# Individualisierte Therapie beim mCRC

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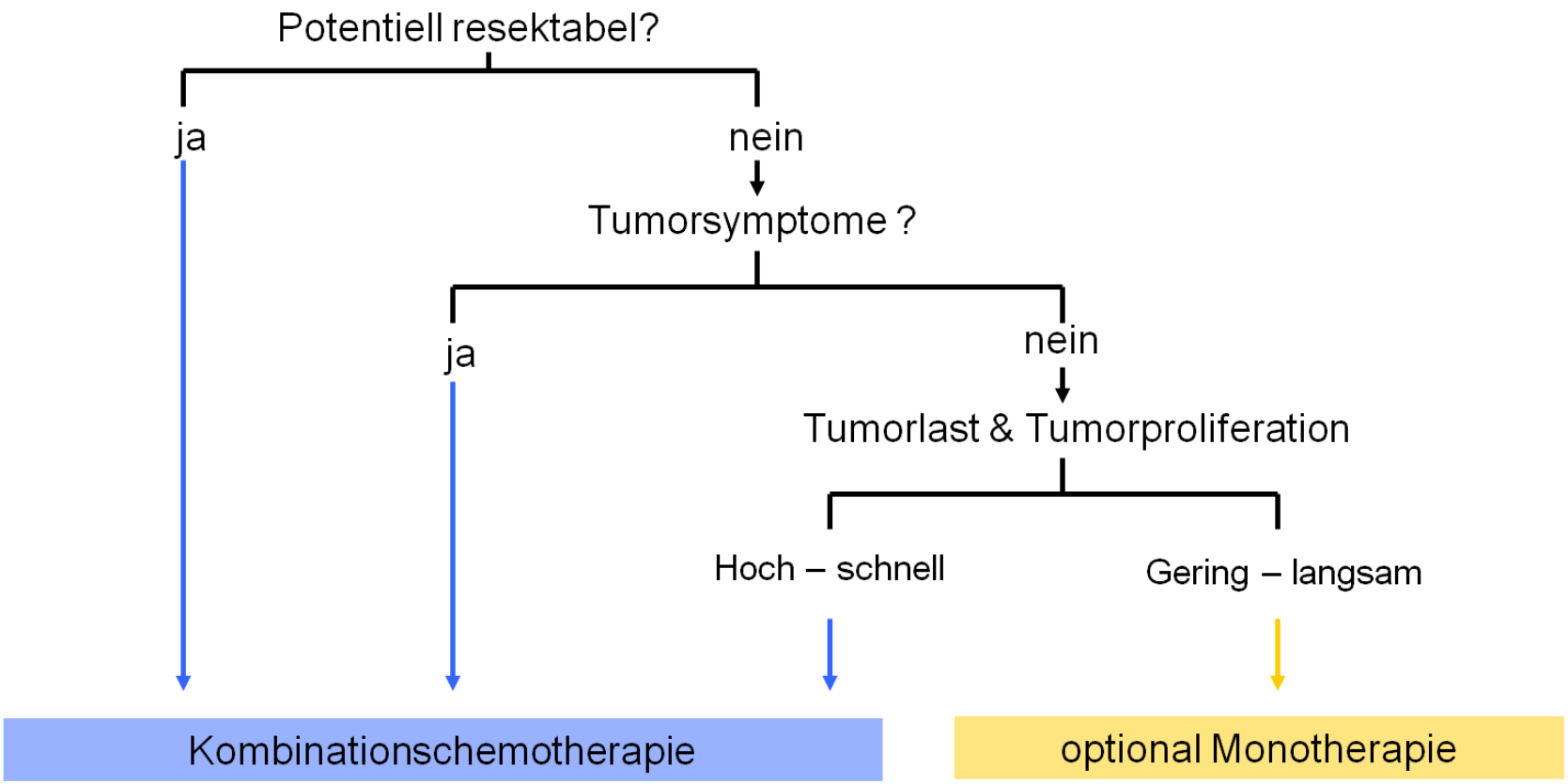
Med. Klinik III, Comprehensive Cancer Center der LMU





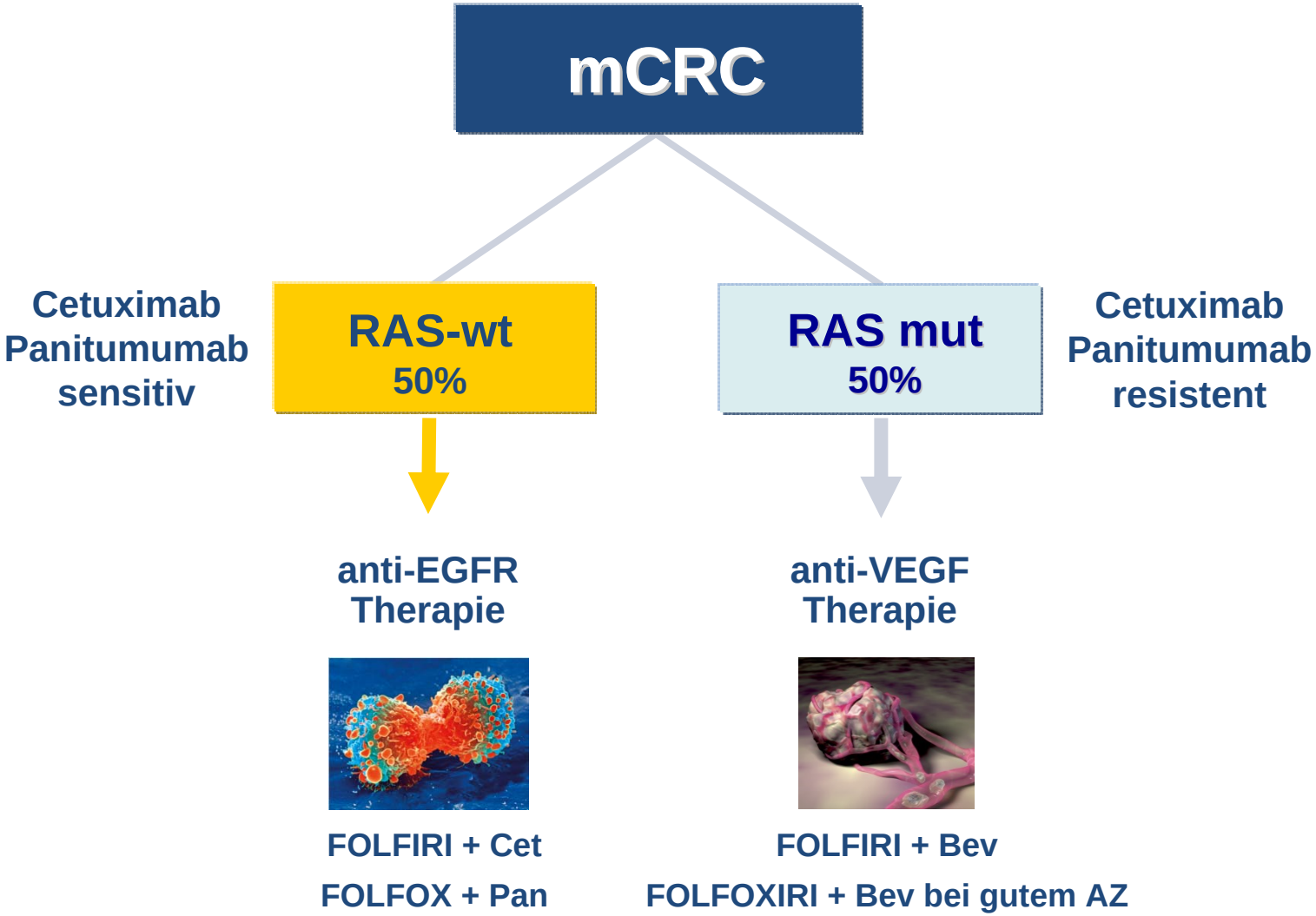
# Therapiealgorithmus nach den ESMO Guidelines



# Klinische Gruppen entsprechend der aktuellen ESMO Guideline

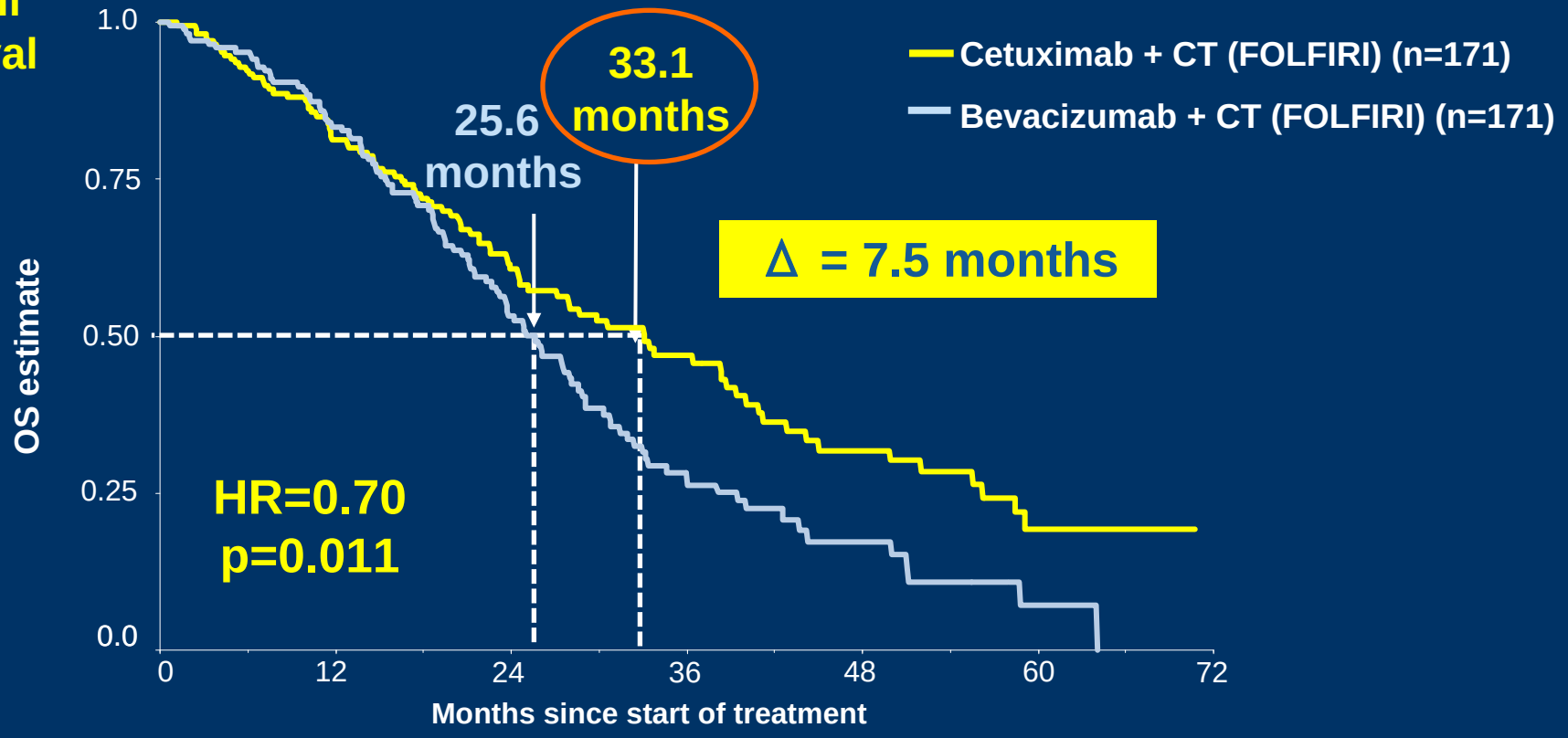
| Gruppe 0 | Gruppe 1 | Gruppe 2 | Gruppe 3 |
|---|---|---|---|
| 10-15% | 10-15% | 10% | 60-70% |
| primär resektabel | potentiell resektabel | rasche Progression<br>symptomatisch | nicht resektabel<br>asymptomatisch<br>Komorbidität |
| Operation | intensive Chemotherapie<br>↓<br>OP | intensive Chemotherapie | Intensive Chemotherapie oder sequenzielle Chemotherapie |

