Regulatory Perspectives on ctDNA-Based Drug Development
（ctDNAによる患者選択への期待と課題）

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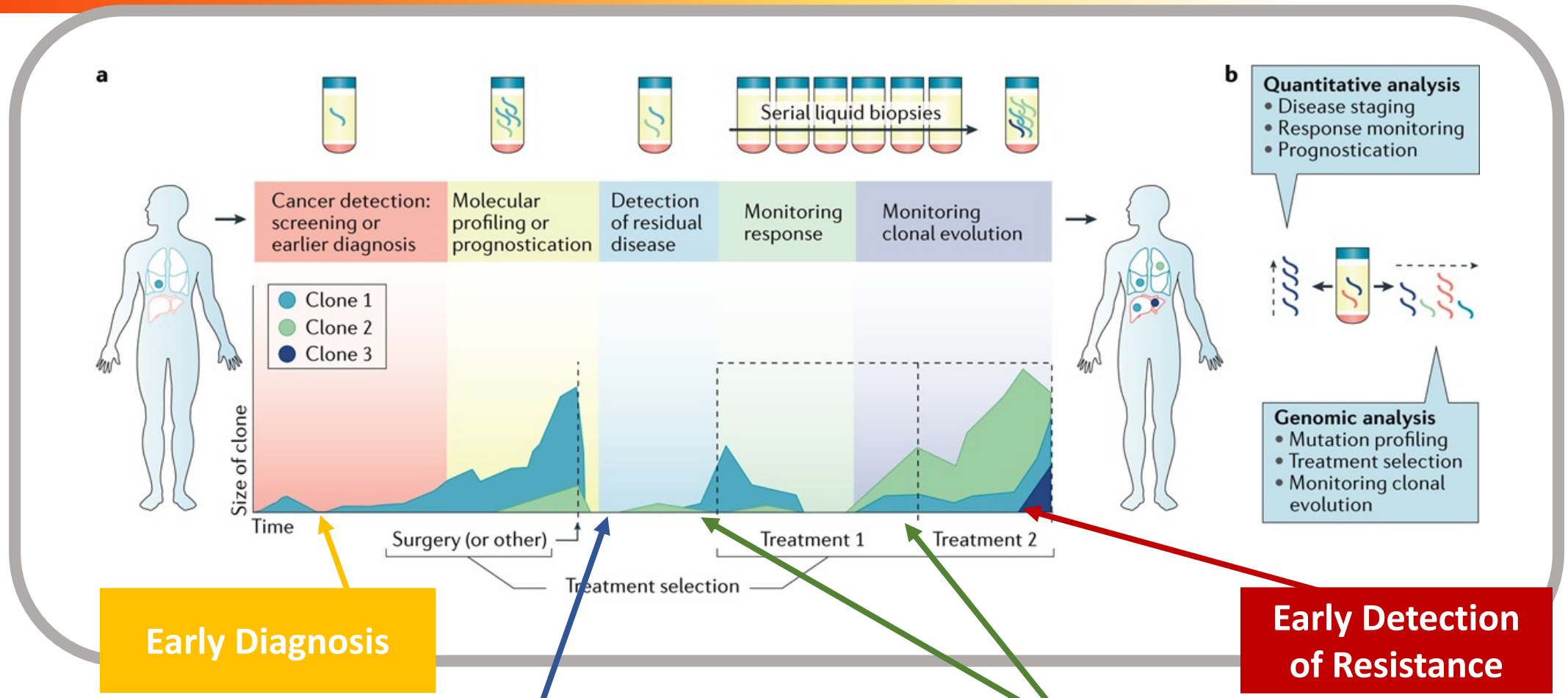
