CDDF WORKSHOP

25 - 26 April 2022

HYBRID WORKSHOP

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

ctDNA and MRD, an academic point of view

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EORTC

Disclaimer

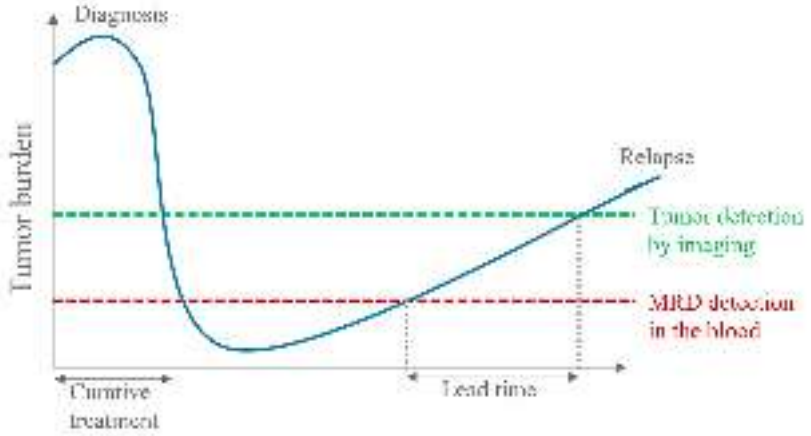
- No conflict of interest

Circulating biomarkers in the clinic

Liquid biomarkers in the clinic: successes and challenges

MRD: Concept develop in liquid tumor

How to translate it to solid tumors?
What circulating biomarkers to use?



Example of prostate cancer and PSA: routine use of biochemical recurrence (BCR) to screen patients, and monitor relapse after radical prostatectomy or RT+ hormono-therapy

Liquid biomarkers in the clinic: successes and challenges

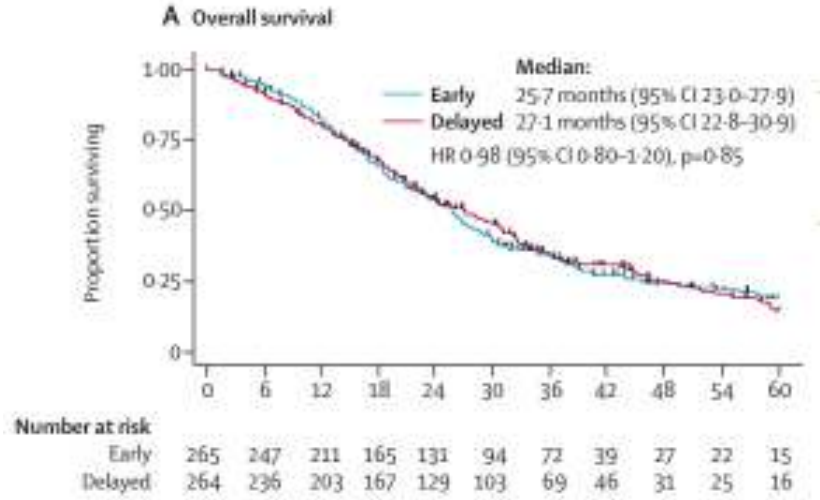
Example of ovarian cancer and CA125

Table 1. The ability of serum CA 125 to predict early progression in 124 patients by using only one rising value from ⩽40 U/ml to ⩾60 U/ml, and from ⩽40 U/ml to ⩾100 U/ml.

	1 value ⩾60 U/ml	1 value ⩾100 U/ml
True positive (TP)	58 (+5*) = 73	60 (+4*) = 64
False positive (FP)	7 (−5*) = 2	4 (−4*) = 0
True negative (TN)	44	46
False negative (FN)	5	14
Sensitivity (SE)	93.2%–93.6%	81.1%–82.1%
Specificity (SP)	86.3%–95.7%)	92.0%–100%
Positive predictive value (PPV)	90.7%–97.3%)	93.8%–100%
Negative predictive value (NPV)	89.8%	76.7%
Median lead-time* (range)	−63 days (−350 to +77)	−31.5 days (−245 to +105)

Rustin et al., Annals of Oncol, 1996

Randomisation when CA125 concentration increased to twice the site upper limit of normal