# Behandlung in Abhängigkeit vom RAS-Mutationstatus



# FIRE-3: Greater selection of patients further improves OS benefit to 7.5 months with cetuximab (RAS wt)

**Overall survival**

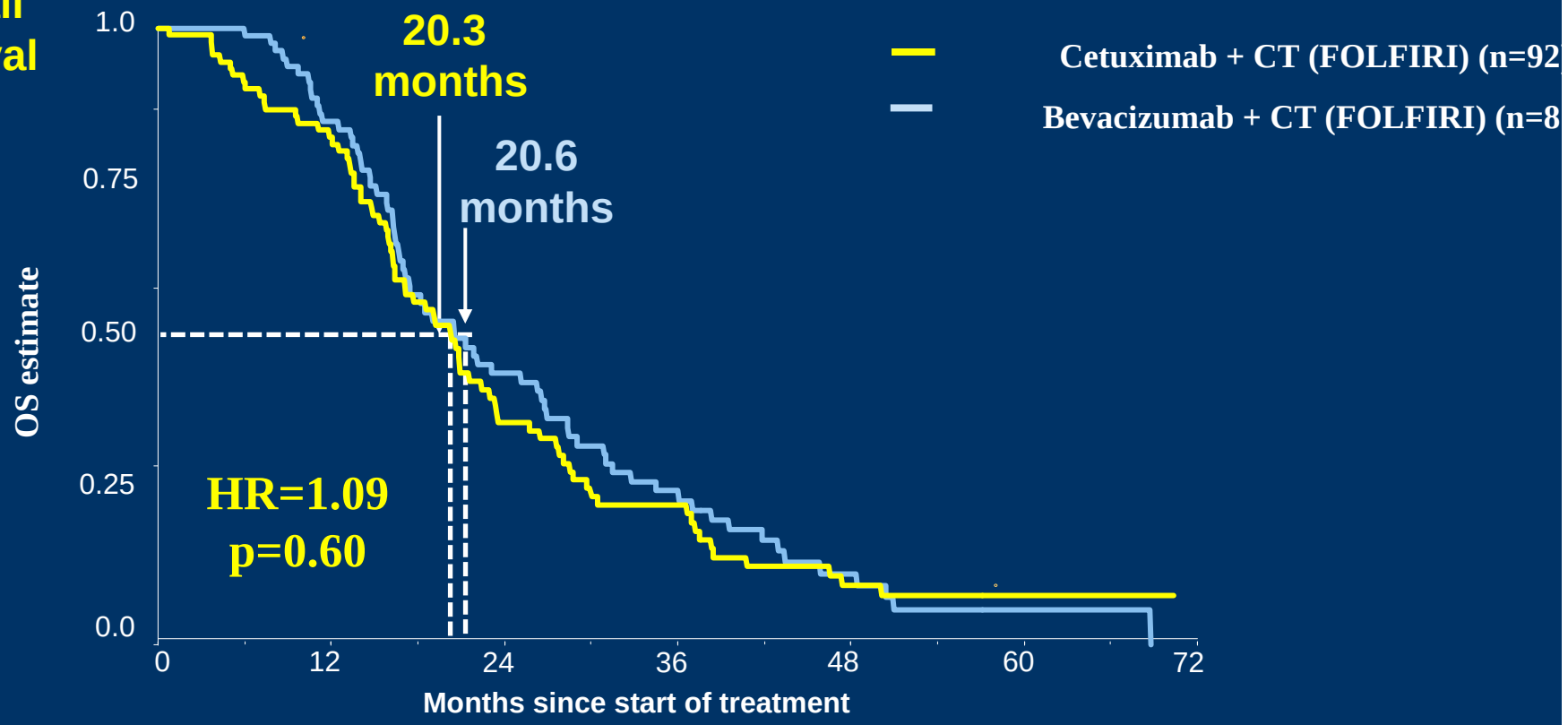



| | Cetuximab + CT | Bevacizumab + CT | p value |
|---|---|---|---|
| **Overall response rate** **primary endpoint not met** | 65.5% | 59.6% | 0.32 |
| **Progression-free survival** | 10.4 months | 10.2 months | 0.54 |

**Stintzing S, et al. ECC 2013 (Abstract No. LBA17)**

# FIRE-3: Patients with any RAS mutation
## (mutations in KRAS or NRAS exons 2, 3 or 4)

**Overall survival**

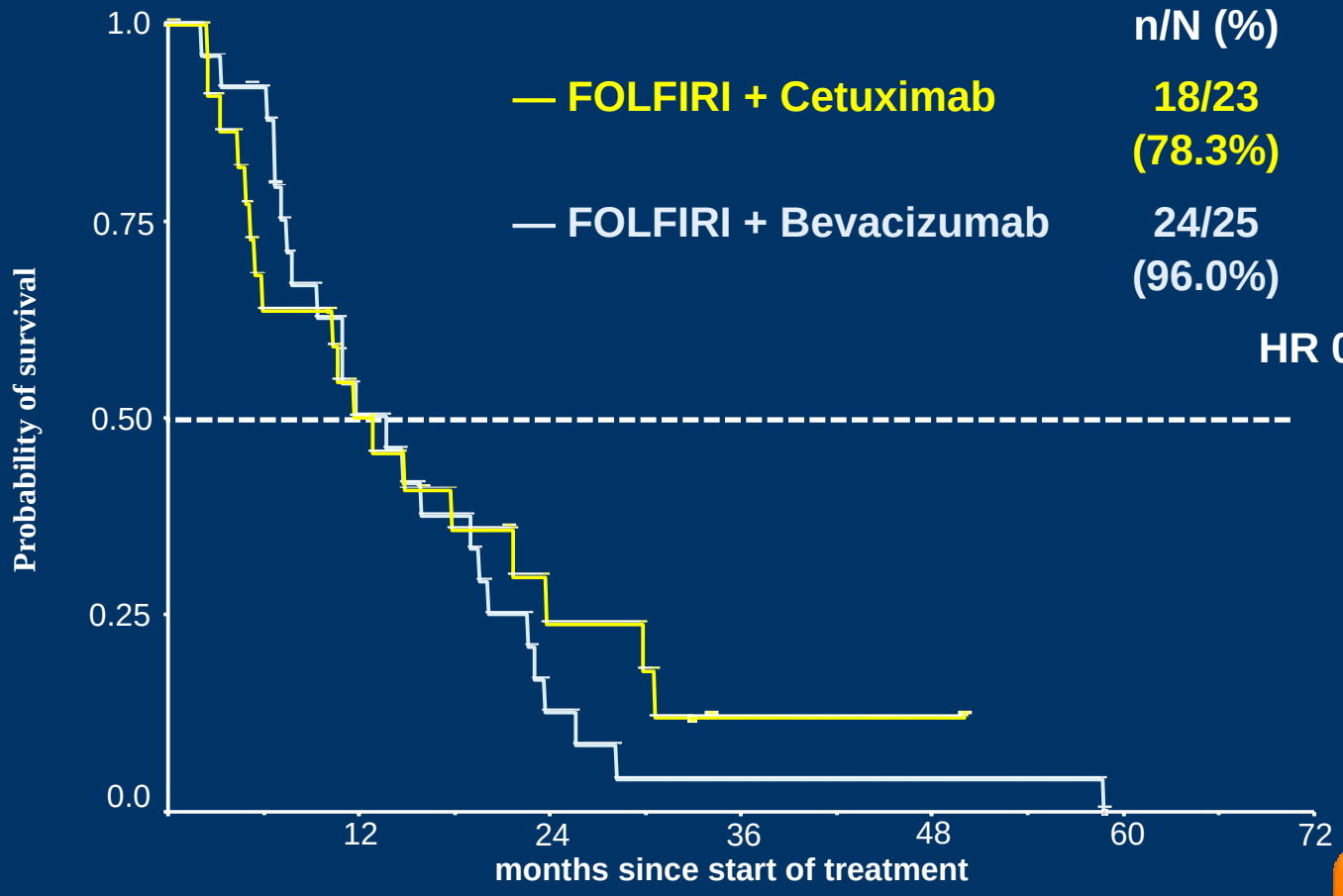



| N = 178 | Cetuximab + CT | Bevacizumab + CT | p value |
|---|---|---|---|
| **Overall response rate** | 38% | 51.2% | 0.097 |
| **Progression-free survival** | 7.5 months | 10.1 months | 0.085 |

*Compared with bevacizumab containing regimen

Stintzing S, et al. ECC 2013 (Abstract No. LBA17)

# Overall survival
# BRAF mutant population



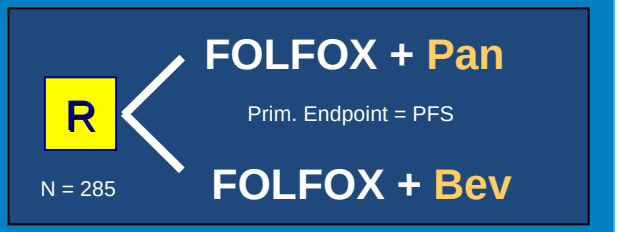

| | Events n/N (%) | Median (months) | 95% CI |
|---|---|---|---|
| — FOLFIRI + Cetuximab | 18/23 (78.3%) | 12.3 | 5.5 – 21.7 |
| — FOLFIRI + Bevacizumab | 24/25 (96.0%) | 13.7 | 7.8 – 19.5 |