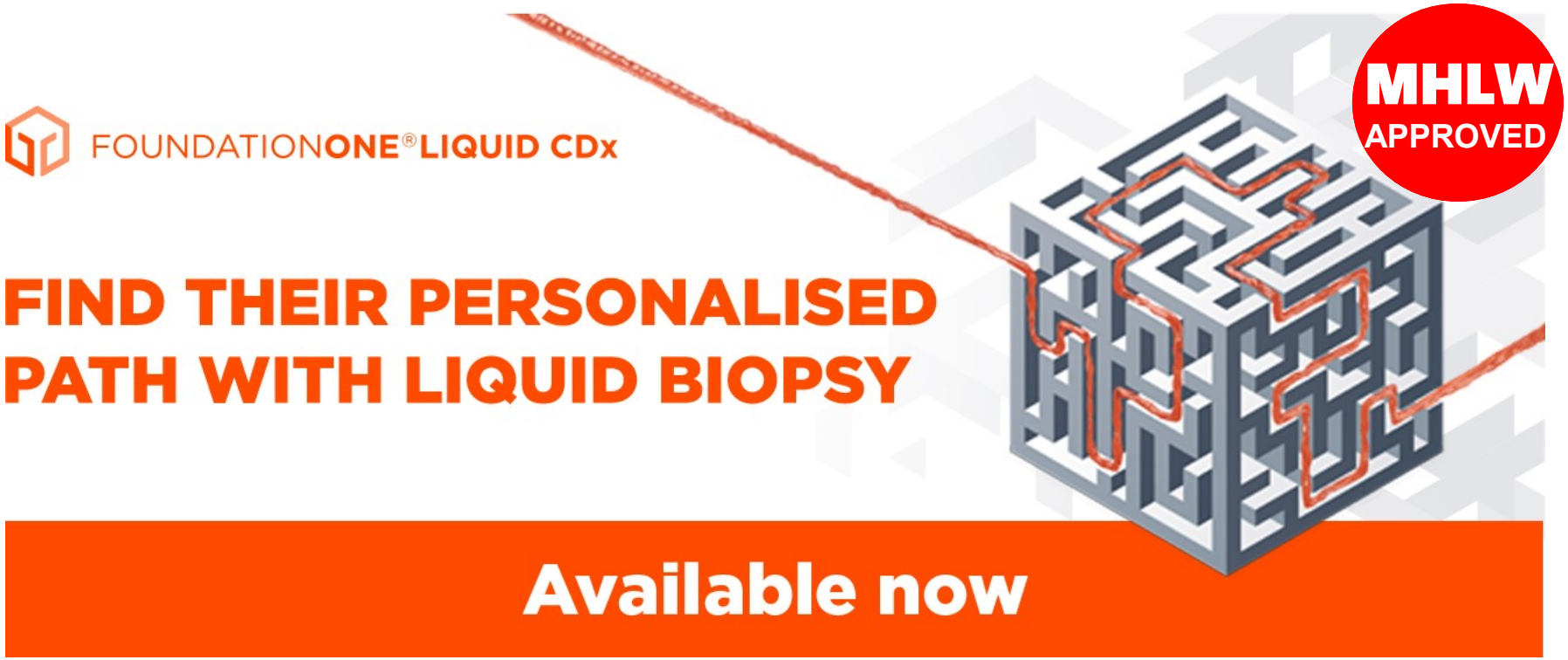
The views and opinions expressed in this presentation are those of the presenter and should not necessarily represent the views and opinions of the PMDA.

