# Multimodale Therapieansätze: Oligometastasierung

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ASKLEPIOS TUMORZENTRUM HAMBURG

# DIRK ARNOLD, DOI 2022-2024

Remunerated *Advisory Boards* and/or *Education Activities/ Honoraria for Presentations*

Industry:

Amgen, Arcus, Astra Zeneca, Bayer, BMS, Boston Scientific, Daichii Sankyo, Eli Lilly, GSK, Gilead

Janssen, Johnson and Johnson, Merck Serono, MSD, Roche, Sanofi, Servier, Seagen, Sirtex, Takeda

CME providers:

Aptutude Health, Art Tempi, PriME Oncology, MedScape, onkowissen, TRM Oncology

Travel support

Daichii Sankyo

Non-remunerated activities:

Advisory Role and/or PI function: Oncolytics, Phanes

# Understanding oligometastatic disease

# The benefit of local treatment in mCRC

# Expanding the concept

# Understanding oligometastatic disease

## The benefit of local treatment in mCRC

## Expanding the concept

# S3-Leitlinie Kolorektales Karzinom

Version 3.01 – XX 2024
AWMF-Registernummer: 021-007OL

## Definition Oligometastasierung

- 1-5 Metastasen ggf. mehr falls komplette Eradikation möglich
- Bis zu 2 Organmanifestationen
- Primärtumor resektabel oder schon entfernt
- Alle Metastasen müssen einer lokalen Therapie zugänglich sein

# Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

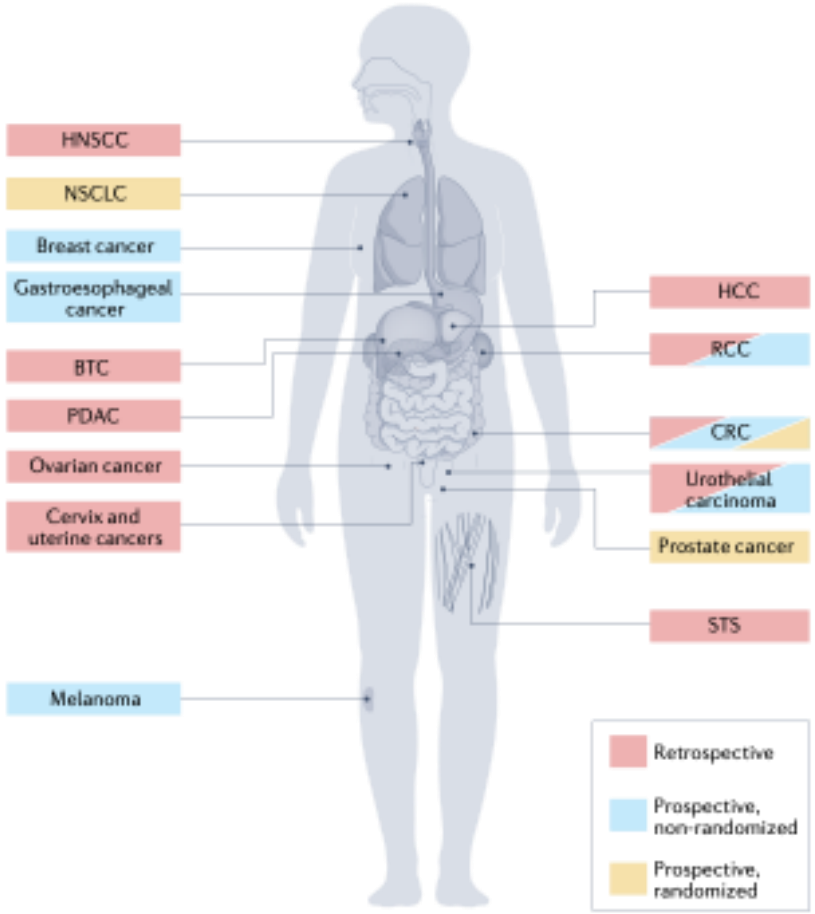
A. Cervantes[1,2], R. Adam[3], S. Roselló[1,2], D. Arnold[4], N. Normanno[5], J. Taïeb[6,7], J. Seligmann[8], T. De Baere[9,10,11], P. Osterlund[12,13], T. Yoshino[14] & E. Martinelli[15], on behalf of the ESMO Guidelines Committee*

Generally, a traditional clinical definition of OMD is:

- **One to five** metastatic lesions
  - occasionally more if complete eradication is possible
- Up to **two metastatic sites**
- Controlled primary tumor (optionally resected)
- All metastatic sites must be safely **treatable by LT .**

Cervantes et al., Ann Oncol 2023

# The oligometastatic stage




Katipally RR et al., Nat Rev Clin Oncol 2022

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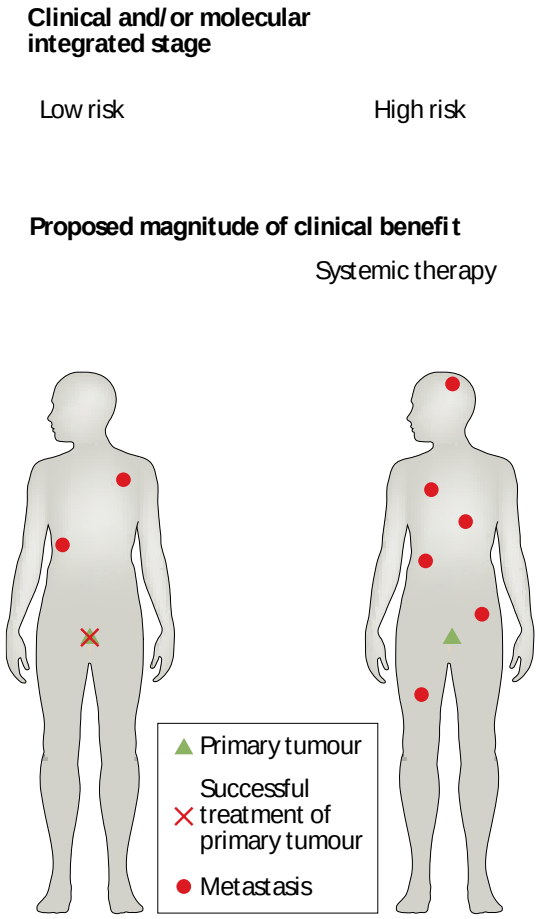


Pitroda and Weichselbaum, Nat Rev Clin Oncol 2019

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- OMD status has therefore been established **by radiological appearances** and **clinical judgement**.
- Notably, OMD status can occur in **multiple clinical scenarios** in the **continuum of care** e.g. during different treatment lines.
  - Therefore, careful and continuous re-assessment is recommended.

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- OMD status has therefore been established by radiological appearances and clinical judgement.
- Notably, OMD status can occur in multiple clinical scenarios in the continuum of care e.g. during different treatment lines.
  - Therefore, careful and continuous re-assessment is recommended.

- Currently, **biological factors do not contribute** to this definition
  - this may change considering, for example, molecular subtypes with specific prognostic background and/or treatment implications.

Cervantes et al., Ann Oncol 2023

# „Characteristics of indolent disease“

**Clinical**

- low number (typically 1–5 lesions)
- metachronous presentation
- No involvement of lymph nodes
- Slow rate of progression (<0.6 new lesions per year)
- limited organ sites (typically 1–2 sites)
- Favourable histology (including, but not limited to, breast, prostate and kidney)

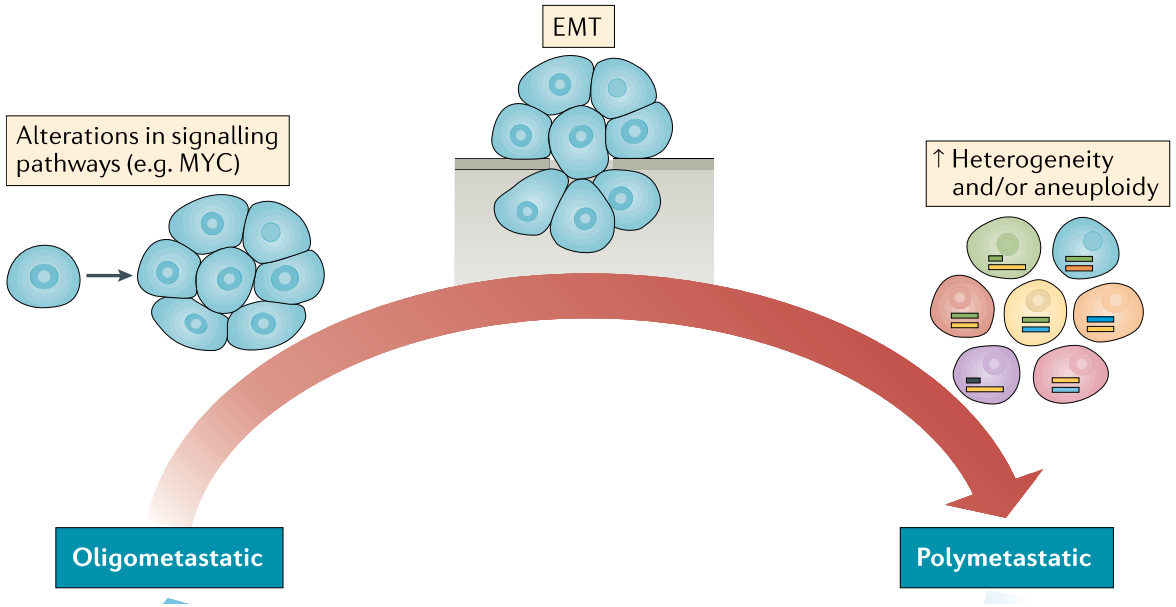
**Biological**

- Activation of innate and adaptive immunity
- Absence of mesenchymal features
- low degree of tumour aneuploidy
- low degree of intratumoural heterogeneity
- Intact 14q chromosomal arm
- expression of microRNAs that suppress genes associated with metastasis

**Treatment**
local ablative interventions (with SBRT, RFTA, surgey) tend to be more beneficial than systemic therapy

Pitroda and Weichselbaum, Nat Rev Clin Oncol 2019

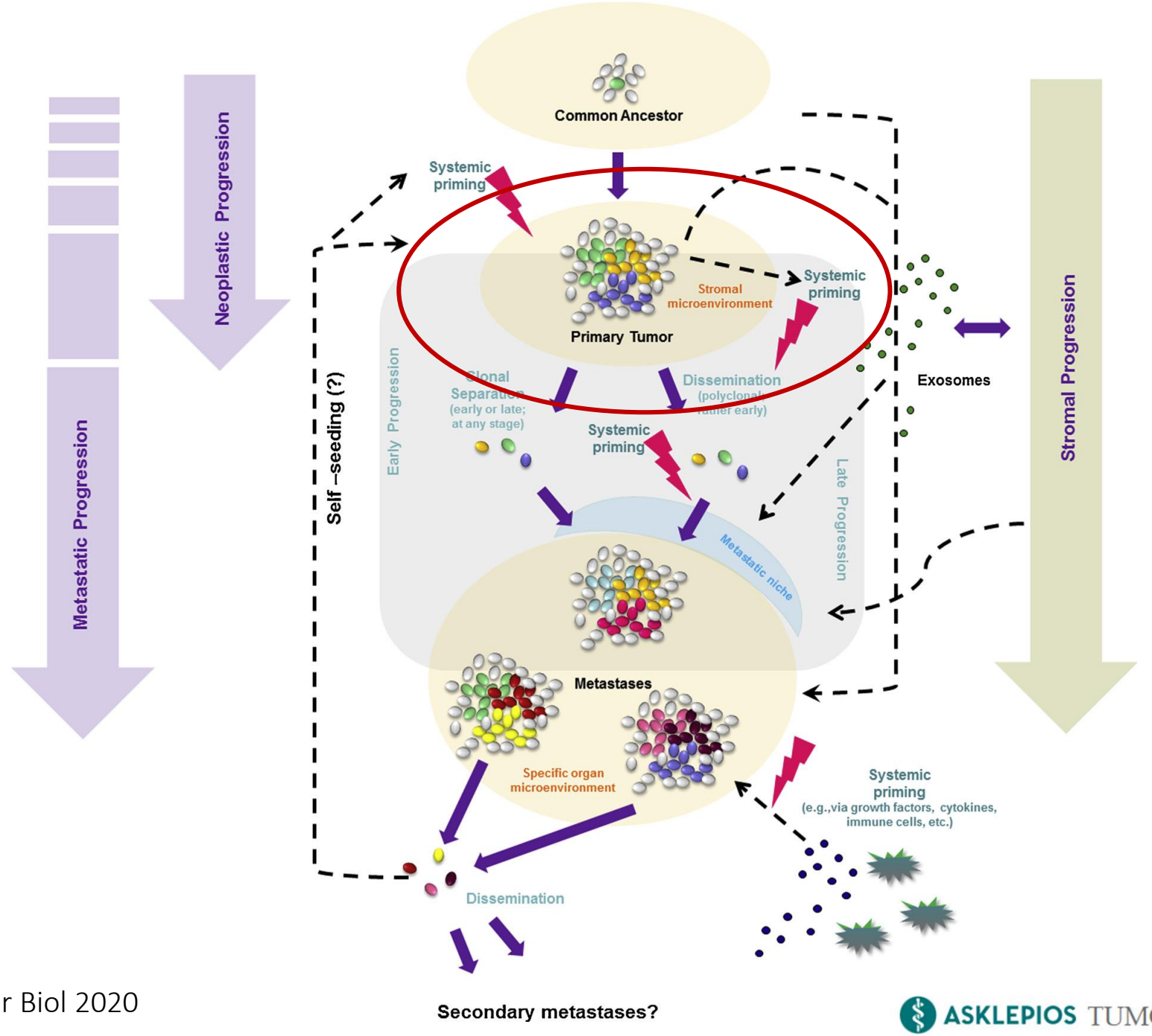
# Mechanistic determinants of metastatic heterogeneity




Katipally RR et al., Nat Rev Clin Oncol 2022

# The tumour

# The oligometastatic phenotype



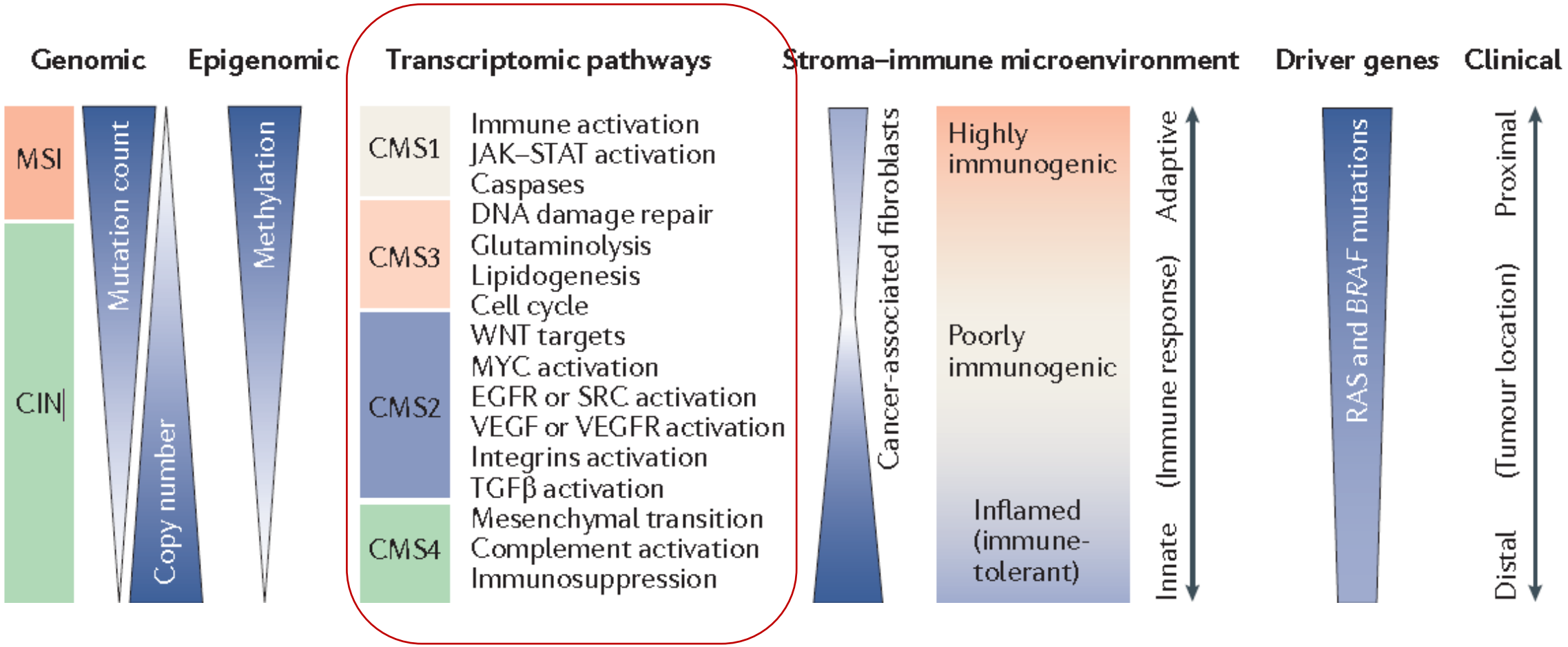

Allgayer et al., Semin Cancer Biol 2020

# Mutational pattern of oligometastatic mCRC

| Biomarker | Clinical Significance |
|---|---|
| Loss of *KRAS* and *SMAD4* alterations from primary to metastatic lesions. High granzyme-B+ T-cell infiltration into metastatic tumor. | The patients with these characteristics remain with liver-limited OMD for long time. |
| Gain in *KRAS*, *PIK3CA* and *SMAD4* alterations. Scarce granzyme-B+ T-cells infiltration. | The patients with these characteristics develop poly-metastatic widely diffusive disease. |
| *KRAS* regression from primary to metastatic lesions. HLA-C7 aplotype. | The patients with these characteristics remain oligometastatic for long time. |