HR 0.87 (95% CI: 0.47 – 1.61)
p (log-rank)= 0.65

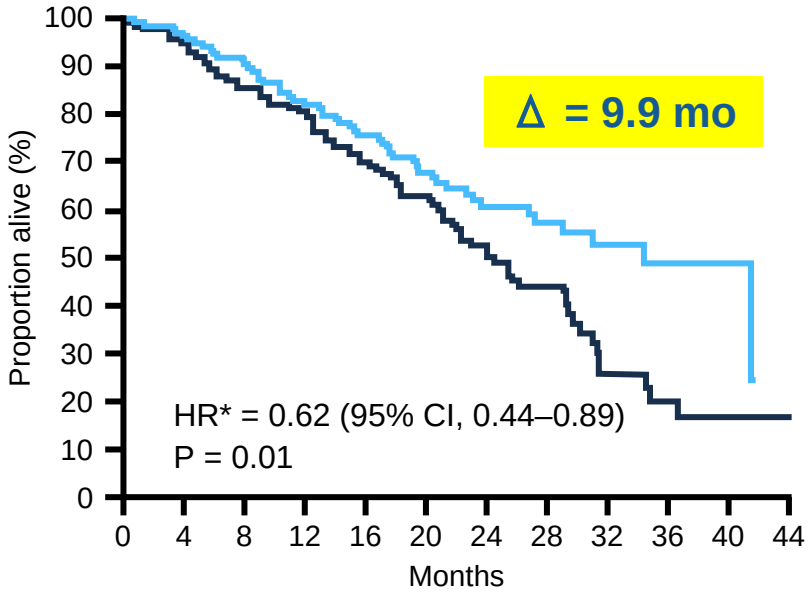
| No. at risk | | | | | |
|---|---|---|---|---|---|
| | 23 | 11 | 4 | 1 | 1 |
| | 25 | 12 | 3 | 1 | |

**10%** BRAF Mutationen

# PEAK study *RAS* analysis
## OS (longer follow-up analysis)

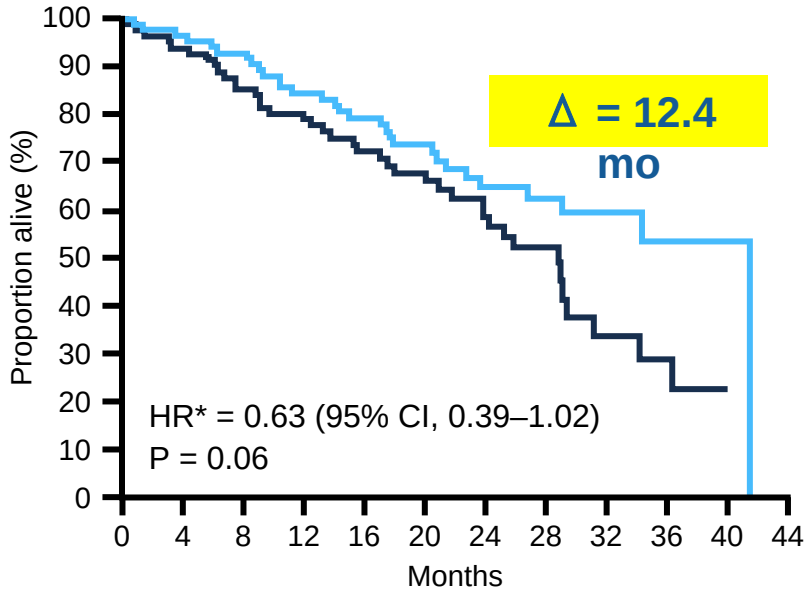



### WT *KRAS* exon 2




| | Events n (%) | Median (95% CI) months |
|---|---|---|
| Panitumumab + mFOLFOX6 (n = 142) | 52 (37) | **34.2** (26.6–NR) |
| Bevacizumab + mFOLFOX6 (n = 143) | 78 (55) | **24.3** (21.0–29.2) |

### WT *RAS*




| | Events n (%) | Median (95% CI) months |
|---|---|---|
| Panitumumab + mFOLFOX6 (n = 88) | 30 (34) | **41.3** (28.8–41.3) |
| Bevacizumab + mFOLFOX6 (n = 82) | 40 (49) | **28.9** (23.9–31.3) |

*Stratified Cox proportional hazards model; No formal hypothesis testing was planned; WT *RAS*, WT *KRAS* & *NRAS* exons 2/3/4; NR, not reached


aus M, et al. EJC 2013; 49 (suppl 3):abstract 2262 (and poster).

VOLUME 32 · NUMBER 10 · APRIL 1 2014

JOURNAL OF CLINICAL ONCOLOGY | ONCOLOGY GRAND ROUNDS

# Curable Patient With Metastatic Colorectal Cancer: Balancing Effective Therapies and Toxicities

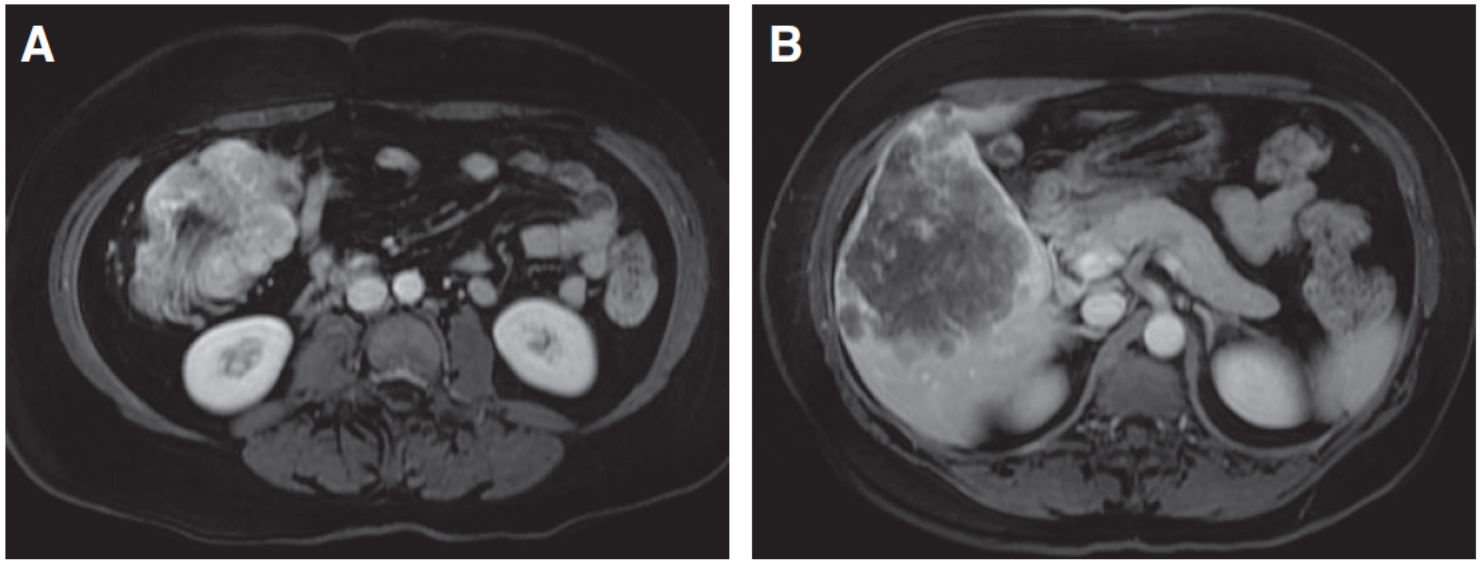
Katherine Van Loon and Alan P. Venook, *Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA*

- 38 Jahre alte Patientin
- Konzertpianistin
- Abdominale Schmerzen im oberen rechten Quadranten

  - Ultraschall
  - MRT Abdomen
  - Koloskopie
  - PET-CT

Van Loon K, Venook AP JCO 2014

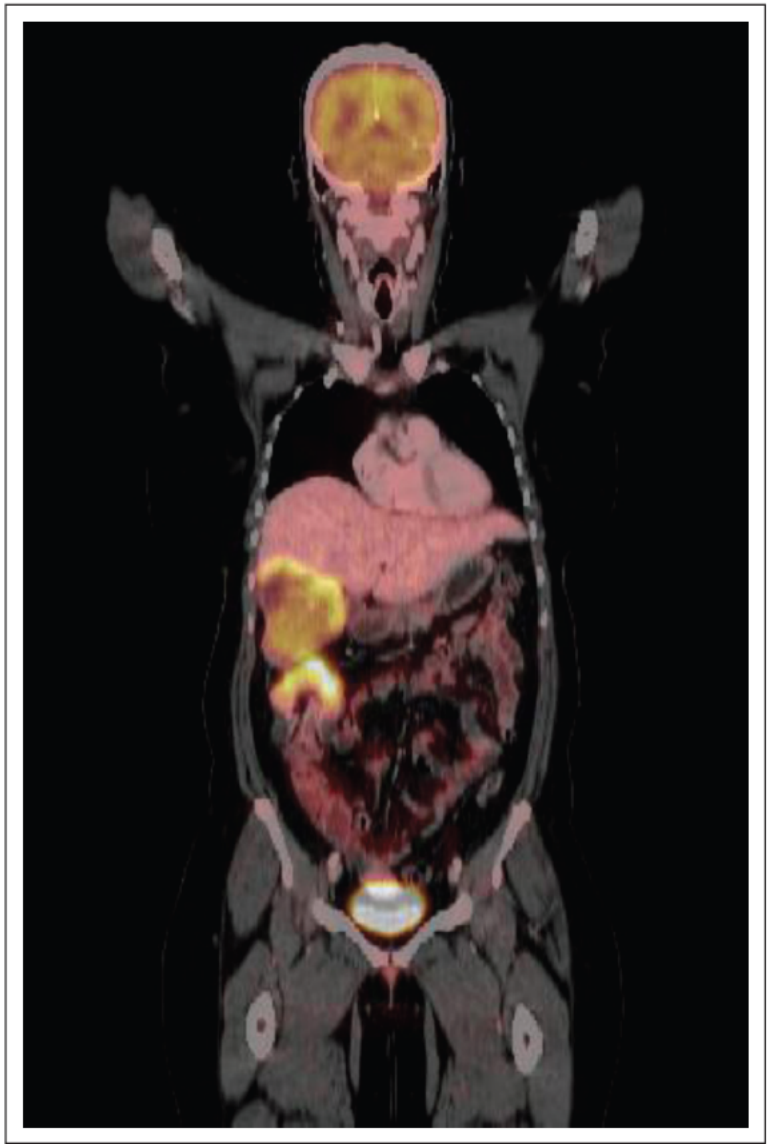
# MRT Untersuchung zum Zeitpunkt der Primärdiagnose




A) Circumferentielle Raumforderung im Bereich der hepatischen Flexur des Colon

B) Ausgedehnter Konglomerattumor im Segment 5/6 der Leber, größter Durchmesser 12.4 x 8 cm

