Current Status and Clinical Application of Circulating Tumour DNA (ctDNA) and its Future Role in Clinical Practice

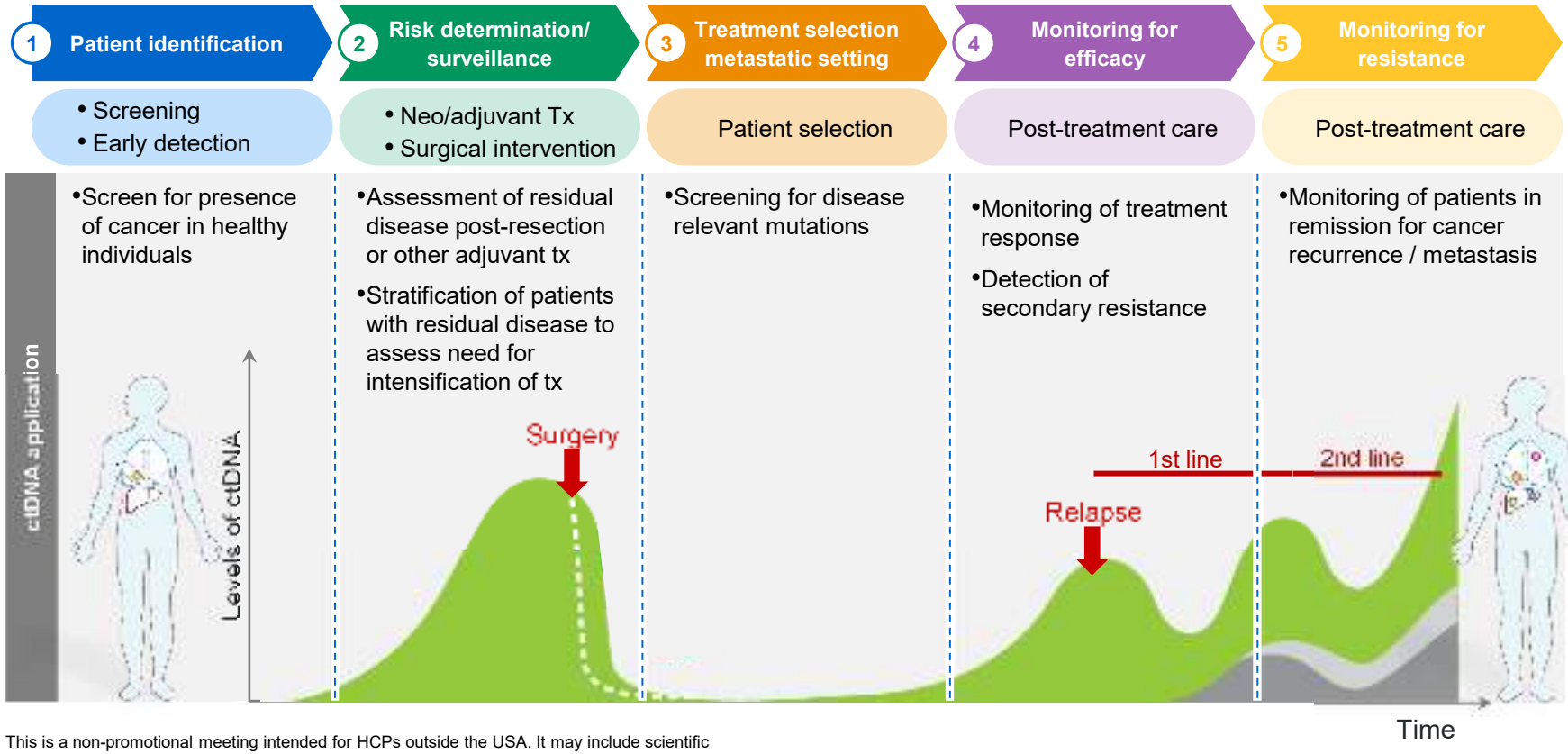
Jürgen E. Gschwend, Professor and Chairman
Department of Urology, Technical University of Munich, Germany

Disclaimer

Lectures: Amgen, Bayer, BMS, Janssen, Merck, MSD, Roche

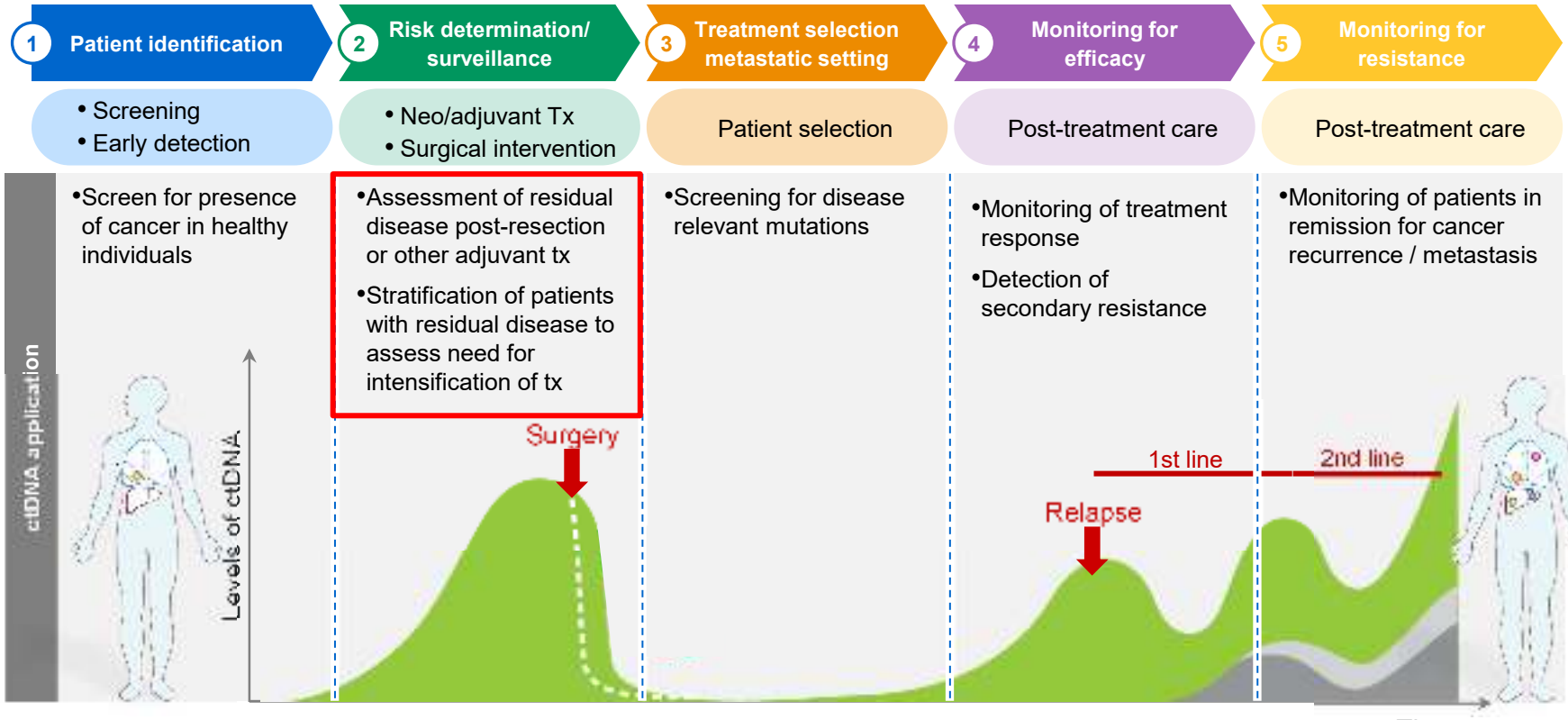
Consultancy: Bayer, BMS, Janssen, Merck, MSD, Pfizer, Roche