Ottaiano et al., Cancers (Basel) 2020; Ottaiano et al, Front Immunol 2022

# Factors impacting on „biology“ of mCRC

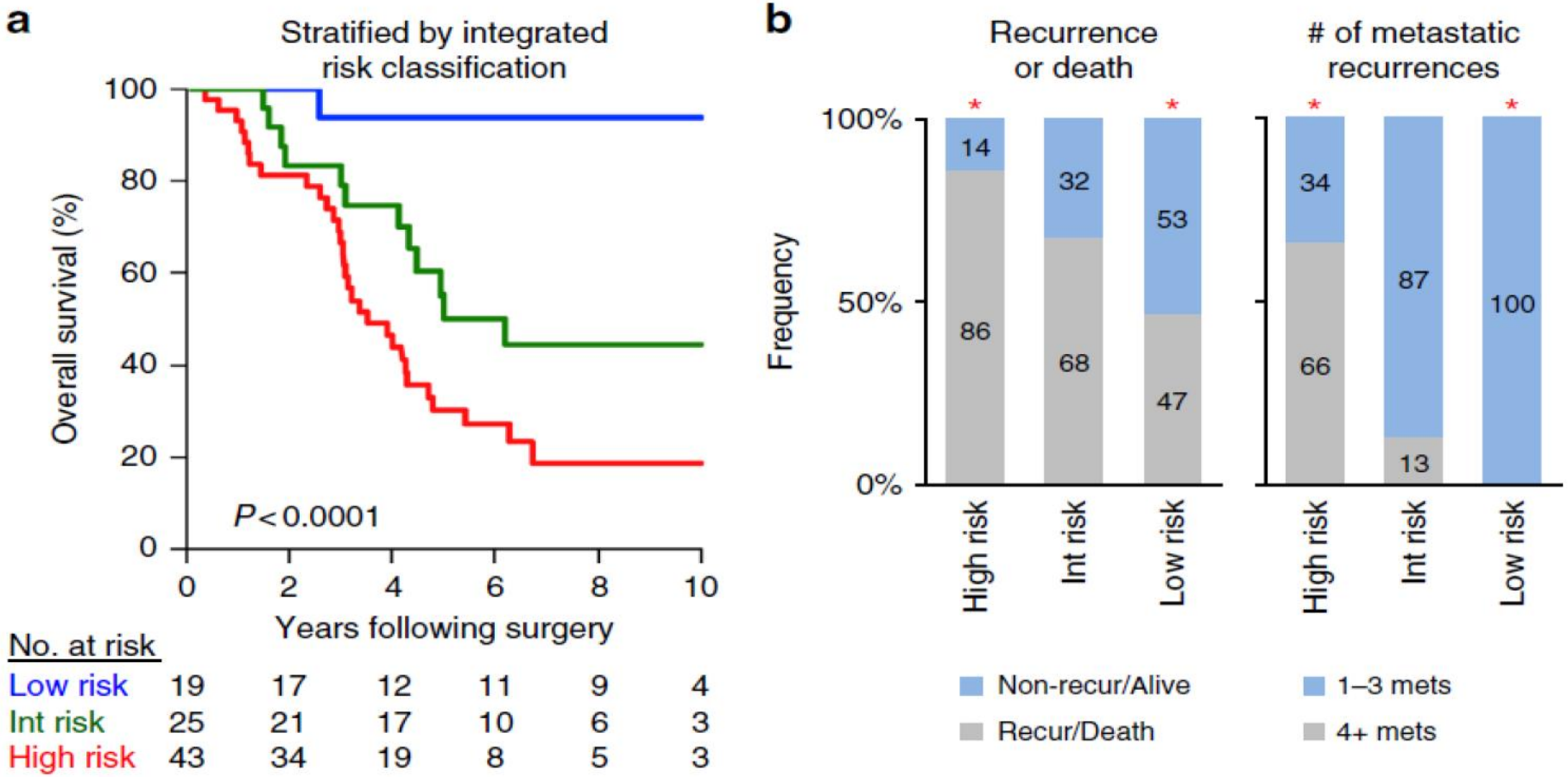


# Integrated molecular subtyping defines a curable oligometastatic state in colorectal liver metastasis

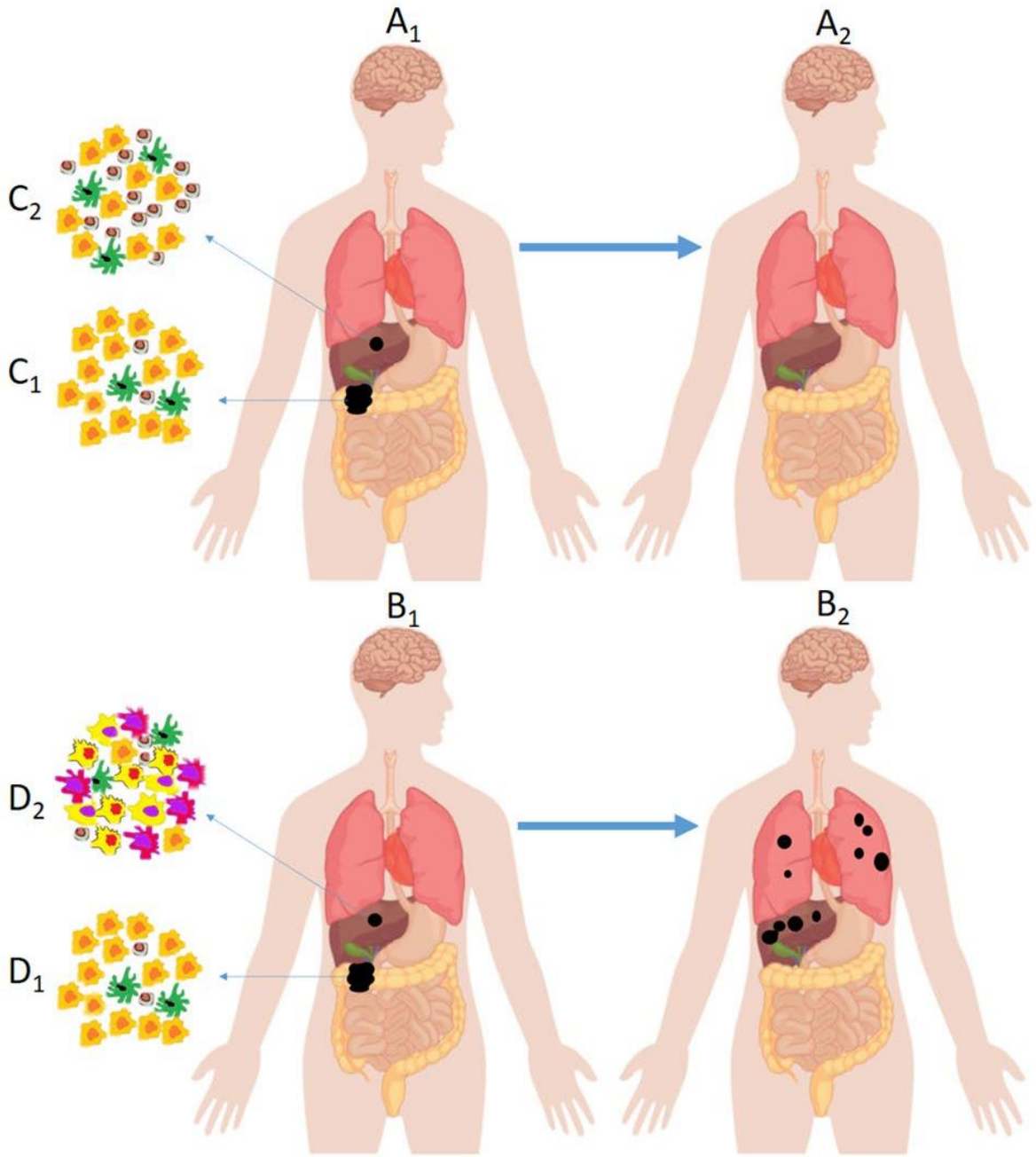
| | Subtype 1<br>Canonical | Subtype 2<br>Immune | Subtype 3<br>Stromal |
|---|---|---|---|
| Frequency | 33% | 29% | 39% |
| Molecular signature | ↓Immune and stroma<br>E2F/MYC signaling<br>DNA damage and cell cycle | ↑Immune<br>Interferon signaling<br>p53 pathway | ↑Stroma<br>KRAS signaling<br>EMT and angiogenesis |
| Specific mutations | NOTCH1 and PIK3C2B | NRAS, CDK12, and EBF1 | MAD3 |
| Met. reccurences | Many | Few | Many |
| Overall survival | Intermediate | Favorable | Unfavourable |

Pitroda et al., Nature Communications 2018

# Integrated molecular subtyping defines a curable oligometastatic state in colorectal liver metastasis




Pitroda et al., Nature Communications 2018




Neoplastic cell with key-driver wild-type genes

GrzB+ CD8+ T-cell

Mutated neoplastic clones:

KRAS mut

PIK3CA mut

Both KRAS and PIK3CA mut

Mononuclear phagocyte system cell

Ottaiano et al., Cancers (Basel) 2023

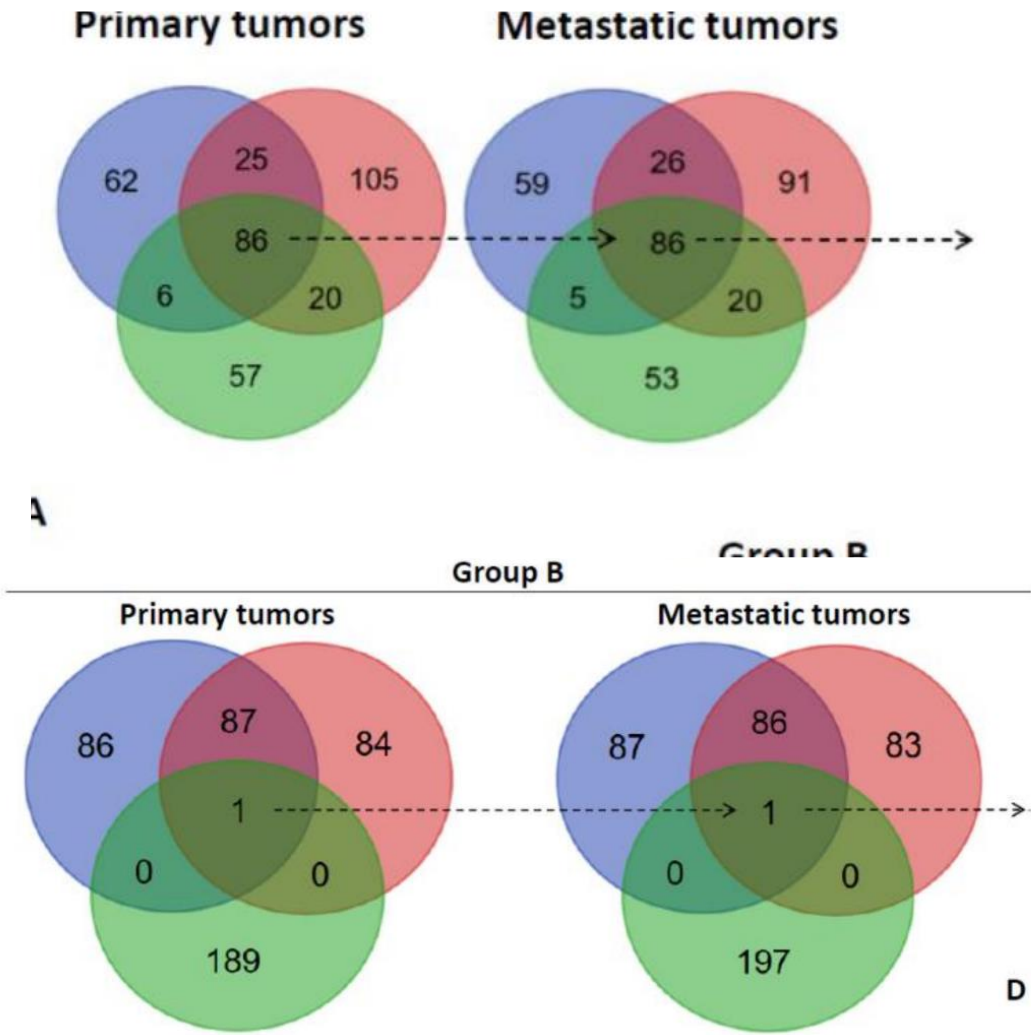
# Mutational pattern of oligometastatic mCRC

6 out of 98 patients liver oligometastases

(≤3 lesions)

(A) without recurrence at 3y follow-up

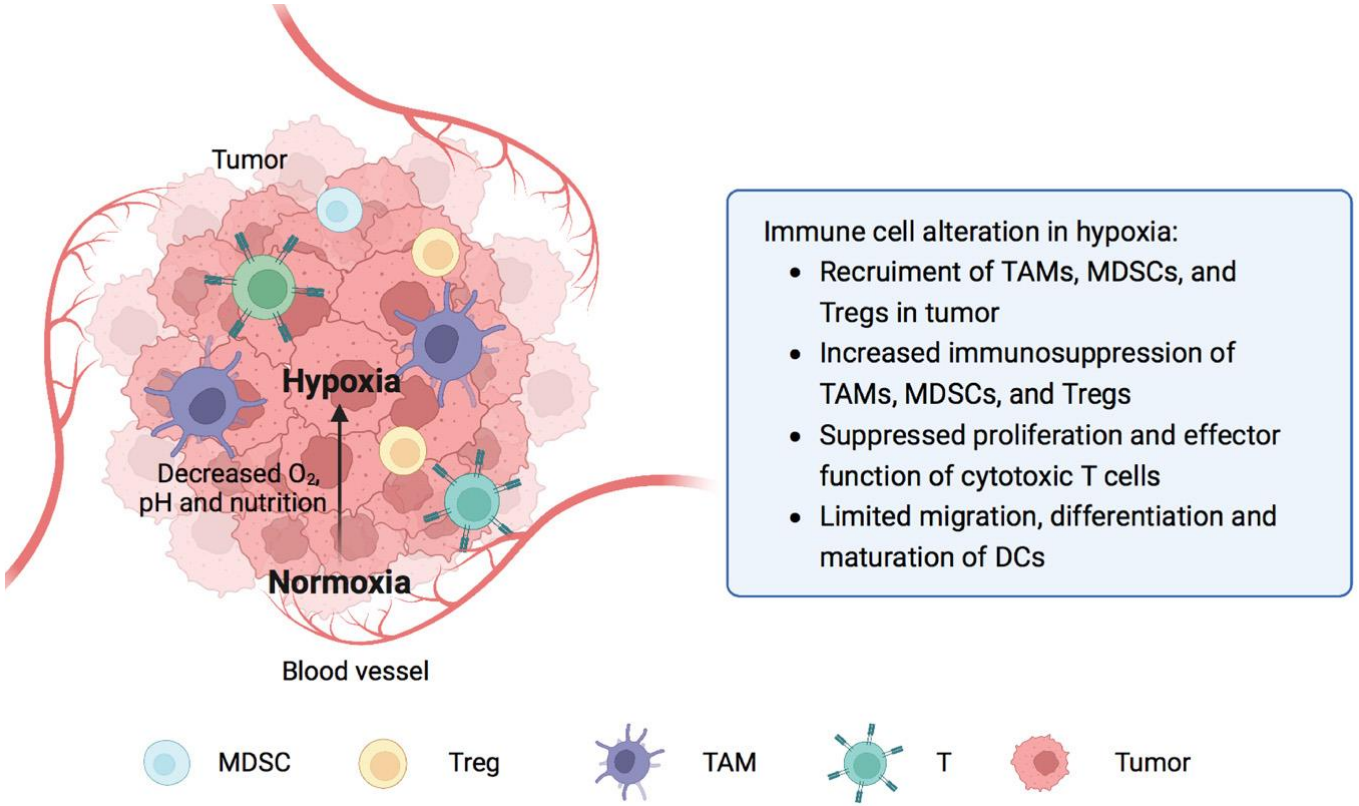
(B) recurred within 1y




Ottaiano et al., Cancers (Basel) 2020

# The environment

# The environment: Tumour microenvironment (TME)

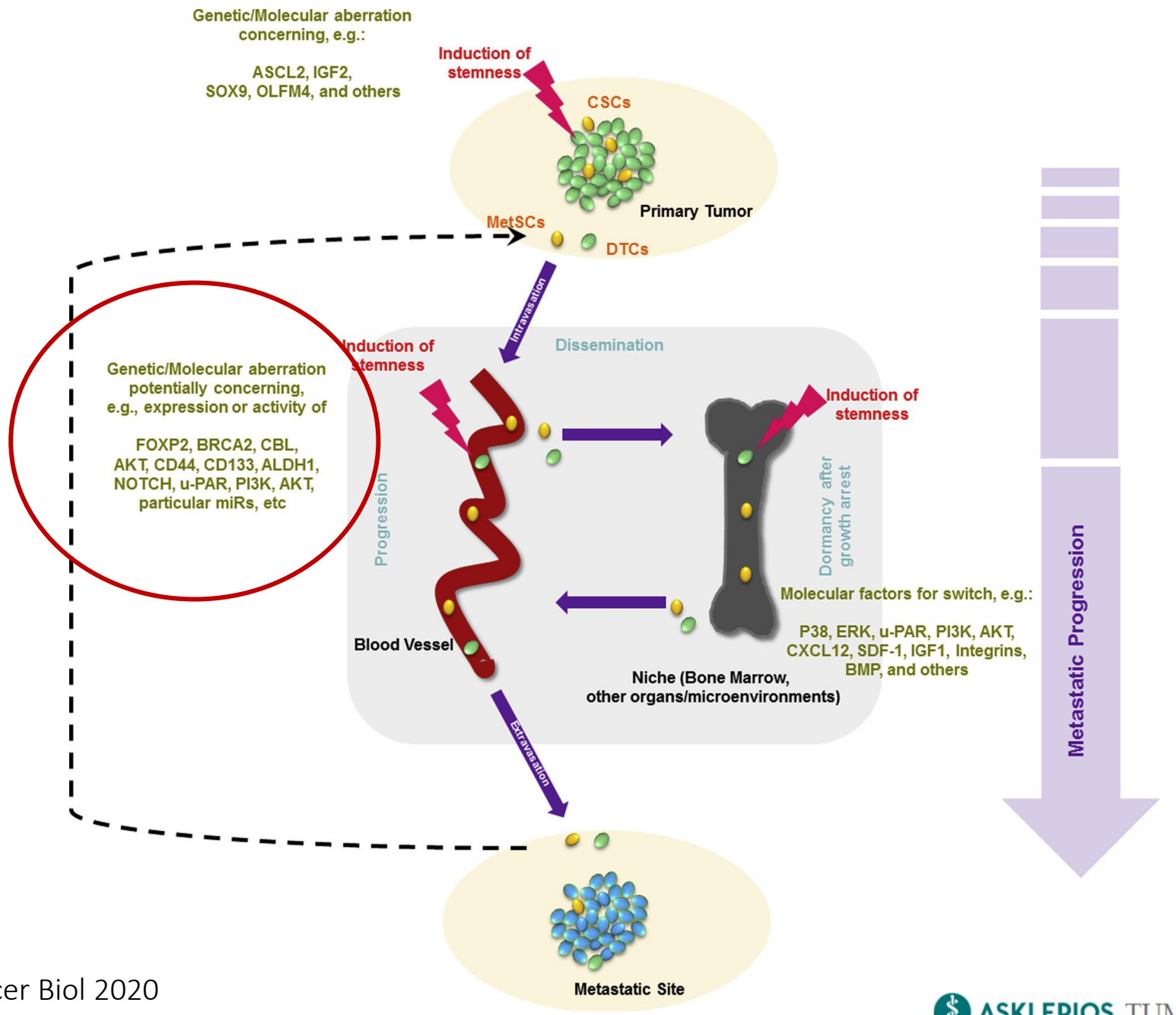



The TME includes

- immune cells,
- extracellular matrix,
- other cells, like fibroblasts
- (blood vessels)

