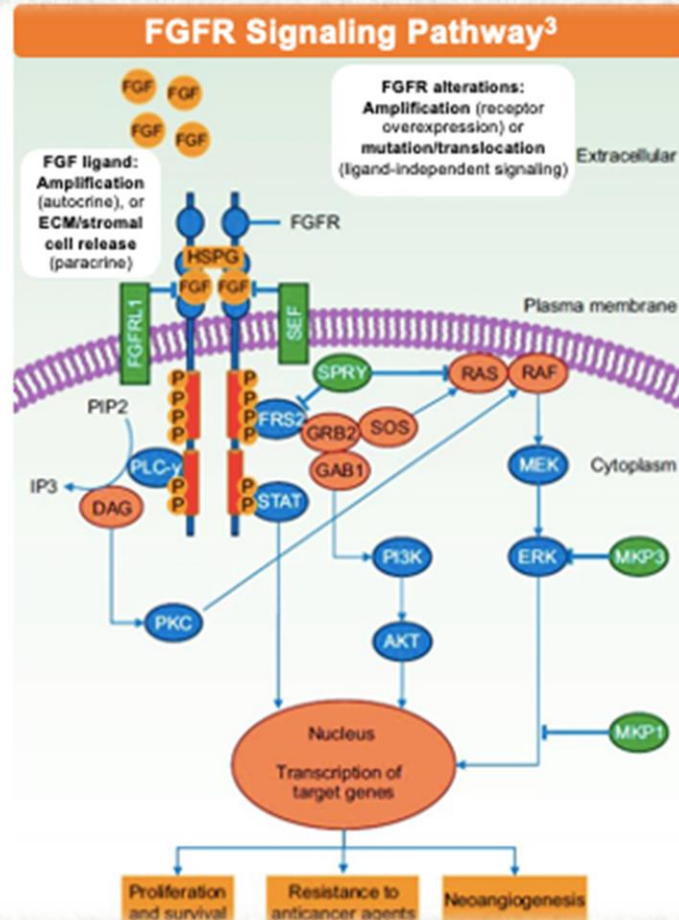
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PFS, progression-free survival; Q21D, every 21 days; EFS event-free survival
EudraCT Number: 2018-001967-22

SunRISe-1: Phase 2b Clinical Study Evaluating Efficacy and Safety of TAR-200 in Combination with Cetrelimab, TAR-200 Alone, or Cetrelimab Alone in HR NMIBC Unresponsive to Intravesical BCG who are Ineligible to Undergo Radical Cystectomy (RC)



ECOG PS, Eastern Cooperative Oncology Group performance status; NMIBC non muscle-invasive bladder cancer: HR high risk LA/mUC, locally advanced/metastatic urothelial carcinoma; ORR, overall response rate; OS, overall survival; QoL, quality of life; CPI checkpoint inhibitor PFS, progression-free survival; Q21D, every 21 days; EFS event-free survival
EudraCT Number: 2020-002646-16

Rationale for targeting FGFR in UC^{1,2}

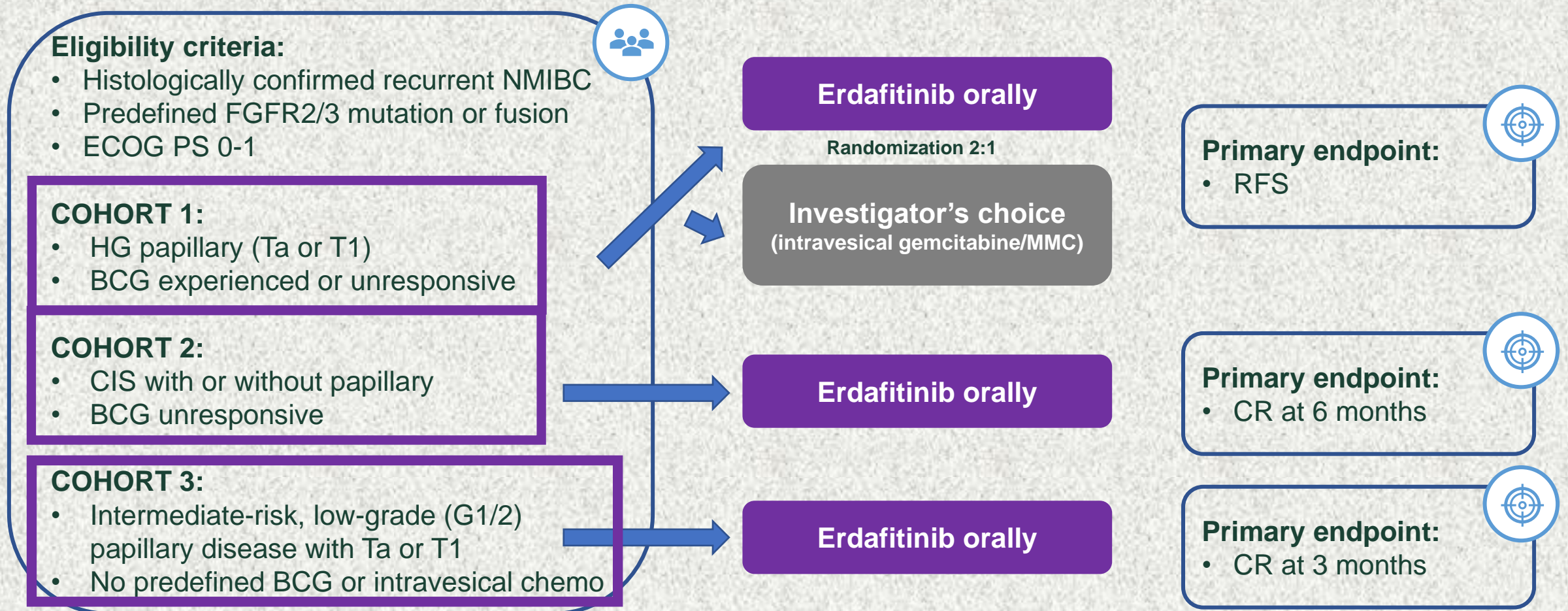


- *FGFR* is altered in 15%-20% of advanced UC⁴
 - Mutated *FGFR3* is present in 37% of upper-tract UC⁵

Cancer Type	Frequency of <i>FGFR</i> Alterations ¹
Metastatic UC	15%-20%
NMIBC	40%-70%
Cholangiocarcinoma	14%-22%
NSCLC	4%
HCC (<i>FGF19</i> amp by FISH)	21%
Glioblastoma	23%
Breast cancer	3-5%
Ovarian cancer	7%
Head and neck cancer	9%-17%

1. <https://tcga-data.nci.nih.gov/docs/publications/tcga> 2. Knowles MA et al. *Nat Rev Cancer* 2015. 3. Touat M et al. *Clin Cancer Res*. 2015.
 4. Rodriguez-Vida A et al. *J. Hematol Oncol*. 2015. 5. Li Q et al. *Curr Urol Rep*. 2016

THOR-2: Randomized Phase 2 Study of Erdafitinib vs Investigator Choice of Intravesical Chemotherapy in Subjects Who Received BCG and Recurred With HR NMIBC and FGFR Mutations or Fusions



ECOG PS, Eastern Cooperative Oncology Group performance status; NMIBC non muscle-invasive bladder cancer: HR high risk
LA/mUC, locally advanced/metastatic urothelial carcinoma; ORR, overall response rate; OS, overall survival; QoL, quality of life; CPI checkpoint inhibitor
PFS, progression-free survival; Q21D, every 21 days; RFS relapse-free survival; CR complete response
EudraCT Number: 2019-002449-39