ctDNA has substantial potential to be used throughout the patient journey



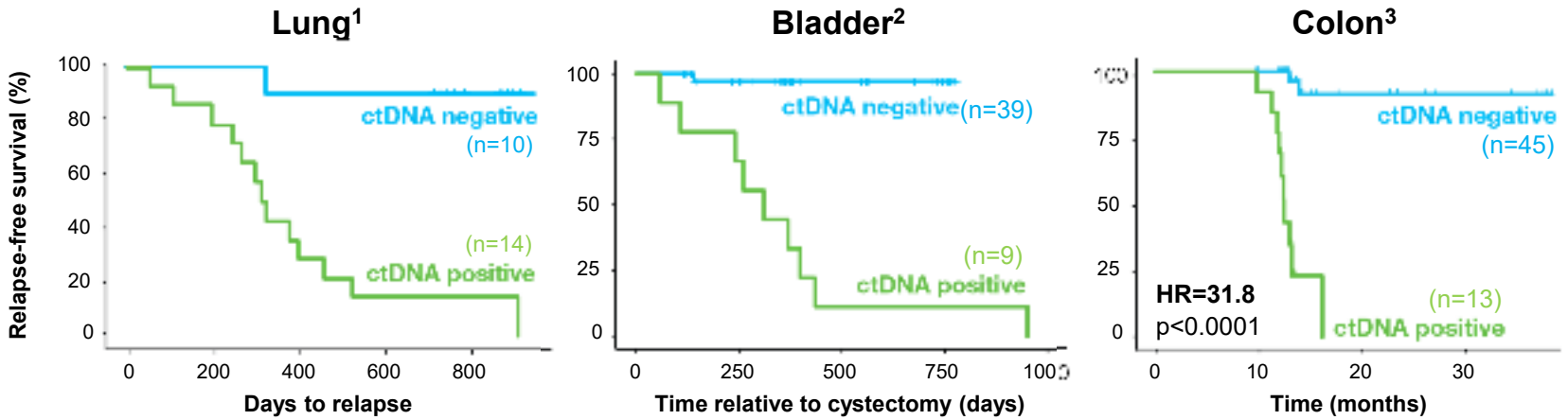
Adapted from Wan et al. Nat Rev Cancer 2017

ctDNA has substantial potential to be used throughout the patient journey



Adapted from Wan et al. Nat Rev Cancer 2017

ctDNA detection after surgery: an indication of molecular disease progression that precedes clinical relapse



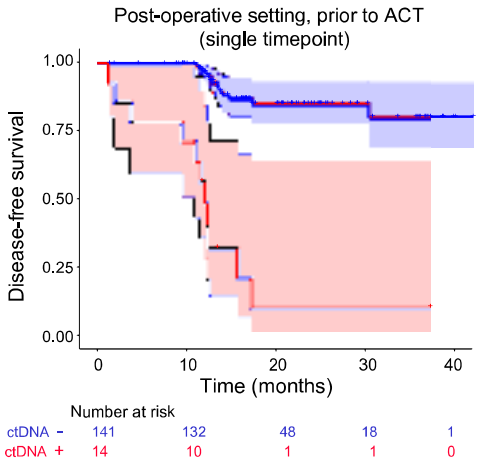
	Lung[1]	Bladder[2]	Colon[3]
Time post-surgery	• Avg lead time 4 months • PPV 100% relapse <12 months	• Avg lead time 4 months • PPV 100% relapse <9 months	• Avg lead time 7 months • PPV 100% relapse <15 months

Shortens drug development/clinical trial timelines
Avoids treating patients who do not require additional therapy

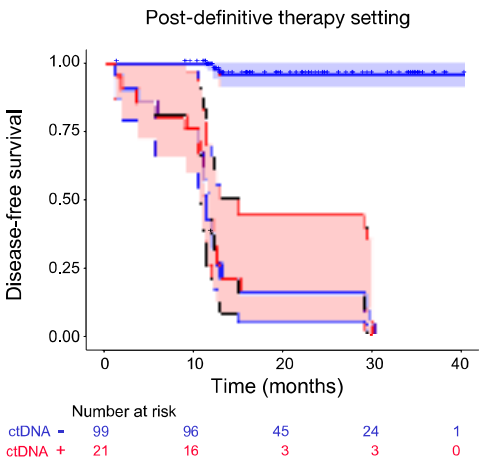
Example from CRC: using ctDNA to assess minimal residual disease after treatment

Relapse-risk stratification by ctDNA status

Post-operatively and prior to ACT, 9% (14/155) of patients showed MRD-positivity, and 78.5% (11/14) relapsed (HR=14; 95% CI: 6.1–30; p<0.001)