Van Loon K, Venook AP JCO 2014



## Baseline Staging PET-CT

- 13-cm Raumforderung im Bereich des rechten Leberlappens mit unregelmäßig gesteigertem FDG-Uptake (SUVmax 11.8)

- Tumor im Bereich der hepatischen Flexur des Colons mit deutlich gesteigertem Stoffwechsel

Van Loon K, Venook AP JCO 2014

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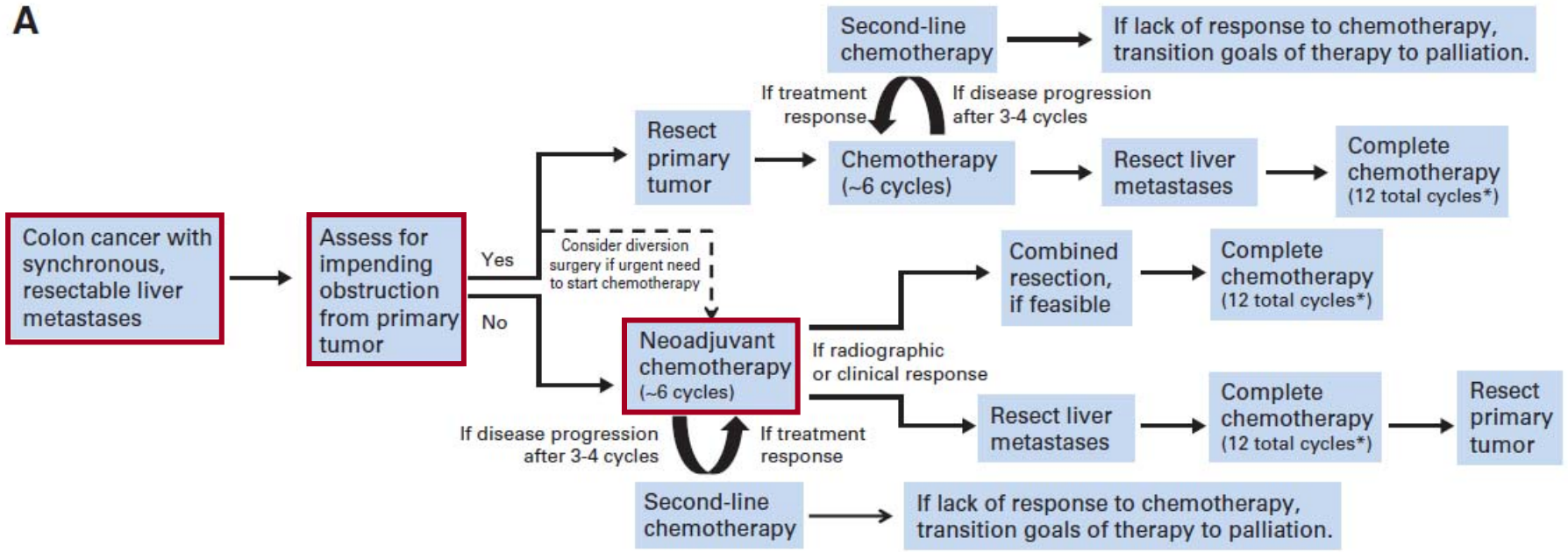
- Abdominale Schmerzen im oberen rechten Quadranten

- Diagnostische Biopsie endoskopisch nicht erfolgreich
- Leberbiopsie: Diagnose metastasiertes Adenokarzinoms des Colons

- Molekularpathologie: KRAS-wt, BRAF-wt, MSS

Van Loon K, Venook AP JCO 2014

# Plausible Behandlungsparadigmen

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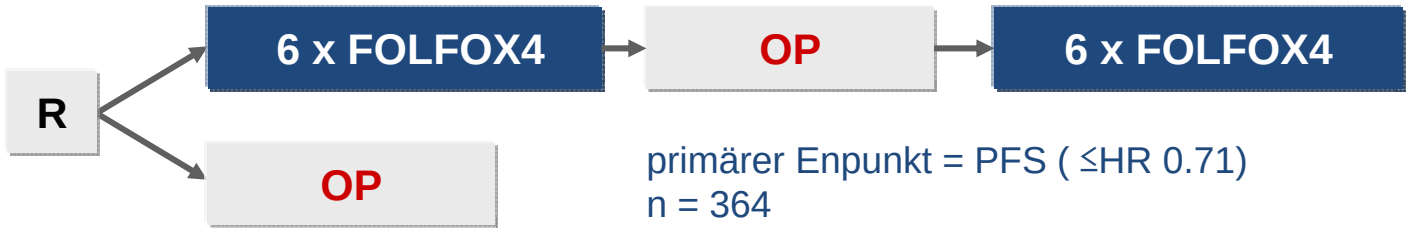
# Perioperative Chemotherapie
## bei resektablen Lebermetastasen




primärer Enpunkt = PFS ( ≤HR 0.71)
n = 364

Median Follow-up = 8.5 Jahre

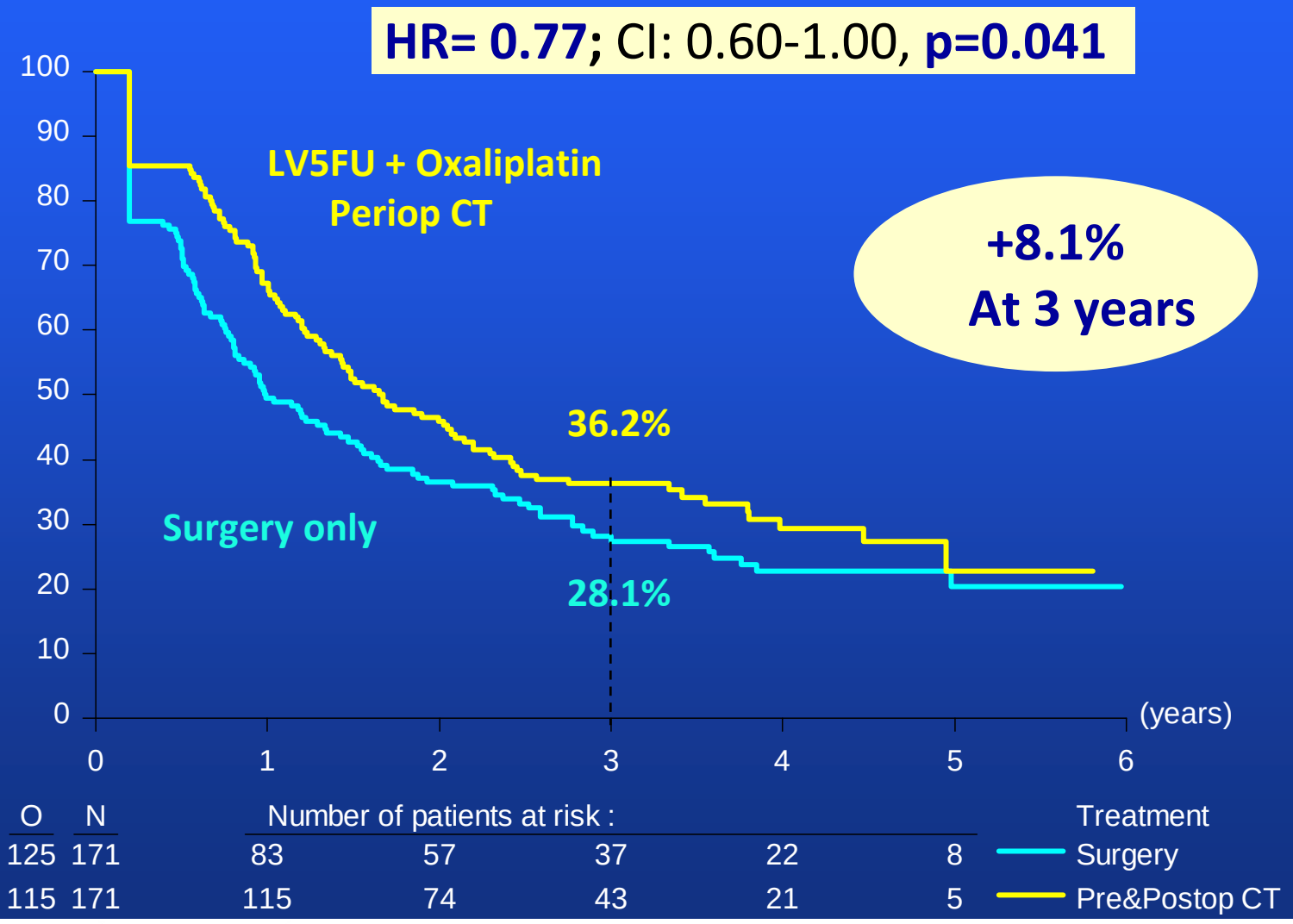
| | Perioperative CT | Primäre OP | Signifikanz |
|---|---|---|---|
| **3-year-PFS**<br>Resezierte Patienten | **42.4%** | 33.2% | HR=0.73<br>**P=0.025** |
| **3-year-PFS**<br>eligible patients | **36.2%** | 28.1% | HR=0.77<br>**P=0.041** |
| **5-year OS rate**<br>eligible patients | **52.4%** | 48.3% | **n.s.** |
| **Median OS** | **HR = 0.88** (95% CI 0.68-1.14) | | **n.s.** |