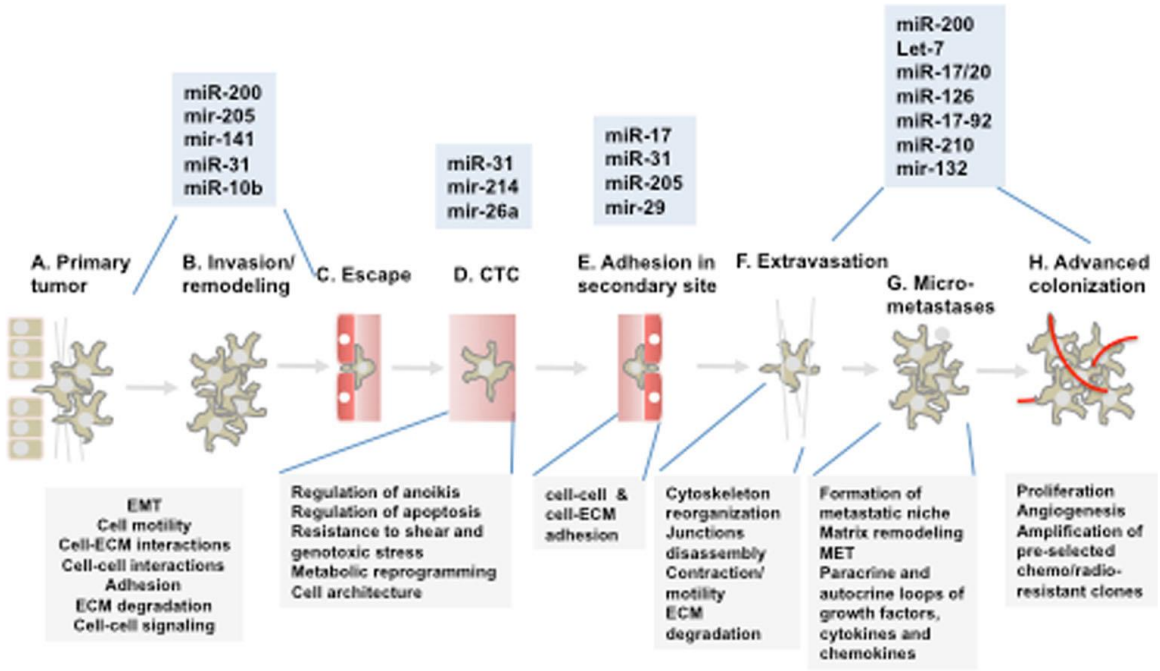
Zhu et al., Organoids 2022

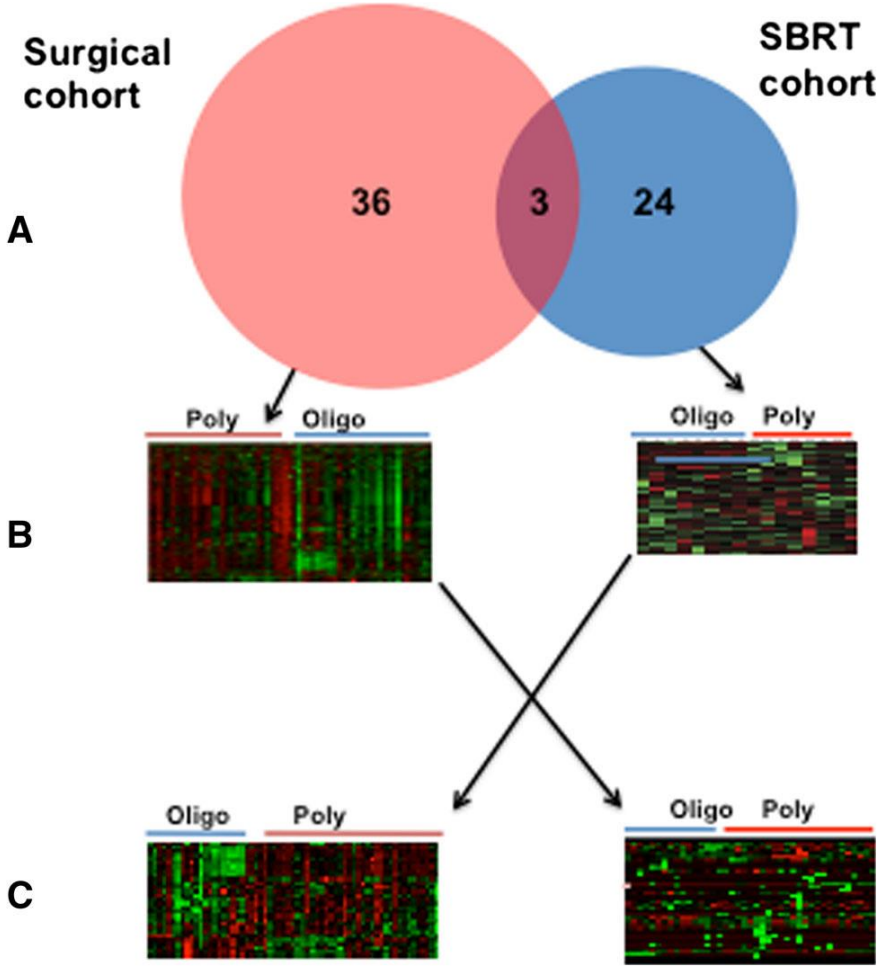
# The oligometastatic phenotype




Allgayer et al., Semin Cancer Biol 2020

# Towards a molecular basis of oligometastatic disease: potential role of micro-RNAs




MicroRNAs expression patterns are associated with OMD (or specific subtype of OMD)

Uppal et al., Clin Exp Metastases 2014

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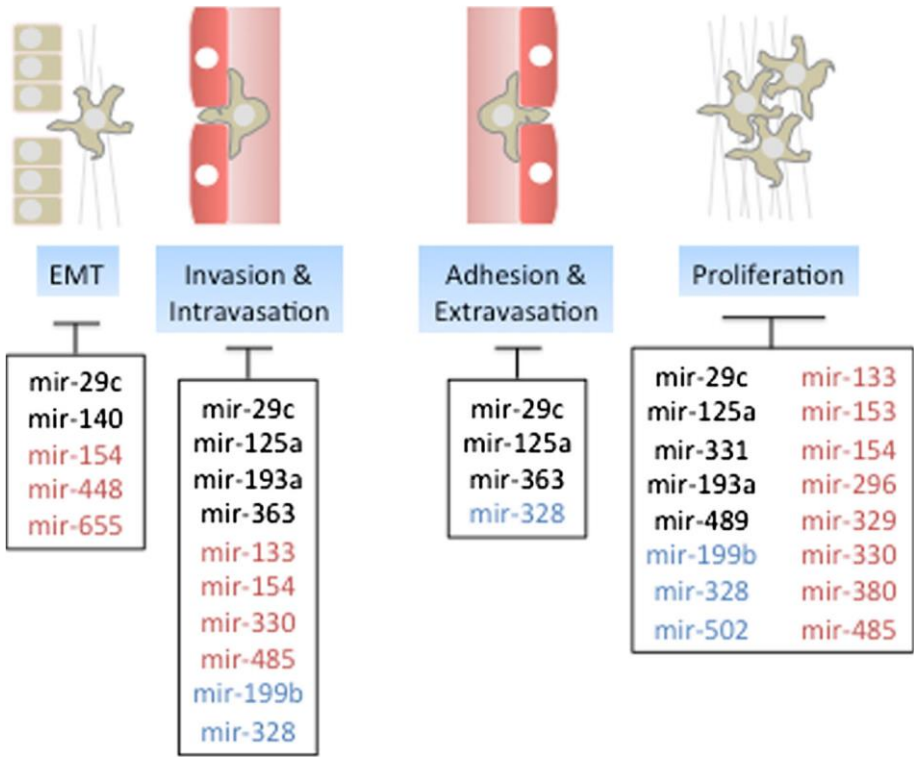


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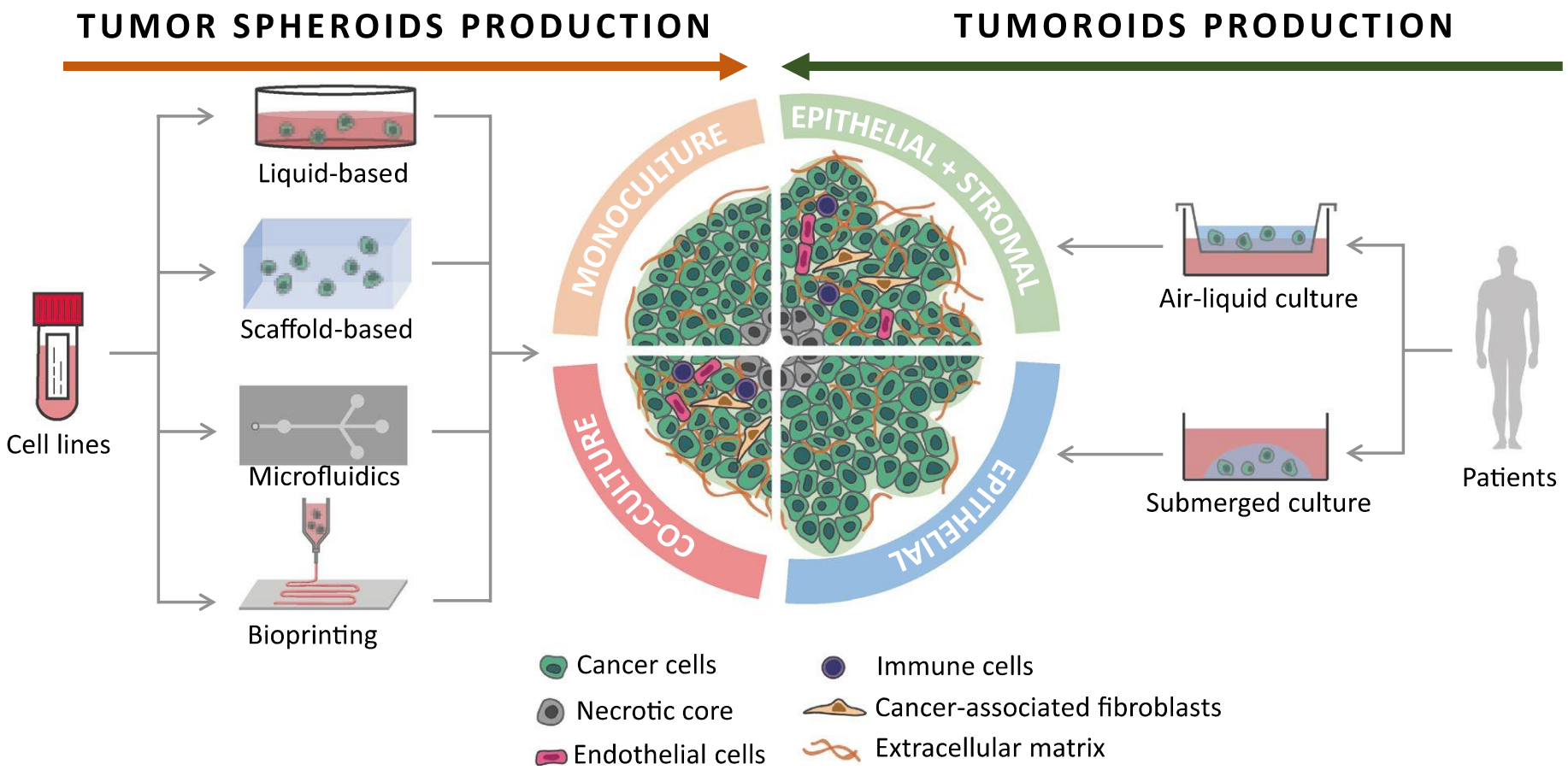
Uppal et al., Clin Exp Metastases 2014

# TME: Chemokine clusters

| | Cluster name | Chemokines | Chemokine receptors | Functions |
|---|---|---|---|---|
| Major clusters | GRO cluster[a] | CXCL1–8 | CXCR1, 2 | Neutrophils, inflammation, type 3 immunity, angiogenesis |
| | MCP/MIP cluster[a] | CCL1, 2, 7, 8, 11–13<br>CCL3–5, 6, 9, 14–16, 18, 23 | CCR1–3, 5, 8 | Monocytes, inflammation, type 1 immunity, type 2 immunity |
| Minor clusters | IP-10 cluster[a] | CXCL9–11 | CXCR3 | Type 1 immunity |
| | MDC cluster[a] | CCL17, 22 | CCR4 | Tolerance, type 2 immunity |
| | SLC cluster[a] | CCL19, 21 | CCR7 | Lymphoid tissue |
| | Eotaxin-like cluster[a] | CCL24, 26 | CCR3 | Type 2 immunity |
| | Lymphotactin cluster[a] | XCL1, 2 | XCR1 | Type 1 immunity |
| Non-cluster | NA | CCL20 | CCR6 | Type 3 immunity |
| | NA | CCL25 | CCR9 | Gut homing, lymphoid tissue |
| | NA | CCL27 | CCR10 | Skin homing |
| | NA | CCL28 | CCR3, 10 | Type 2 immunity |
| | NA | CXCL12 | CXCR4 | Development, haematopoiesis, lymphoid tissue, angiogenesis |

Mempel TR et al., Nat Rev Cancer 2024

# Three-dimensional in vitro culture models in oncology research




Jubelin et al., Cell and Bioscience 2022

Understanding oligometastatic disease

The benefit of local treatment in mCRC

Expanding the concept

# LIVERMETSURVEY

Launched by Prof. René Adam in 2006 and sponsored since October 2017 by Fondation A.R.CA.D- Aide et Recherche en CAncérologie Digestive- LMS Program is a prospective international database with more than 70 participating countries.

It focuses on patients operated for colorectal liver metastasis, whether resected or not.

Its objective is to collect on a multi-institutional basis the most significant data concerning the history, the treatment (chemotherapy, surgery, combined ablation) and the outcome of operated patients.

The final purpose is to evaluate patient outcomes and prognostic factors for resected patients, so as to define guidelines of optimal treatment and strategy.

LMS Program is opened to all centers across the world, whether private or public; no selection criteria will be applied regarding prior surgical experience and/ or size of the center. Investigators are requested to include all their operated patients consecutively and to provide their follow-up at long-term.