HR: 14; 95% CI: 6.1 - 30; p <0.001



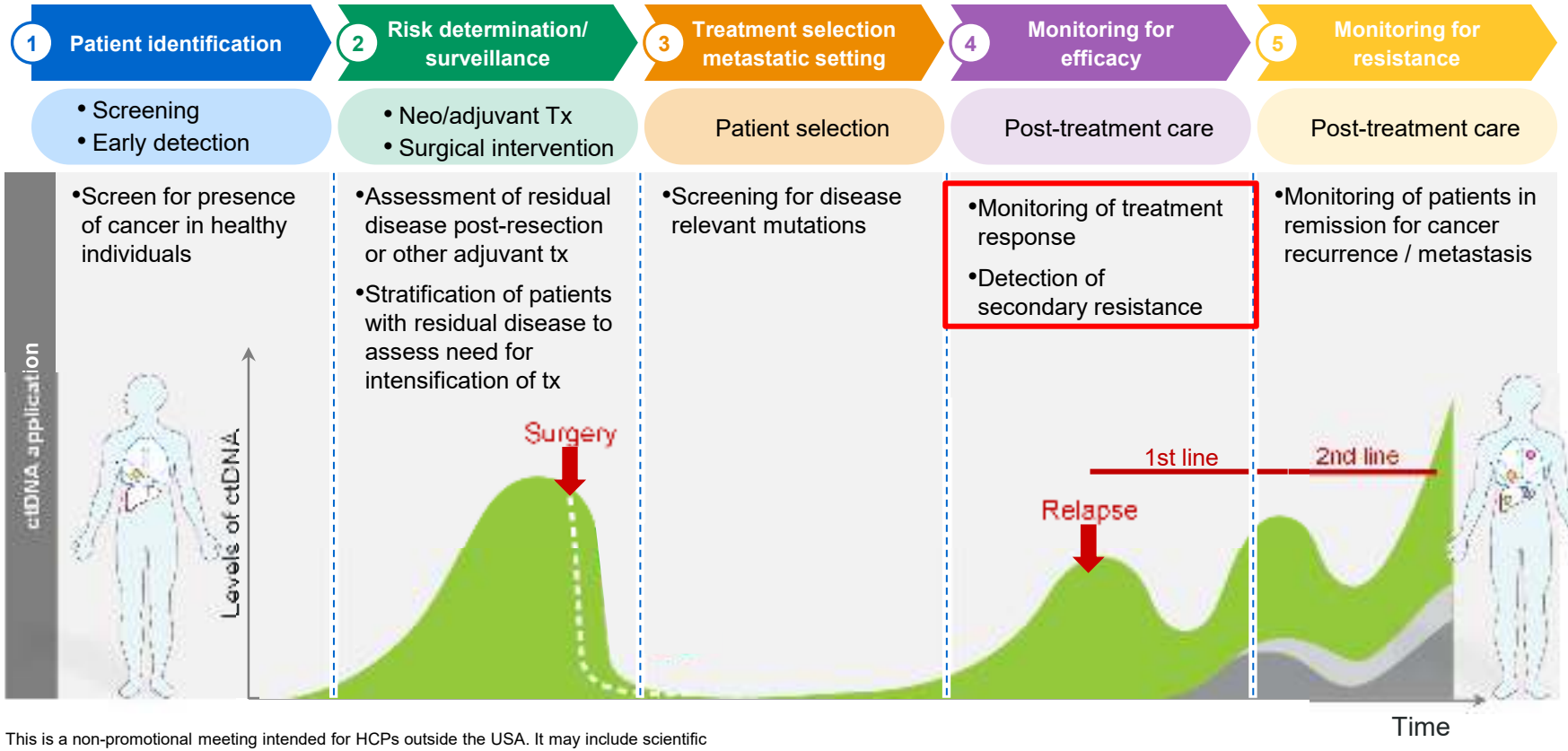
HR: 58; 95% CI: 17 - 196; p <0.001

A shift to ctDNA-positivity during longitudinal monitoring (n=120) was associated with poor clinical outcome (HR=58; 95% CI: 17–196; p<0.001)

Signatera™ bespoke, multiplex-PCR NGS assay

This is a non-promotional meeting intended for HCPs outside the USA. It may include scientific information about investigational compounds that may not be approved or valid in your jurisdiction

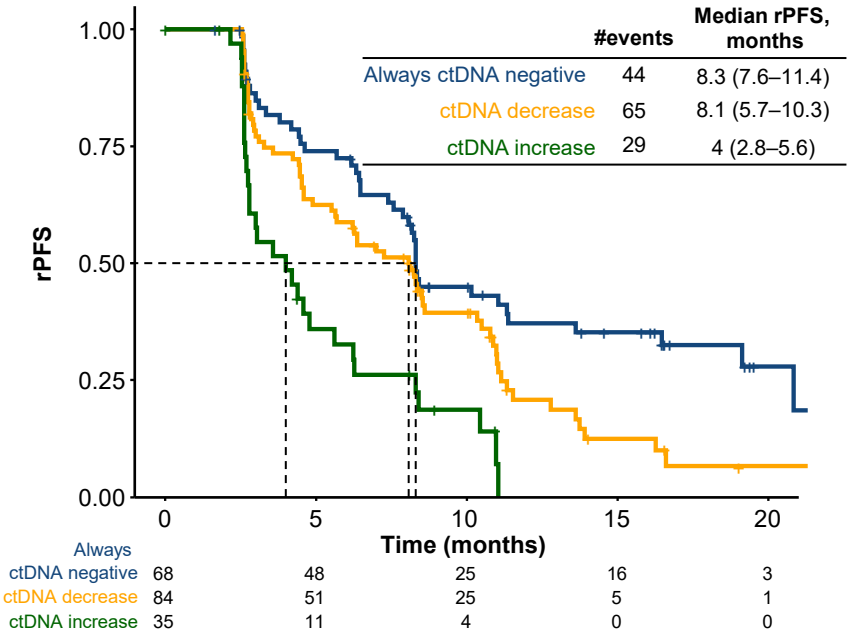
ctDNA has substantial potential to be used throughout the patient journey



Adapted from Wan et al. Nat Rev Cancer 2017

Example from mCRPC: using ctDNA to assess treatment response in the metastatic setting

A.MARTIN (randomised, phase II study of ipatasertib and abiraterone vs abiraterone alone in mCRPC after docetaxel chemotherapy)



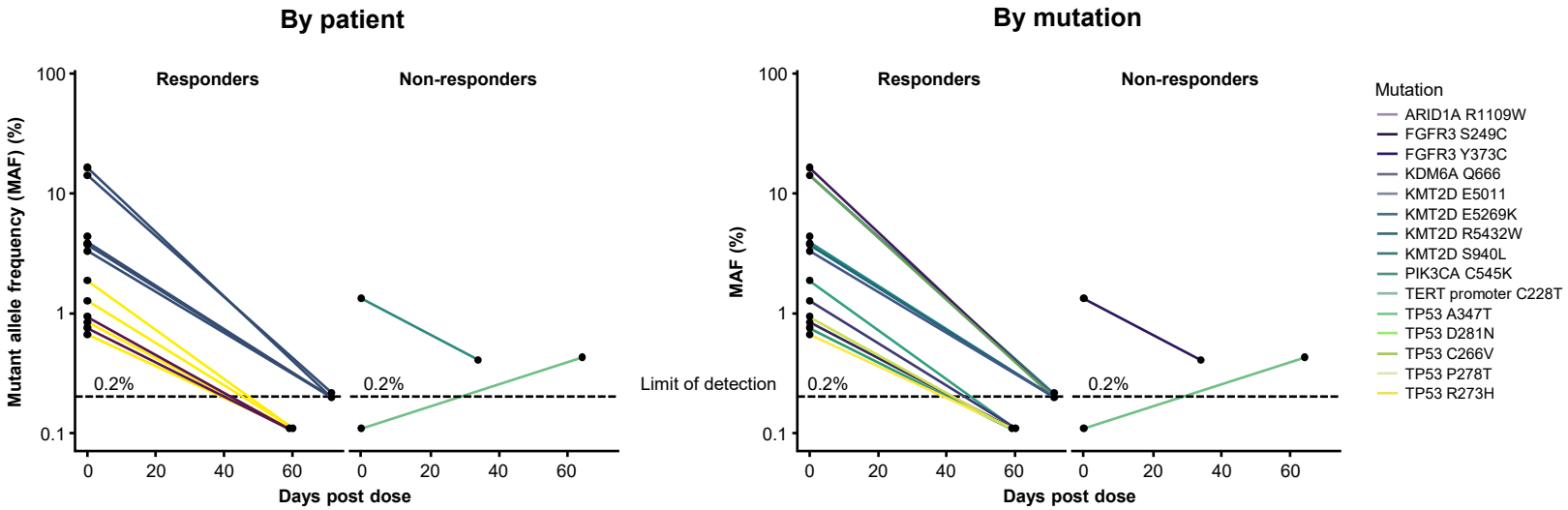
- Patients who remained ctDNA negative had the best rPFS, followed by patients experiencing a reduction in ctDNA
- Higher post-treatment ctDNA significantly correlated with worse rPFS

Comparison	HR	p value
ctDNA increase vs always ctDNA negative	2.89 (1.74–4.78)	<0.0001
ctDNA increase vs ctDNA decrease	2.16 (1.36–3.42)	0.0008
ctDNA decrease vs always ctDNA negative	1.55 (1.05–2.29)	0.0279

Example from metastatic urothelial cancer: using ctDNA to assess treatment response in the metastatic setting

BISCAY (phase Ib study of durvalumab + targeted therapies)