**K**eine signifikante Überlebensverlängerung durch perioperative CT

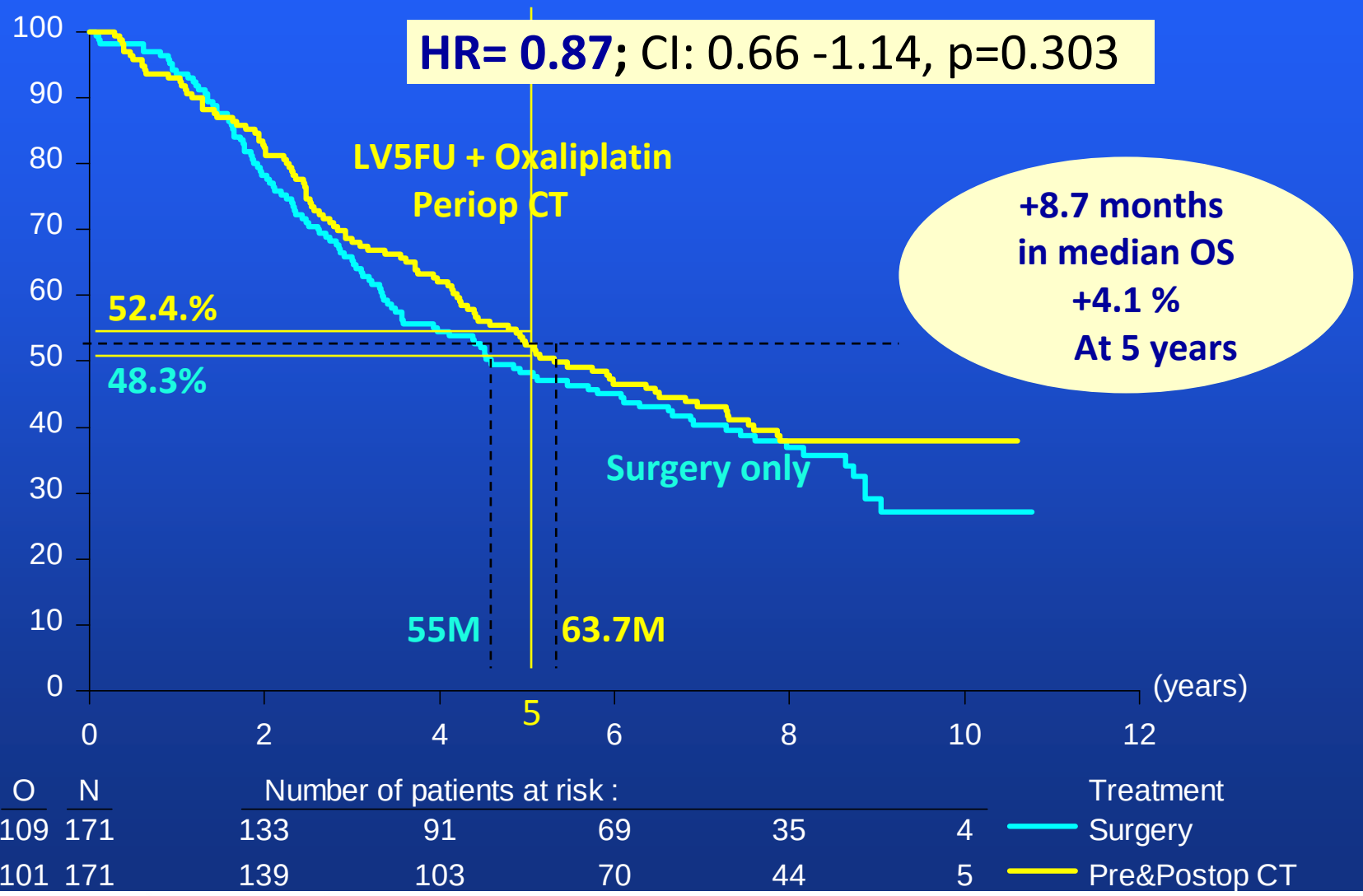
Nordlinger et al. Lancet 2008
Nordlinger, ASCO 2012, #3508

# Progression-free survival in eligible patients

Nordlinger et al. Lancet 2008



# Overall survival in eligible patients



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- 38 Jahre alte Patientin
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- Abdominale Schmerzen im oberen rechten Quadranten

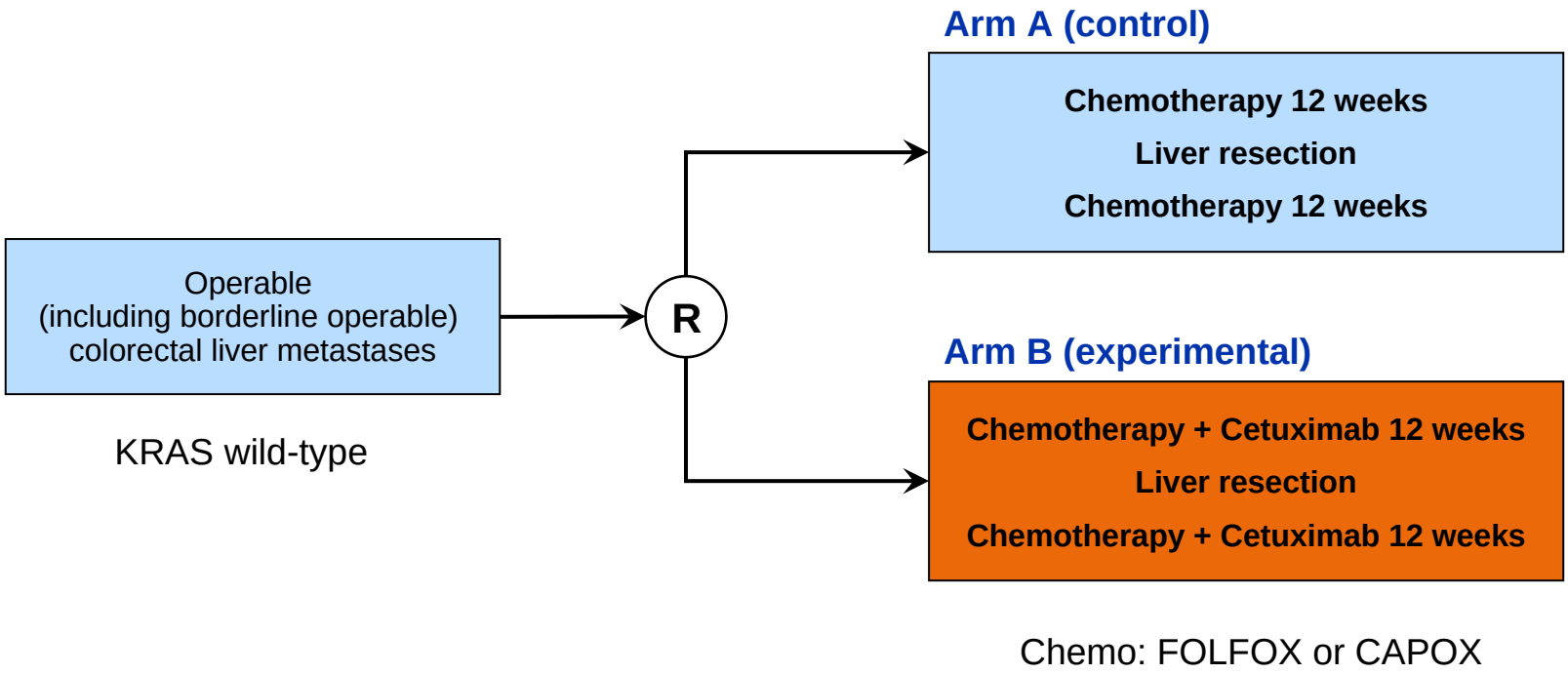
**Individueller Therapieansatz**

- Kein Oxaliplatin wegen PNP-Risiko ➔ FOLFIRI
- Kein Bevacizumab wegen kurzfristig geplanter OP
- Kein Cetuximab aufgrund der negativen Daten der New EPOC-Studie

Van Loon K, Venook AP JCO 2014

# New EPOC Study: Trial Design

Patienten mit resektabler Lebermetastasierung




Primrose J, et al. ASCO 2013

# **New EPOC**: Kein Vorteil für Cetuximab

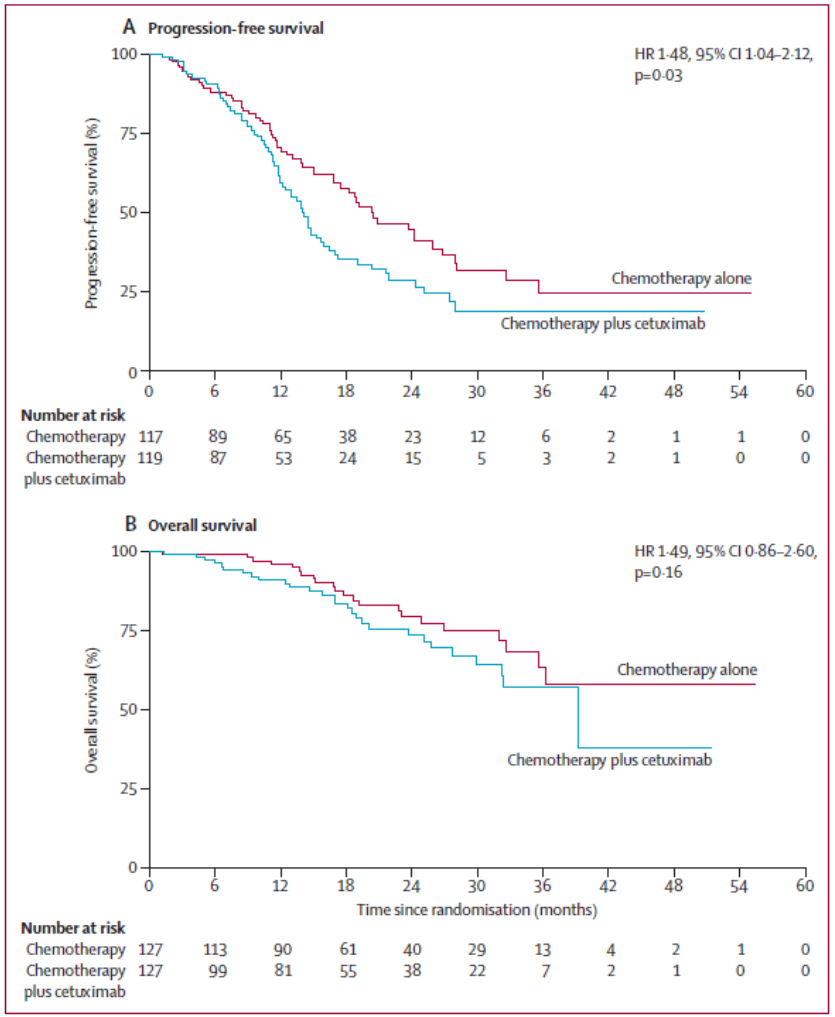



*Figure 2:* Kaplan-Meier curves of progression-free survival (A) and overall survival (B) by treatment group in *KRAS* exon 2 wild-type patients only