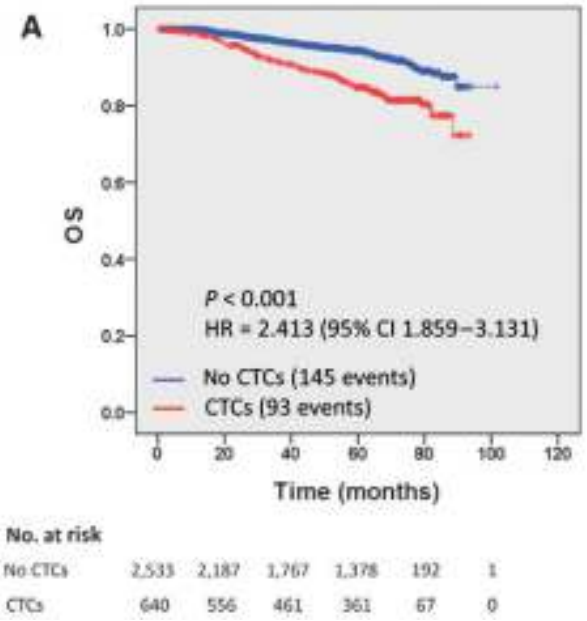


Rustin et al., Lancet, 2010

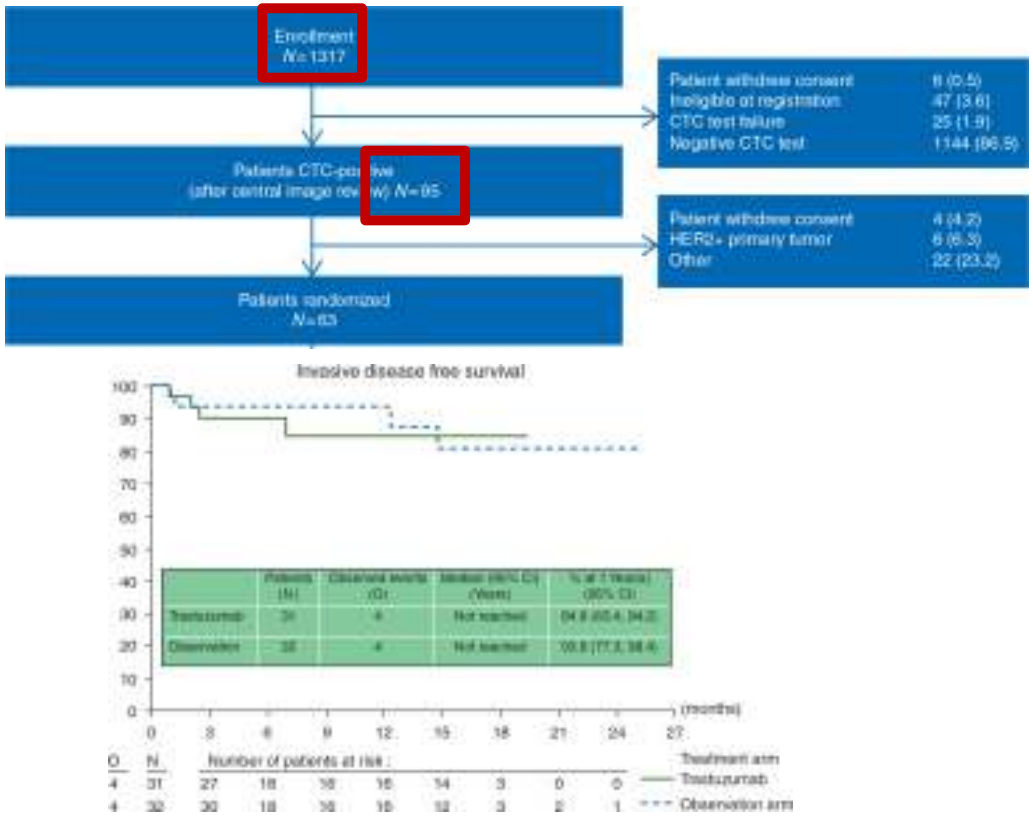
Change in CA125 is not predictive of OS

Issue with lead time?

Liquid biomarkers in the clinic: successes and challenges



Janni et al., CCR, 2016



Ignatiadis et al., Annals on Oncol 2018

Considerations for implementing ctDNA in clinical care

ctDNA and clinical utility

Impact of initiation of treatment and baseline tumor size?

IFCT-0302: randomized trial on follow-up of resected NSCLC patients (Westeel et al., ESMO, 2017)

Months	Min	Max
6	CXR	Chest CT
12	CXR	Chest CT
18	CXR	Chest CT
24	CXR	Chest CT
30		
36	CXR	Chest CT
42		
48	CXR	Chest CT
54		
60	CXR	Chest CT

Minimal follow-up (Min):

- History + physical examination
- Chest X ray (CXR)
- Only if symptoms or abnormal CXR: CT scan allowed

→ Detect a mass of 15 mm

Maximal follow-up (Max):

- History + physical examination
- Chest X ray
- **CT scan + contrast** (Thorax + upper abdomen)
- Fiberoptic bronchoscopy (mandatory for squamous + large cell carcinomas)

Stratification:

- **center**
- **stage**
- **histology**
- **perioperative treatments**

→ Detect a mass of 3 mm

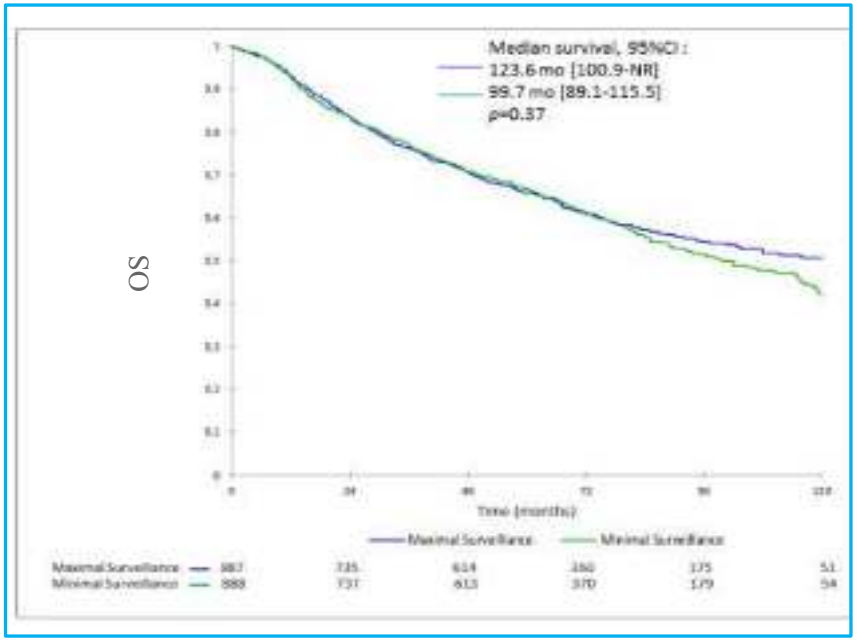
Impact of initiation of treatment and baseline tumor size?