LOGIN

## Register a center

To register a center, please send the following information to info@livermetsurvey-arcad.org:

- Center name
- Center postal address
- Zip code
- Country
- Principal investigator (PI) first name
- PI family name
- PI title (Pr/Dr/Mr/Mrs.)
- PI Email

## Register as a co-investigator

To register as a co-investigator, please send the following information to info@livermetsurvey-arcad.org:

- Center name
- Name of the pre-registered center
- Center password
- Title (Pr/Dr/Mr/Mrs.)
- First name
- Family name
- Postal address
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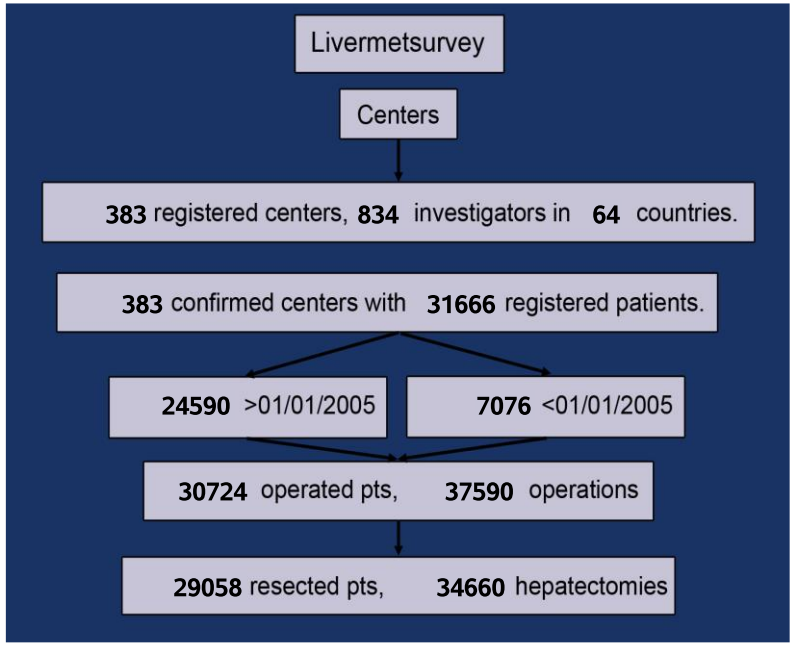


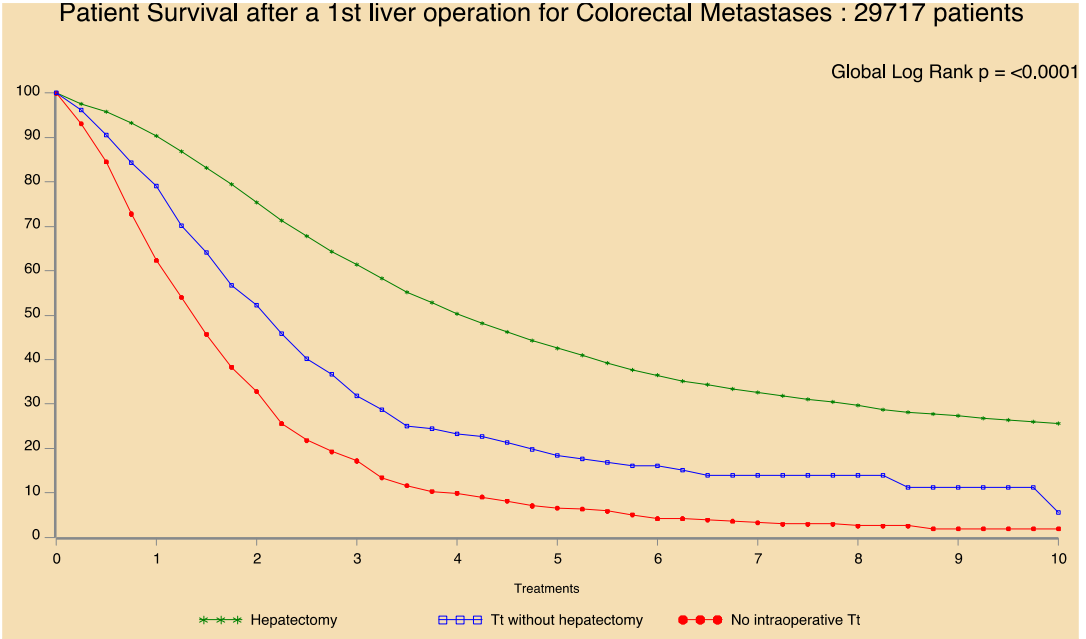


www.livermetsurvey.arcad.org

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# Kurativ intendierte Therapie: S3 Leitlinie

## 10.2 Resektable Metastasierung

| 10.8 | Konsensbasiertes Statement | neu 2024 |
|---|---|---|
| **EK** | Bei primär resektabler Metastasierung (inklusive Oligometastasierung) ist die Anwendung lokaler Therapieverfahren zu prüfen. Neben einer Operation sind andere lokalen Therapieverfahren zu berücksichtigen. | |
| | Starker Konsens | |

| 10.9 | Konsensbasierte Empfehlung | neu 2024 |
|---|---|---|
| **EK** | Die Beurteilung der Resektabilität oder des Einsatzes anderer lokaler Therapieverfahren soll unter Beteiligung eines in der Metastasenchirurgie erfahrenen Chirurgen bzw. in der Anwendung lokalen Therapieverfahren (SRBT, RFA, TACE, intraarterielle CTx) erfahrenen Therapeuten erfolgen. | |
| | Starker K | |

| 10.10 | Konsensbasierte Empfehlung | neu 2024 |
|---|---|---|
| **EK** | Eine neoadjuvante Therapie von primär resektablen Lebermetastasen kann insbesondere bei prognostisch ungünstiger Tumorbiologie (z. B. kurzes krankheitsfreies Intervall oder synchrone Metastasierung, Anzahl und Lokalisation der Metastasen etc.) erfolgen.<br><br>Kann durch diese systemische Therapie eine Stabilisierung der Erkrankung erreicht werden, so sollte die Resektion möglichst zeitnah (d. h. nach 2 – 3 Monaten Therapie) angestrebt werden. | |

# Management of limited metastases: Surgery or RFTA?

COLLISION
Colorectal Liver Metastases: surgery vs thermal ablation

Patients with Resectable Colorectal Liver Metastases (CRLM)

- No extrahepatic mets
- Total number of CRLM ≤ 10
- ≥1 resectable & ablatable CRLM ≤ 3cm
- Additional resection(s) >3cm allowed
- Additional ablations for unresectable CRLM allowed

*n = 599*

Expert panel

Limited burden

Interm. burden

High burden

IOUS

RANDOMIZATION

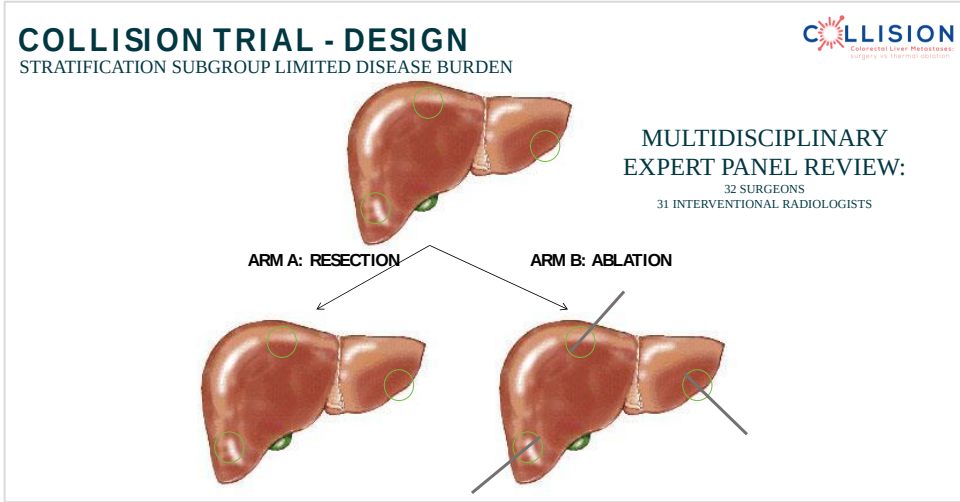
Arm A: Resection

Arm B: Ablation

FOLLOW UP

DEATH

Phase III international multicenter randomized controlled trial to prove / disprove hypothesis of non-inferiority of thermal ablation compared to surgical resection for small-size colorectal liver metastases (CRLM)



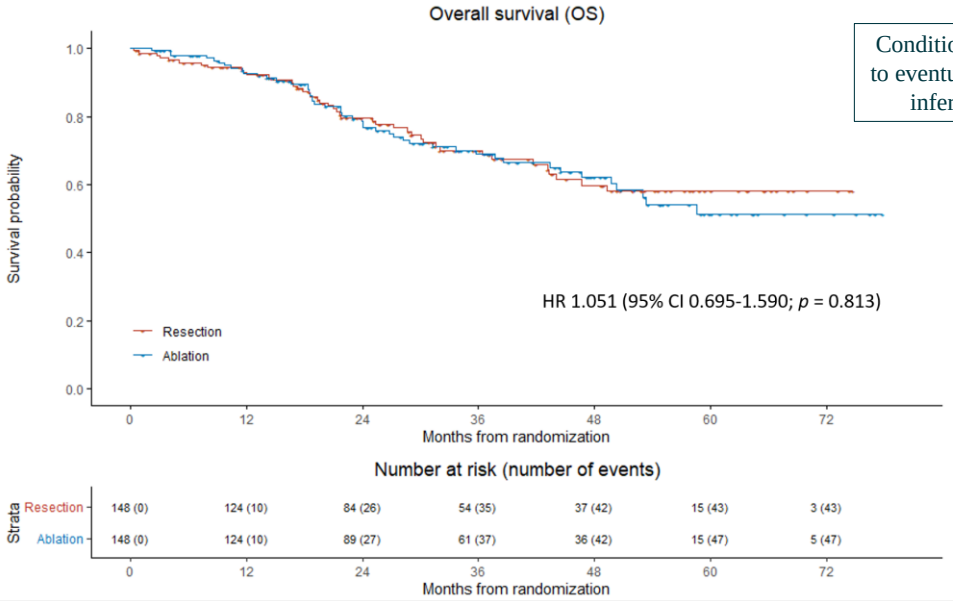

Meijerink M et al., ASCO 2024

# Management of limited metastases: Surgery or RFTA?

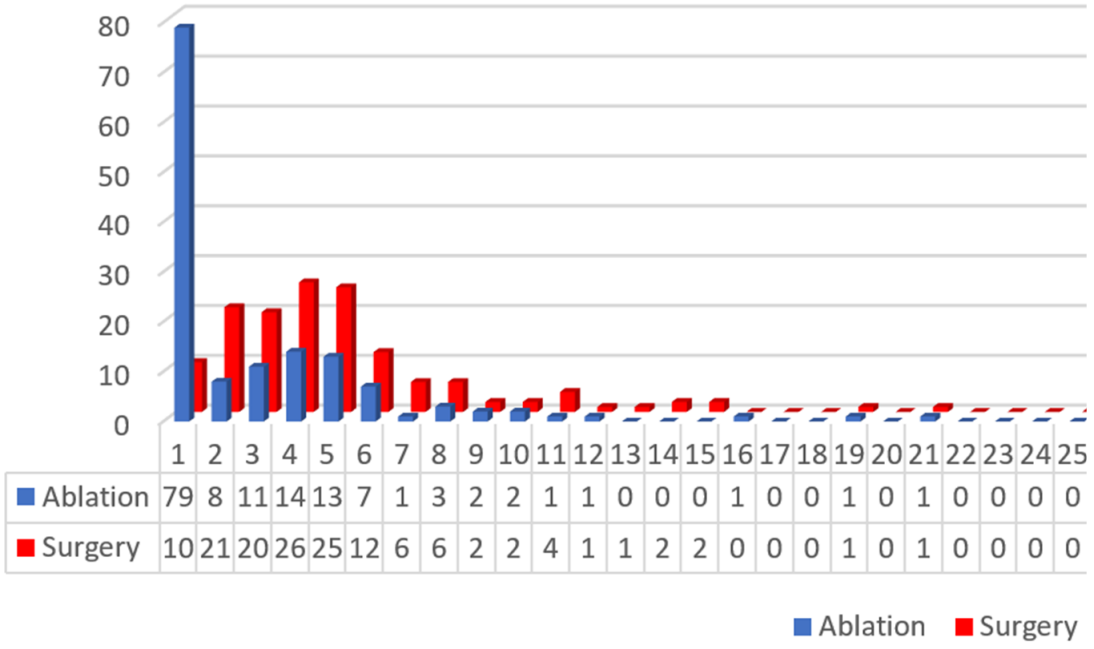
## RESULTS

OVERALL SURVIVAL – PRIMARY ENDPOINT

COLLISION Colorectal Liver Metastases: surgery vs thermal ablation




Conditional probability to eventually prove non-inferiority 91%!




Meijerink M et al., ASCO 2024

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# Statement der interdisziplinären AG GIT der DKG

- .....stellt die thermische Ablation eine onkologisch nicht inferiore Therapiealternative zur chirurgischen Resektion von resektablen Lebermetastasen dar.

  Dies gilt für klinische Situationen, in denen max. 10 Metastasen vorhanden und von denen mindestens eine ≤3cm groß ist.

- ... multifokale hepatische Metastasierung mit minimalem Parenchym-Verlust in eine makroskopische Tumorfreiheit...zu bringen.
- ...darf in diesem Zusammenhang auch als Argument für ein kombiniertes Verfahren aus Resektion und Ablation zur Vermeidung großer Parenchymverluste verstanden werden.

www.aio-portal.de; 02.09.2024

# How can we eradicate metastases?

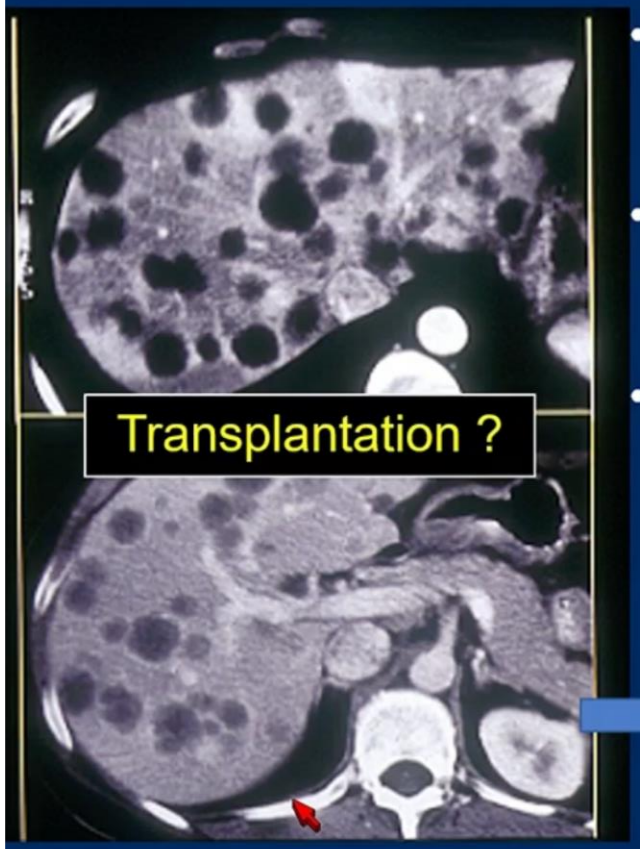
Local ablative treatments of metastases

| | |
|---|---|
| • Surgery | Eradication rate: 100% |
| • Local ablation techniques | Eradication rate: >95%* |
| • SBRT | Eradication rate: 70-100% |
| • Intra-arterial therapies | Eradication rate: 40-90%* |

*Depends on: size, localisation, physical effects (cooling,....), and: skills and techniques

# Management of liver limited metastases: Transplantation?

## Definitively Non Resectable Liver Metastases : Rationale



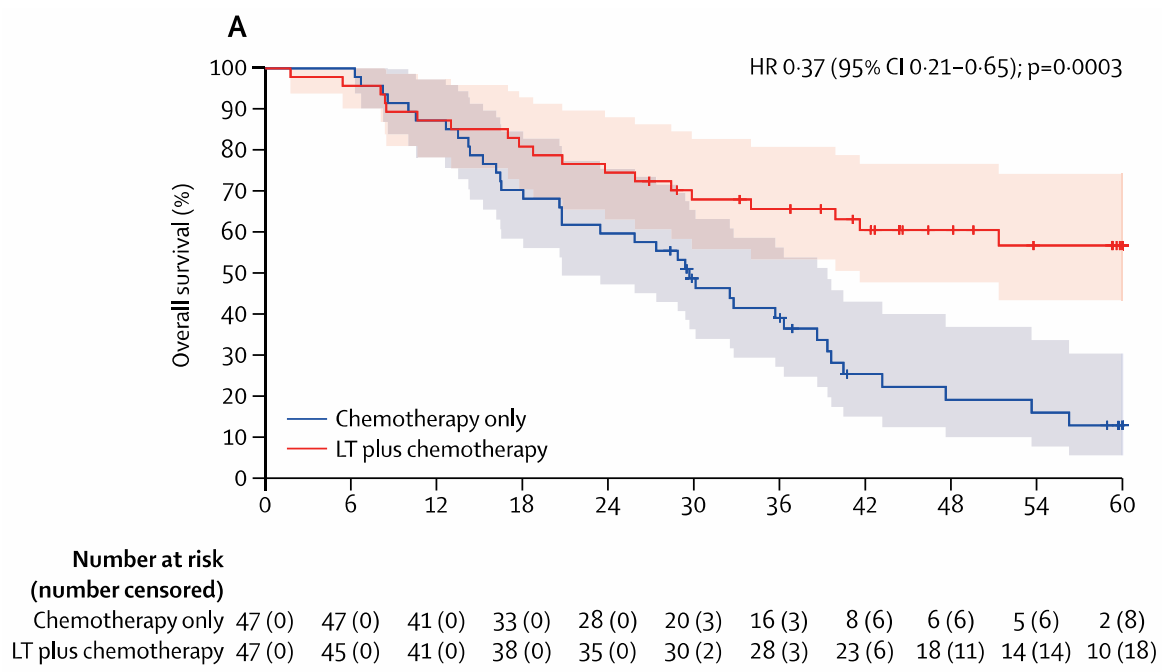

- Absolute contraindication in the 2000's because of the low 5-year survival (18%)[1]
- More recently : improved outcome with better patient selection and increased efficacy of chemotherapy (C)[2]
- However, strong evidence for clinical benefit : critical
  - Scarcity of organs
  - Perception "no role for local treatment in an advanced metastatic disease"