Durvalumab monotherapy treatment arm (Module D)



ctDNA monitoring at C3D1 indicates clearance of ctDNA in responding patients

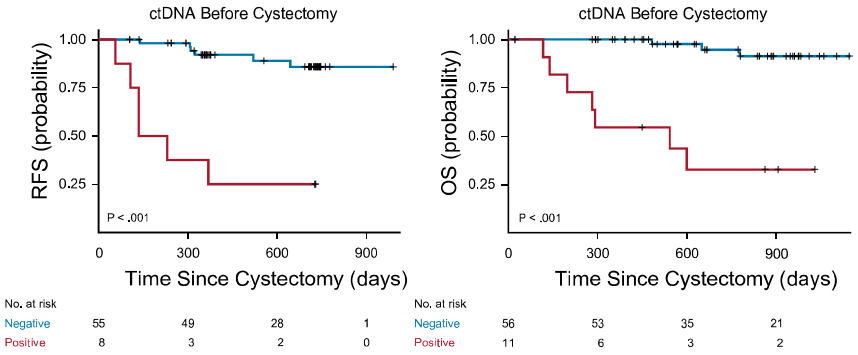
Bespoke NGS panel of 10 genes

Carroll et al. ASCO 2019

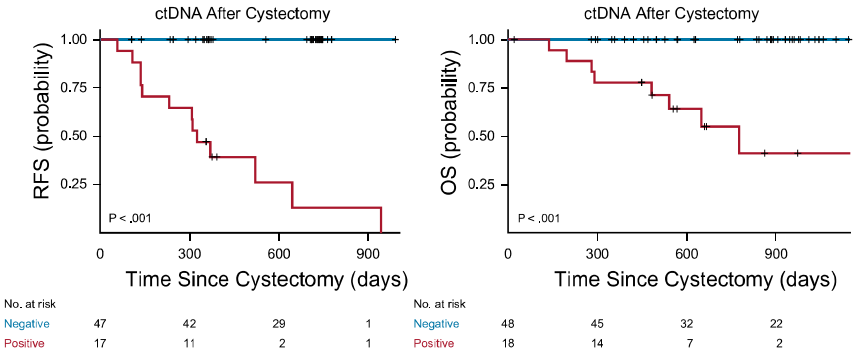
Example from MIBC: using ctDNA to assess treatment response in the early setting

Analysis of plasma samples from 68 patients with MIBC

ctDNA status after chemotherapy and before cystectomy



ctDNA status during disease surveillance after cystectomy

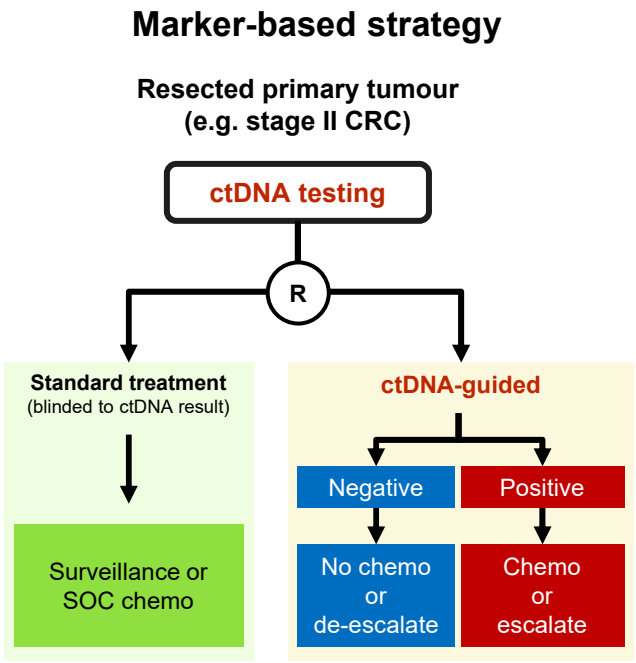


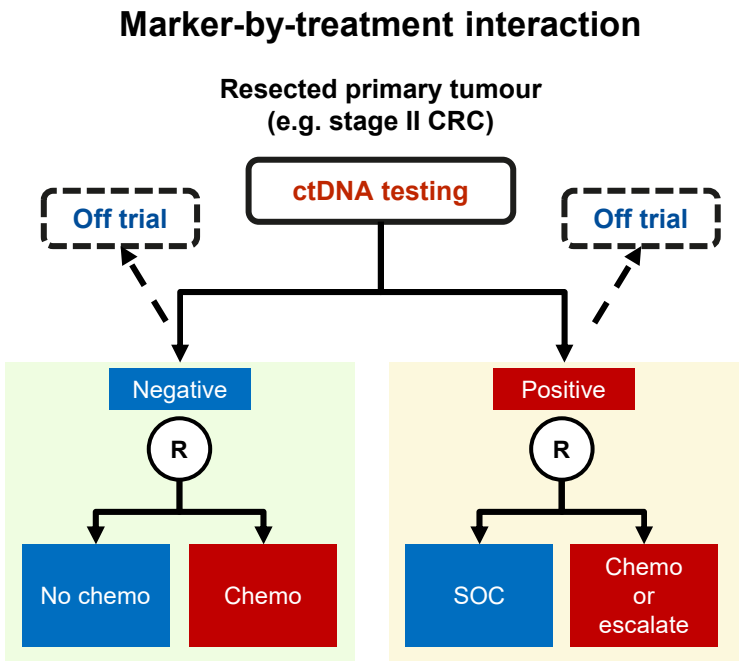
Both ctDNA status before cystectomy and ctDNA status after cystectomy were prognostic for patient outcome (RFS and OS)

NGS

Christensen et al. J Clin Oncol 2019

ctDNA is being investigated to select patients for adjuvant treatment in clinical trials





Tie et al. ESMO 2020

Example CRC: Selected ctDNA-guided randomised adjuvant trials

Country	Australia	Australia/ Canada	Australia	US/ Canada	Germany/ Austria/ Sweden	France	UK	Netherlands
Trial name (registration number)	DYNAMIC (ACTRN1261500 381583)	DYNAMIC-III (ACTRN1261700 1566325)	DYNAMIC-RECTAL (ACTRN1261700 1560381)	COBRA (NCT04068103)	CIRCULATE (NCT04089631)	PRODIGE 70 – CIRCULATE (NCT04120701)	TRACC (NCT04050345)	MEDOCC-CrEATE (NL6281/ NTR6455)
Study population	Stage II	Stage III	Rectal	Stage II (low risk)	Stage II	Stage II	Stage II/III	Stage II (low risk)
Assay	Safe-SeqS	Safe-SeqS	Safe-SeqS	Guardant LUNAR-1	Dresden NGS	ddPCR (methylation markers x 2)	In-house NGS	PGDx elio
Sample size	450	1000	408	1408	3609	1980	1621	1320
Design	SOC vs ctDNA guided	SOC vs ctDNA guided	SOC vs ctDNA guided	SOC vs ctDNA guided	ctDNA-by-treatment interaction	ctDNA-by-treatment interaction	SOC vs ctDNA guided	SOC vs ctDNA guided
Intervention	ctDNA+ (chemo) ctDNA– (no chemo)	De-escalate / escalate	ctDNA+ (chemo) ctDNA– (no chemo)	ctDNA+ (chemo) ctDNA– (no chemo)	ctDNA+ (chemo vs no chemo)	ctDNA+ (chemo vs no chemo)	De-escalate	ctDNA+ (chemo) ctDNA– (no chemo)

Tie et al. ESMO 2020

CDDF WORKSHOP

25 - 26 April 2022

HYBRID WORKSHOP

Measurable Residual Disease (MRD) and Circulating Tumour Nucleotides (ct DNA) in cancer drug development

Clinical Application of ctDNA in Bladder Cancer:

Phase 3 IMvigor010 trial

Background Phase 3 IMvigor010

- MIUC carries a substantial risk for death such that nearly 50% of patients develop recurrence within 2 years of cystectomy[1-3]
- Circulating tumor DNA (ctDNA)-positive patients represent a high-risk population in MIUC[4]
- IMvigor010, a global Phase III trial, evaluated adjuvant treatment with atezolizumab (anti–PD-L1) compared with observation in MIUC[5]
- A ctDNA exploratory analysis was included prospectively to evaluate if:
  - Plasma ctDNA is associated with worse prognosis in this data set ?
  - Atezolizumab provides DFS or OS benefit vs observation in patients with detectable ctDNA (ctDNA+) ?
  - ctDNA clearance occurs at a higher rate with atezolizumab vs observation ?