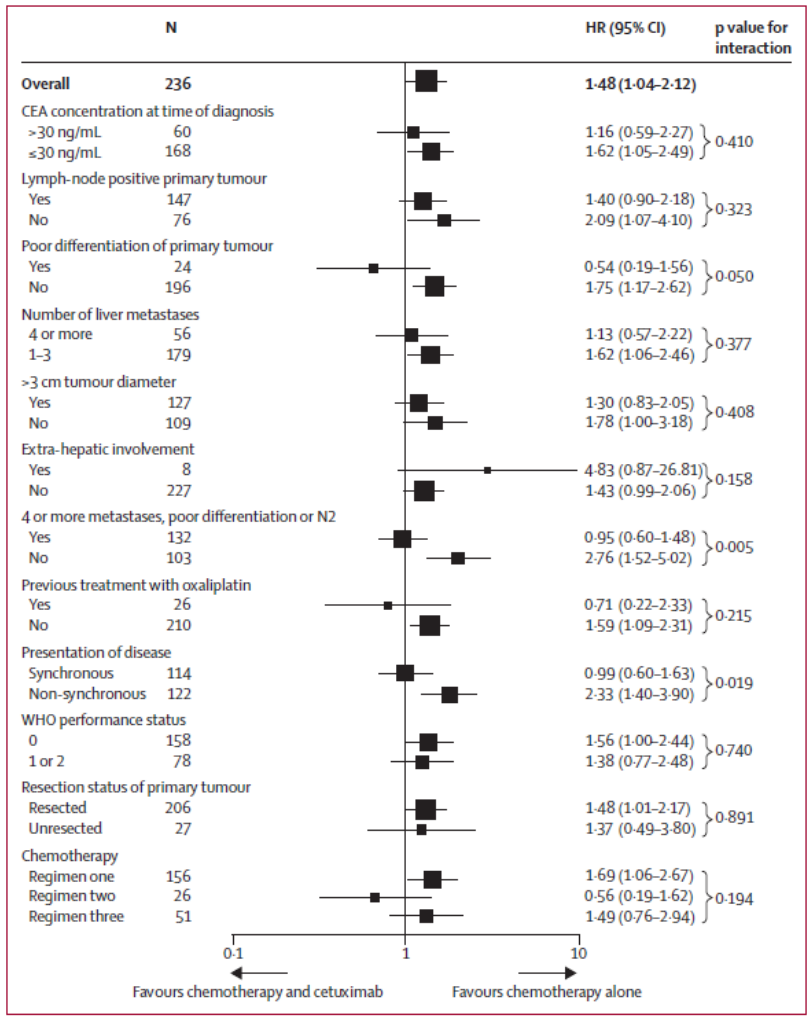
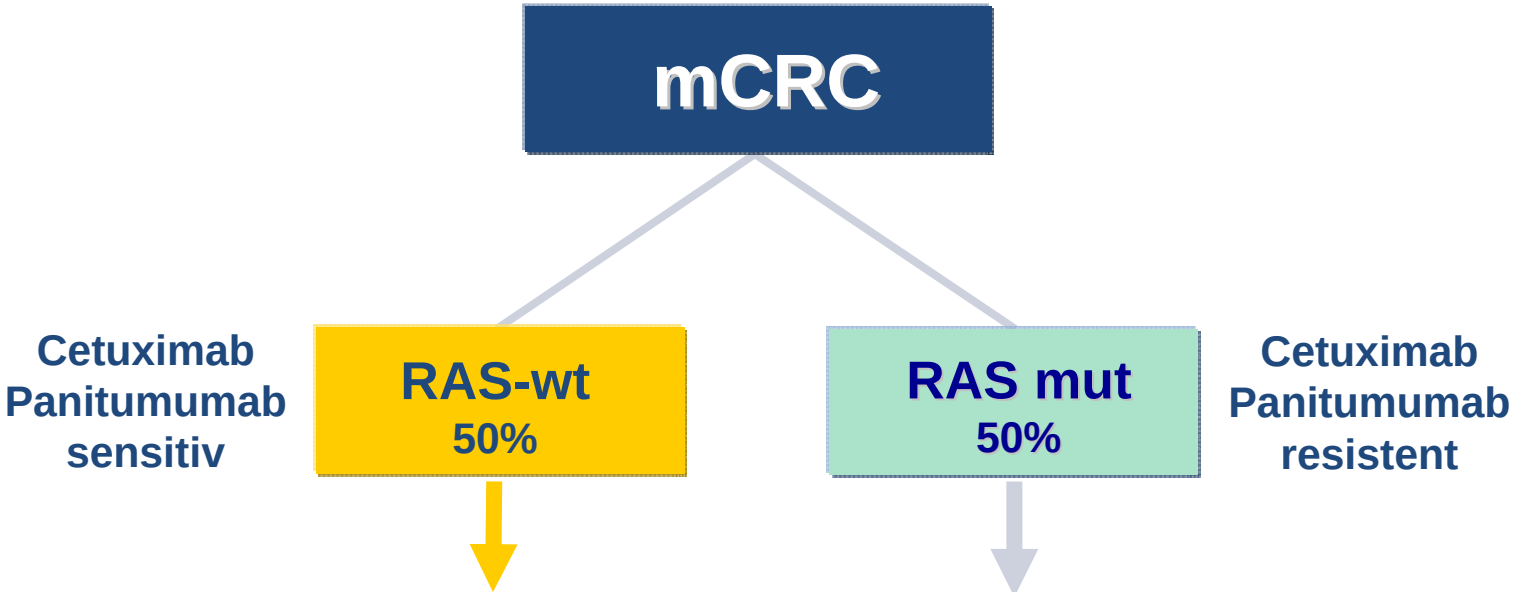



*Figure 3:* HRs for progression-free survival with chemotherapy alone versus chemotherapy and cetuximab, according to prespecified subgroups