IFCT-0302: randomized trial on follow-up of resected NSCLC patients (early stage)

Treatment: chemotherapy

Survival rate (95% CI)	3 years	5 years	8 years
Min	77.3% (74.5 – 80%)	66.7% (63.6 – 69.9%)	51.7% (47.8 – 55.5%)
Max	76.1% (73.3 – 78.9%)	65.8% (62.6 – 68.9%)	54.6 % (50.9 – 58.3%)

- HR_{Max} = 0.94 [0.81-1.08]
- HR_{Max} adjusted = 0.95 [0.82-1.09]



Westeel et al., ESMO, 2017

No benefit from early chemotherapy treatment start on OS

Impact of initiation of treatment and baseline tumor size?

IO efficacy and tumor burden evaluated through RECIST target size (metastatic patients).

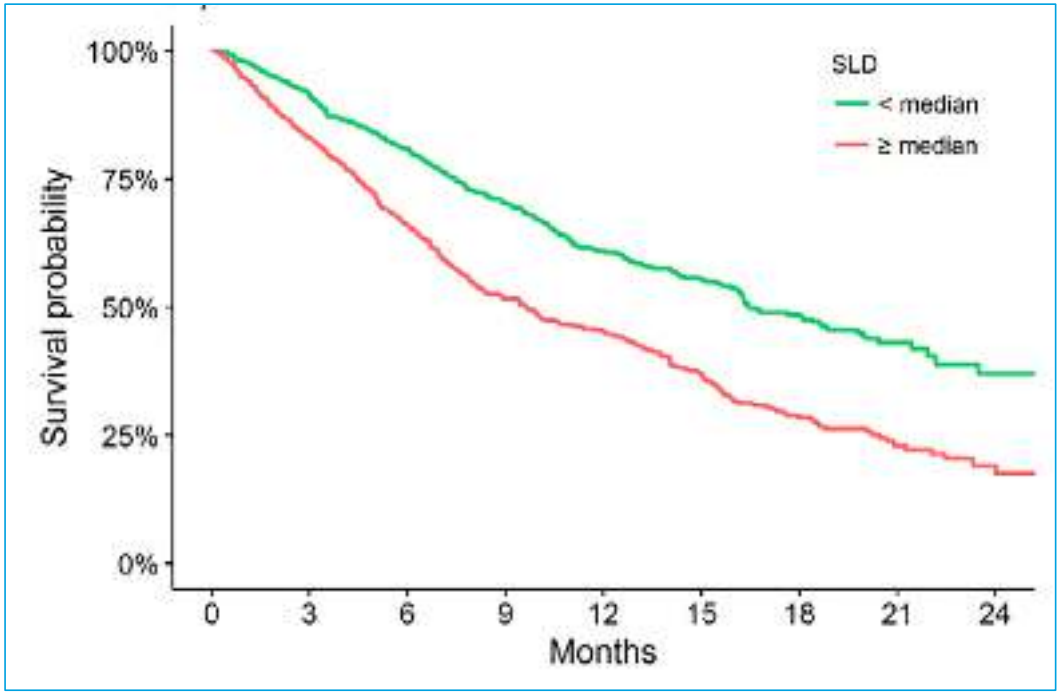
Meta-analysis from

- OAK (NCT02008227, July 7, 2016 data cutoff),
- POPLAR (NCT01903993, May 8, 2015 data cutoff),
- BIRCH (NCT02031458, May 28, 2015 data cutoff)
- FIR (NCT01846416, January 7, 2015 data cutoff).

All analyses were based upon patients with NSCLC who received atezolizumab treatment.

N=1461 pts

Baseline SLD is an independent predictor of survival outcomes



SLD = sum of longest diameters of target lesions.