DFS, disease-free survival; MIUC, muscle-invasive UC.

1. Raghavan D, et al. *NEJM*. 1990;322:1129-38. 2. Stein JP, et al. *JCO*. 2001;19:666-75.
3. Stenzl A et al. *Eur Urol*. 2009;55:815-25 4. Christensen E, et al. *JCO*. 2019;37.
5. Hussain M, et al. ASCO 2020 [abs 5000].

Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial

*Joaquim Bellmunt, Maha Hussain, Jürgen E Gschwend, Peter Albers, Stephane Oudard, Daniel Castellano, Siamak Daneshmand, Hirayuki Nishiyama, Martin Majchrowicz, Viraj Degaonkar, Yi Shi, Sanjeev Mariathasan, Petros Grivas, Alexandra Drakaki, Peter H O'Donnell, Jonathan E Rosenberg, Daniel M Geynisman, Daniel P Petrylak, Jean Hoffman-Censits, Jens Bedke, Arash Rezazadeh Kalebasty, Yousef Zakharia, Michiel S van der Heijden, Cora N Sternberg, Nicole N Davarpanah, Thomas Powles, for the IMvigor010 Study Group**

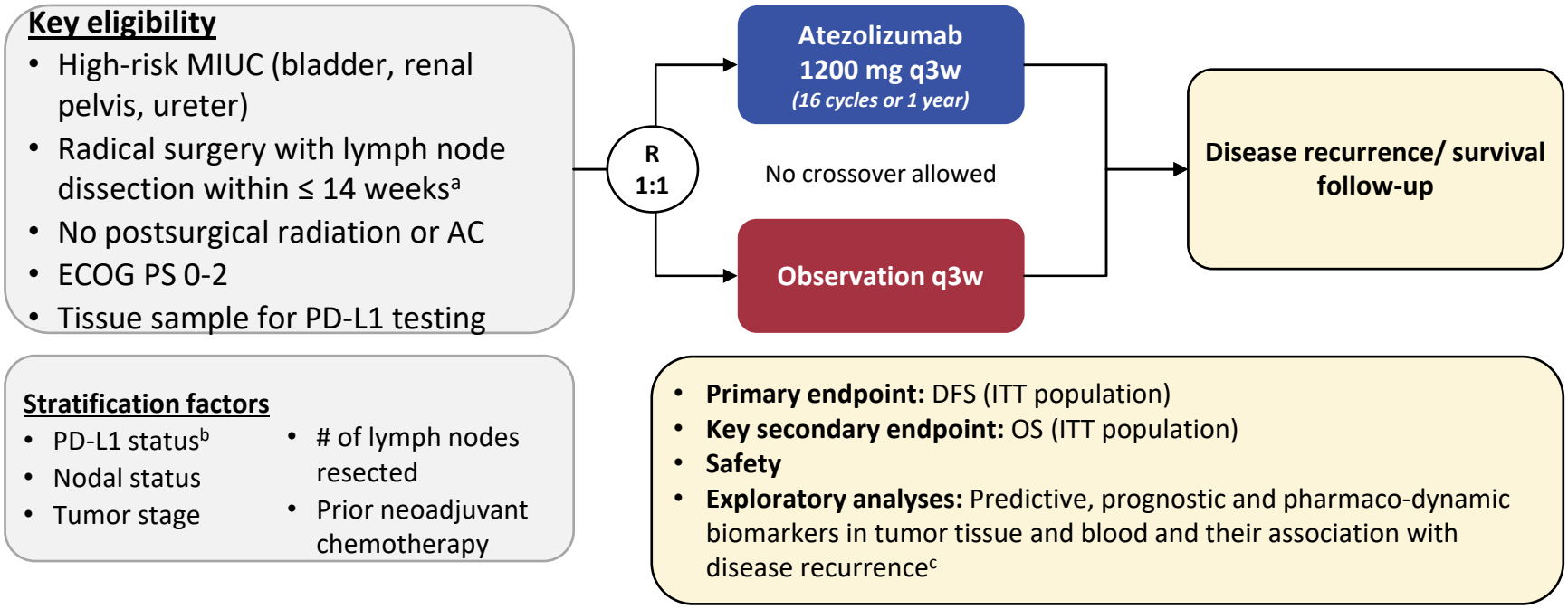
Summary

Background Despite standard curative-intent treatment with neoadjuvant cisplatin-based chemotherapy, followed by radical surgery in eligible patients, muscle-invasive urothelial carcinoma has a high recurrence rate and no level 1 evidence for adjuvant therapy. We aimed to evaluate atezolizumab as adjuvant therapy in patients with high-risk muscle-invasive urothelial carcinoma.

Lancet Oncol 2021

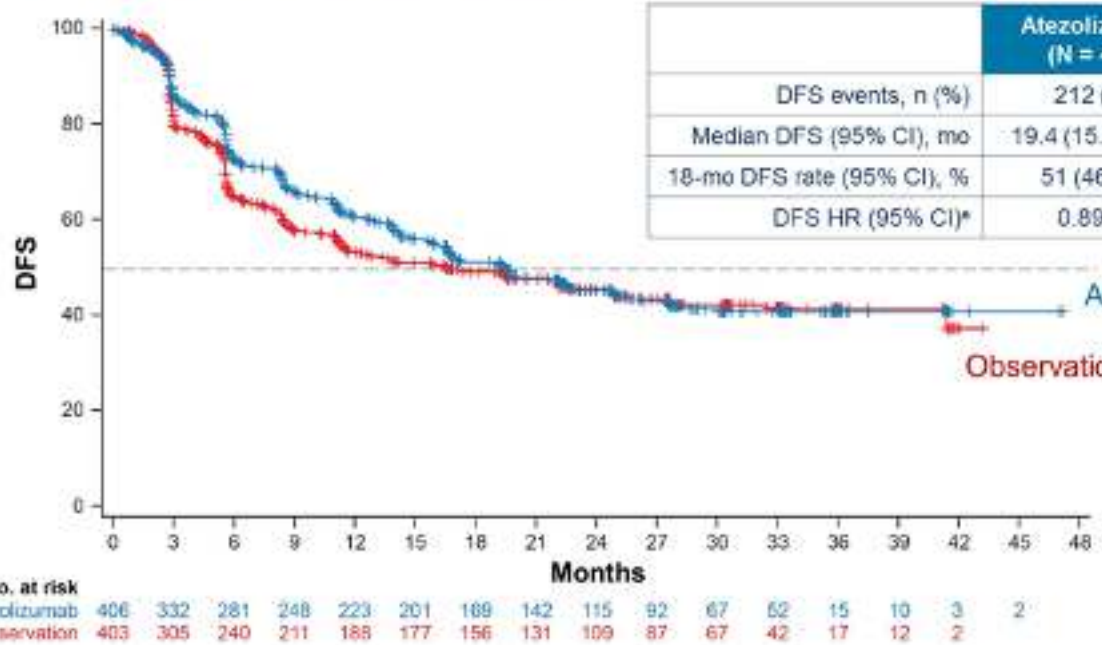
Published Online March 12, 2021 https://doi.org/10.1016/S1470-2045(21)00004-8