Agenda



- ❖ Non-muscle invasive Bladder Cancer (NMIBC)
- ❖ **Muscle invasive Bladder Cancer (MIBC)**
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Muscle-invasive bladder cancer: background



Neoadjuvant cisplatin-based CT is still the SOC in MIBC



Adjuvant nivolumab improves DFS in HR MIBC



Neoadjuvant IO approach is very active in MIBC



Urgent need of new predictive biomarkers in MIBC

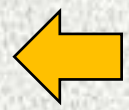
MIBC



RC candidate

Bladder preservation

CIS-ineligible



OPTIMUS

KEYNOTE 905

VOLGA

KEYNOTE B15

NURE COMBO

SURE-01/02

NAC (CIS-eligible)



Radical Cystectomy

Trimodality therapy



Pts with NO prior NAC:
pT3, pT4a or pN+
AND cis-ineligible/refusal

Pts with prior NAC:
ypT2 to ypT4a or pN+

Adjuvant CT
(selected)

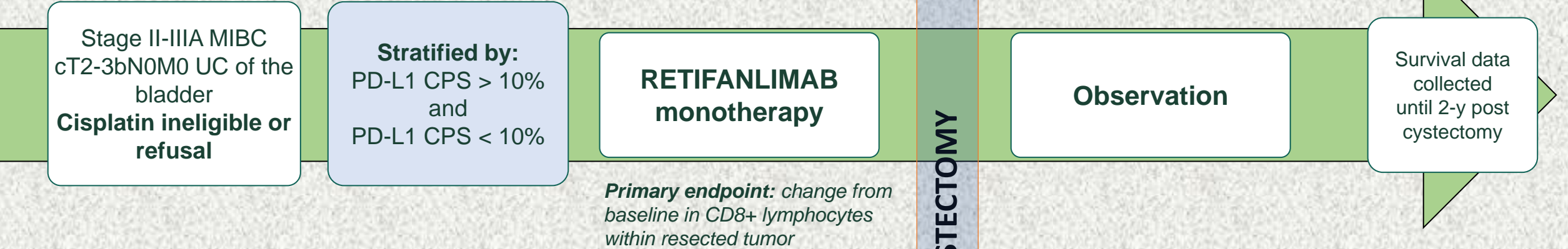


Adjuvant Nivolumab



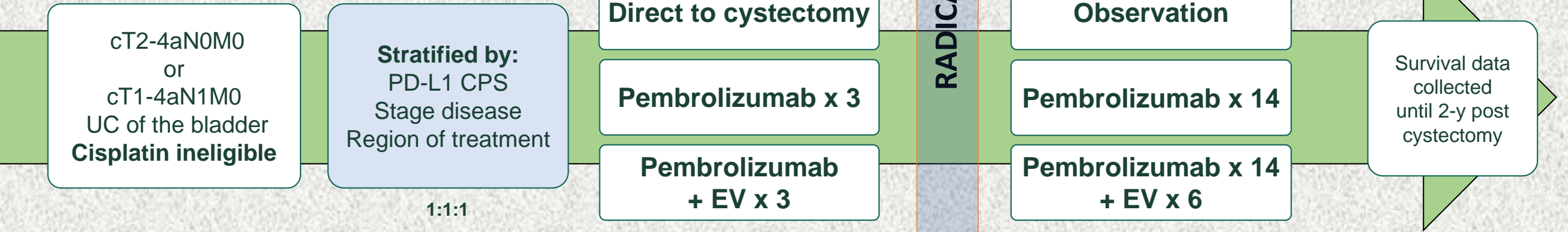
Ongoing sponsored trials-1

OPTIMUS phase 2 trial



Primary endpoint: change from baseline in CD8+ lymphocytes within resected tumor

KEYNOTE-905 phase 3 trial



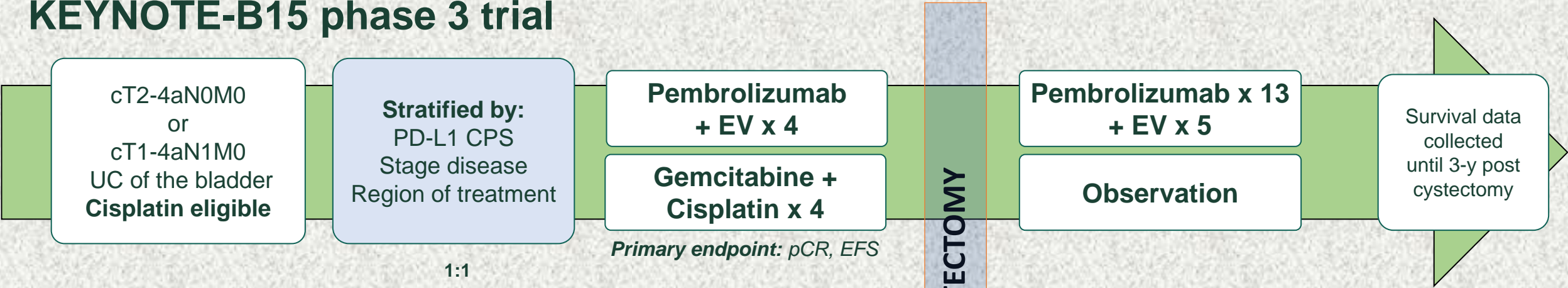
Primary endpoint: pCR, EFS

CPS combined positive score; pCR pathologic complete response; UC urothelial carcinoma; EFS event-free survival; EV enfortumab vedotin

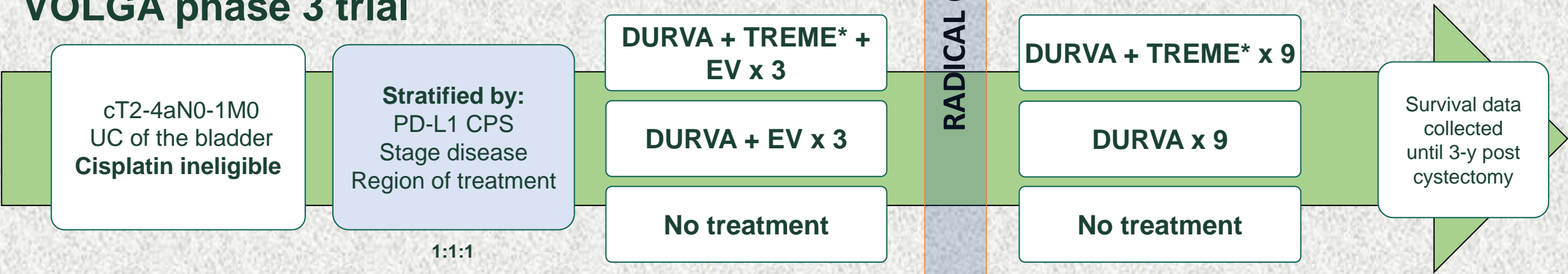
Ongoing sponsored trials-2



KEYNOTE-B15 phase 3 trial



VOLGA phase 3 trial



CPS combined positive score; pCR pathologic complete response; UC urothelial carcinoma; EV enfortumab vedotin
EFS event-free survival

*Tremelimumab (neoadjuvant C1,2 only; adjuvant C1 only)

Ongoing academic trials: SURE-01 and SURE-02 studies

Open-label, single-arm, phase II studies



Sponsor: IRCCS Ospedale San Raffaele
EudraCT Number: 2020-004844-27

- Combined Bladder MRI/PET
- t/a CT scan
- Combined Bladder MRI/PET
- t/a CT scan

- Histologically-confirmed UC or UC+VH
- cT-stage 2-4
- cN-stage 0
- No previous CT
- Ineligibility/refusal of cis chemo
- Adequate organ function tests