Hopkins Semin Oncol 2019

Considerations for implementing ctDNA in clinical care

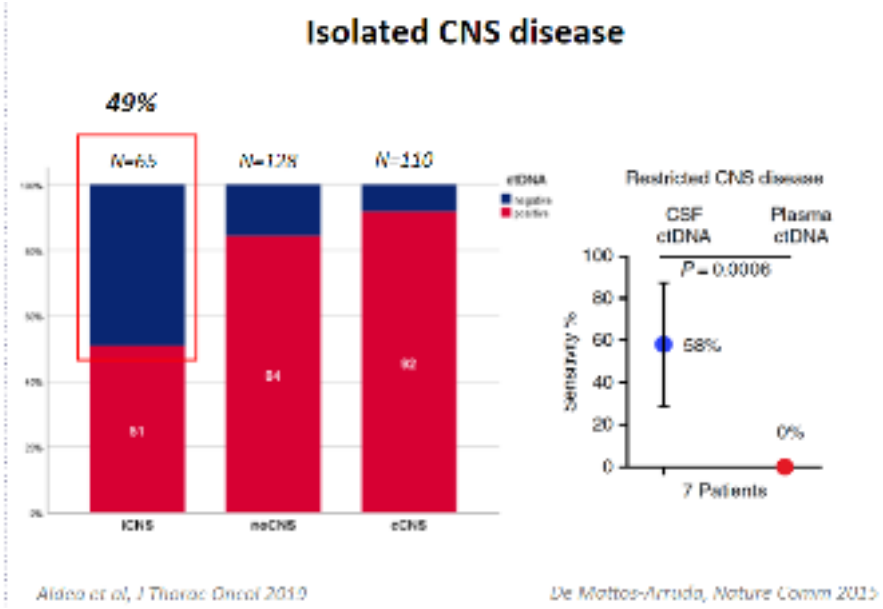
Pattern of relapse

Patterns of relapse and limit of ctDNA assays

Would ctDNA bring the same value in detecting relapse in different cancers?

- NSCLC: around 50% risk of relapse after radical treatment (IMpower-31)
  - **40%** local relapse
  - **40%** distant metastasis
  - 20% both
- CRC: 38.1% risk of relapse after surgery (at 27.6 months, Mejri et al., Clin Trans Oncol, 2017)
  - 23.8% local relapse
  - **69.8%** distant metastasis
  - 6.4% both
- Locally advanced HNSCC: around 50% risk of relapse after radical treatment
  - **40%** local relapse
  - **60%** local relapse and distant metastasis

What about brain metastasis?

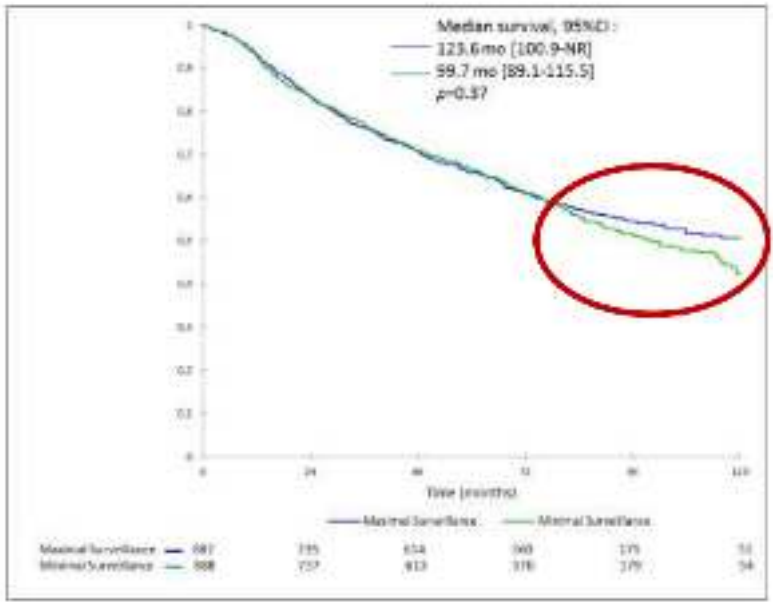


Aldea et al, J Thorac Oncol 2019

De Mattos-Arruda, Nature Comm 2020

Limited detection rate for patients with brain metastasis

The issue of second primary malignancies



Westeel et al., ESMO, 2017

After 2 yrs: benefits from CT scan for early detection of second primary malignancies

Personalized ctDNA assays: efficacy after 2 yrs in lung cancer?

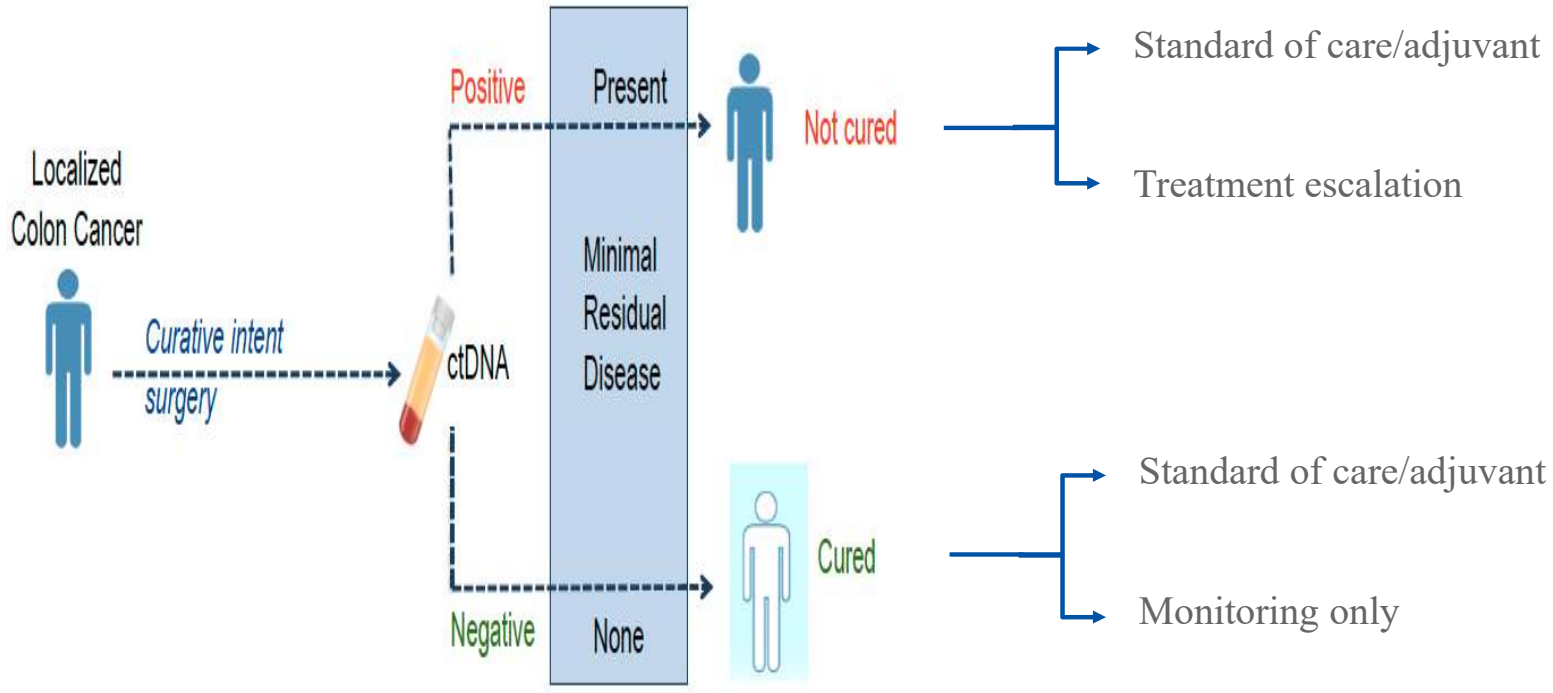
Sensitivity regarding detection of new primary malignancies?