**ORR: 54% vs 58% (Chemo vs Chemo + Cet)**

Primrose J, et al. Lancet Oncology 2014

# Behandlung in Abhängigkeit vom RAS-Mutationstatus



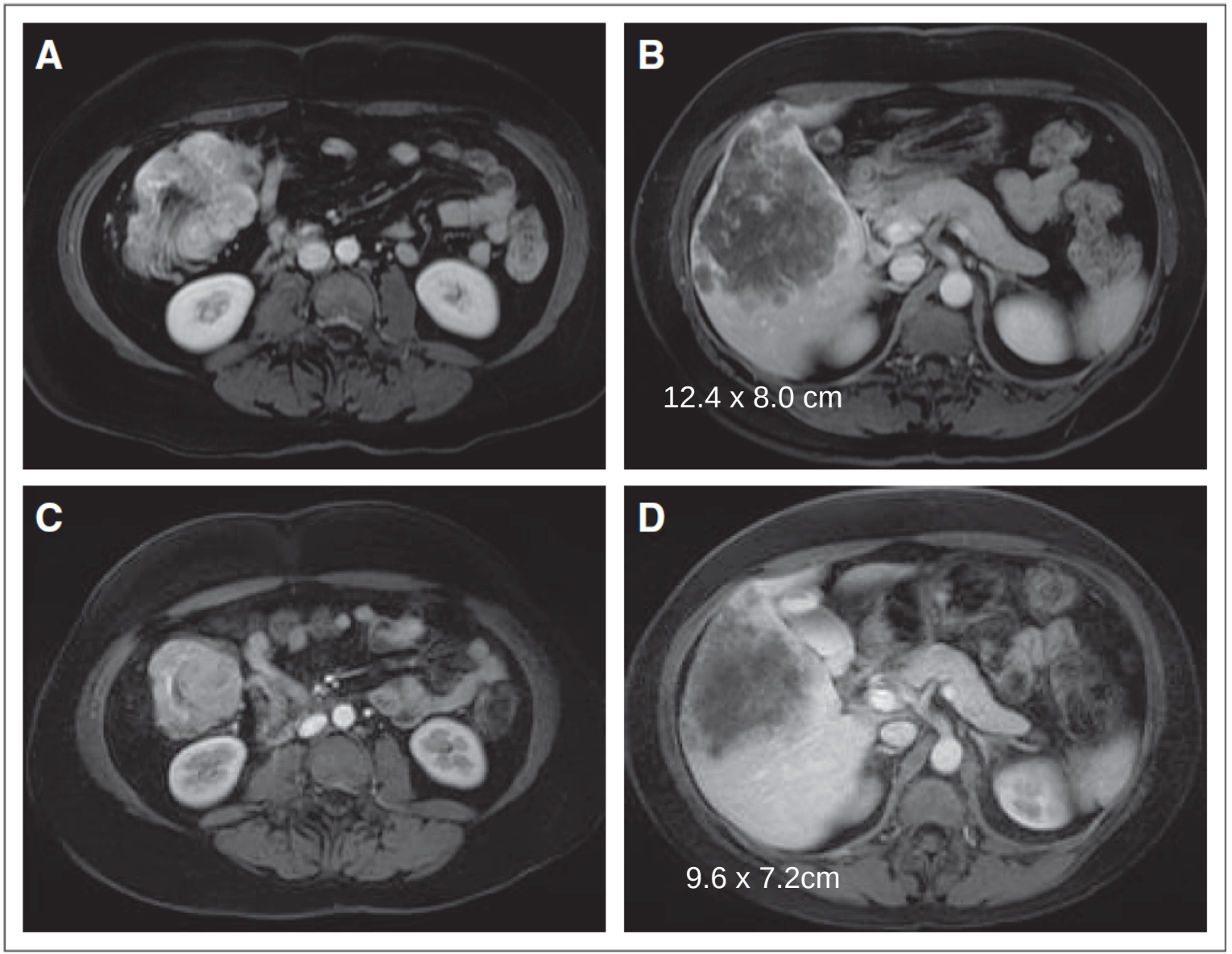

**Einzelfallentscheidung**

- 4 Zyklen FOLFIRI, gut toleriert
- Restaging

# MRT Untersuchung zum Zeitpunkt der Primärdiagnose

**Baseline**

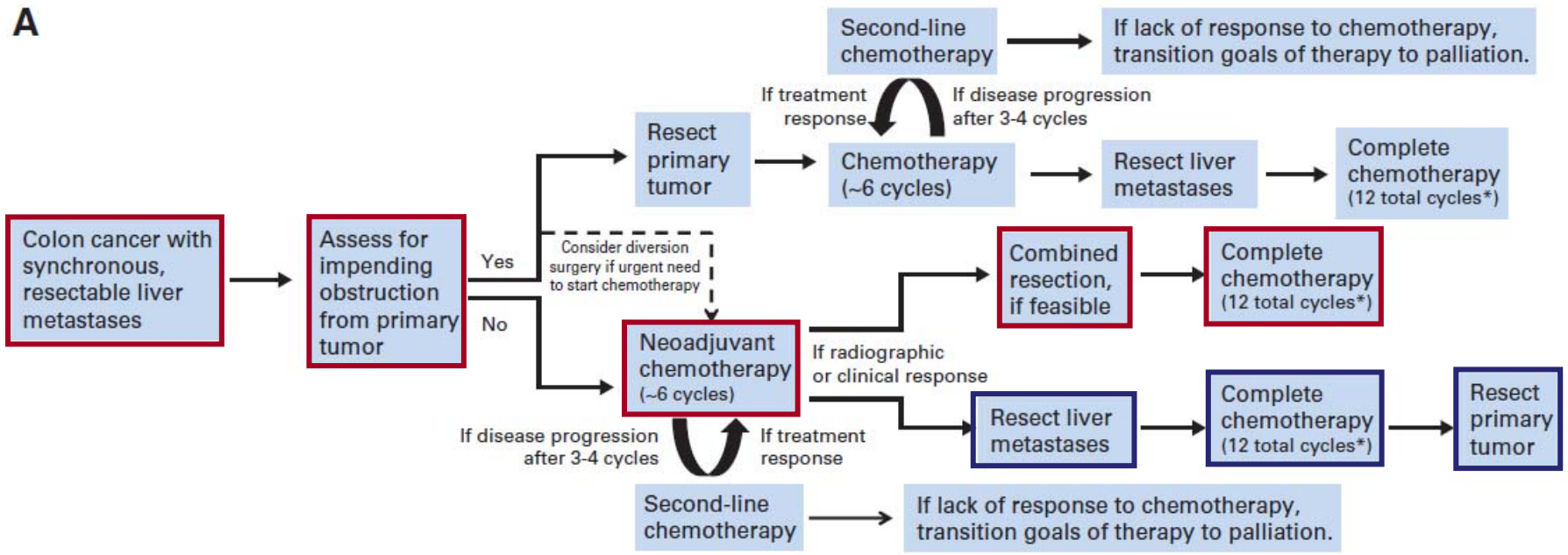
**Nach 4 Zyklen FOLFIRI**




Van Loon K, Venook AP JCO 2014

# Plausibles Behandlungsparadigma

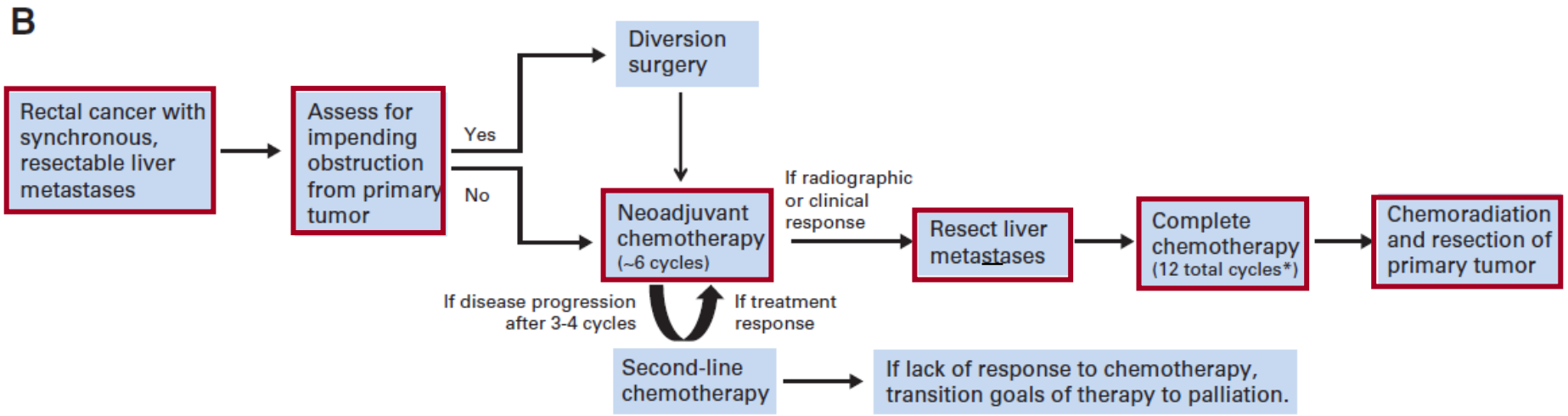
## Synchron metastasiertes Colon-CA




Van Loon K, Venook AP JCO 2014

# Plausibles Behandlungsparadigma

## Synchron metastasiertes Rektum-CA




Van Loon K, Venook AP JCO 2014

# Vorgehen bei primär nicht sicher resektablen Lebermetastasen

# Primäre Resektion des Primärtumors bei synchroner Metastasierung

- Gepoolte Analyse aus 4 klinische Studien
- **N = 810**
- Patienten mit nicht-resektabler synchroner Metastasierung
- 1st-Line Chemotherapie: Fluoropyrimidin, Oxaliplatin, Irinotecan, Bevacizumab

- Primäre Resektion: n = 478 (59%)
- Keine primäre Resektion: n = 332 (41%)

- **Multivariat-Analyse**
  - adjustiert für CEA, ALP, WBC, PS, Zahl der Metastasten

- **<u>Resultat</u>: Die Resektion des Primärtumors ist ein unabhängiger Prädiktor des Überlebens**
  - **OS:** **HR 0.63** (0.53 - 0,75), p<0.0001
  - **PFS:** **HR 0.82** (0.70 - 0.95), p<0.0007

Faron M et al. ASCO 2012, #3507

DGC
STUDIENZENTRUM DER DEUTSCHEN GESELLSCHAFT FÜR CHIRURGIE

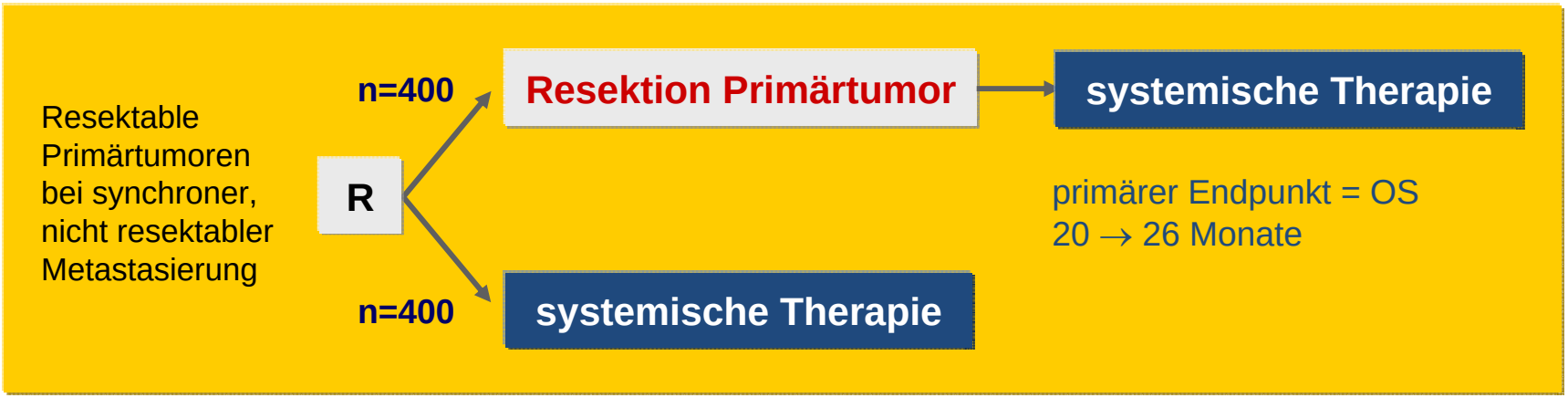
# SYNCHRONOUS

AIO

**Resection of the primary tumor versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases (UICC stage IV)**

**-**

**A randomized controlled multicenter trial (SYNCHRONOUS-Trial)**



# Chemotherapie +/- Cetuximab bei nicht resektablen CLM

**Published Ahead of Print on April 8, 2013 as 10.1200/JCO.2012.44.8308**
**The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2012.44.8308**

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

## Randomized Controlled Trial of Cetuximab Plus Chemotherapy for Patients With *KRAS* Wild-Type Unresectable Colorectal Liver-Limited Metastases

*Le-Chi Ye, Tian-Shu Liu, Li Ren, Ye Wei, De-Xiang Zhu, Sheng-Yong Zai, Qing-Hai Ye, Yiyi Yu, Bo Xu, Xin-Yu Qin, and Jianmin Xu*

Processed as a Rapid Communication manuscript

All authors: Zhongshan Hospital, Fudan University, Shanghai, People's Republic of China.

Published online ahead of print at www.jco.org on April 8, 2013.

Supported by Key Projects of the Clinical Disciplines, administered by the Ministry of Health.

L.-C.Y., T.-S.L., L.R., and Y.W. contributed equally to this work.

Presented orally at the 10th Annual Meeting of the Japanese Society of Medical Oncology, Osaka, Japan, July 26-28, 2012; at the 13th Korea-Japan-China Colorectal Cancer Symposium, Seoul, Korea, September 8-9, 2012;

A B S T R A C T

**Purpose**
To assess the effects of cetuximab plus chemotherapy as first-line treatment for unresectable colorectal liver metastases (CLMs).

**Patients and Methods**
After resection of their primary tumors, patients with *KRAS* wild-type synchronous nonresectable liver-limited metastases from colorectal cancer were randomly assigned to receive chemotherapy (FOLFIRI [fluorouracil, leucovorin, and irinotecan] or mFOLFOX6 [modified fluorouracil, leucovorin, and oxaliplatin]) plus cetuximab (arm A) or chemotherapy alone (arm B). The primary end point was the rate of patients converted to resection for liver metastases. Secondary end points included tumor response and survival.

**Results**
The intent-to-treat population comprised 138 patients; 70 patients were randomly assigned to arm

# Chemotherapie +/- Cetuximab bei primär nicht resektablen Lebermetastasen

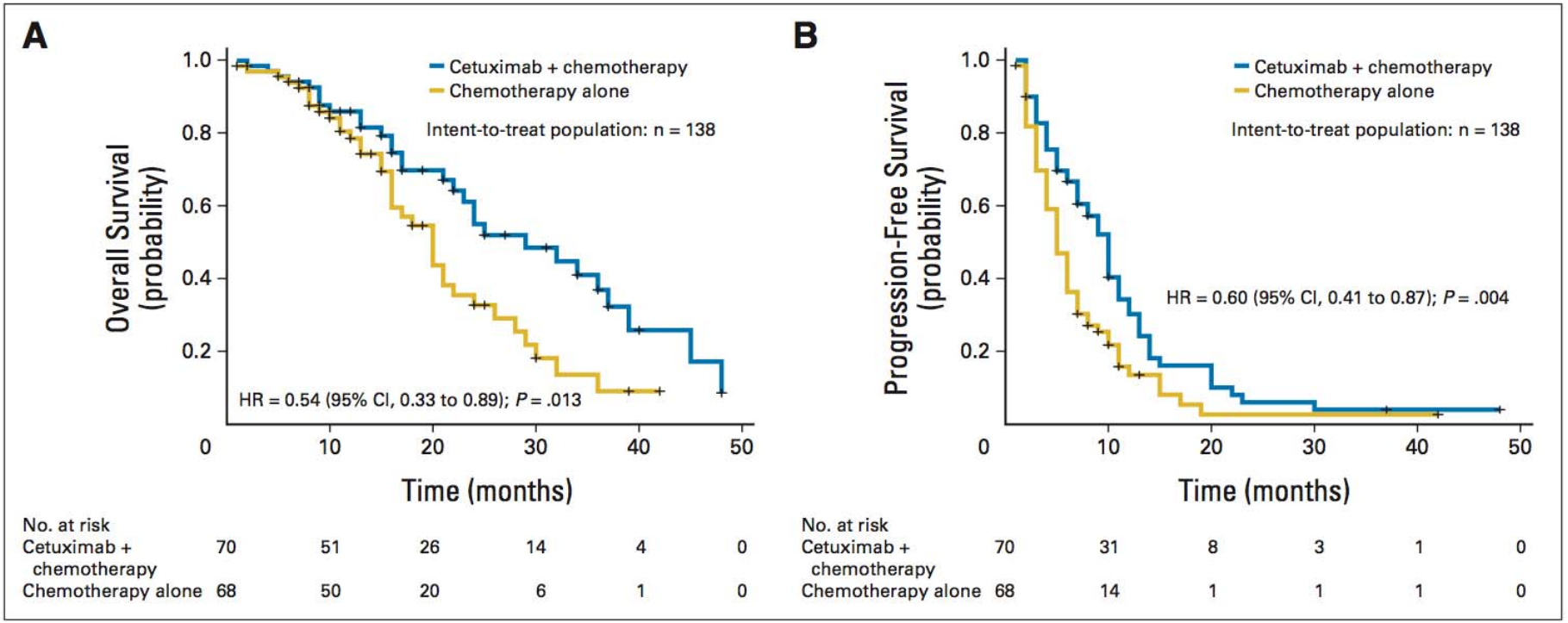



**Fig 2.** (A) Overall survival curves and (B) Kaplan-Meier progression-free survival for the intent-to-treat population in the cetuximab plus chemotherapy and chemotherapy-alone treatment arms. HR, hazard ratio.