4x3 weekly cycles
of SG
monotherapy



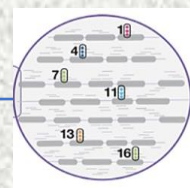
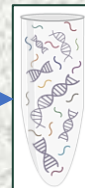
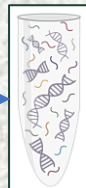
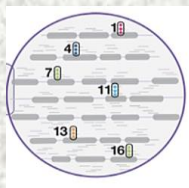
RADICAL CYSTECTOMY

Standard-of-care
management

4x3 weekly cycles
of SG+Pembro

12-month adjuvant pembro

1y FUP



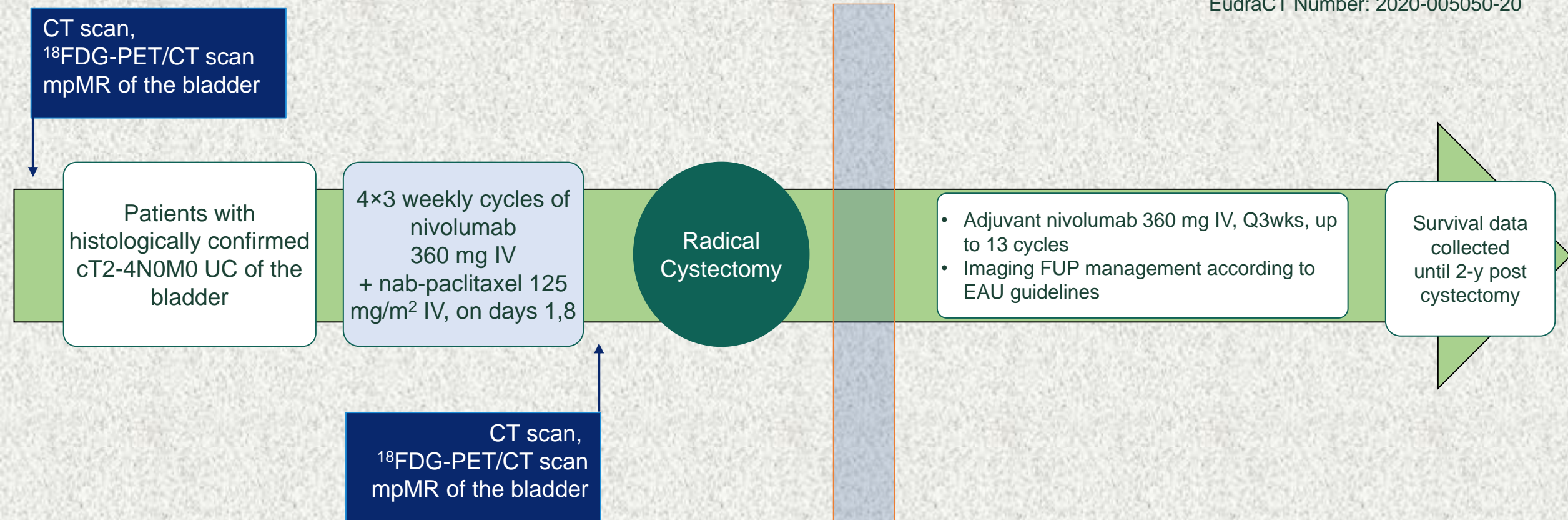
- **Primary endpoint:** pathologic complete response
- **Secondary endpoints:** pathologic downstaging; EFS, OS, safety and tolerability

Ongoing academic trials: NURE-Combo

Open-label, single-arm, phase II study



Sponsor: IRCCS Ospedale San Raffaele
EudraCT Number: 2020-005050-20



CT: computed tomography
FDG-PET: fluorine-fluorodeoxyglucose positron emission tomography
mpMR: multiparametric Magnetic Resonance
UC: urothelial carcinoma

- **Primary endpoint:** pathologic complete response
- **Secondary endpoints:** pathologic downstaging; EFS, OS, safety and tolerability

Ongoing academic trials: NURE-Combo

First interim and safety analyses: characteristics, efficacy



Sponsor: IRCCS Ospedale San Raffaele
EudraCT Number: 2020-005050-20

Baseline characteristics	N = 13
Median Age (IQR)	63 (46-74)
Male (%)	12 (92.3)
Clinical T, n (%)	
-> T2N0	8 (61.5)
-> T3N0	5 (38.5)
Hydronephrosis, n (%)	1 (7.7)
Previous BCG, n (%)	2 (15.4)
Histology, n (%)	
-> Pure UC	6 (46.2)
-> UC + squamous	1 (7.7)
-> Plasmacytoid	2 (15.4)
-> Nested	2 (15.4)
-> Micropapillary	2 (15.4)
Cystectomy, n (%)	11 (84.6)
Time from end neoadj-RC (median days, IQR)	44.5 (24-78)

UC: urothelial carcinoma; RC radical cystectomy

Efficacy	N = 11
Pathological complete response, n (%)	3 (27.3)
Pathological downstaging to pT < 2, n (%)	8 (72.7) 3 ypT0; 3 ypTis; 2 ypT1
Treatment failure, n (%)	
-> ypT2-T4 ypN0	2 (18.2)
-> ypTany ypN+	1 (9)

- **Primary endpoint:** pathologic complete response
- **Secondary endpoints:** pathologic downstaging; EFS, OS, safety and tolerability

Ongoing academic trials: NURE-Combo

First interim and safety analyses: safety profile

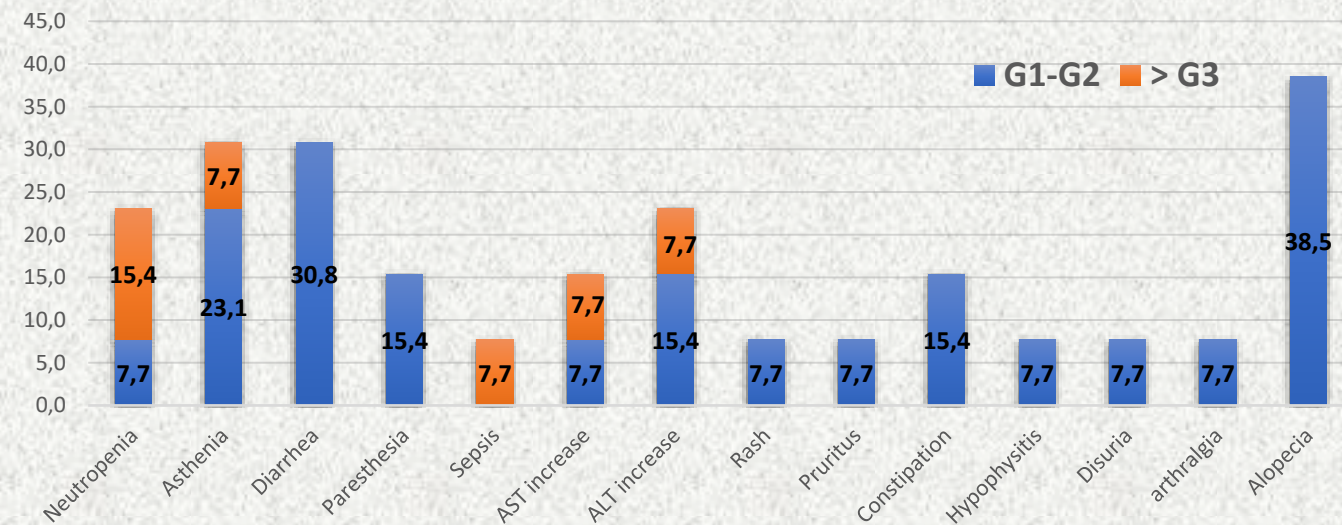


Sponsor: IRCCS Ospedale San Raffaele
EudraCT Number: 2020-005050-20

Safety	N=13
Radical cystectomy rate	13 (100)
Discontinued treatment, n (%)	3 (23)
• Nivolumab	2 (15)
• Nab-paclitaxel	1 (7)
Completed neoadjuvant treatment, n (%)	
• Nivolumab	13 (100)
• Nab-paclitaxel	12 (92)
AEs \geq G3, n (%)	5 (38)
• Hematological	2 (15)
• Non Hematological	3 (23)
Dose reduction, n (%)	1 (7)
Serious Adverse Events, n (%)	2 (15)
Use of high-dose corticosteroids, n (%)	1 (7)
Death, n (%)	1 (7)