Considerations for implementing ctDNA in clinical care

ctDNA for treatment escalation/de-escalation

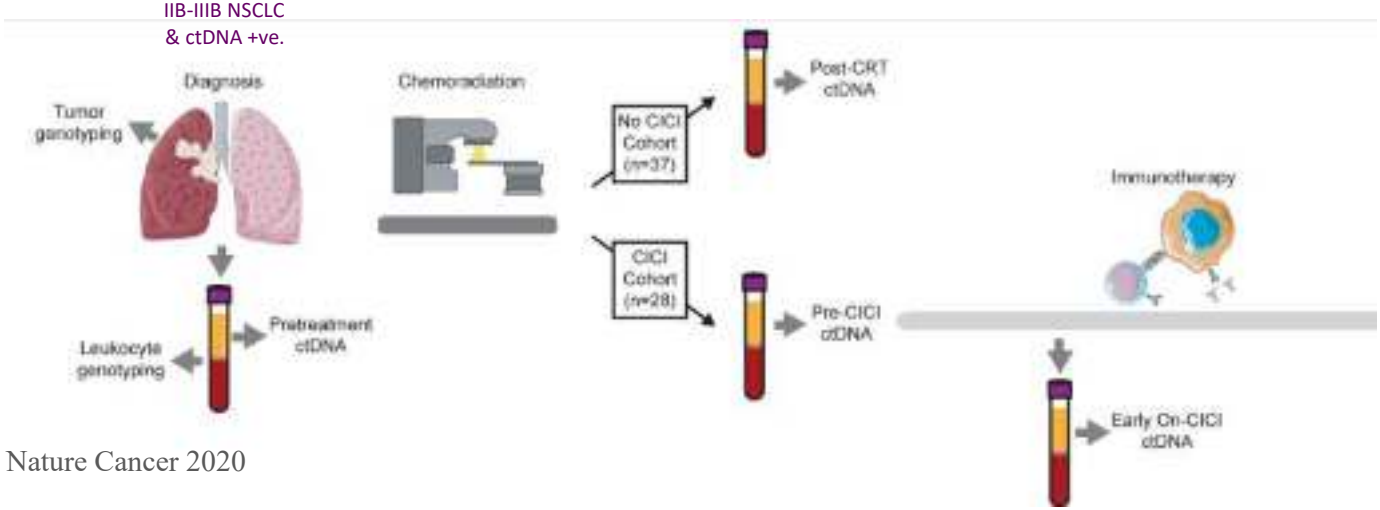
ctDNA positivity to select patients for adjuvant therapy?

- Design currently proposed for several trials (mainly CRC cohorts):

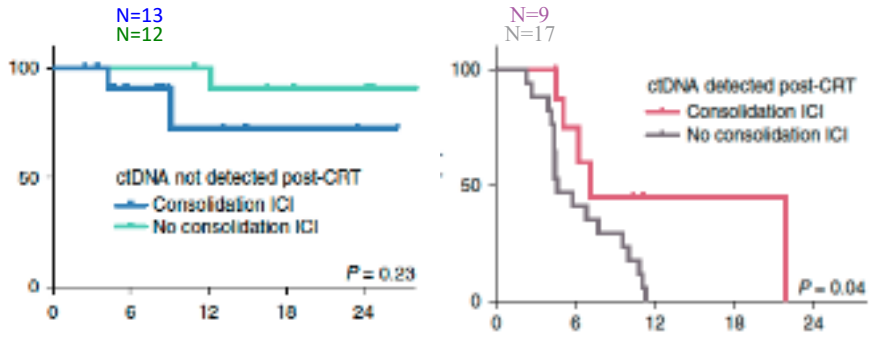


ctDNA positivity to select patients for adjuvant therapy?

IIB-IIIB NSCLC
& ctDNA +ve.