Phase 3 IMvigor010 adjuvant study in MIUC



- IMvigor010 did not meet its primary endpoint of DFS in the ITT population[1]

DFS in ITT Population

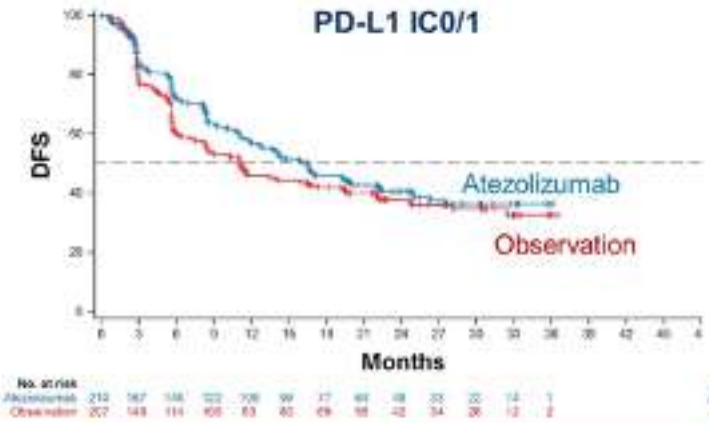


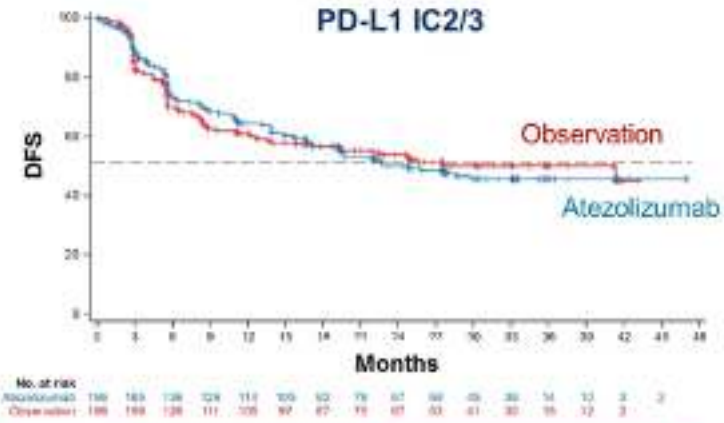
	Atezolizumab (N = 406)	Observation (N = 403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS (95% CI), mo	19.4 (15.9, 24.8)	16.6 (11.2, 24.8)
18-mo DFS rate (95% CI), %	51 (46, 56)	49 (44, 54)
DFS HR (95% CI)[a]	0.89 (0.74, 1.08); *P* = 0.2446[b]	

Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. [a]Stratified by post-resection tumor stage, nodal status and PD-L1 status. [b]2-sided.

Presented By Maha Hussain at ASCO 2020

DFS by PD-L1 Status





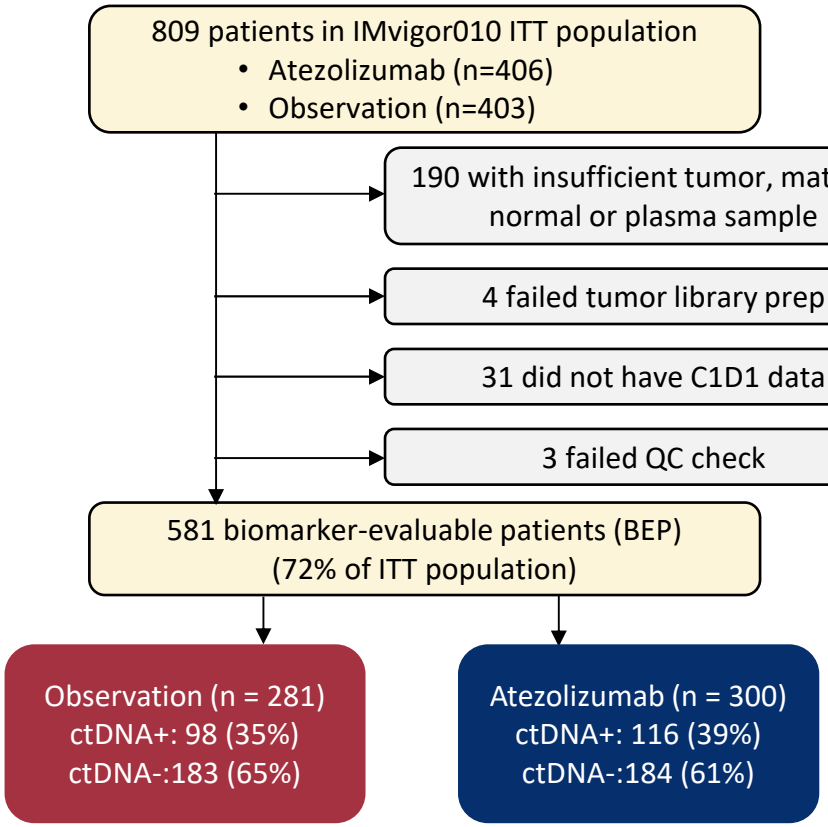
	Atezolizumab (n = 210)	Observation (n = 207)
DFS events, n (%)	118 (56)	120 (58)
HR (95% CI)[a]	0.81 (0.63, 1.05)	

Atezolizumab (n = 196)	Observation (n = 196)
94 (48)	88 (45)
1.01 (0.75, 1.35)	

Data cutoff: November 30, 2019. IC2/3, PD-L1–expressing IC on ≥ 5% of tumor area (VENTANA SP142 assay); IC0/1, < 5%. [a]Stratified by tumor stage and nodal status.

Presented By Maha Hussain at ASCO 2020

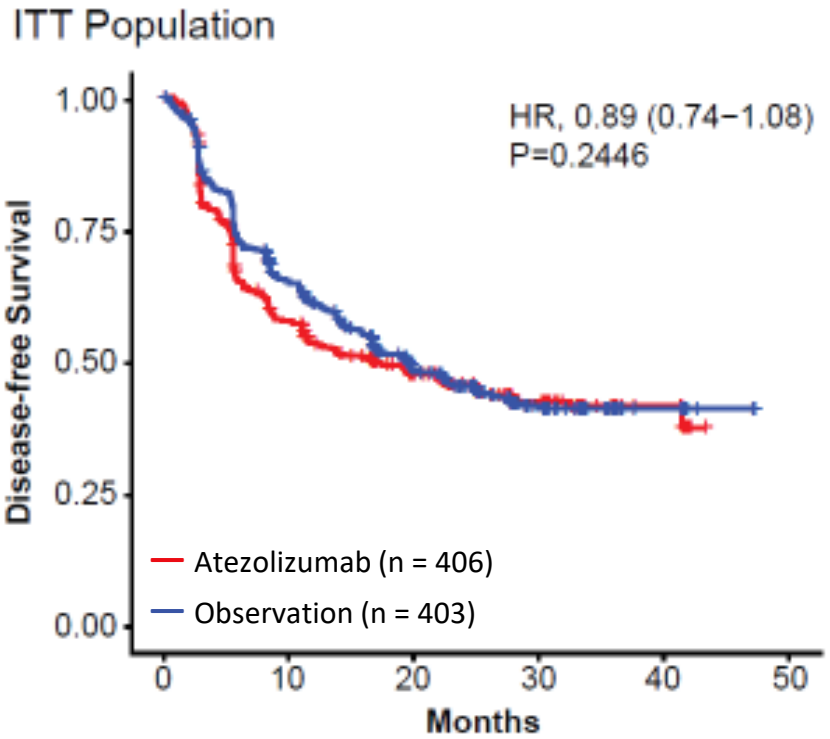
IMvigor010 ctDNA-evaluable patients were representative of the ITT population