Randomised study to assess the efficacy of LT+C compared to C alone

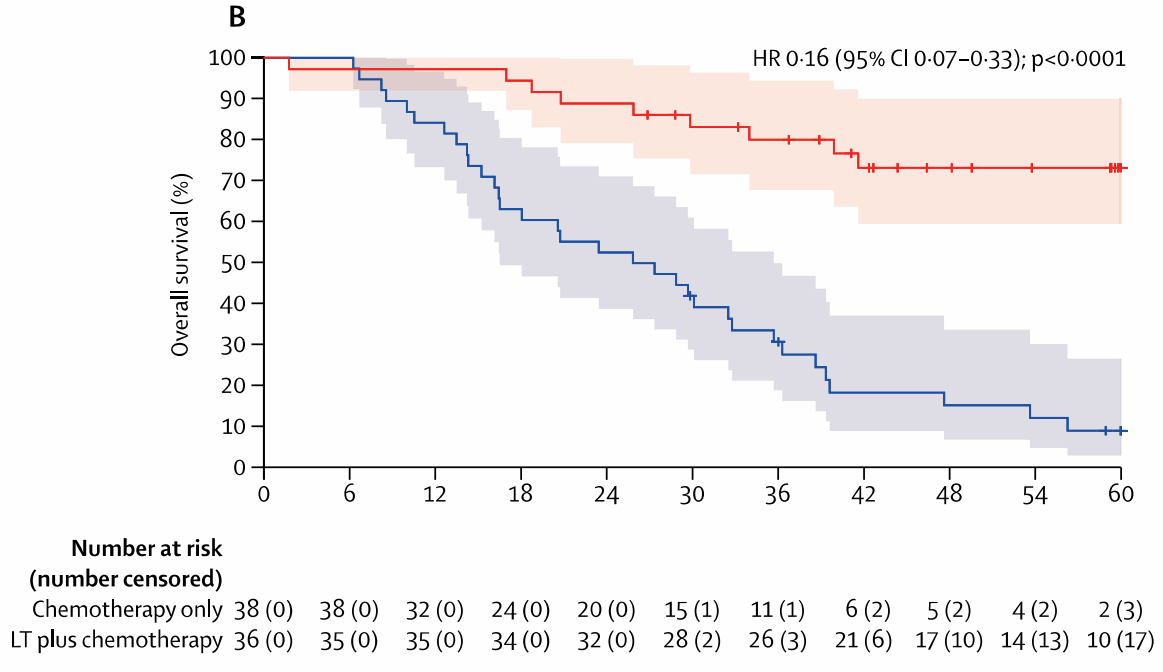
*(1) Foss et al, Tranplant Int 2010* *(2) Hagness et al, Ann Surg 2013*

Adam R et al., ASCO 2024

# Liver transplantation in mCRC: Randomized TRANSMET study




Overall survival, ITT population




Overall survival, PP population

Adam R et al., The Lancet 2024

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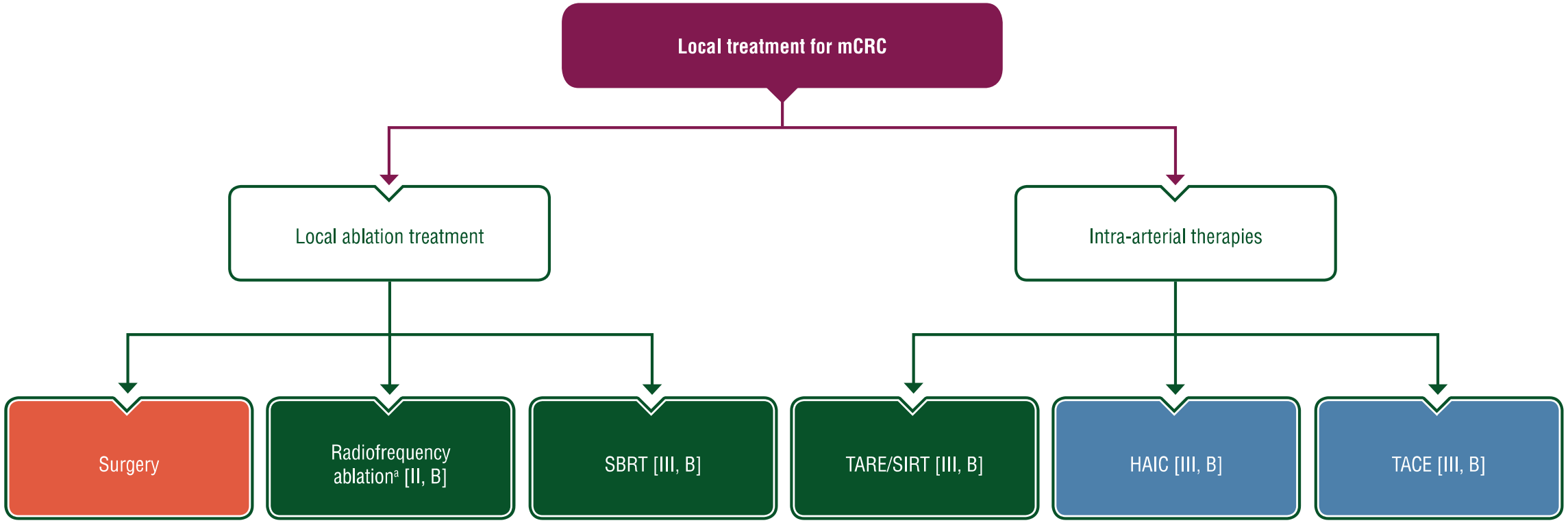
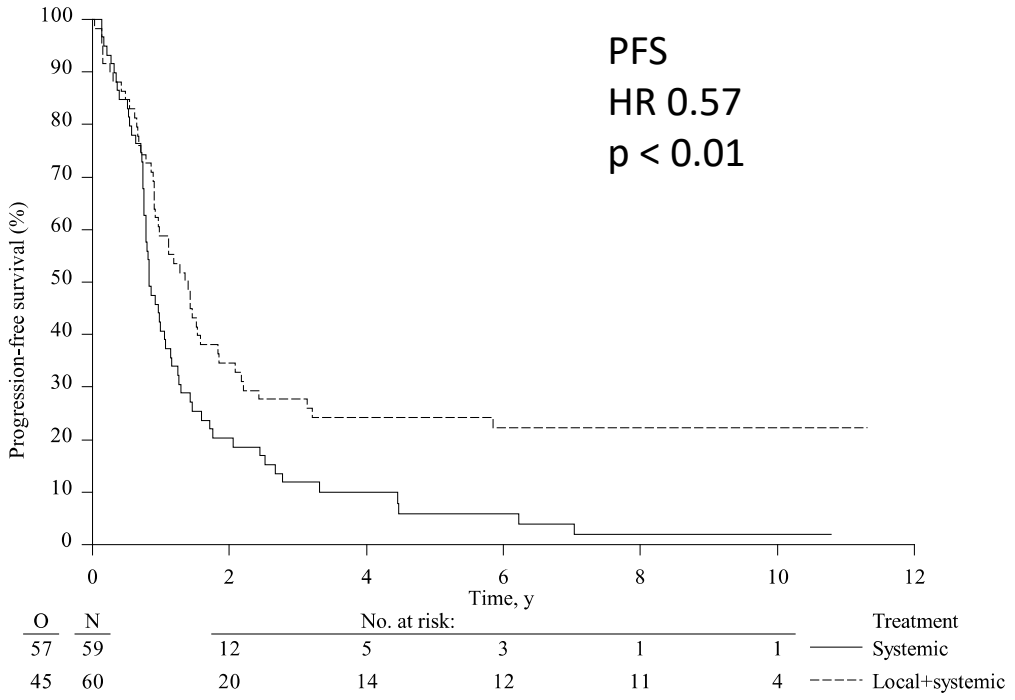
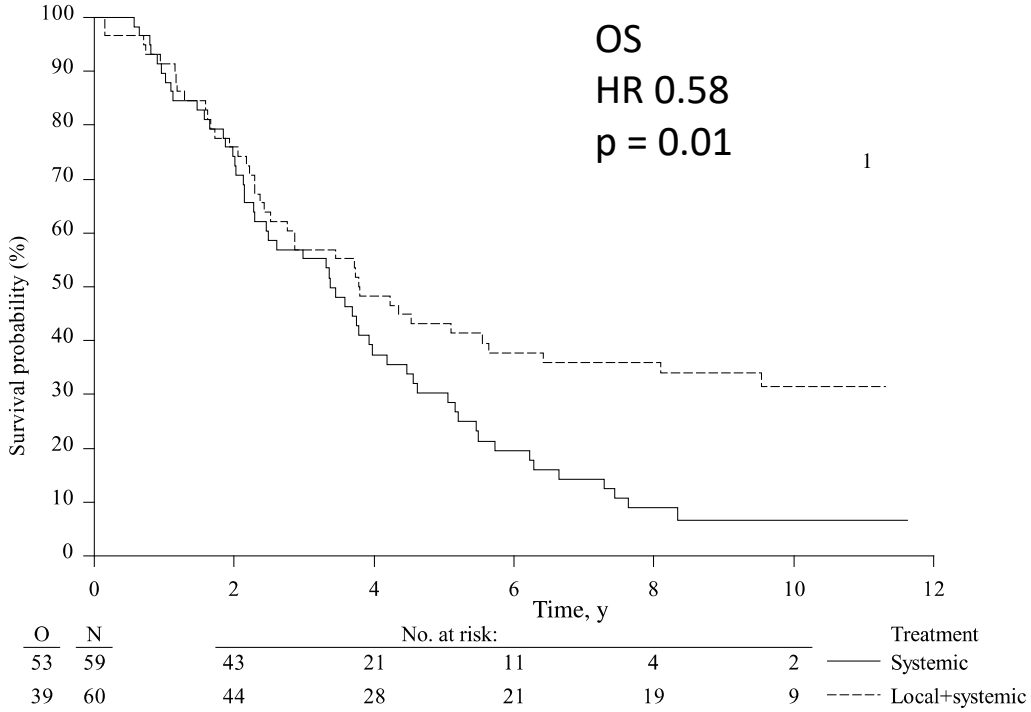



Cervantes et al., Ann Oncol 2023

# Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial

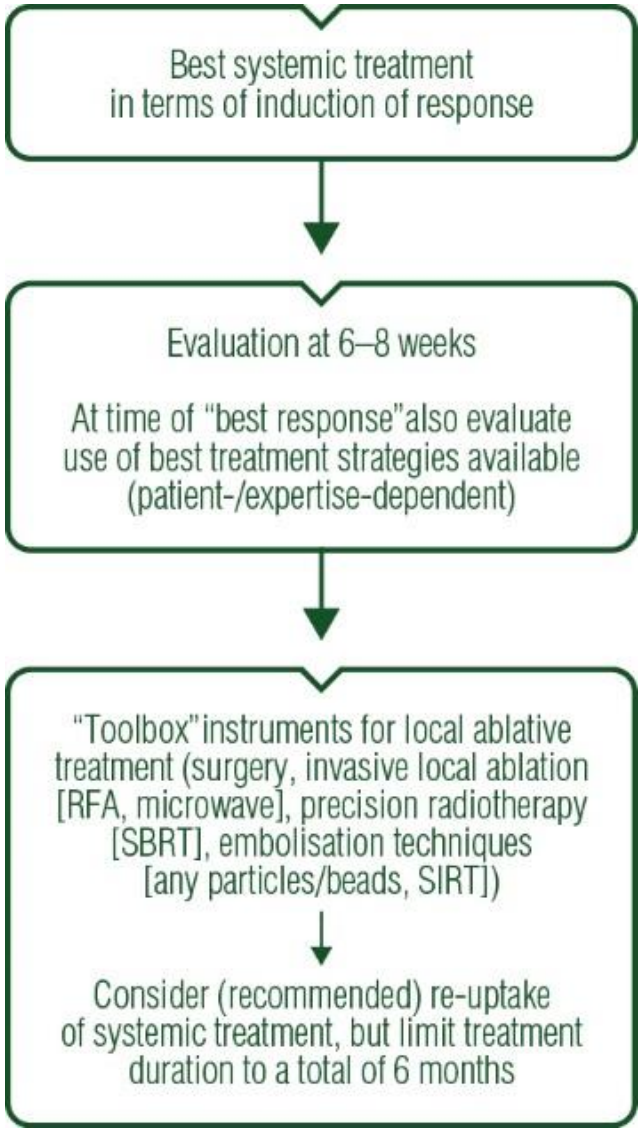
119 pts., “liver only” met disease; not suitable for resection; <10 lesions




CLOCC Trial, Ruers et al., JNCI 2017

Median follow-up 9.7 yrs




**Local ablative treatments....should be selected…..according to**

- Localisation and treatment goal
- 'the more curative the more surgery'/higher importance of local/complete control),
- treatment-related morbidity,
- local expertise and availability,
- patient-related factors.

Van Cutsem E et al., ESMO Consensus 2016; Ann Oncol 2016

# Local vs. systemic control: EORTC CLOCC and EPOC trials

Table 4
Follow-up and first progressions.

| | Radiofrequency ablation (RFA) – CLOCC ($N = 55$) | Resection (RES) – EPOC ($N = 81$) |
|---|---|---|
| Median fluorouracil (FU) from RFA/ surgery | 4.7 years | 8.2 years |
| Recurrences | 38 (69.1%) | 48 (59.3%) |
| Local recurrence per patient treated (LR)* | 8/55 (14.5%) | 6/81 (7.4%) |
| Local recurrence rate per lesion treated | 10/167 (6.0%) | 6/110 (5.5%) |
| Non-local liver recurrence# | 17 (30.9%) | 18 (22.3%) |
| Extra hepatic recurrence only | 13 (23.6%) | 24 (29.6%) |

*Includes for RFA: three treated patients with combined non-local liver recurrences.
*Includes for RES: one patient with a combined extra-hepatic recurrences.

**65%**

Tanis et al., Eur J Cancer 2014

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**6%**

Tanis et al., Eur J Cancer 2014

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**6%**

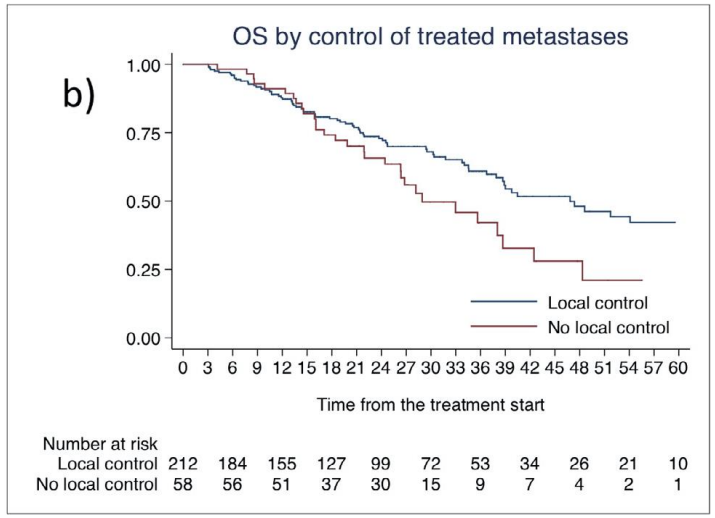
**50-55%**

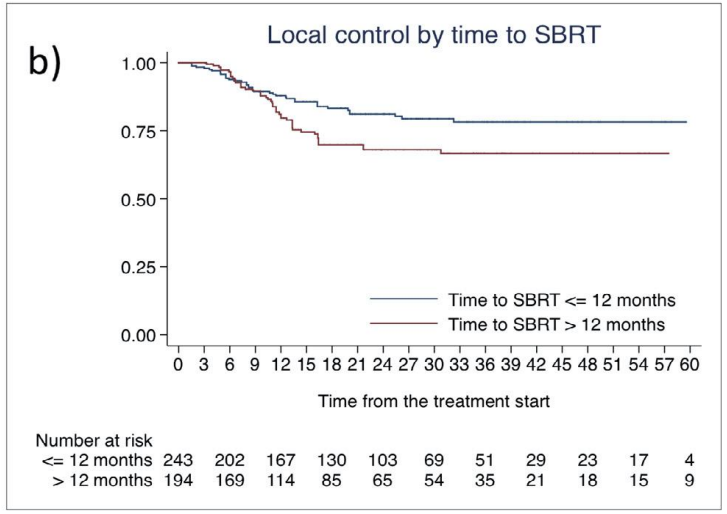
Tanis et al., Eur J Cancer 2014

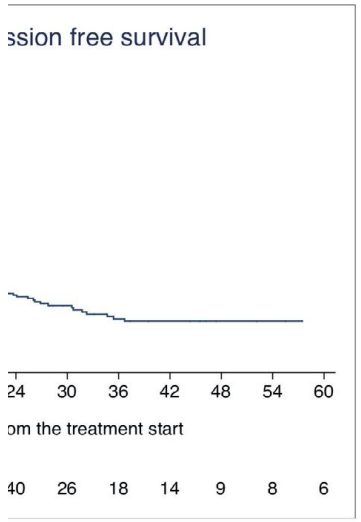
# Known prognostic factors: Control of systemic disease, and completeness of intervention

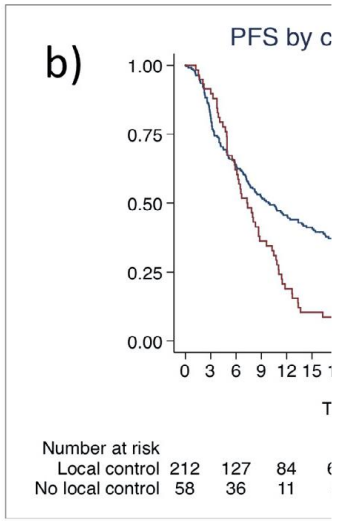
Original Article

## Predictive factors for survival of oligometastatic colorectal cancer treated with Stereotactic body radiation therapy



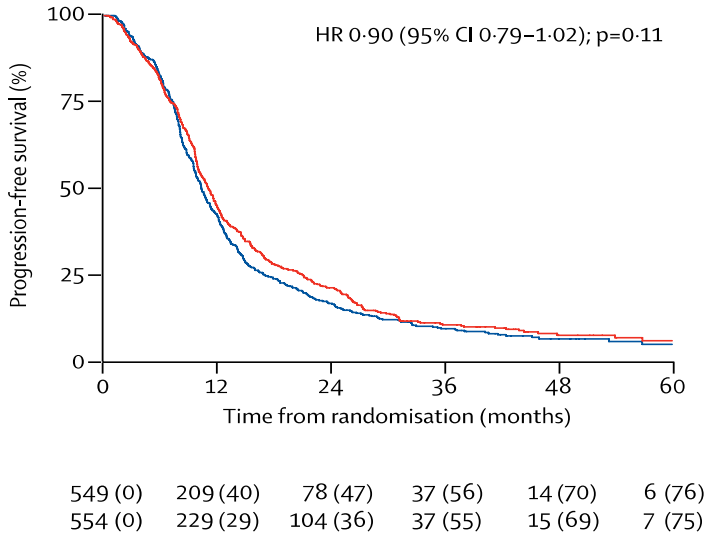




Franzese et al., Radiotherapy Oncol 2022

# Beispiel: transarterielle Radioembolisation beim KRK

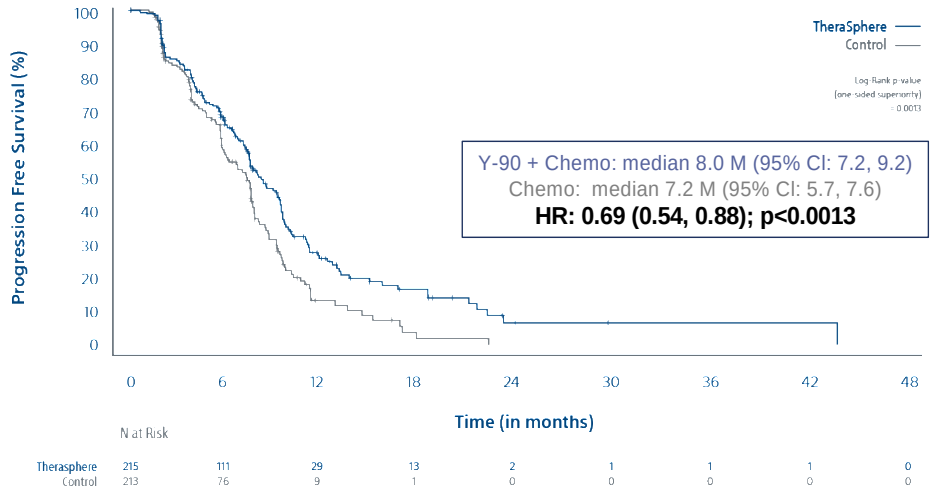
**First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials**




1st line, upfront TARE

## Radioembolization with Chemotherapy for Colorectal Liver Metastases: a randomized, open-label, international, multicenter, phase 3 trial

**EPOCH study**




2nd line, oligomets.