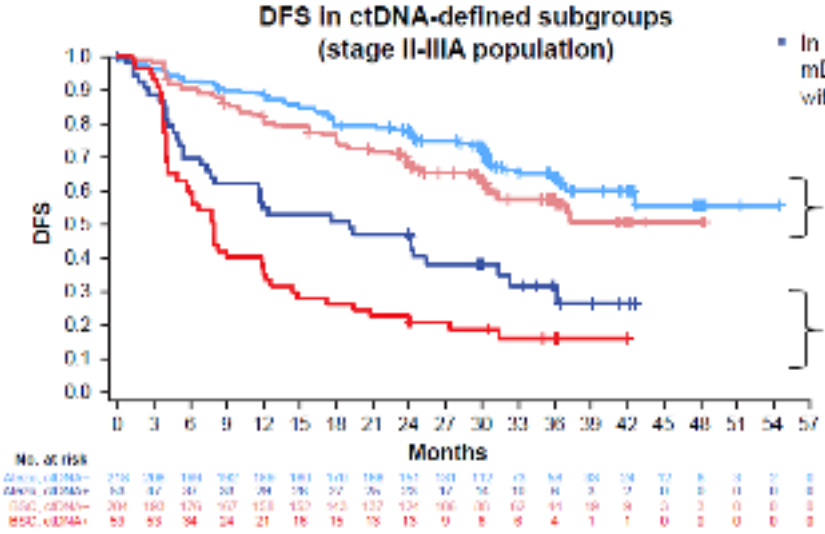


Moding – Nature Cancer 2020



Undetectable ctDNA post-CTRT good prognosis regardless ICI
Clear benefit for ctDNA positive population from ICI maintenance
Limited sample size

ctDNA as a stratification factor – IMpower10 trial



- In all ctDNA-evaluable stage II-IIIA patients, mDFS was NR (atezo) vs 31.4 months (BSC), with an HR of 0.69 (95% CI: 0.53, 0.89)

ctDNA–	Atezo (n=218)	BSC (n=204)
mDFS, mo	NR	NR
HR (95% CI)	0.72 (0.52, 1.00)	

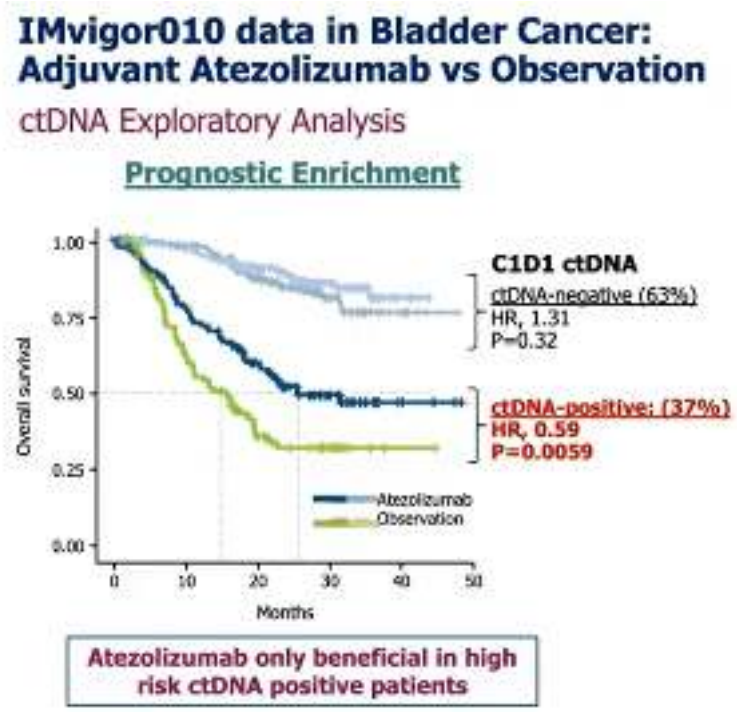
ctDNA+	Atezo (n=53)	BSC (n=59)
mDFS, mo	18.1	7.9
HR (95% CI)	0.61 (0.39, 0.94)	

Clinical cutoff: 21 January 2021. Unstratified HRs are shown.

Subgroup analysis:

- Impact on ctDNA+ population (HR=0.61)
- But also effect on ctDNA- population (HR=0.72)

ctDNA as a stratification factor – IMvigor010 trial



ESMO-IO, Dec 2020; Powles et al. Nature, 2021.

Subgroup analysis:

- **Impact on ctDNA+ population (HR=0.59)**
- **No effect on ctDNA- population (HR=1.31)**

Single timepoint vs longitunal monitoring of ctDNA

- Monitoring ctDNA instead of a single timepoint?