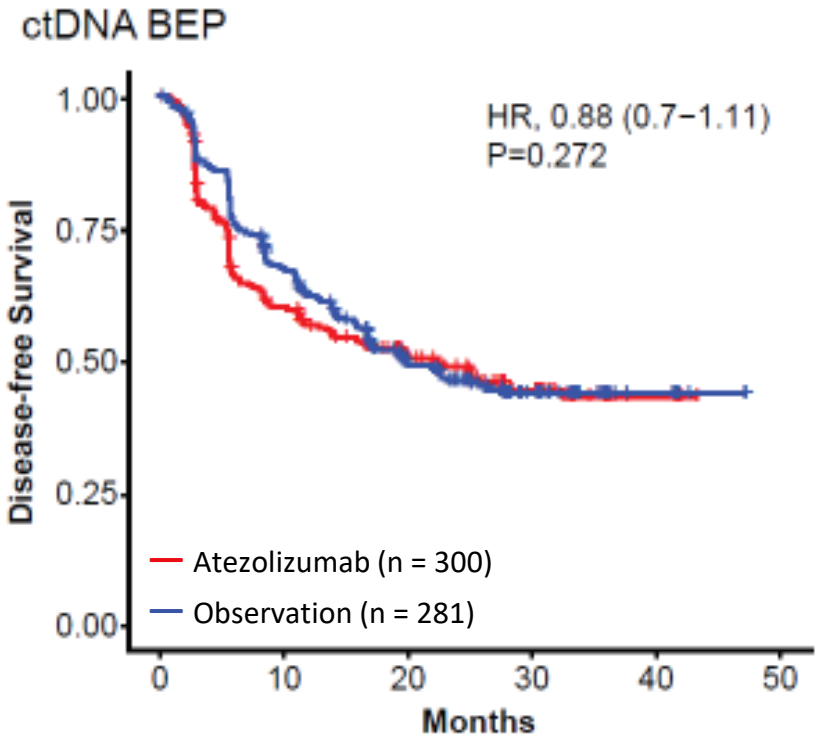


Data cutoff: November 30, 2019.

- Baseline clinical features were balanced between the ITT and BEP and between the BEP arms
- Baseline ctDNA status (cycle 1, day 1) was similar between arms

DFS was similar between the ITT and BEP

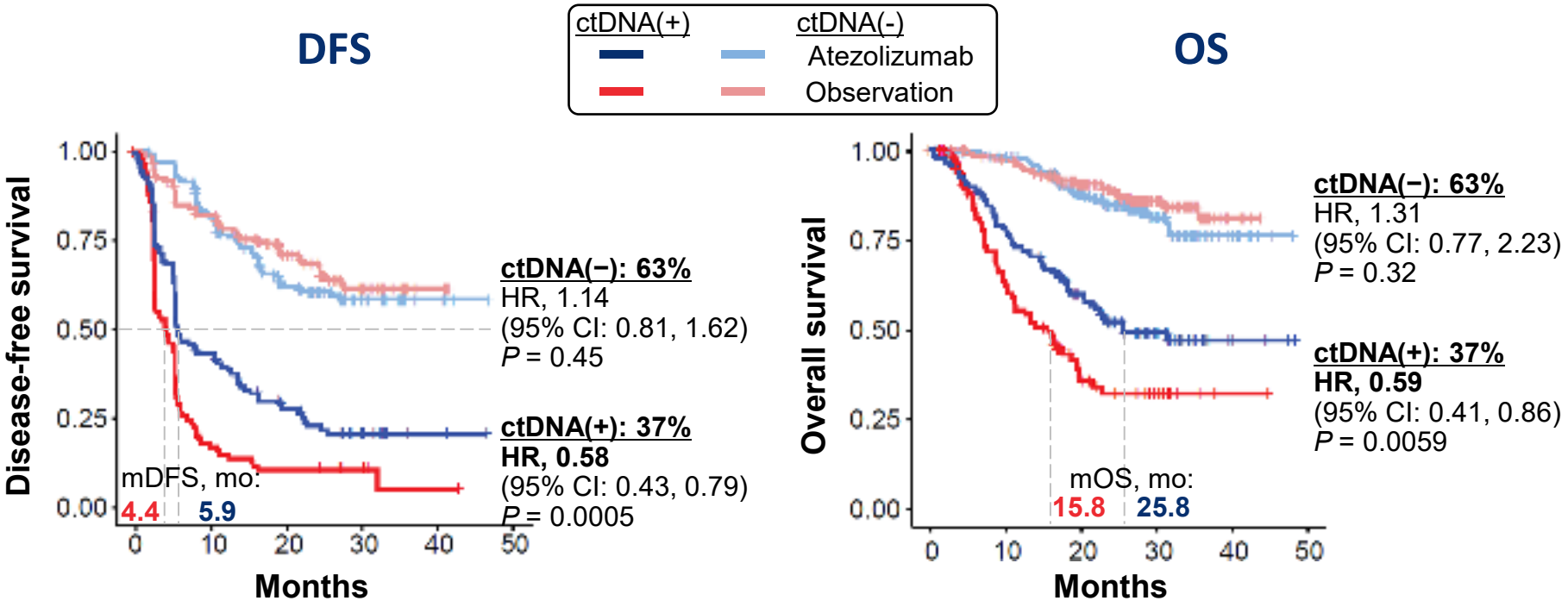




- OS data were similar

HRs are stratified by nodal status, PD-L1 status and tumor stage.
P values are for descriptive purposes only.