ctDNA assays are implemented in medical practice



Nature Reviews Cancer 17 pp 223-238 (2017)

FoundationOne Liquid CDx (F1CDxL) was approved in March 2021



Modified from https://www.foundationmedicine.in/foundationone-liquid-cdx.html

Critical Issues in Review of F1CDxL (1)

- It was required to provide appropriate information to the medical community on when and in what situations the use of liquid biopsy is recommended for testing for solid tumors instead of tissue biopsy.

- **Joint taskforce of JSMO, JSCO and JCA released "Policy recommendations for the appropriate use of ctDNA-based genome profiling tests" in Jan 2021 .**

- **There are no restrictions on intended use compared to F1CDx, and it is possible to use F1CDx and F1CDxL at the discretion of the physician based on guidance and policy recommendations of joint TF.**

Product photos from https://www.foundationmedicine.in/foundationone-liquid-cdx.html

Critical Issues in Review of F1CDxL (2)

		
SNV	Approved	Approved
Indels	Approved	Approved
Copy number Amplification	Approved	Not Approved
Rearrangement	Approved	Approved
MSI	Approved	Not Approved
TMB	Approved	Not Approved

- Not included in the scope of approval, but can be reported for research use at the request of a physician.
- Further accumulation of clinical data using liquid biopsy is awaited to establish the clinical validity.

Product photos from https://www.foundationmedicine.in/foundationone-liquid-cdx.html

Approved CDx using Liquid Biopsy

CDx	BM (drug)	Major evaluated studies in the review
Cobas EGFR Mutation Test v2	EGFR (Osimertinib)	Efficacy of ctDNA-positive sub-population of AURA2 study. Comparison with paired tissue biopsy test results of AURA2 study.
	EGFR (Erlotinib, Gefitinib, Afatinib)	Comparison with paired tissue biopsy test results of ENSURE study (clinical study of Erlotinib).
Oncobeam RAS CRC	KRAS, NRAS（Cetuximab, Panitumumab）	Comparison with paired tissue biopsy test results collected from medical institutions in Japan
ArcherMET	Met exon14 (tepotinib)	Efficacy of ctDNA-positive patients of VISION study. Comparison with paired tissue biopsy test results of VISION study.
F1CDxL	EGFR (Erlotinib, Gefitinib, Afatinib, Osimertinib)	Concordance study with approved liquid-biopsy-CDx
	ALK (Alectinib, Crizotinib, Ceritinib)	Efficacy of ctDNA-positive sub-population of B-FAST study (clinical study of Alectinib)
	ROS1 (Entrektinib)	Comparison with paired tissue biopsy test results of STARTRK-2 study. Efficacy of ctDNA-positive sub-population of STARTRK-2 study.
	NTRK (Entrektinib)	Comparison with paired tissue biopsy test results of STARTRK-2 study. Efficacy of ctDNA-positive sub-population of STARTRK-2 study.

Approach to CDx Approval for Liquid Biopsy

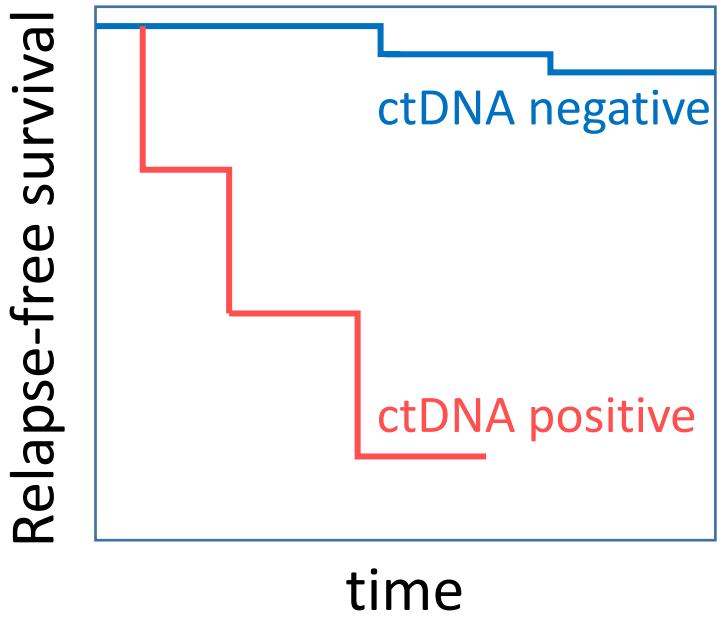
- For new drugs, it is strongly encouraged to obtain data on efficacy in ctDNA-positive populations.