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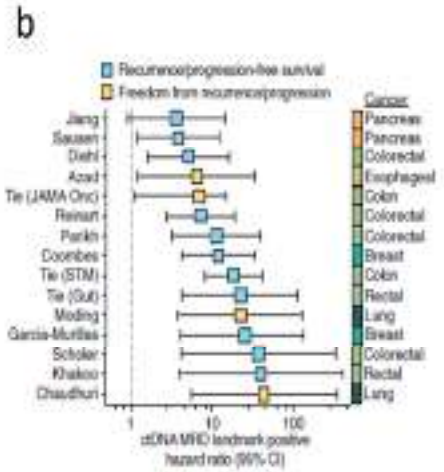
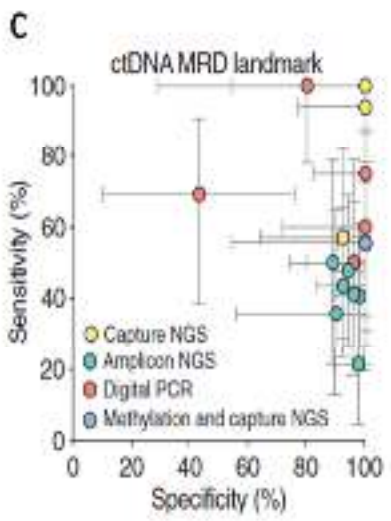
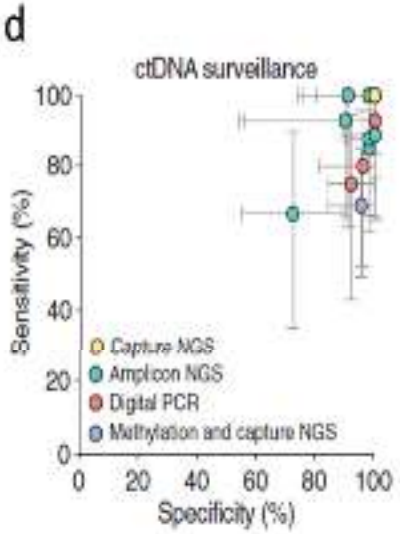
Cancer	Reference	# Patients	Analysis Landmark	Analysis Surveillance
Lung	Peng (111)	48	Yes	Yes
Lung	Chaudhuri (62)	37	Yes	Yes
Lung	Abbosh (31)	24	Yes	Yes
Lung	Moding (90)	12	Yes	No
Breast	Garcia-murillas (113)	101	No	Yes
Breast	Coombes (34)	43	Yes	Yes
Breast	Garcia-murillas (27)	43	Yes	Yes
Breast	Olsson (112)	20	No	Yes
Colon	Tie (91)	178	Yes	Yes
Rectal	Tie (89)	159	Yes	No
Colorectal	Reinert (36)	94	Yes	Yes
Colon	Tie (92)	68	Yes	No
Colorectal	Parkin (52)	72	Yes	Yes
Colon	Wang (114)	40	No	Yes
Colorectal	Schøler (28)	26	Yes	Yes
Rectal	Khakoo (109)	33	Yes	No
Colorectal	Diehl (107)	20	Yes	No
Esophageal	Azad (69)	20	Yes	No
Pancreas	Jiang (110)	27	Yes	No
Pancreas	Sausen (108)	20	Yes	No
Bladder	Christensen (36)	99	Yes	Yes
	Total	1187	18	19







Moding et al., Cancer Discovery, 2021

- Entry in clinical trial upon ctDNA positivity?

Considerations for implementing ctDNA in clinical care

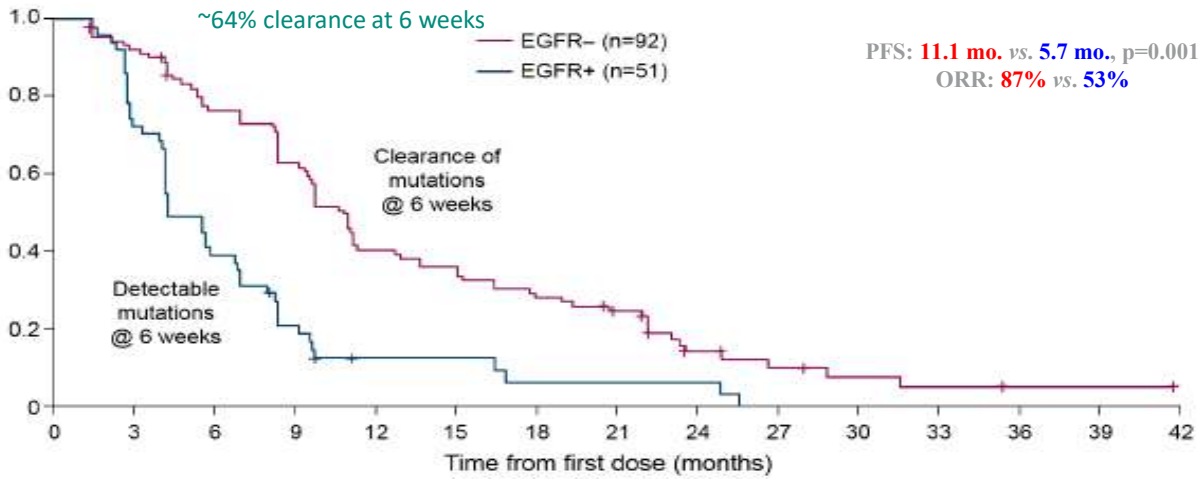
ctDNA to monitor treatment efficacy/early endpoint