- **Nivolumab suspended** in two patients (**adjuvant phase only**), ALT/AST increase; UTI with sepsis
- **Nab-paclitaxel suspended** in one patient (**C4**), paresthesia and asthenia
- Hypophisitis: one case, grade 2, diagnosed after cystectomy. Rapid improvement after hormonal reposition
- **Dose reduction: nab-paclitaxel** in one patient
- **Death**: one patient died after cystectomy (**not related**), suspected arterial intestinal ischemia

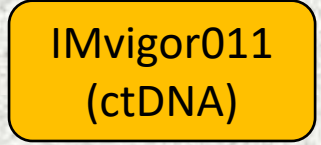
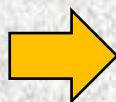
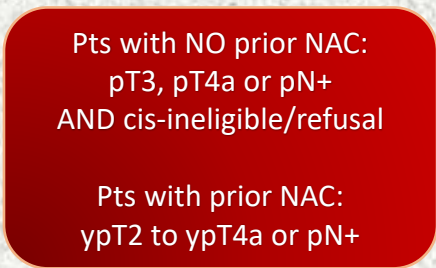
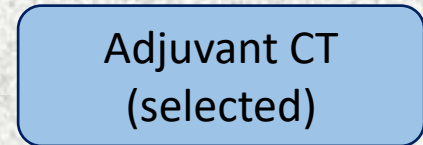
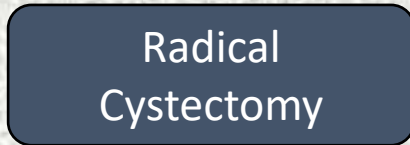
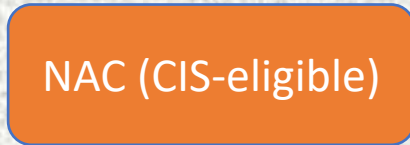
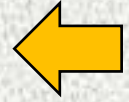
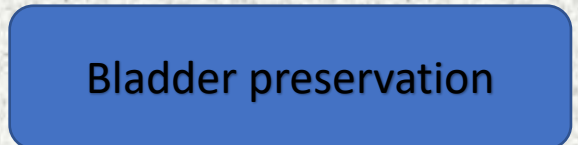
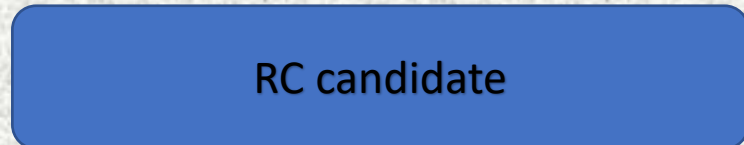
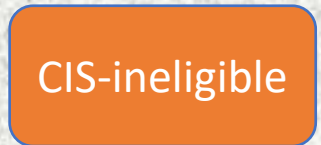
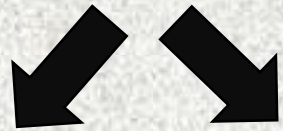
Adverse Events



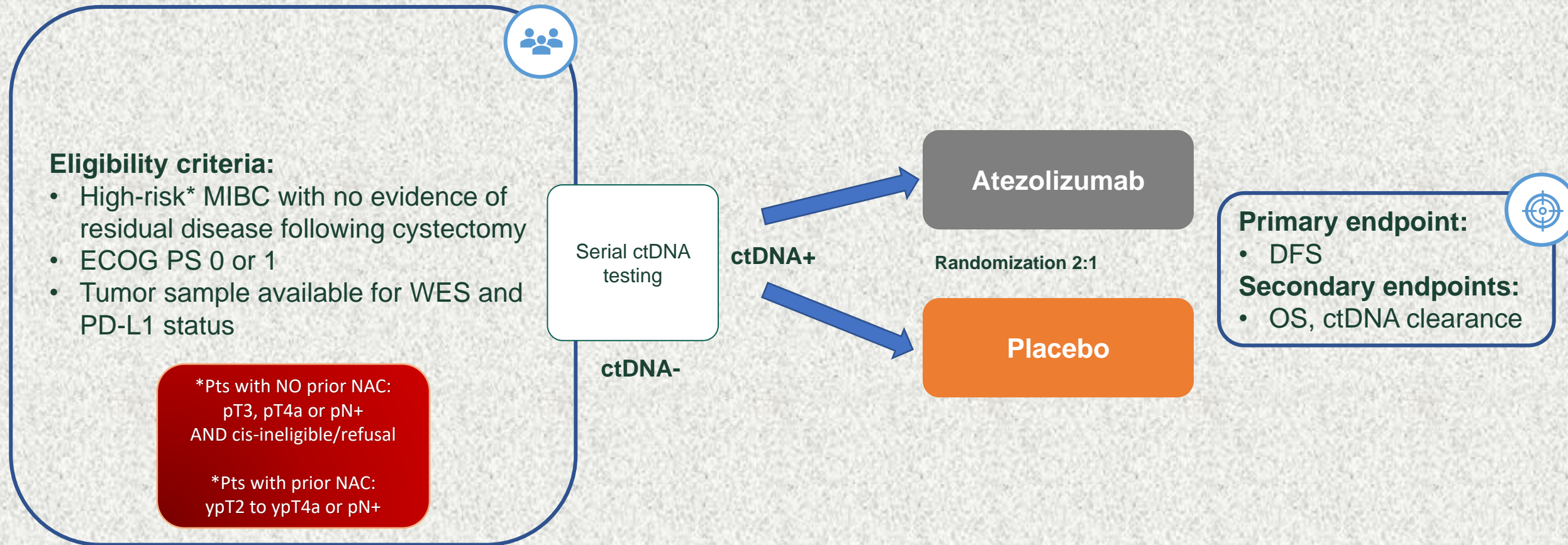
UC: urothelial carcinoma; RC radical cystectomy
AEs, adverse events: UTI urinary tract infection

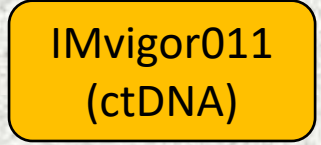
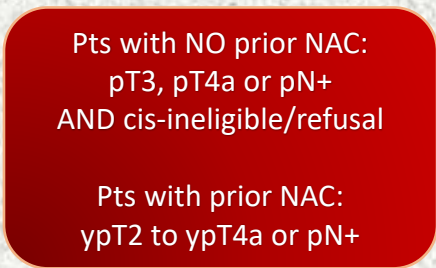
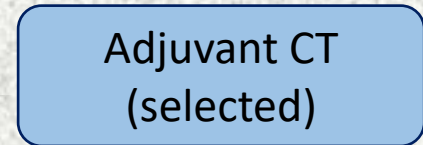
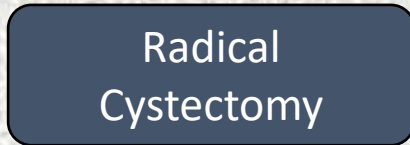
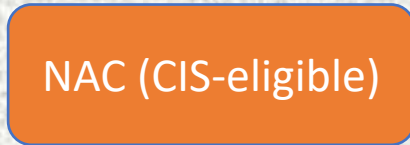
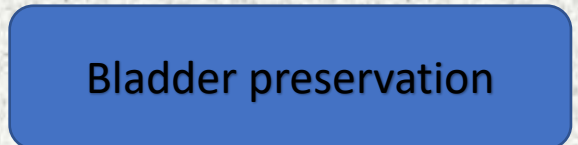
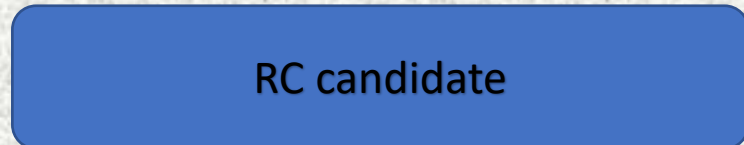
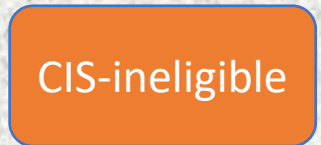