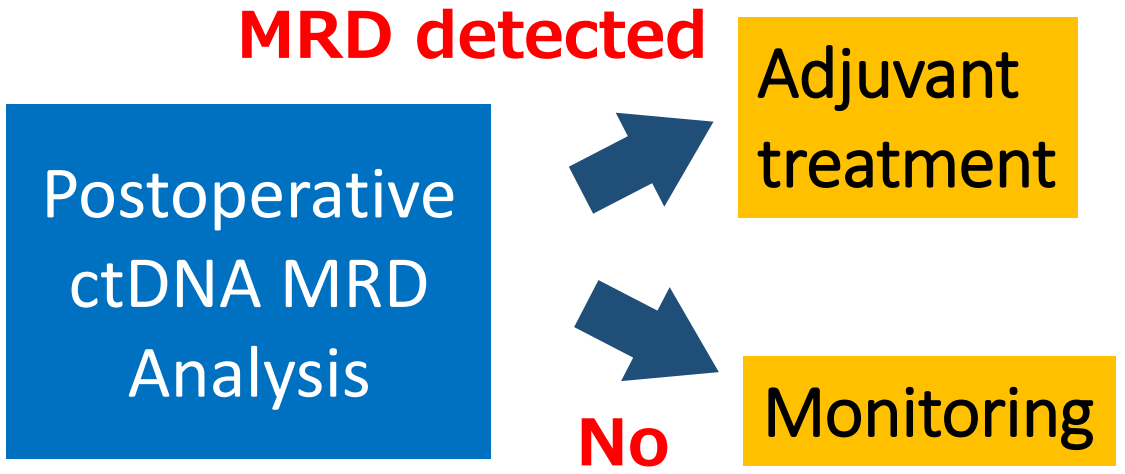
- Consistency of paired liquid and tissue biopsy test results in the target population of a drug could be the basis for approval of liquid biopsy as CDx.

- For drugs developed in the old days when liquid biopsy was a dream, clinical utility of liquid biopsy may be extrapolated to drugs with the same mechanism of action, since the inclusive relation of ctDNA-positive populations in tissue-biopsy positive populations could be the same.

The Next Trend : NGS-based MRD test assays

- **Detect MRD and stratify for high or low risk of recurrence.**
- **Provide adjuvant treatment to high risk patients.**





CtDNA Assays for CDx vs MRD (1)

	CDx for malignant tumor drugs	MRD
Target of detection	Driver gene that closely related to the MOA of relevant drug	Genes not related drugs
	Usually one gene (except for TMB, MSI, etc.)	Usually multiple genes (personalized in some cases)

Follow-on products can be developed based on analytical equivalence.

It is difficult to develop a follow-on product.