ctDNA clearance as an early endpoint

Monitoring of response or detecting early resistance to TKI

AURA

Osimertinib in NSCLC patients progressing on TKI



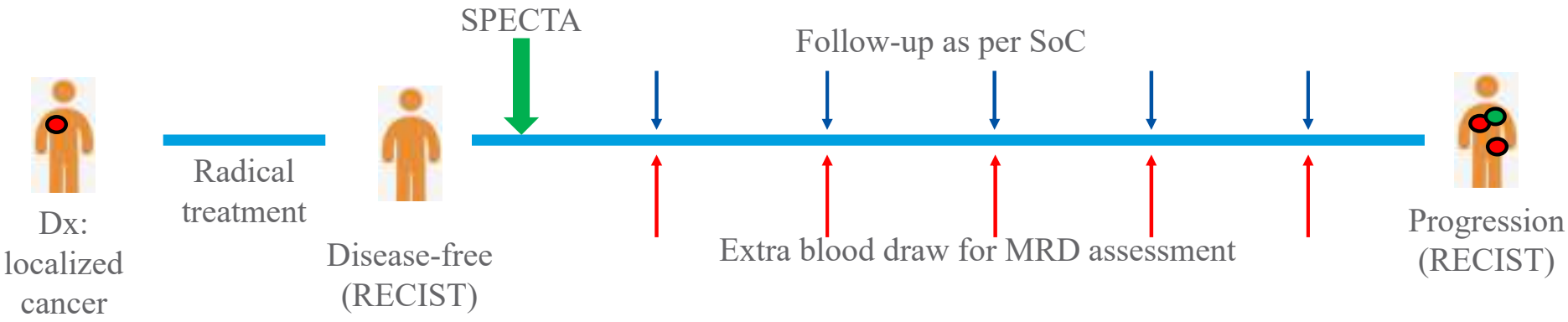
PFS: **11.1 mo.** *vs.* **5.7 mo.**, p=0.001
ORR: **87%** *vs.* **53%**

Thress – ASCO 2017

Open questions

- How to integrate with response criteria?
  - As an additional test to integrate into the ruleset? E.g. as date of PD to be confirmed by imaging?
  - As a new endpoint for RECIST? Next to RR, PFS, etc. Similar to pCR?
  - Other options?
- ctDNA and MRD detection
  - Prognostic value of ctDNA positivity at a single time point for risk of recurrence
  - Surrogate marker for treatment efficacy (ctDNA clearance associated with response)
  - Clinical utility: to be demonstrated
- Limitations
  - Variability within tumor types (shedding, patterns of relapse, etc)
  - LOD
  - Would the impact be similar for all treatments?
- For a clinician:
  - how to interpret ctDNA positivity?
  - Perform additional imaging?
  - Start of a new line of treatment?
  - How to inform the patient?
  - What will be the effect on patient quality of life?

Data generation – EORTC MRD project



Primary endpoint: PPV

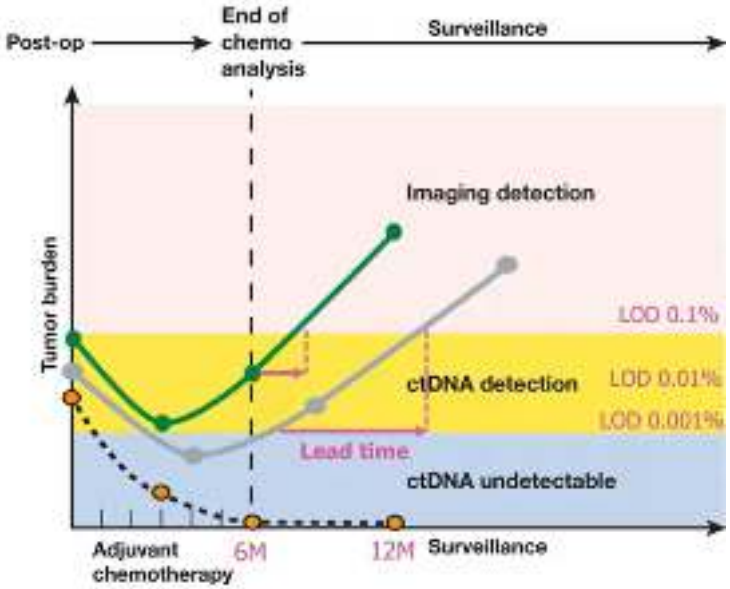
Secondary endpoints: NPV and lead time

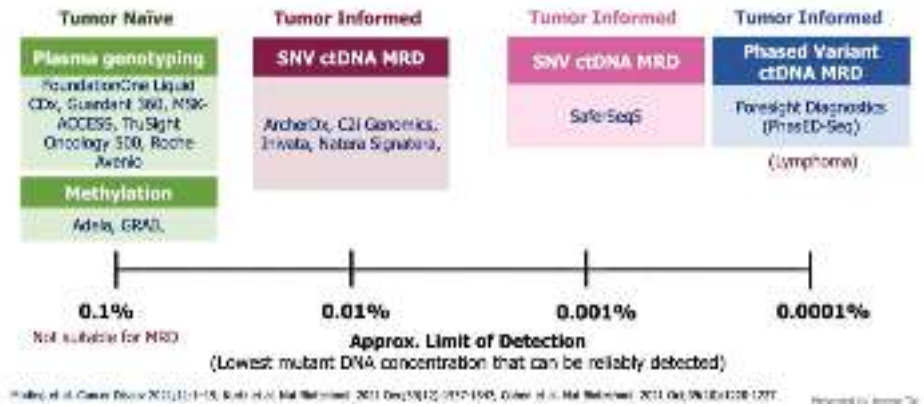
Cohorts: NSCLC, melanoma, HNSCC, TNBC, HER2-positive BC, Prostate, RCC and rare cancers (HPV-positive HNSCC, pancreatic cancer, etc.)

MRD assay: under discussion (personalised assay, methylation, etc)

Thank you

The importance of LOD and assay selection





Jeanne Tie, AACR, 2022