MIBC



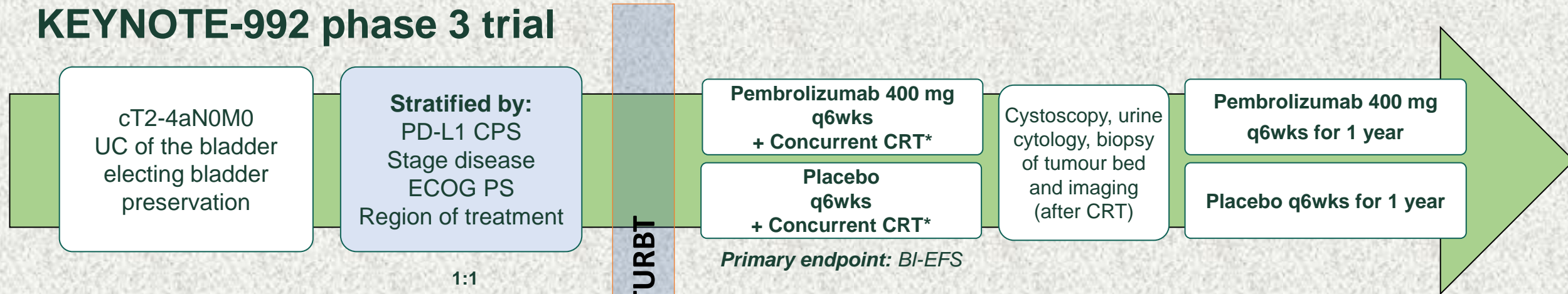
IMvigor011: phase 3, double-blind, randomized study of atezolizumab vs placebo as adjuvant therapy in pts with HR MIBC who are ctDNA positive following cystectomy



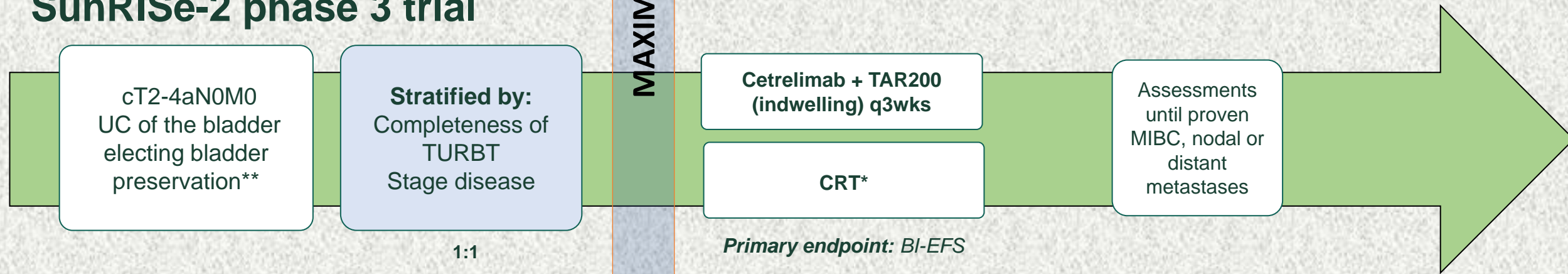


Ongoing sponsored trials-3: bladder preservation

KEYNOTE-992 phase 3 trial



SunRISe-2 phase 3 trial



CPS combined positive score; BI-EFS, bladder-intact event-free survival

* CRT, cisplatin 35 mg/m² q1wk (x 6 wks) or gemcitabine 27 mg/m² q2wks (x 6 wks) + radiotherapy – investigator's choice

** within 3 months from diagnostic TURBT

EudraCT Number: 2019-004023-20
2020-005452-38

Agenda



- ❖ Non-muscle invasive Bladder Cancer (NMIBC)
- ❖ Muscle invasive Bladder Cancer (MIBC)
- ❖ **Metastatic disease (1st or more advanced lines)**

Backbone of first-line treatments



Gemcitabine-cisplatin (GC): median OS 14 months, ORR 49%

ddMVAC: median OS 15 months, ORR 70%

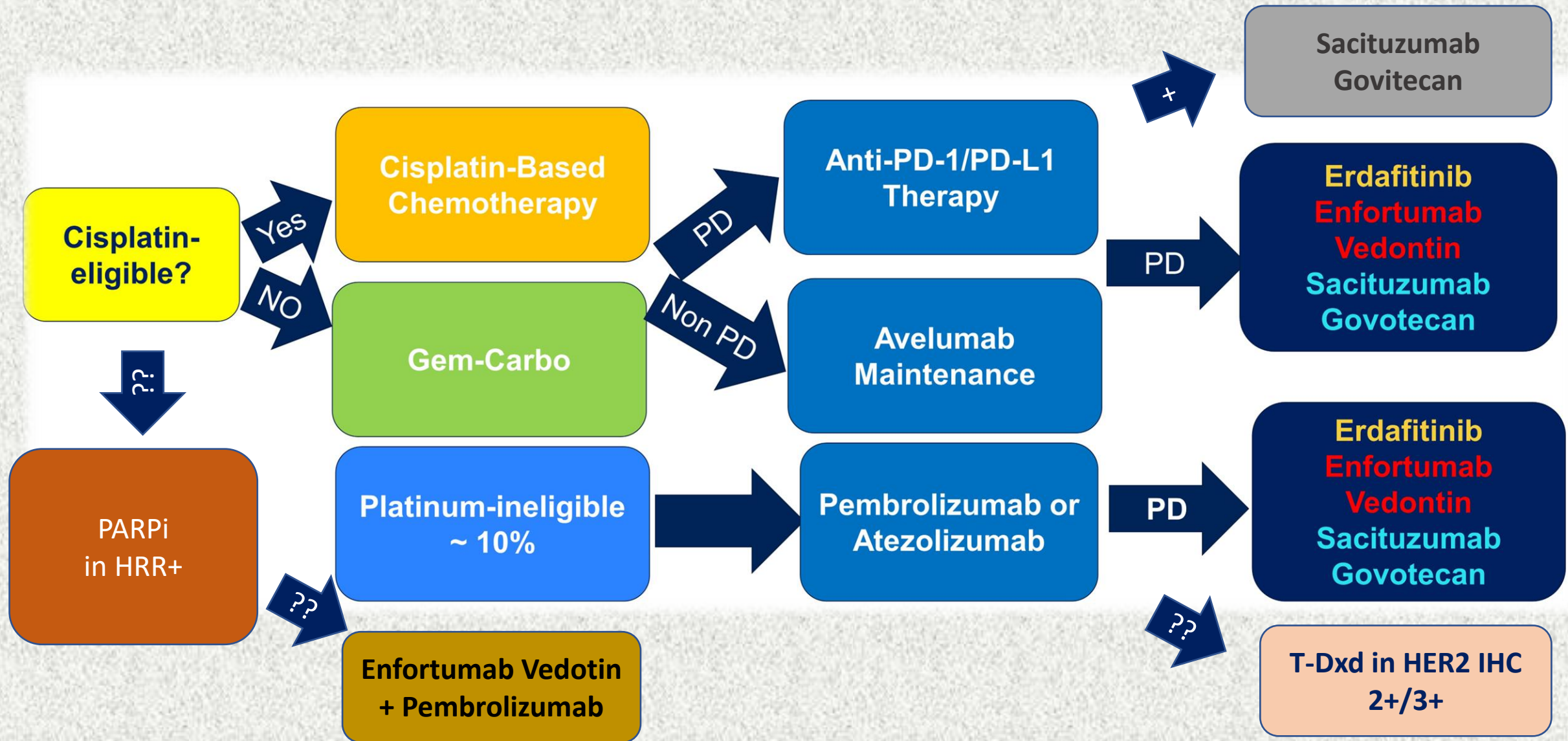
Gemcitabine-carboplatin: recent trials show median OS 13 months, ORR 43%