Wasan et al., Lancet Oncol 2017; Mulcahy et al., J Clin Oncol 2021

# Oligometastatic disease and LAT:  What can be improved?

**Not likely** to be „super relevant“:

(Technically) better surgery

(Technically) better Local Ablative Treatment (LAT)

Different systemic treatment

# Oligometastatic disease and LAT:  What can be improved?

**Not likely** to be „super relevant“:

(Technically) better surgery

(Technically) better Local Ablative Treatment (LAT)

Different systemic treatment

**More likely:**

Selection of patients with „biologically“ localized disease

Best integration of LAT - with surgery and systemic treatment

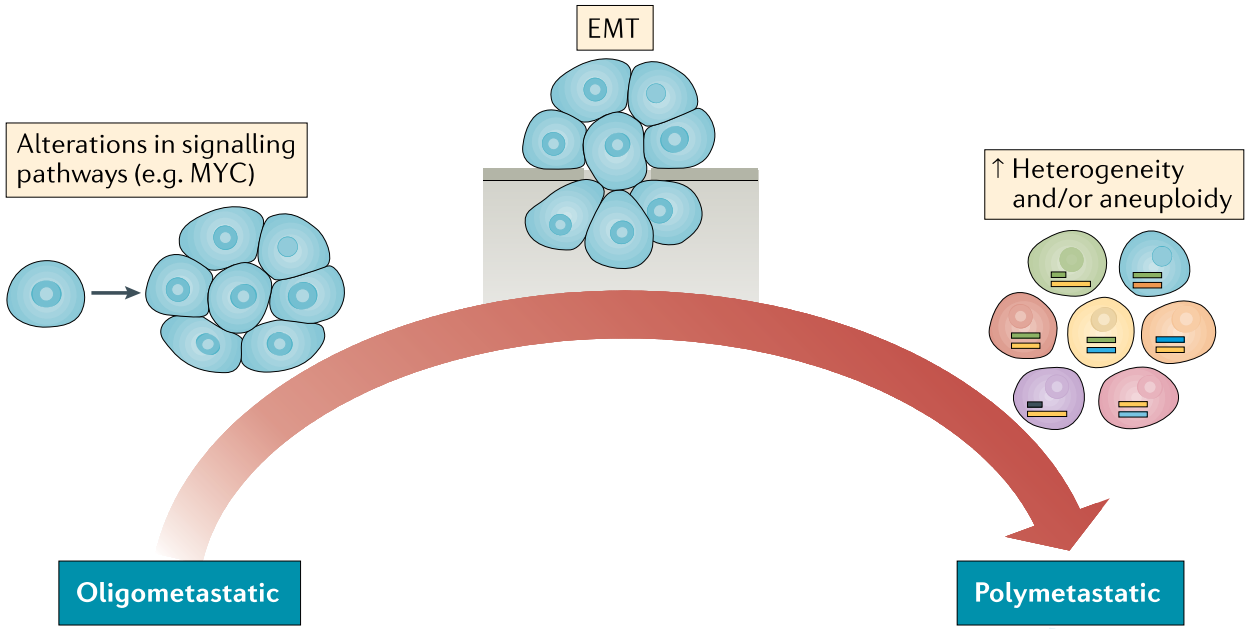
Evaluation of common, but not fully evaluated clinical scenarios

Understanding oligometastatic disease

The benefit of local treatment in mCRC

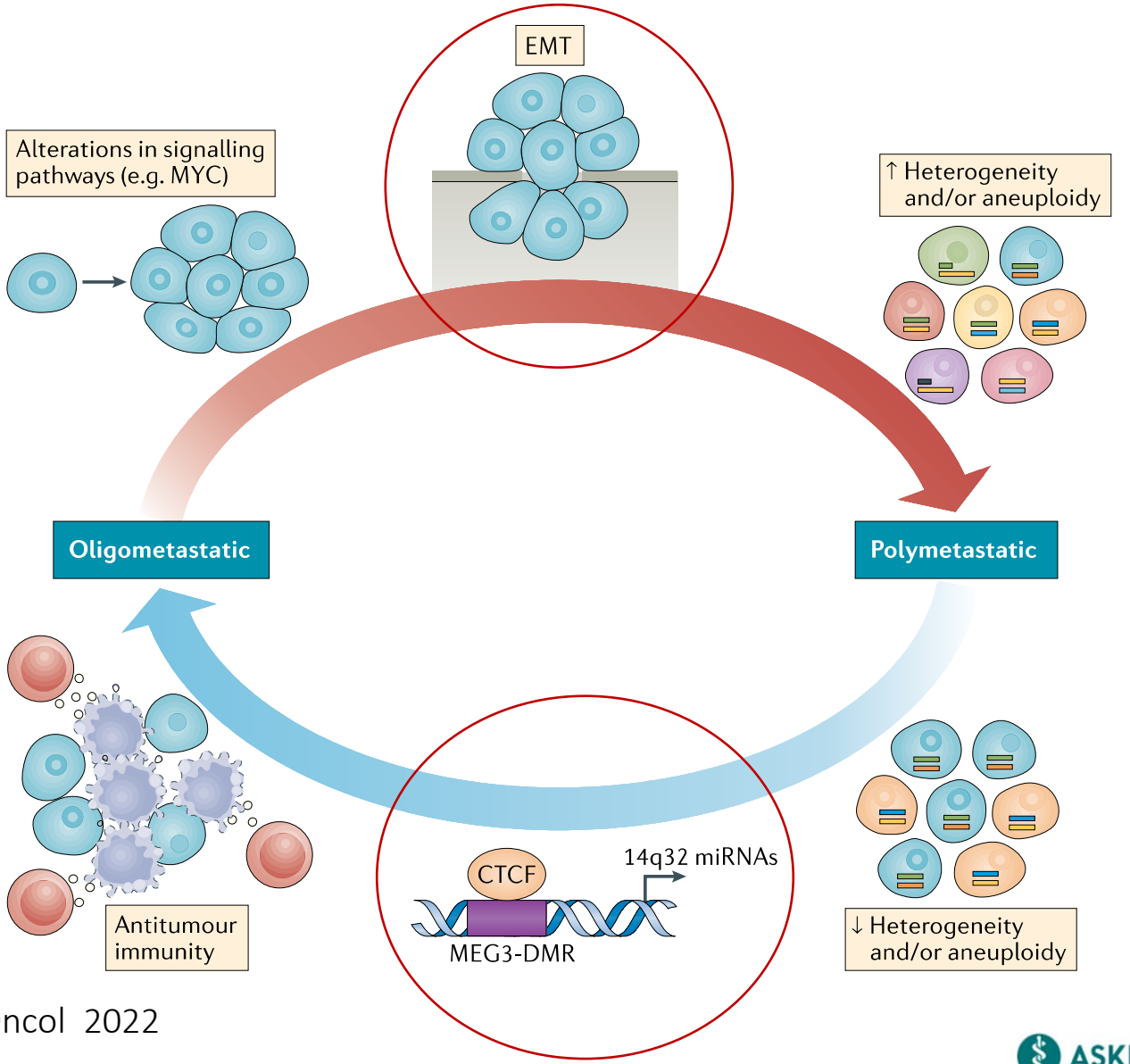
Improving the concept

# Mechanistic determinants of metastatic heterogeneity




Katipally RR et al., Nat Rev Clin Oncol 2022

# Mechanistic determinants of metastatic heterogeneity



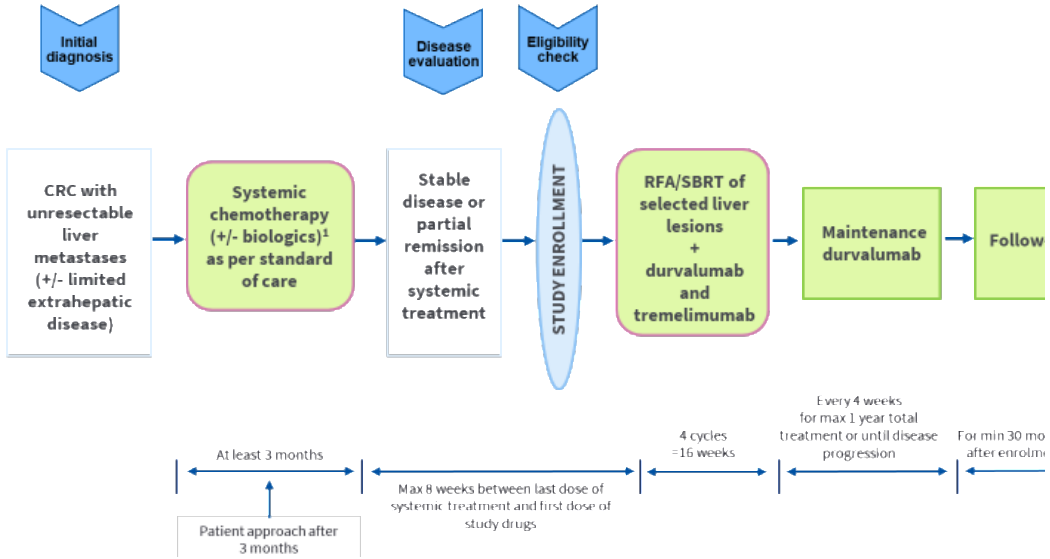

Controlling **EMT**

Gaining **immunogenic control**

Katipally RR et al., Nat Rev Clin Oncol 2022

# Durvalumab and tremelimumab plus local partial tumor ablation (RFA or stereotactic radiotherapy) in patients with unresectable liver metastases from metastatic colorectal cancer: Results of the EORTC-1560-GITCG multicentre single-arm phase II study (ILOC)

Seligmann J[1], Koessler T[2], Mauer M[3], Evrard S[4], Freedman J[5], Gootjes EC[6], Guckenberger M[7], Govaerts AS[3], Giraut A[3], Ricke J[8], Folprecht G[9], Arnold D[10], Giasafaki P[3], Ducreux M[11], Antunes S[3], Ruers T[12]

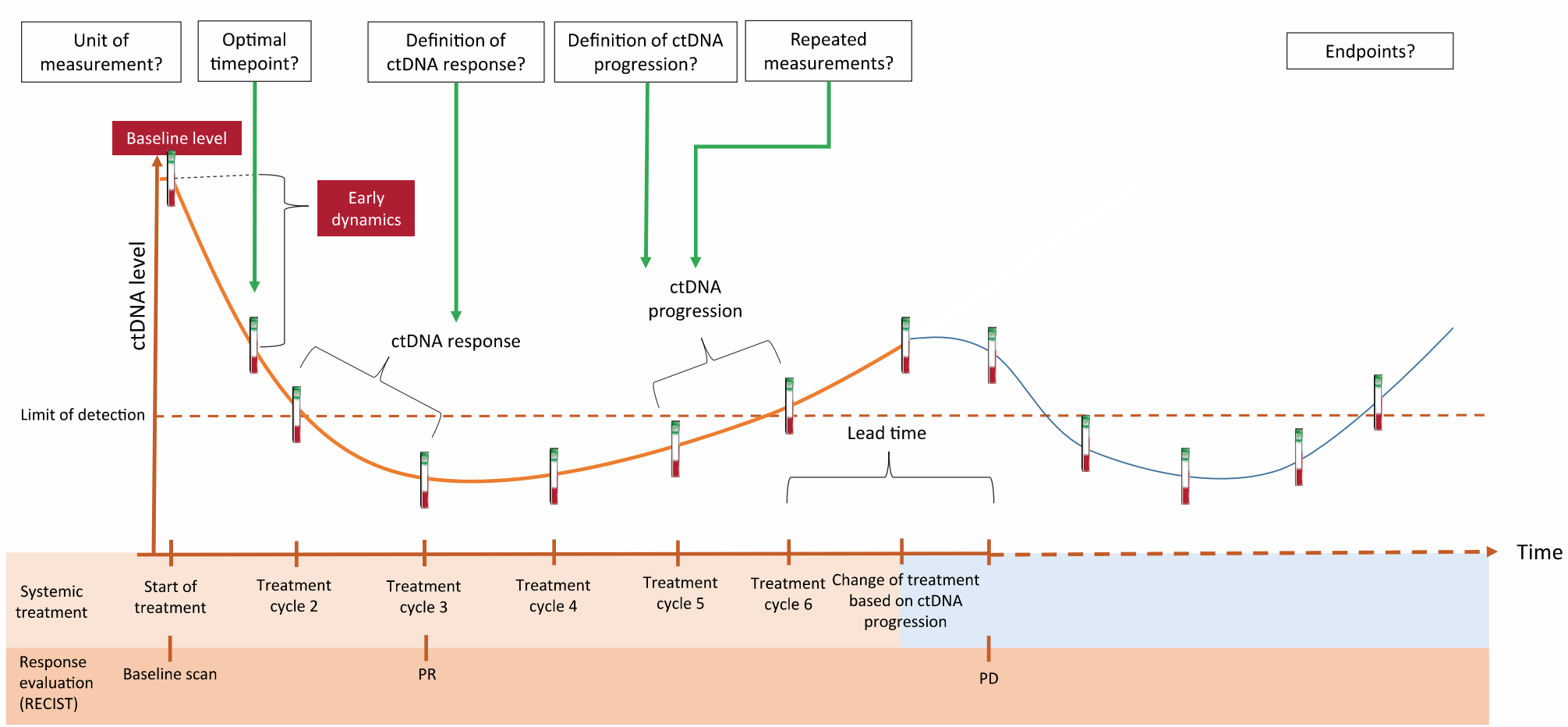



| | Type of local tumor ablation | | |
|---|---|---|---|
| | RFA (radiofrequency ablation) (N=12) | SBRT (stereotactic radiotherapy) (N=8) | Total (N=20) |
| Best overall immune response | N (%) | N (%) | N (%) |
| iCR+iPR | 0 | 0 | 0 |
| iSD | 5 (41.7) | 4 (50.0) | 9 (45.0) |
| iCPD/iUPD | 7 (58.3) | 4 (50.0) | 11 (55.0) |

Seligman J et al., ASCO GI 2024; in press

# Opportunity #2:
# Treatment determination by ctDNA

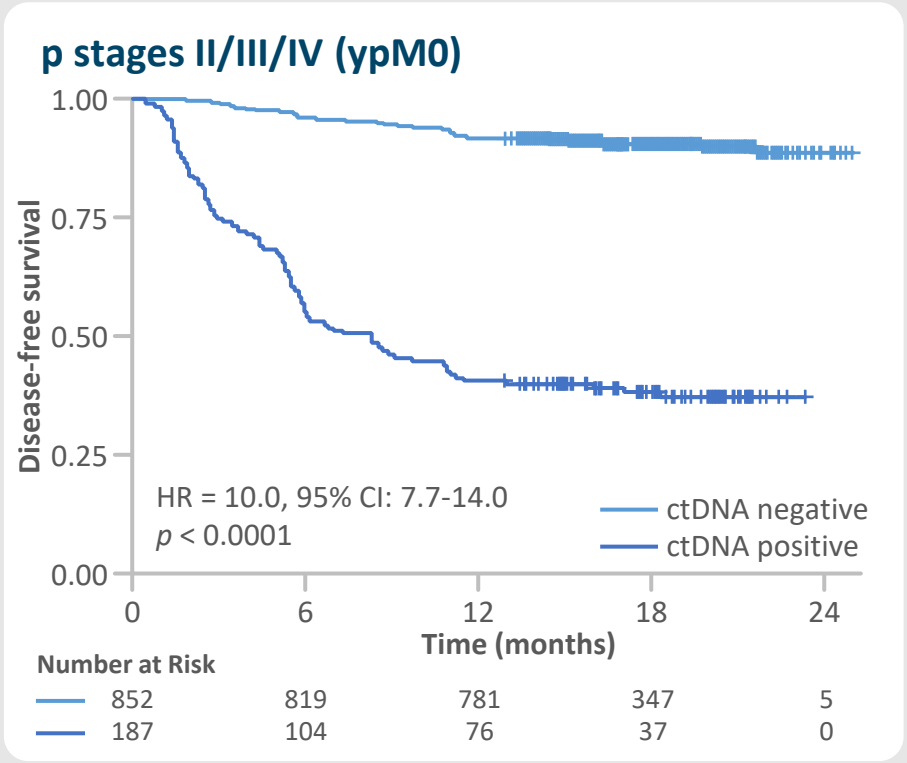
# Continous assessment - treatment needs