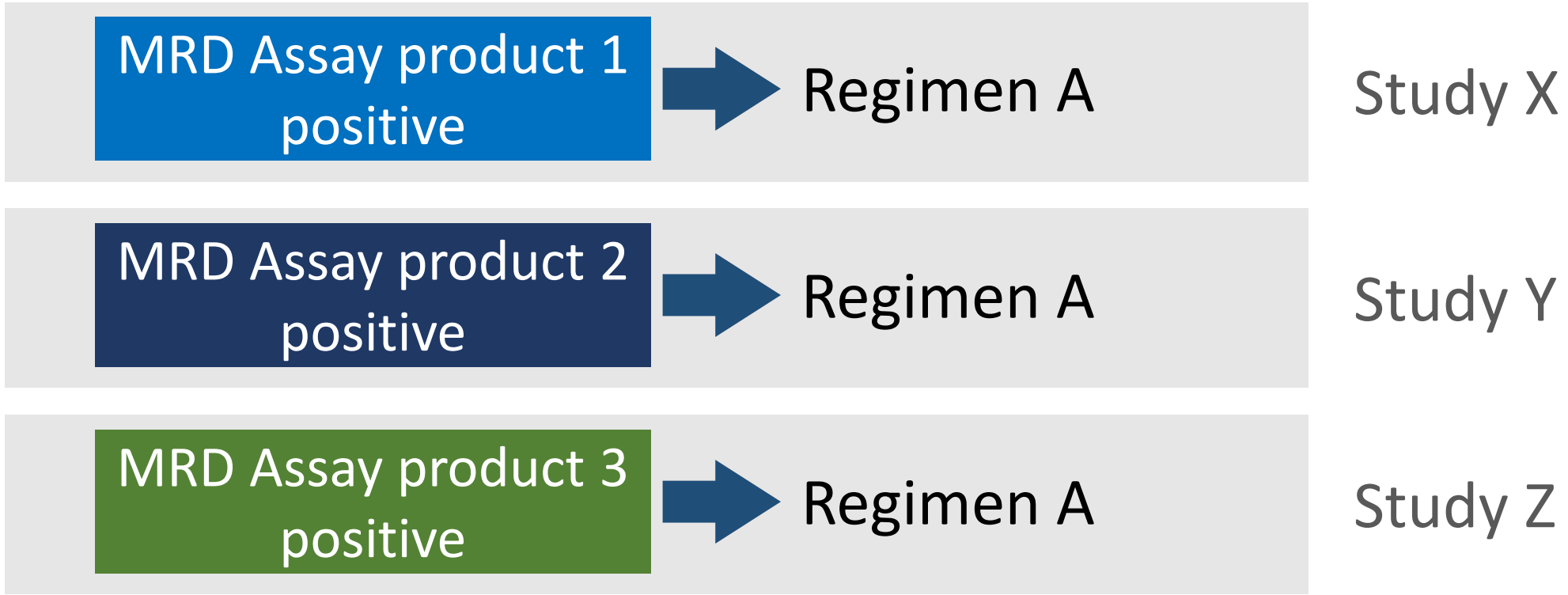
CtDNA Assays for CDx vs MRD (2)

	CDx for malignant tumor drugs	MRD
Primary Intended use	Identification of responders of the drug	Provide the prognostic risk of the patient
		Identification of patients for adjuvant treatment

No CDx product can be approved unless the relevant drug is approved.

MRD product can be approved based on the prognostic performance.