Avelumab maintenance in responders is the new SOC,
median OS 23.8 months (ITT) and 30.9 months (PD-L1+)

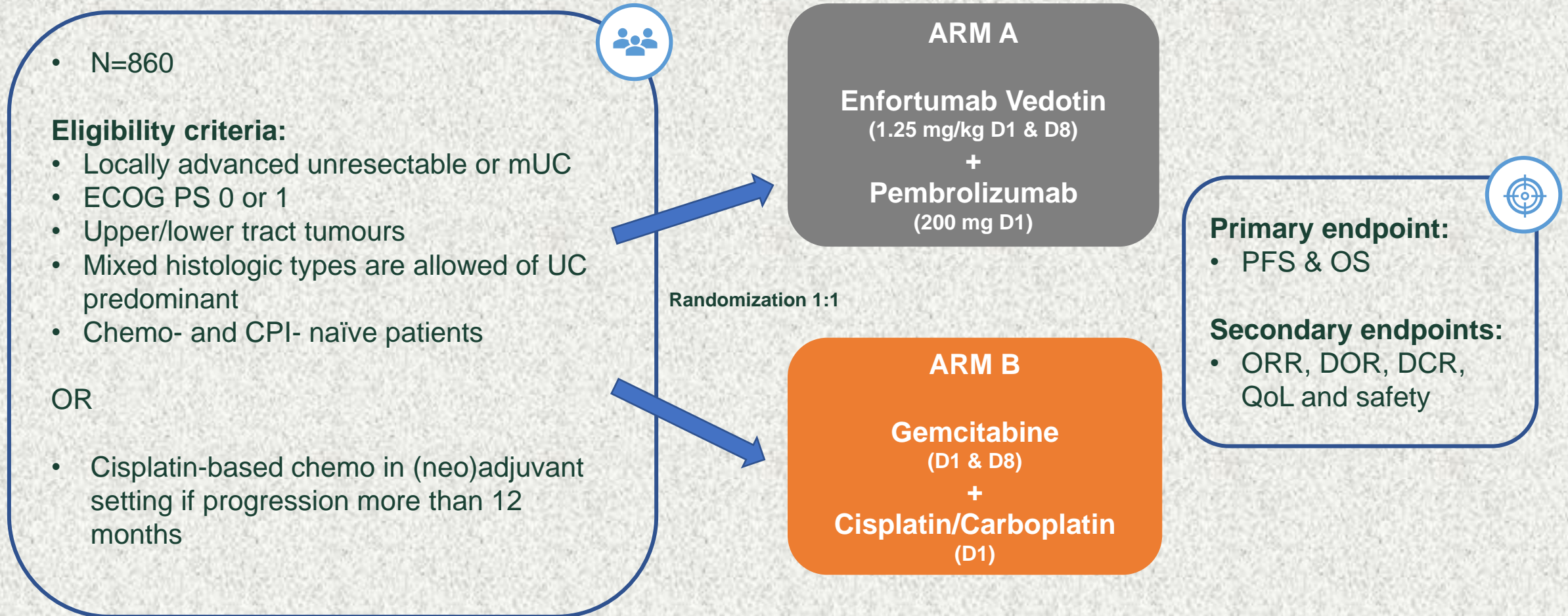
Only a minority of pts receive second-line treatments

An unmet need to improve survival with first-line treatments

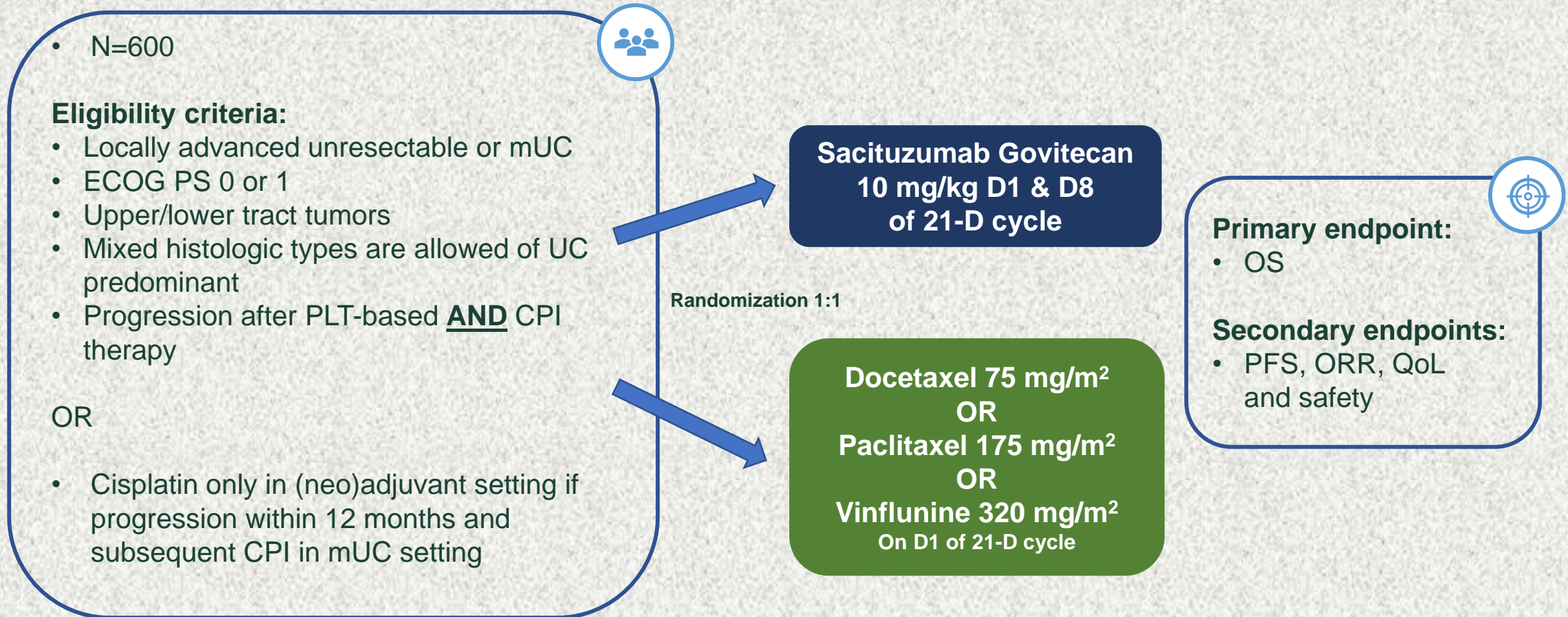
Current treatment paradigm (after ASCO/ESMO 2022)