Brenner Thomssen, Arnold et al., Cancer 2022

# More than 2,000 pts: Japanese GALAXY / CIRCULATE

## Disease free survival (DFS) based on ctDNA status at 4 weeks post-surgery

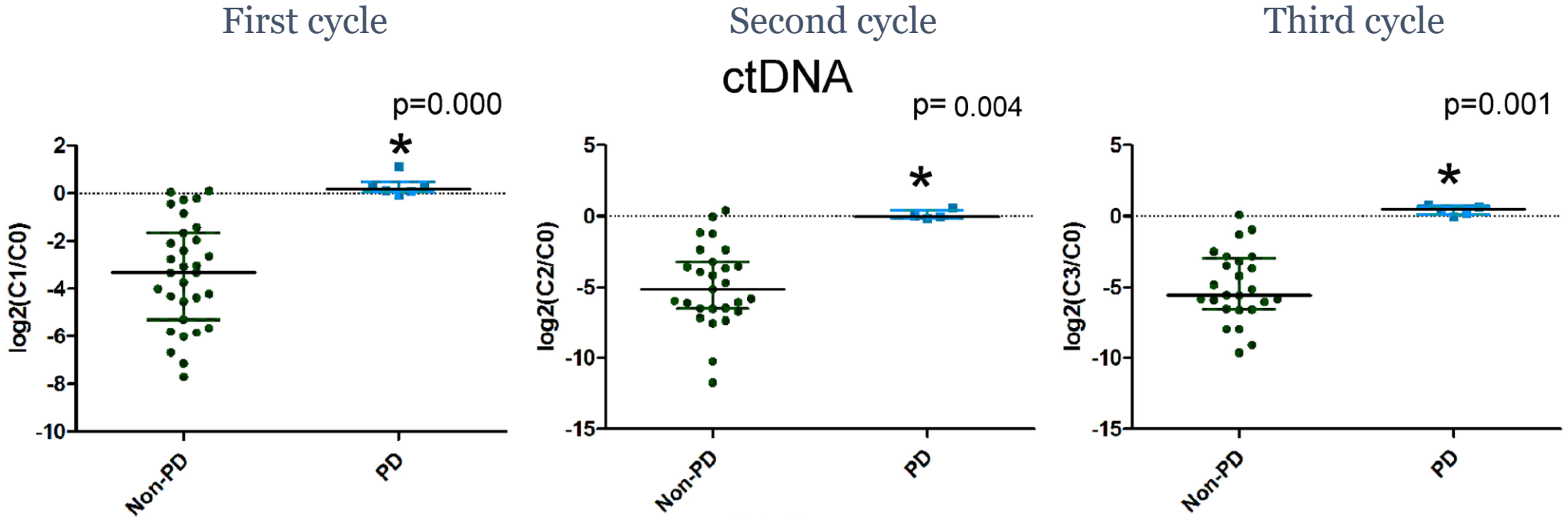



| ctDNA | Events/N | 6M-DFS (95% CI) | 12M-DFS (95% CI) | 18M-DFS (95% CI) |
|---|---|---|---|---|
| ctDNA negative | 81/852 | 96.1% (94.6-97.2) | 91.7% (89.6-93.3) | 90.5% (88.3-92.3) |
| ctDNA positive | 115/188 | 55.6% (48.2-62.64) | 40.6% (33.6-47.6) | 38.4% (31.4-45.5) |

With a single test at 4w post-op, overall 18M-DFS of 38.4% in the MRD-positive group and 90.5% in the MRD-negative group, including all treated and non-treated patients

Kotani D et al., Nature Med 2023

# ctDNA dynamics indicating response to systemic tx.



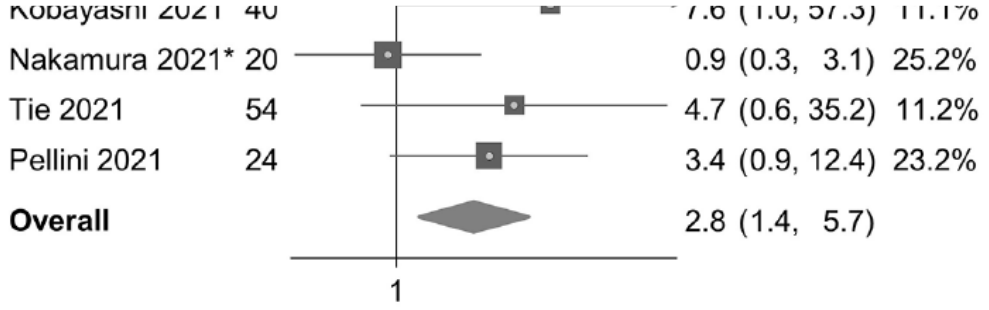

| Variable | AUC | *p* value | Cutoff value | Sensitivity (%) (95% CI) | Specificity (%) (95% CI) | PPV (%) (95% CI) | NPV (%) (95% CI) | Accuracy (%) (95% CI) |
|---|---|---|---|---|---|---|---|---|
| ctDNA log2 (C1/C0) | 0.978 | 0.000 | −0.126 | 100.0 (54.1–100.0) | 93.5 (78.6–99.2) | 75.0 (34.9–96.8) | 100.0 (88.1–100.0) | 94.6 (81.8–99.3) |
| ctDNA log2 (C2/C0) | 0.954 | 0.004 | −0.655 | 100.0 (39.8–100.0) | 92.6 (75.7–99.1) | 66.7 (22.3–95.7) | 100.0 (86.3–100.0) | 93.5 (78.6–99.2) |
| ctDNA log2 (C3/C0) | 0.992 | 0.001 | −0.471 | 100.0 (47.8–100.0) | 96.0 (79.7–99.9) | 83.3 (35.9–99.6) | 100.0 (85.8–100.0) | 96.7 (82.8–99.9) |

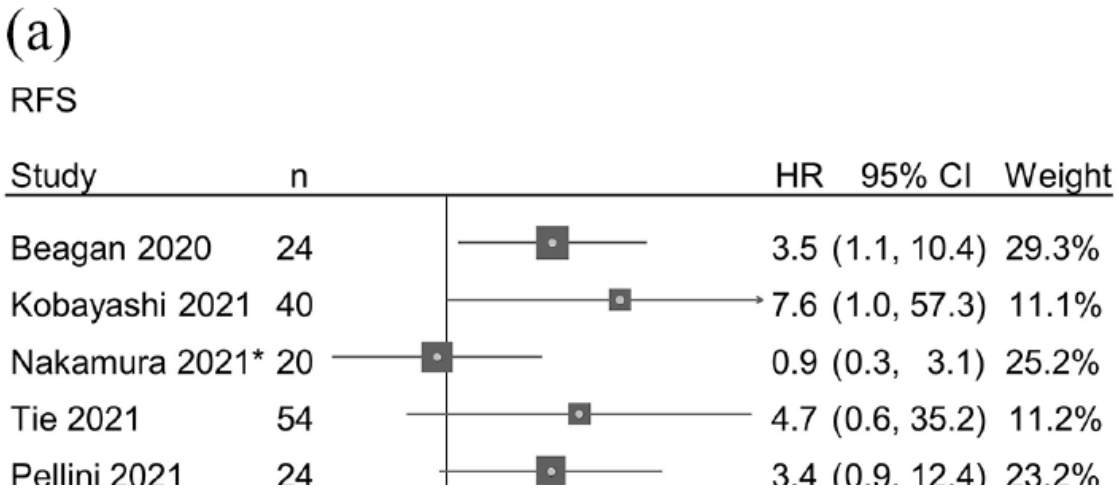
Jia et al., Front Genet 2021

# Circulating DNA in patients undergoing loco-regional treatment of colorectal cancer metastases: a systematic review and meta-analysis

Louise B. Callesen, Tana Takacova, Julian Hamfjord, Florian Würschmidt, Karl J. Oldhafer, Roland Brüning, Dirk Arnold and Karen-Lise G. Spindler

in pre-ablation samples




Callesen et al., Ther Adv Med Oncol 2022

ASKLEPIOS TUMORZENTRUM HAMBURG

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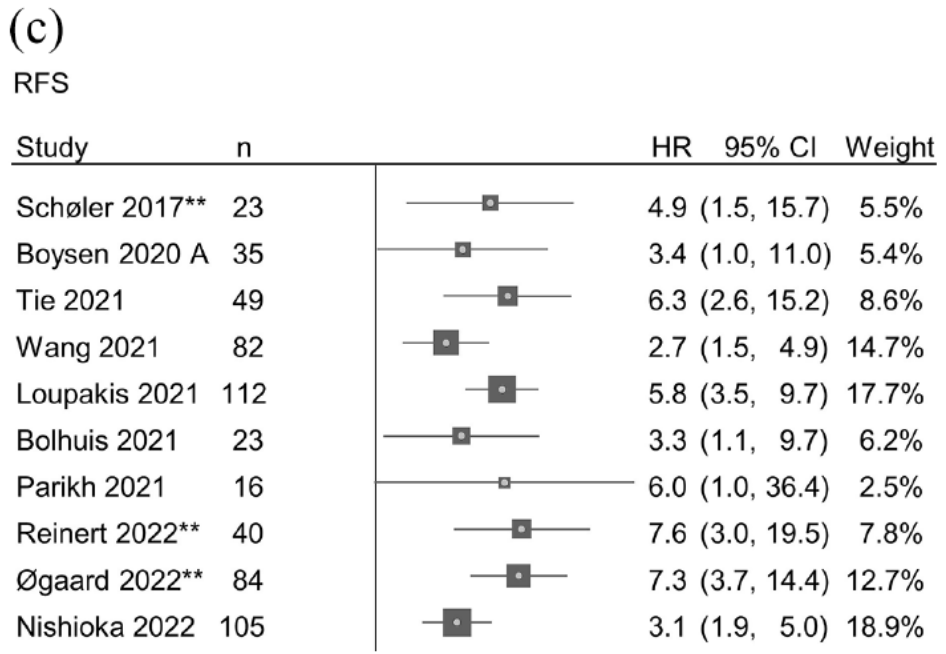
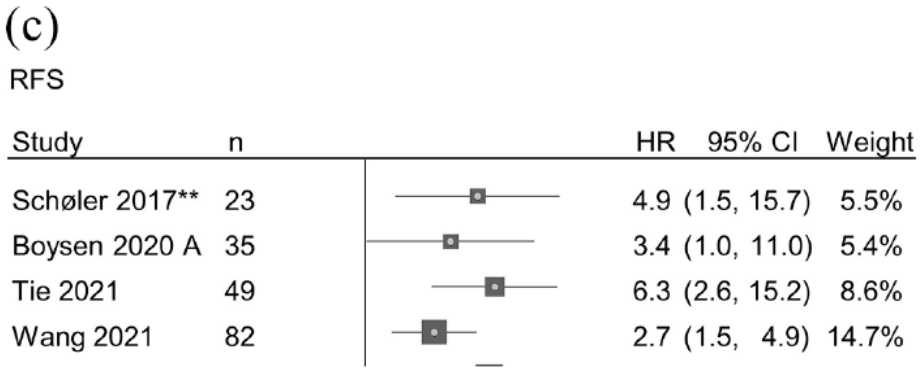
in post-ablation samples