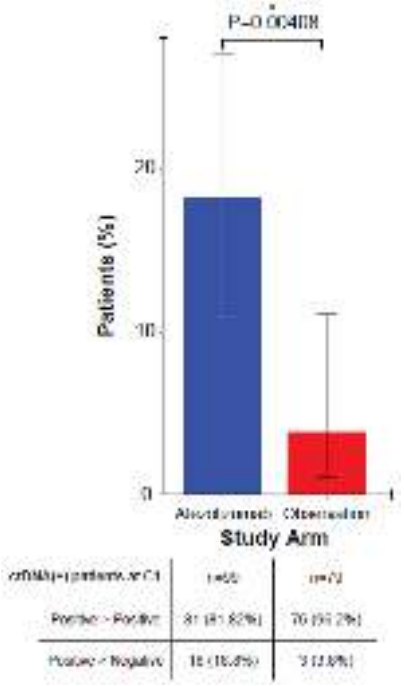
ctDNA(+) patients had improved DFS and OS with atezolizumab vs observation



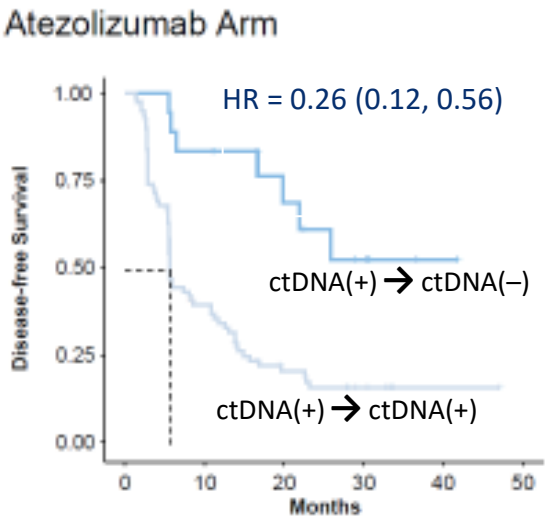
- IMvigor010 confirmed the prognostic value of ctDNA status

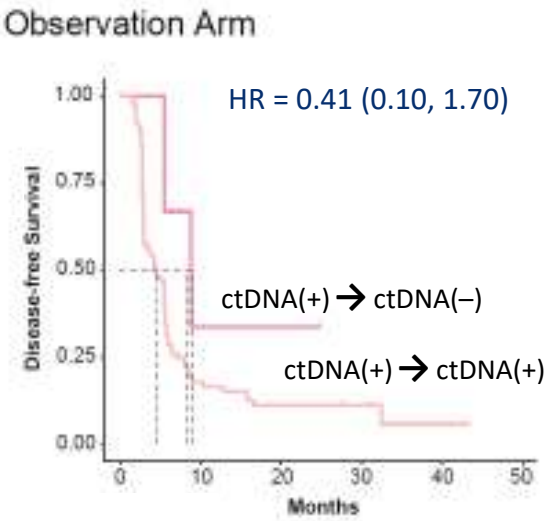
Changes in ctDNA status over time were associated with treatment arm and survival

ctDNA clearance rates (cycle 1 to cycle 3)



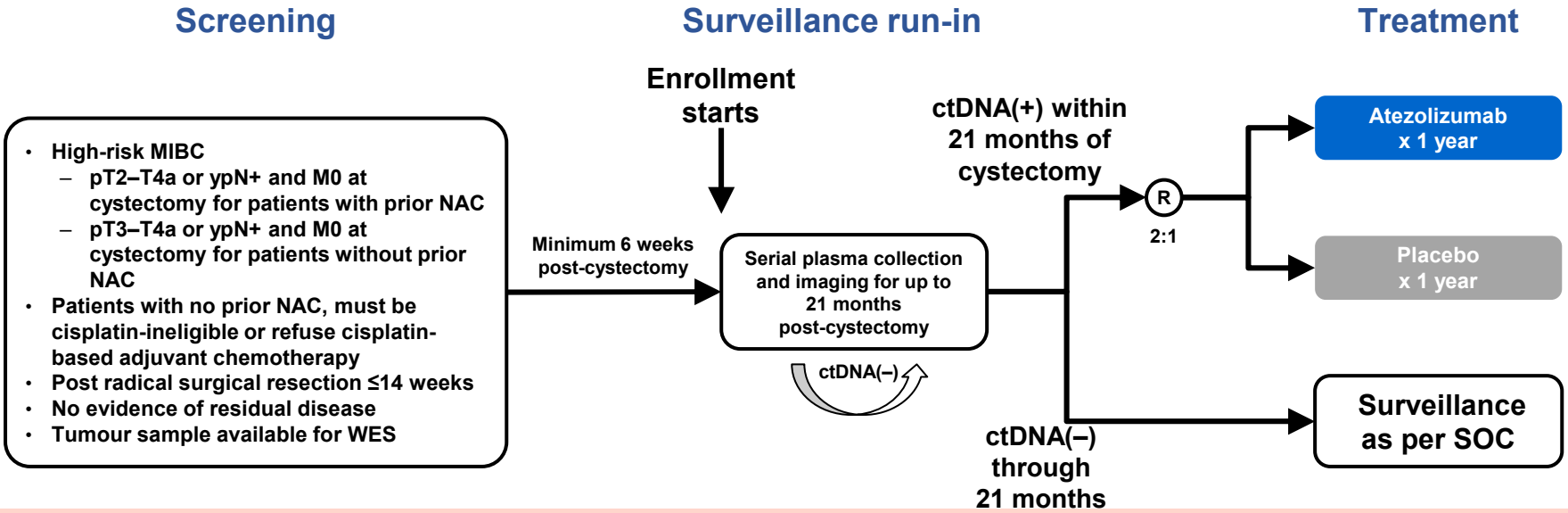
DFS





- OS results were similar

IMvigor011 study design



Stratification factors

- Nodal status (positive vs negative)
- Tumour stage after cystectomy (≤pT2 vs pT3/pT4)
- PD-L1 IHC status (IHC score of IC0/1 vs IC2/3)
- Time from cystectomy to first ctDNA(+) sample (≤20 weeks vs >20 weeks)

NCT04660344

Conclusions IMvigor010

- In IMvigor010, post-surgical ctDNA positivity was associated with a high-risk of recurrence and death
- ctDNA positivity identified patients with MIUC likely to derive DFS and OS improvement from adjuvant atezolizumab
- TMB status was also associated with improved outcomes with adjuvant atezolizumab in the ctDNA+ population
- This work warrants validation in the prospective study IMvigor011
- If confirmed, the results may change our understanding of post-surgical cancer care

Article

ctDNA guiding adjuvant immunotherapy in urothelial carcinoma

https://doi.org/10.1038/s41586-021-03642-9

Received: 8 December 2020

Accepted: 13 May 2021

Published online: 16 June 2021

Check for updates

Thomas Powles[1,18], Zoe June Assaf[2,18], Nicole Davarpanah[2], Romain Banchereau[2], Bernadett E. Szabados[3], Kobe C. Yuen[2], Petros Grivas[4,5,6], Maha Hussain[7], Stephane Oudard[8], Jürgen E. Gschwend[9], Peter Albers[10], Daniel Castellano[11], Hiroyuki Nishiyama[12], Siamak Daneshmand[13], Shruti Sharma[14], Bernhard G. Zimmermann[14], Himanshu Sethi[14], Alexey Aleshin[14], Maurizio Perdicchio[15], Jingbin Zhang[16], David S. Shames[2], Viraj Degaonkar[2], Xiaodong Shen[2], Corey Carter[2], Carlos Bais[2], Joaquim Bellmunt[17,18] & Sanjeev Mariathasan[2,18]

These findings demonstrate the use of ctDNA as a marker for MRD and response to atezolizumab, and link ctDNA to the biology of the tumours. These results may change our understanding of post-surgical cancer care. If validated in this setting, as well as across tumour types, the findings will also change clinical practice.

Summary

- ctDNA has many opportunities to inform our clinical practice
  - Early diagnosis
  - Track minimal residual disease
  - Monitor response and resistance
- Utility of ctDNA has been demonstrated across multiple tumour types and with many different treatment strategies including immunotherapy
- Use of ctDNA as a biomarker may be particularly well suited to monitor early stage disease and may help avoid over treatment of patients (help guide adjuvant therapy)
- ctDNA is being used to select patients in clinical trials