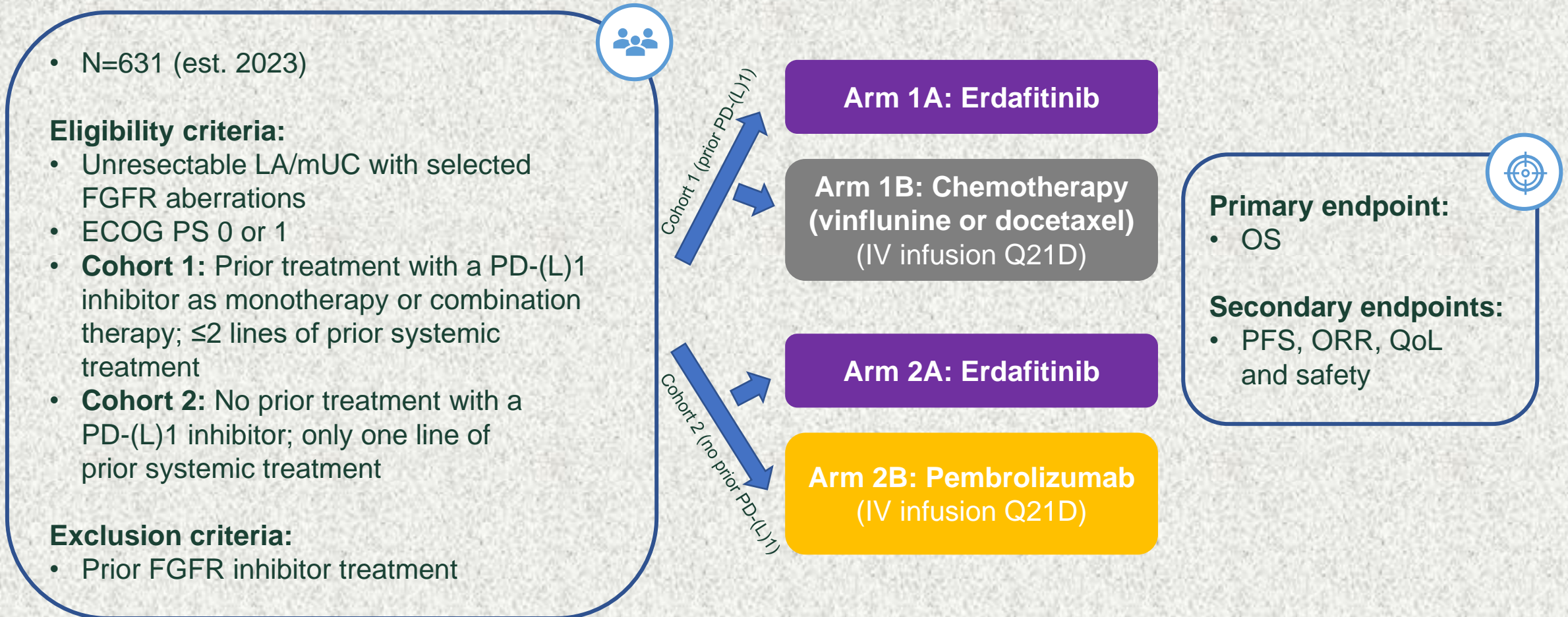
EV-302: An open-label, randomized, controlled phase 3 study of enfortumab vedotin in combination with pembrolizumab versus chemotherapy alone in previously untreated LA/mUC



TROPiCS-04: A Randomized Open-Label Phase 3 Study of Sacituzumab Govitecan Versus Treatment of Physician's Choice in Subjects with LA/mUC



THOR: Phase III, open-label study of erdafitinib in previously treated patients with LA/mUC harbouring selected FGFR aberrations



Industry partnership in Early Drug Development

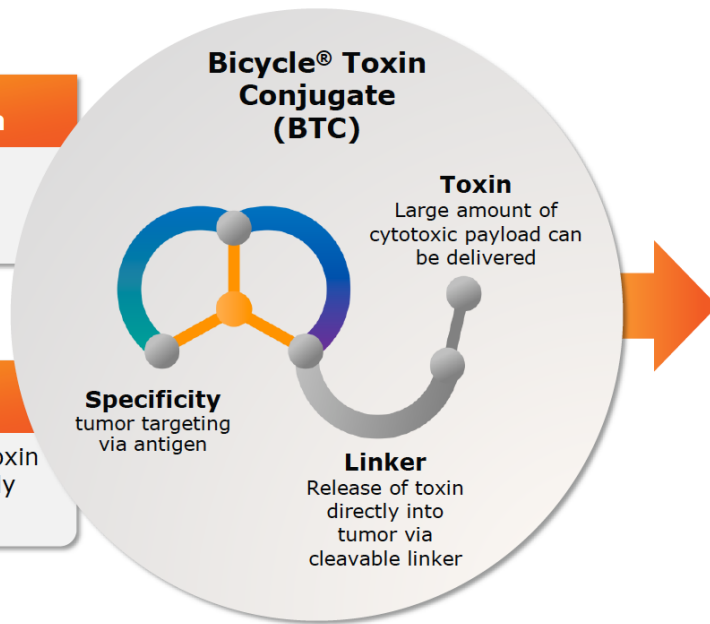
BTCs – preclinical data promises higher potency and specificity with fewer side effects

MWt of 1.5-2kDa

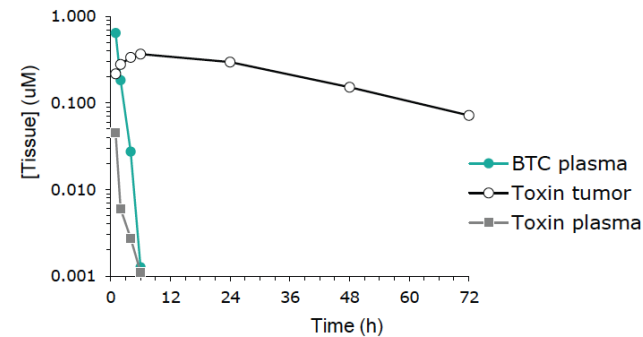
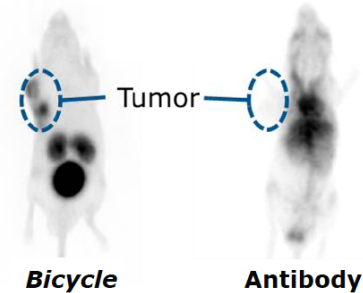
50-100x smaller than antibodies