Treatment to MRD positive patients: Vision of the Future



Treatment to MRD positive patients: Alternative Vision of the Future

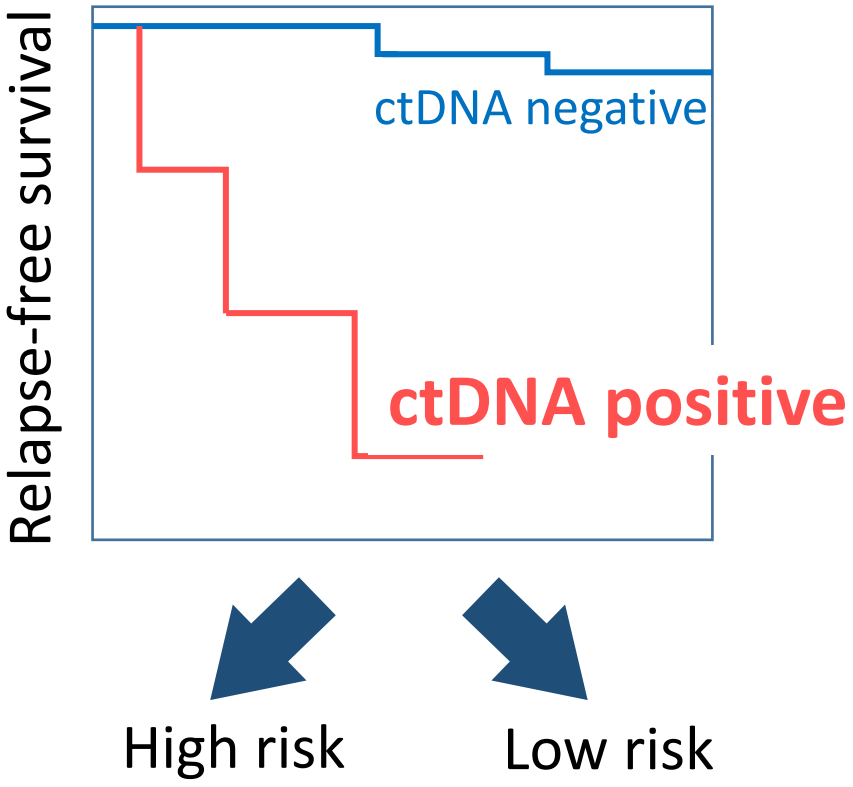
Regimen A

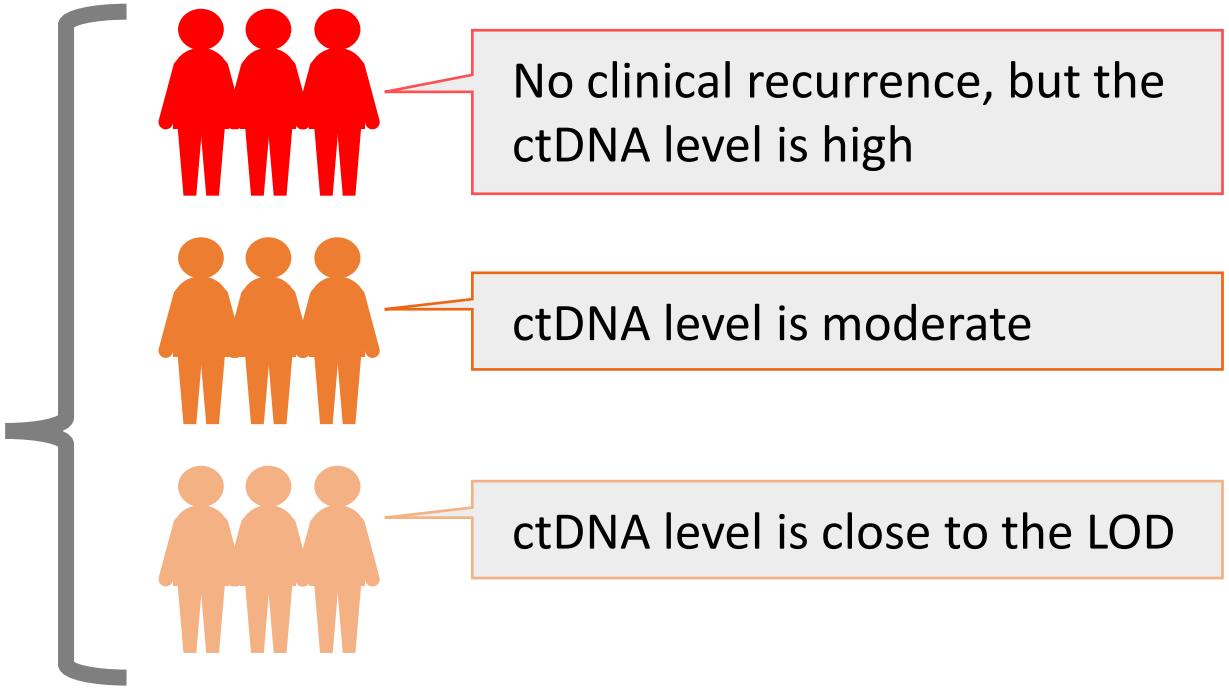
Study X

The critical question is whether Product 2 and Product 3 can be considered clinically equivalent to Product 1.

High Risk of Recurrence

Treatment to MRD positive patients: Is MRD test qualitative or semi-quantitative?





Which populations are likely to benefit from treatment?

Qualitative

Semi-Quantitative?

Conclusion and Perspectives

- With the approval of the ctDNA-based CGP in Japan, we can expect further utilization of liquid biopsy and accumulation of evidence for patient identification using ctDNA. CtDNA-based CDx is also expected to increase.
- Clinical implementation of MRD is also expected, and it will be important to build consensus among stakeholders on how to generalize MRD test results and evidence of drugs for ctDNA-positive patients.
- Regardless of CDx or MRD, in order for a drug to be approved for ctDNA-positive patients, the diagnostic product must be approved, and this should be carefully considered during development.