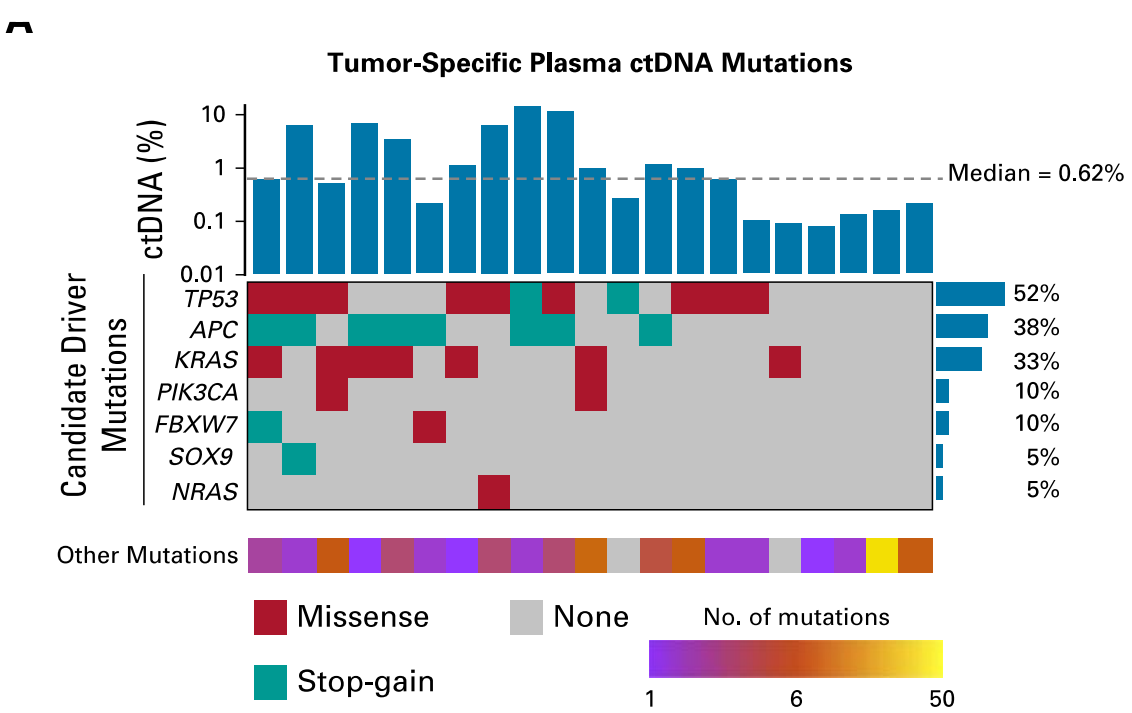


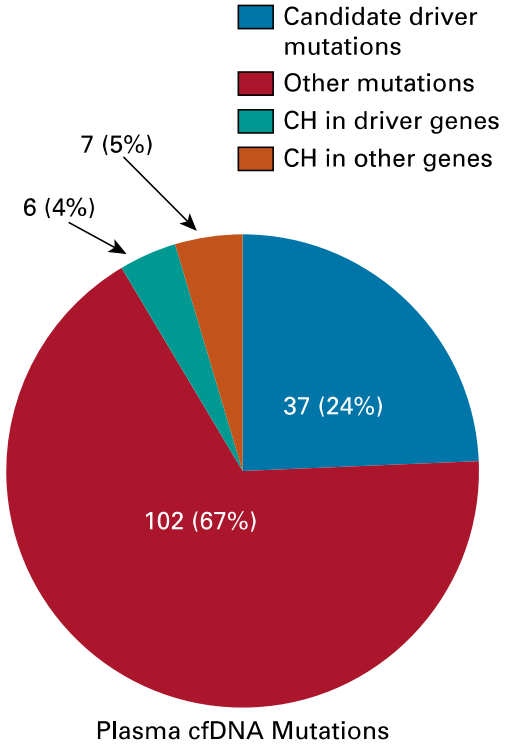



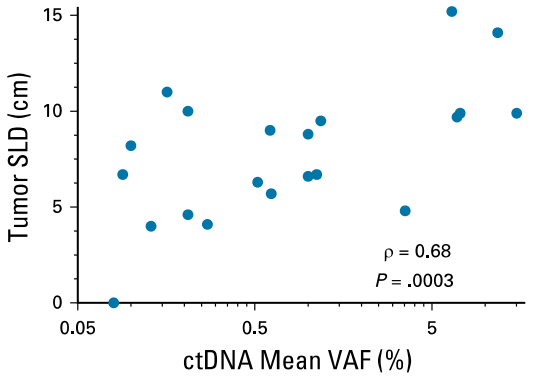

Callesen et al., Ther Adv Med Oncol 2022

BIOMARKERS

# ctDNA MRD Detection and Personalized Oncogenomic Analysis in Oligometastatic Colorectal Cancer From Plasma and Urine



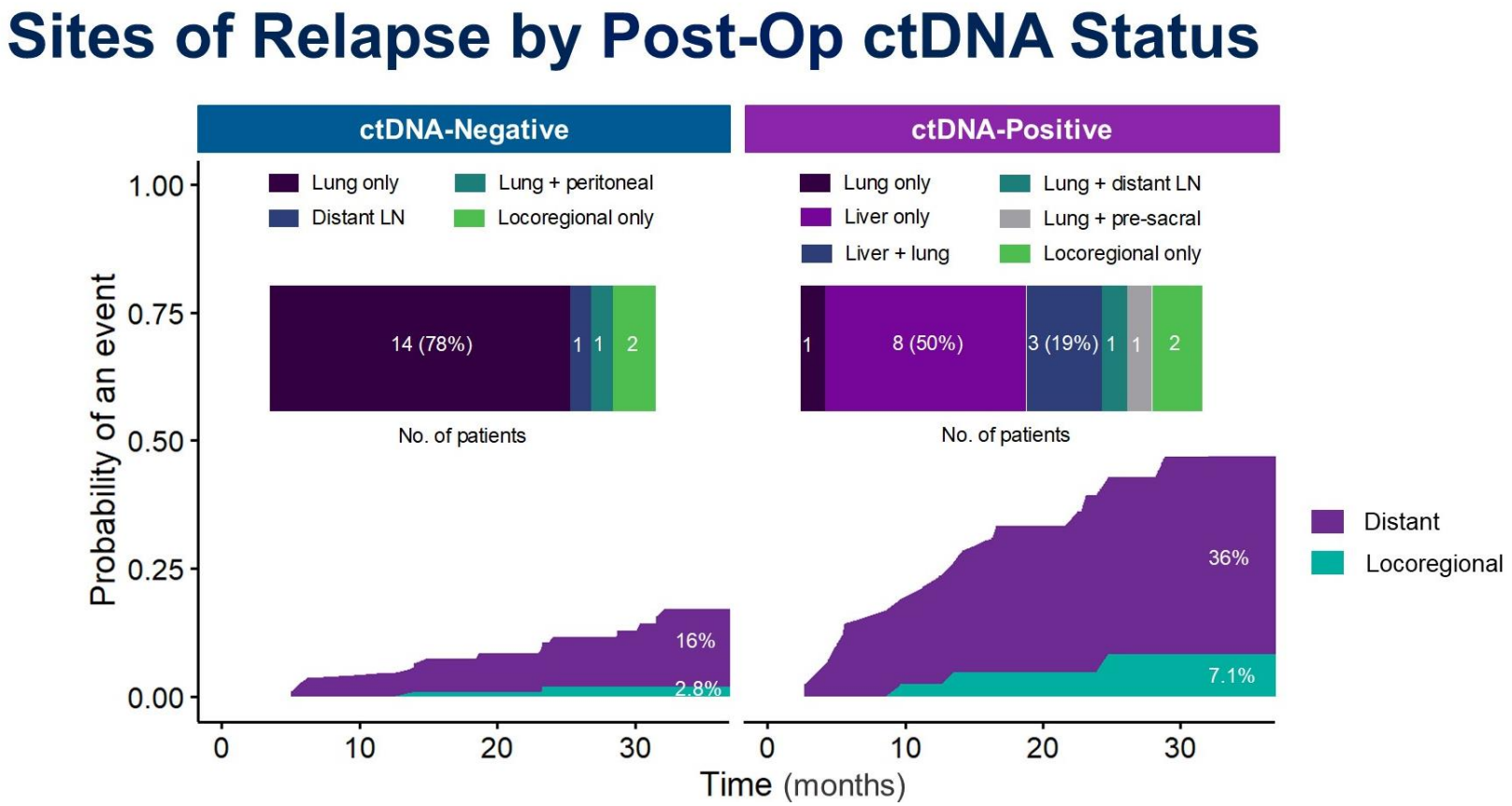




Pellini et al., JCO Precis Oncol 2023

# ctDNA MRD profile may correlated with site of relapse

Australian DYNAMIC Rectal trial




Tie J et al., GI Cancer Symposium 2024

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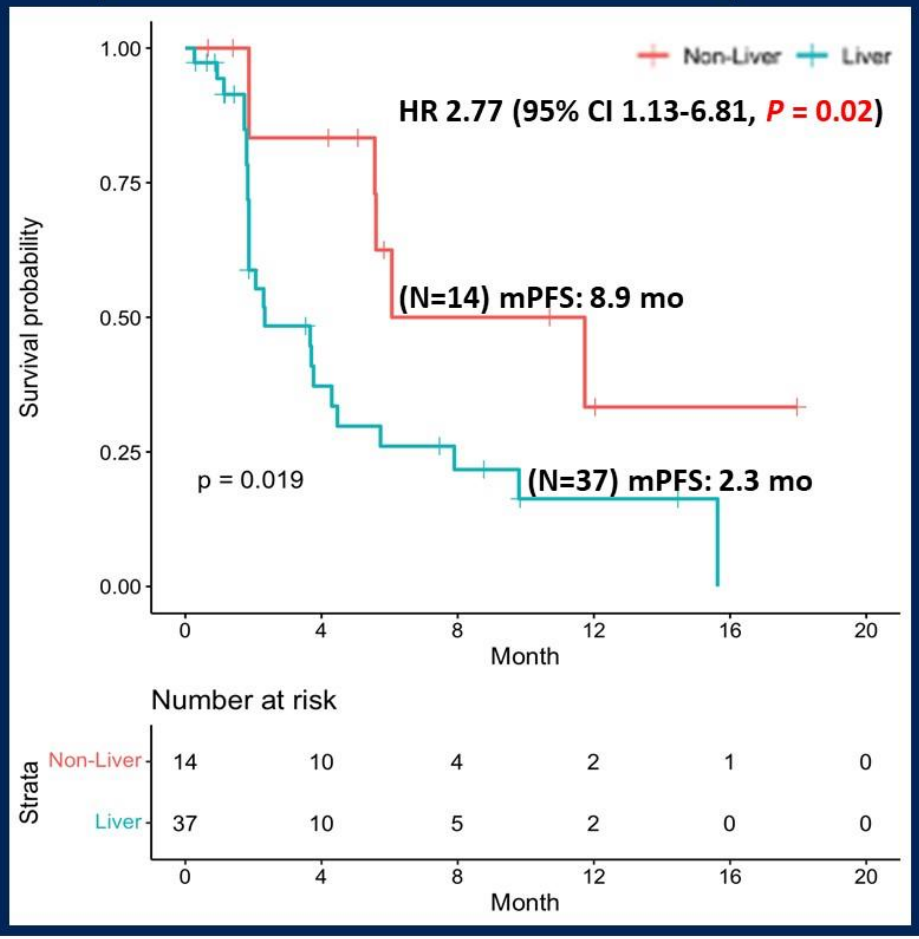
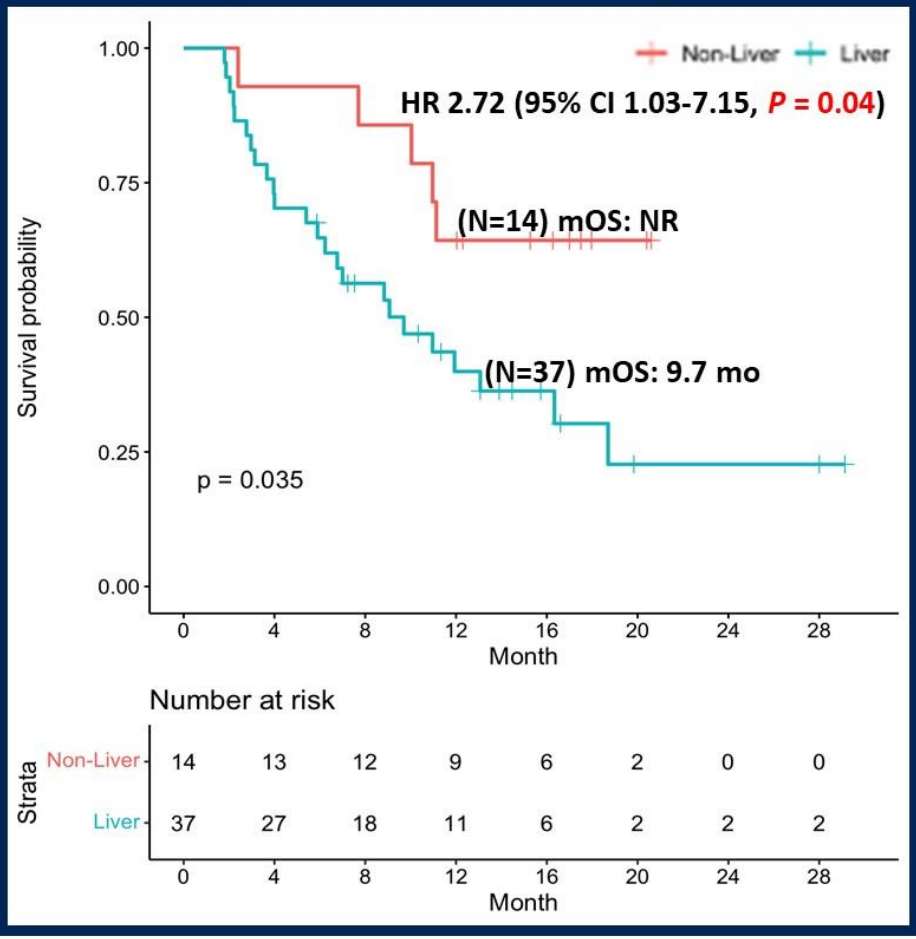
# Opportunity #3:
# Considering different immunology of different metastatic sites

# PFS and OS by Presence and Lack of Liver Metastases in MSS MCRC

## Progression Free Survival

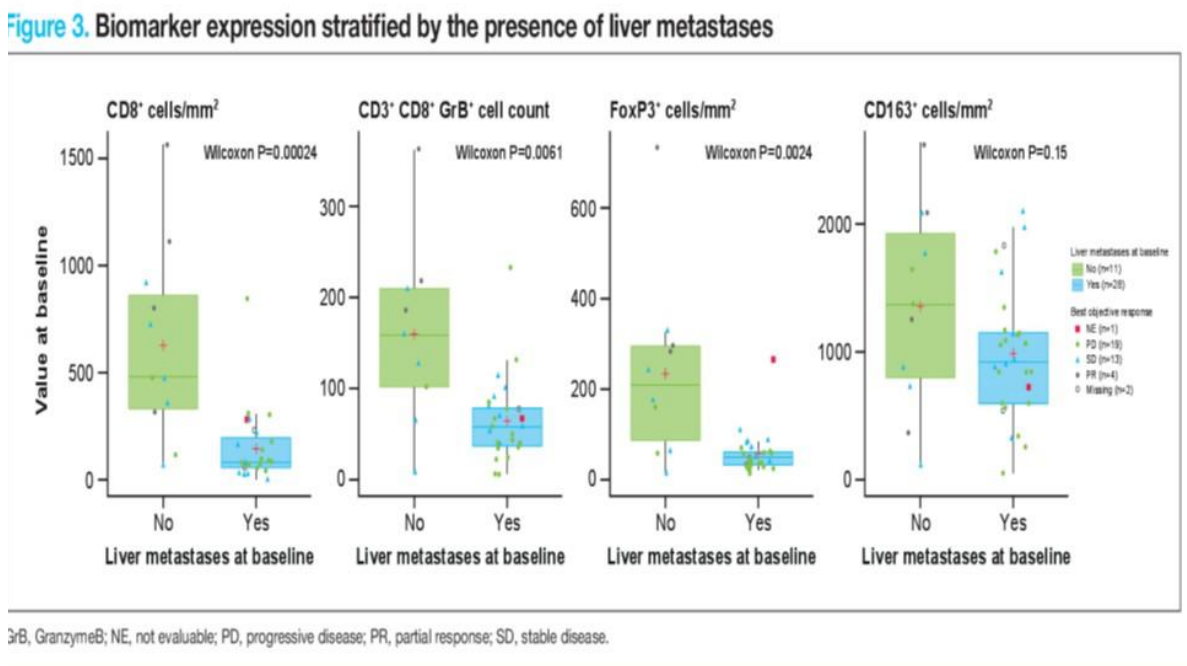


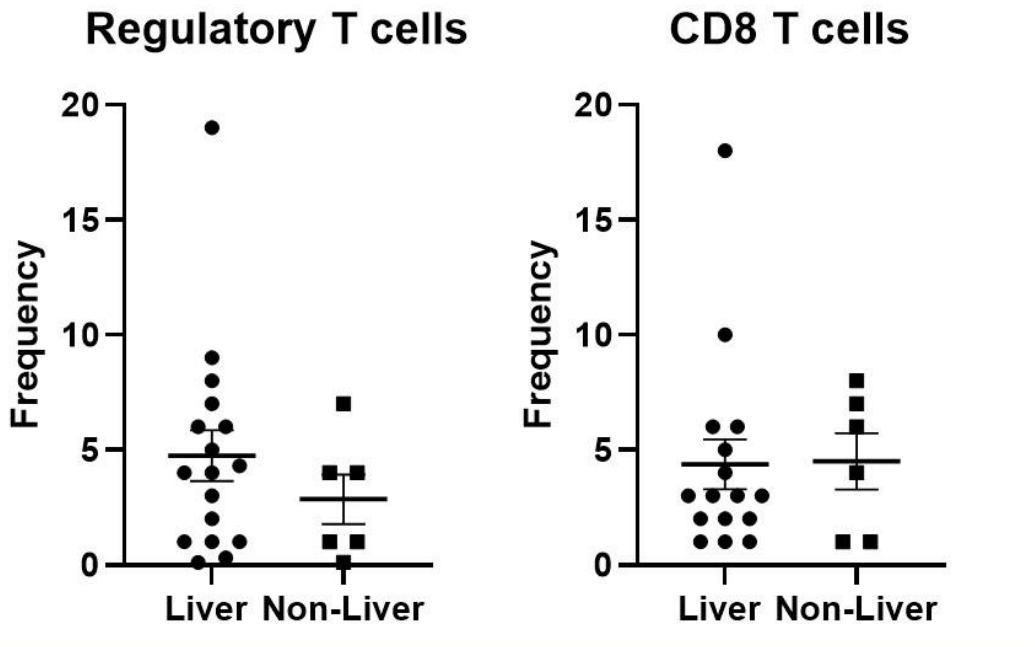

## Overall Survival




Kim R et al., ASCO 2023

# Biological characteristics of colorectal liver metastases



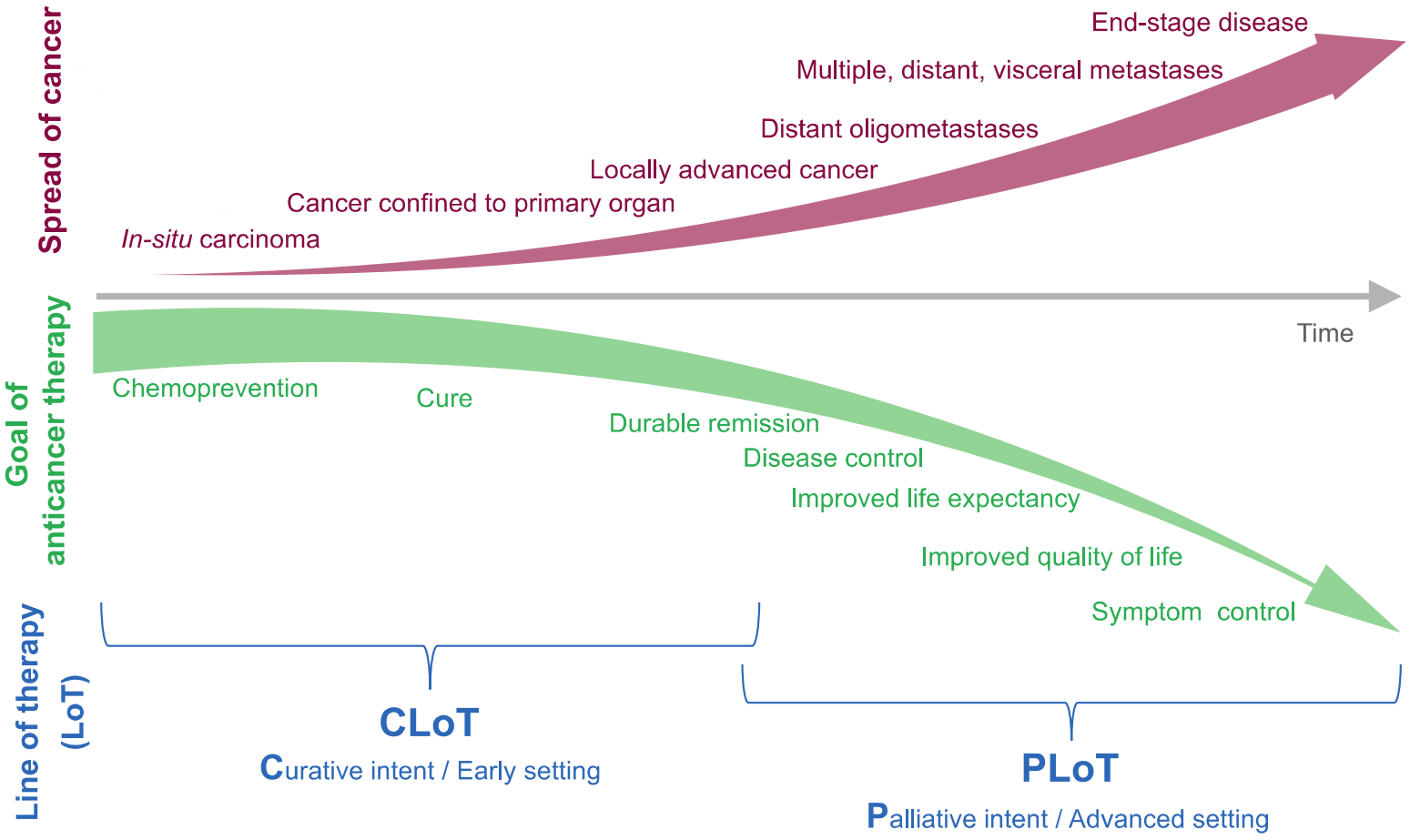




Fakih M et al., ASCO 2022; Kim R et al., Eur J Cancer 2022

# Summary

- OMD is an established concept in management of mCRC
- Various treatment modalities - with the specific pro´s and con´s
- Studies have identified specific molecular and genetic features that underlie the oligometastatic phenotype
  - Genes that encode reduced cancer cell migration and invasion ability
  - Factors that indicate enhanced immune response (likely in the metastatic microenvironment).
  - Prognostic and predictive molecular features
  - Site of metastasation
  - ctDNA may help to determine the best clinical scenario
- However – biology is not yet ready for prime time.....more trials!

# OMD in treatment *lines*: Where are we „in“?




Saini K and Twelves C, Eur J Cancer 2021

**Dirk Arnold**

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ASKLEPIOS TUMORZENTRUM HAMBURG