Chemotherapie: FOLFIRI oder FOLFOX6

**Le-Chi Ye, et al. JCO 2013**

# Chemotherapie +/- Cetuximab bei primär nicht resektablen CLM

| | Chemo + Cet n=70 | Chemo n=68 | p |
|---|---|---|---|
| **ORR** | **57.1%** | **29.4%** | <0.01 |
| **R0-Resection Rate** | **25.7%** | **7.4%** | <0.01 |
| **Overall Survival** | **30.9 mo** | 21.0 mo | 0.013 |
| **3-yr-OS** | **41%** | 18% | 0.013 |
| **OS pts with surgery** | 46.4 mo | 36.0 mo | 0.94 |
| **OS pts no surgery** | 25.7 mo | 19.6 mo | 0.05 |

**Chemo: FOLFOX6 49%, FOLFIRI 31%, both 20%**

**Ye, Le-Chi JCO 2013**

# Zusammenfassung

- Eine individualisierte Therapie des mCRC ist möglich und sinnvoll

- Wichtige Parameter einer individualisierten Therapieführung sind:
  - Zuordnung zu den klinischen Gruppen 0-4
  - Synchrone vs metachrone Metastasierung
  - Resektabilität der Tumormanifestationen
  - Patientenwunsch
  - Molekularpathologische Evaluation
    - RAS-wt: präferentiell anti-EGFR mAB's
    - BRAF-mut: Therapieintensivierung, z.B. FOLFOXIRI
    - MSI: eher keine Fluoropyrimidin-Monotherapie

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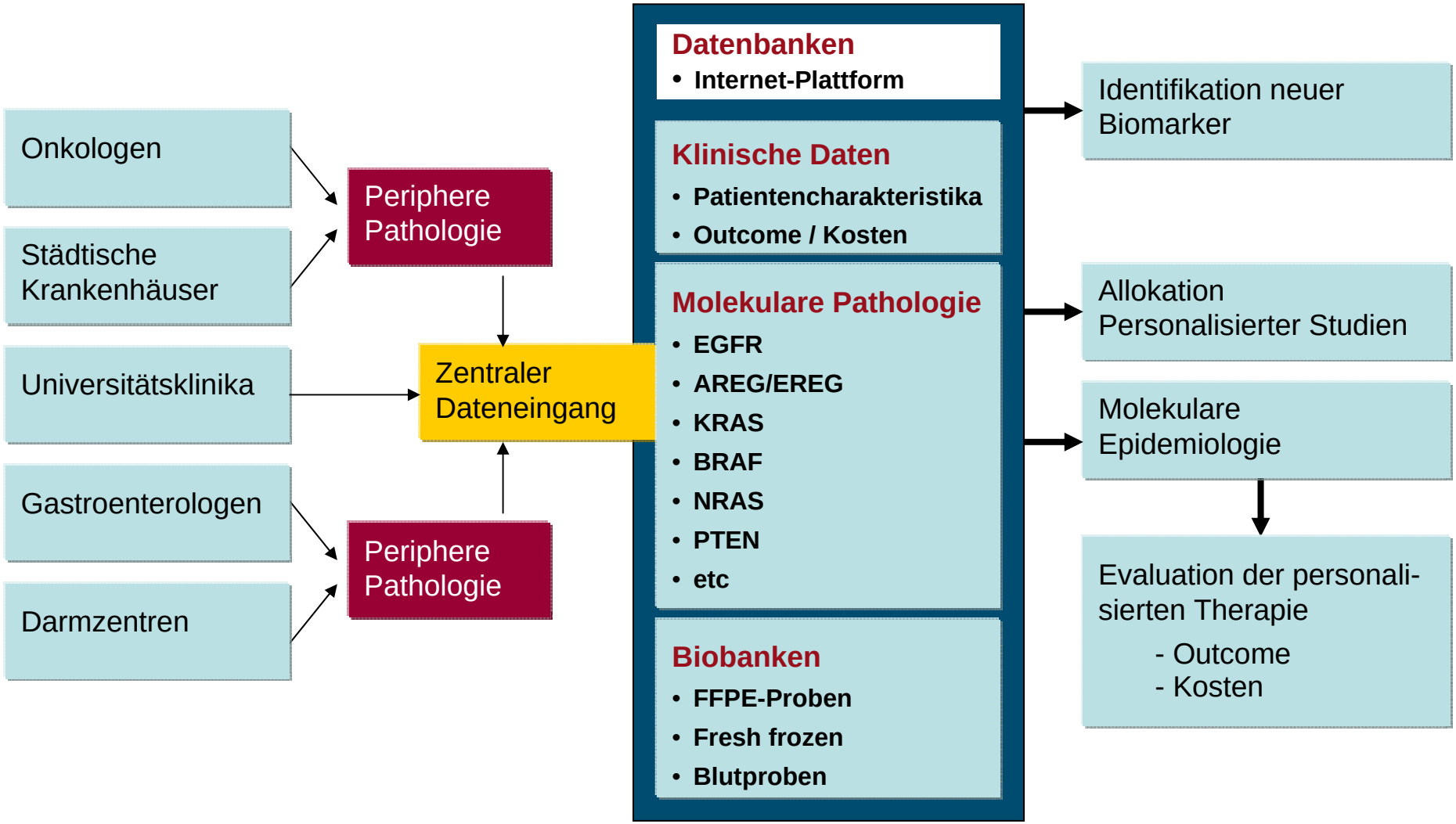
# CRC Screening Platform

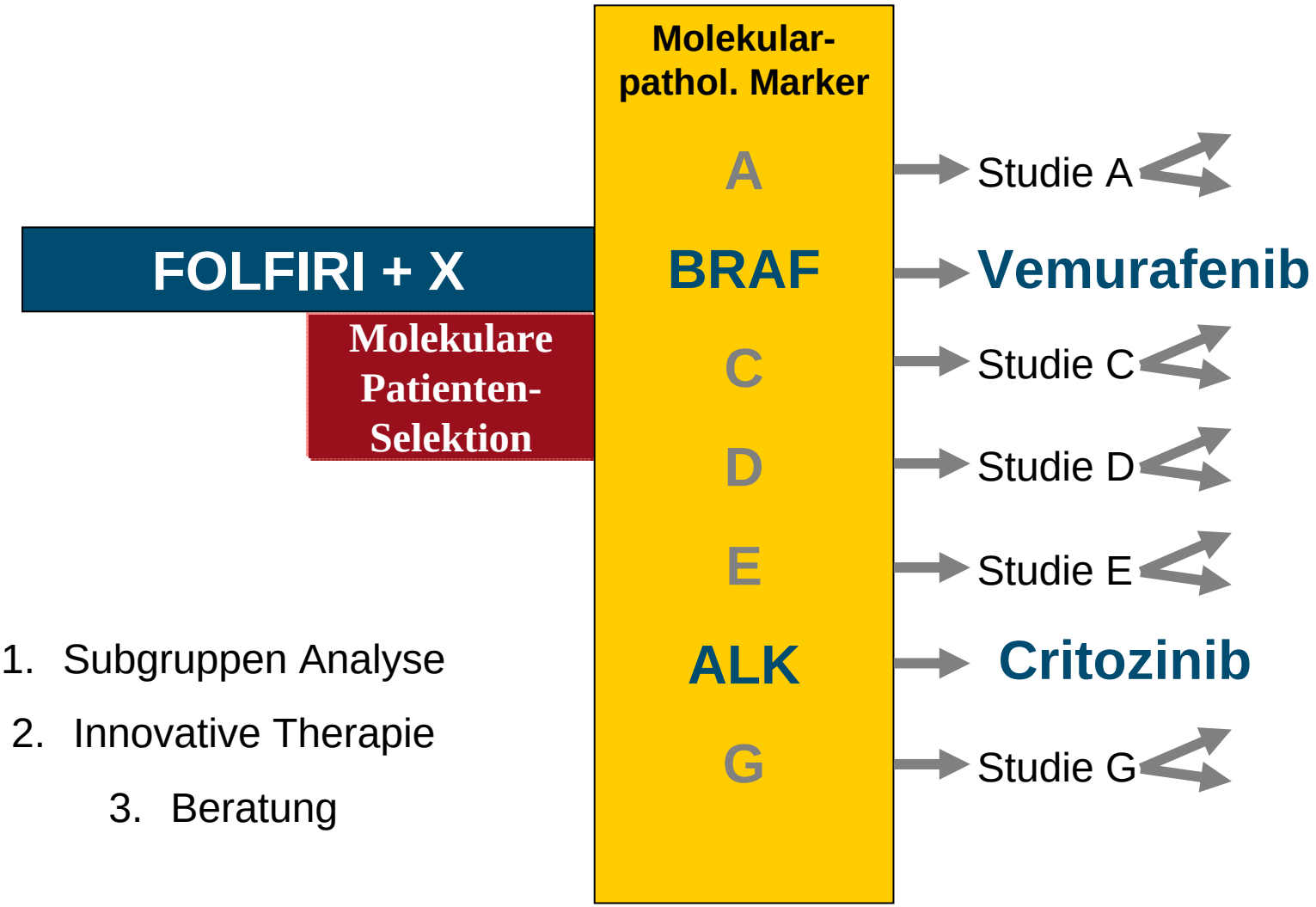
COMPREHENSIVE CANCER CENTER CCC LMU KREBSZENTRUM MÜNCHEN



LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN

# Molekulare Selektion

COMPREHENSIVE CANCER CENTER CCC[LMU]
KREBSZENTRUM MÜNCHEN




1. Subgruppen Analyse
2. Innovative Therapie
3. Beratung