High selectivity

Allows more potent toxin to be delivered directly to tumor

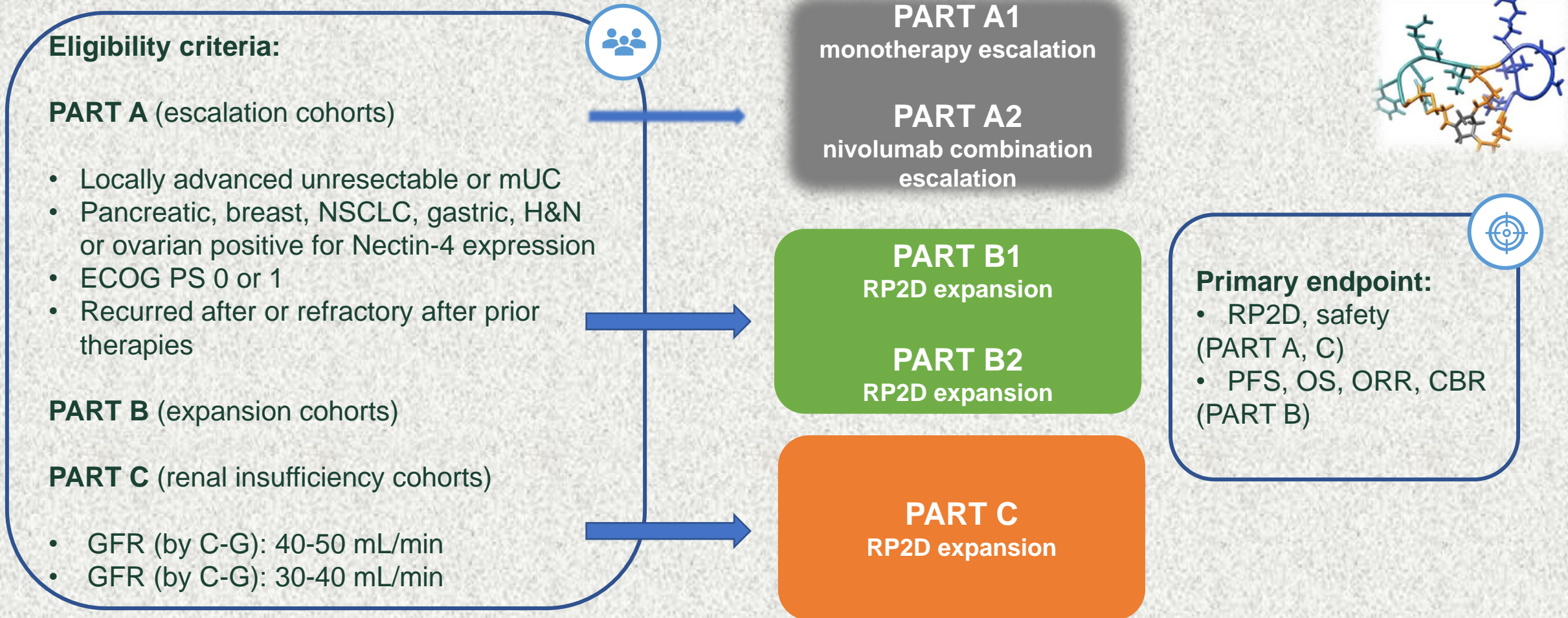


PET Imaging 40-60min

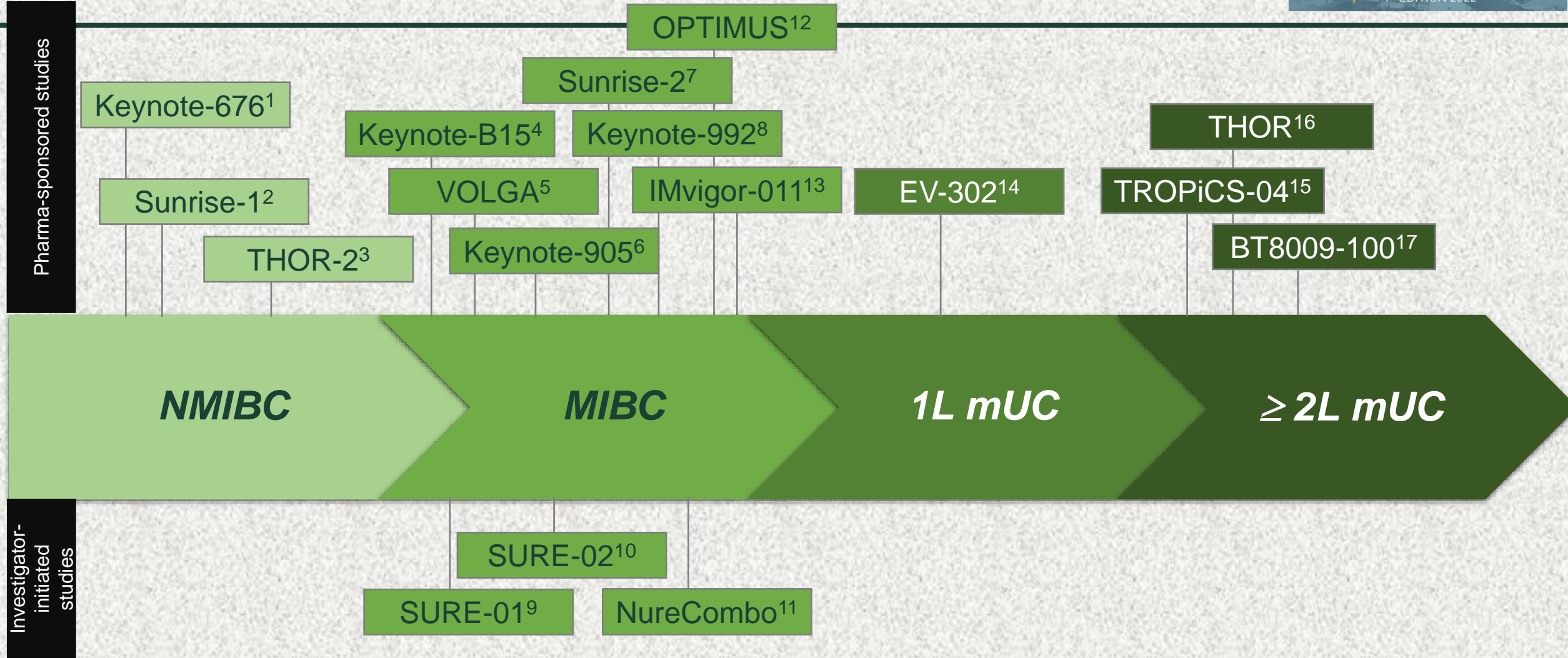


*Phase I/II BT8009-100
(NCT04561362) trial
open at San Raffaele*

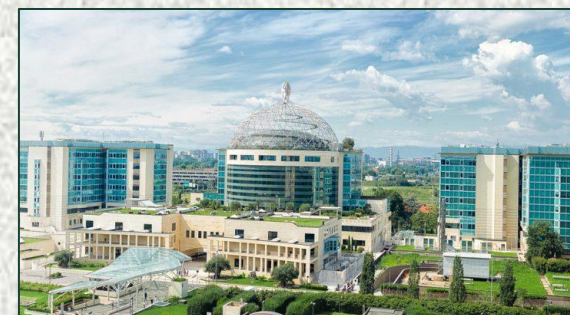
BT8009-100: phase 1/2 study of safety, pharmacokinetics and preliminary clinical activity of BT8009 in patients with Nectin-4 expressing advanced malignancies



Currently enrolling Phase 1-2-3 trials in UC landscape (as of Nov 25th, 2022)



1. Pembrolizumab + BCG vs BCG (NCT03711032); 2. TAR200+cetrelimab vs TAR200 vs Cetrelimab (NCT04640623); 3. Erdafitinib vs Investigator-choice intravesical chemotherapy instillation (NCT04172675); 4. EV+pembrolizumab vs chemo (NCT04700124); 5. Durva+Treme+EV vs Durva+EV vs RC (NCT04960709); 6. EV+ Pembro vs Pembro vs RC (NCT03924895); 7. TAR200 + cetrelimab vs chemoRT (NCT04658862); 8. Pembro+chemoRT vs chemoRT (NCT04241185); 9. sacituzumab govitecan + RC (NCT05226117); 10. sacituzumab govitecan + pembro + RC (NCT05535218); 11. Nivolumab+Nab-paclitaxel + RC (NCT04876313); 12. retifanimab + RC (NCT04586244); 13. Atezolizumab post-RC in ctDNA+ (NCT04660344); 14. EV+Pembro vs chemotherapy (NCT04223856); 15. sacituzumab govitecan vs investigator-choice chemotherapy (NCT04527991); 16. erdafitinib vs investigator-choice chemotherapy in FGFR3-selected patients (NCT03390504); 17. BT8009 monotherapy (NCT04561362);



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