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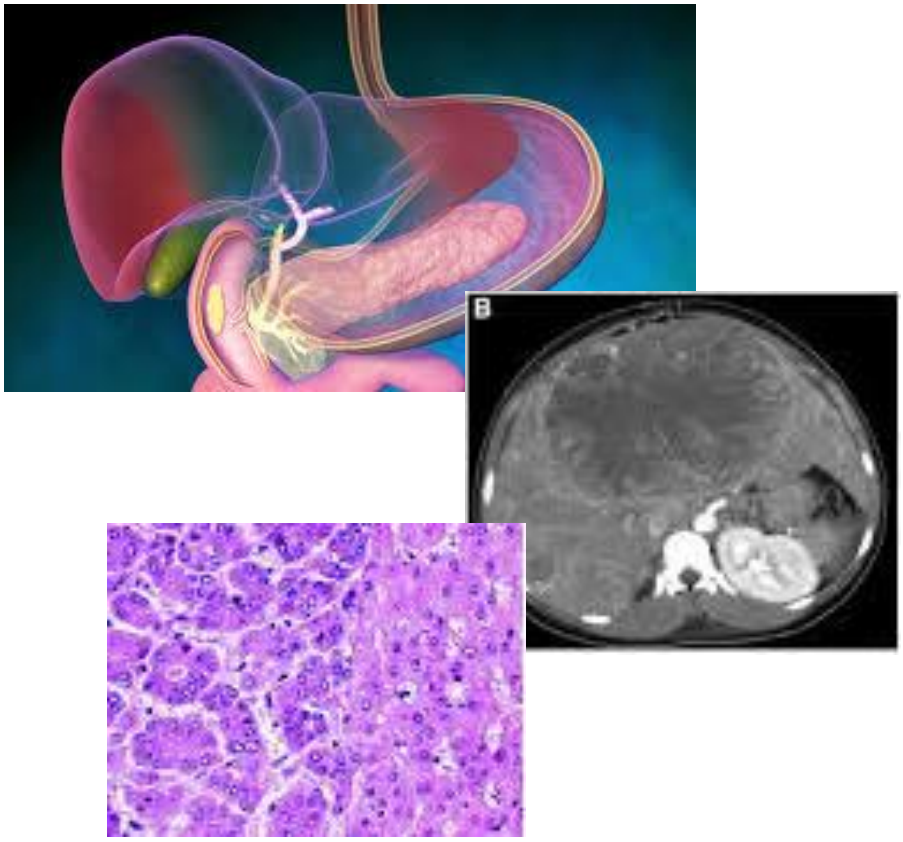
Aktuelle Trends und Empfehlungen bei der Behandlung gastrointestinaler Tumoren



SHG-Tagung

Paracelsus-Klinik Scheidegg

05. Januar 2018

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Themen

- Kolonkarzinom - Adjuvante Therapie des KRK – reduzierte Therapiedauer??
- Kolonkarzinom - Einsatz von TKIs / Immun-Checkpoint-Inhibitoren in der palliativen Therapie
- Neue Therapieoptionen beim Pankreaskarzinom
- Systemische Therapie des HCC – seit über 10 Jahren neue Therapieoptionen
- Adjuvante Therapie von Gallenwegstumoren – neuer Standard??
- Perioperative Therapie des Magen-CAs – FLOT neuer Standard

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Kolonkarzinom - Adjuvante Therapie

Adjuvant Oxaliplatin-based therapy (3 vs. 6 months) in Stage III Colon Cancer

Trial	Regimen(s)	Stage III Colon Cancer Patients*	Enrolling Country
TOSCA	CAPOX or FOLFOX4	2402	Italy
SCOT	CAPOX or mFOLFOX6	3983	UK, Denmark, Spain, Australia Sweden, New Zealand
IDEA France	CAPOX or mFOLFOX6	2010	France
C80702	mFOLFOX6	2440	US, Canada
HORG	CAPOX or FOLFOX4	708	Greece
ACHIEVE	CAPOX or mFOLFOX6	1291	Japan

No patients:
12,834

Total DFS events:	3,263
ECOG 0/ 1	79% / 21%
N1/ N2	72% / 28%
T1+2/ 3/ 4	13/ 66/ 21%
FOLFOX/ CAPOX	60 / 40%

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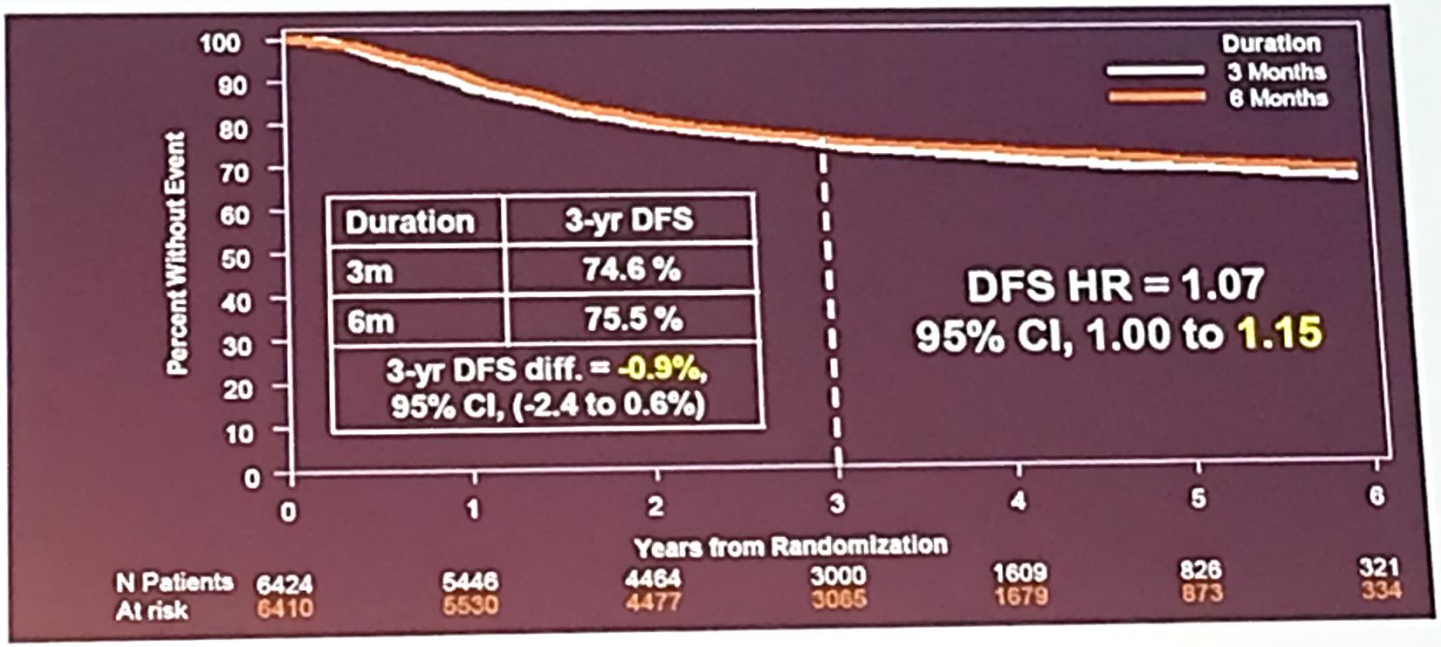
Kolonkarzinom - Adjuvante Therapie

Adjuvant Oxaliplatin-based therapy (3 vs. 6 months) in Stage III Colon Cancer: DFS



Non-inferiority „statistisch nicht erreicht“ aber…

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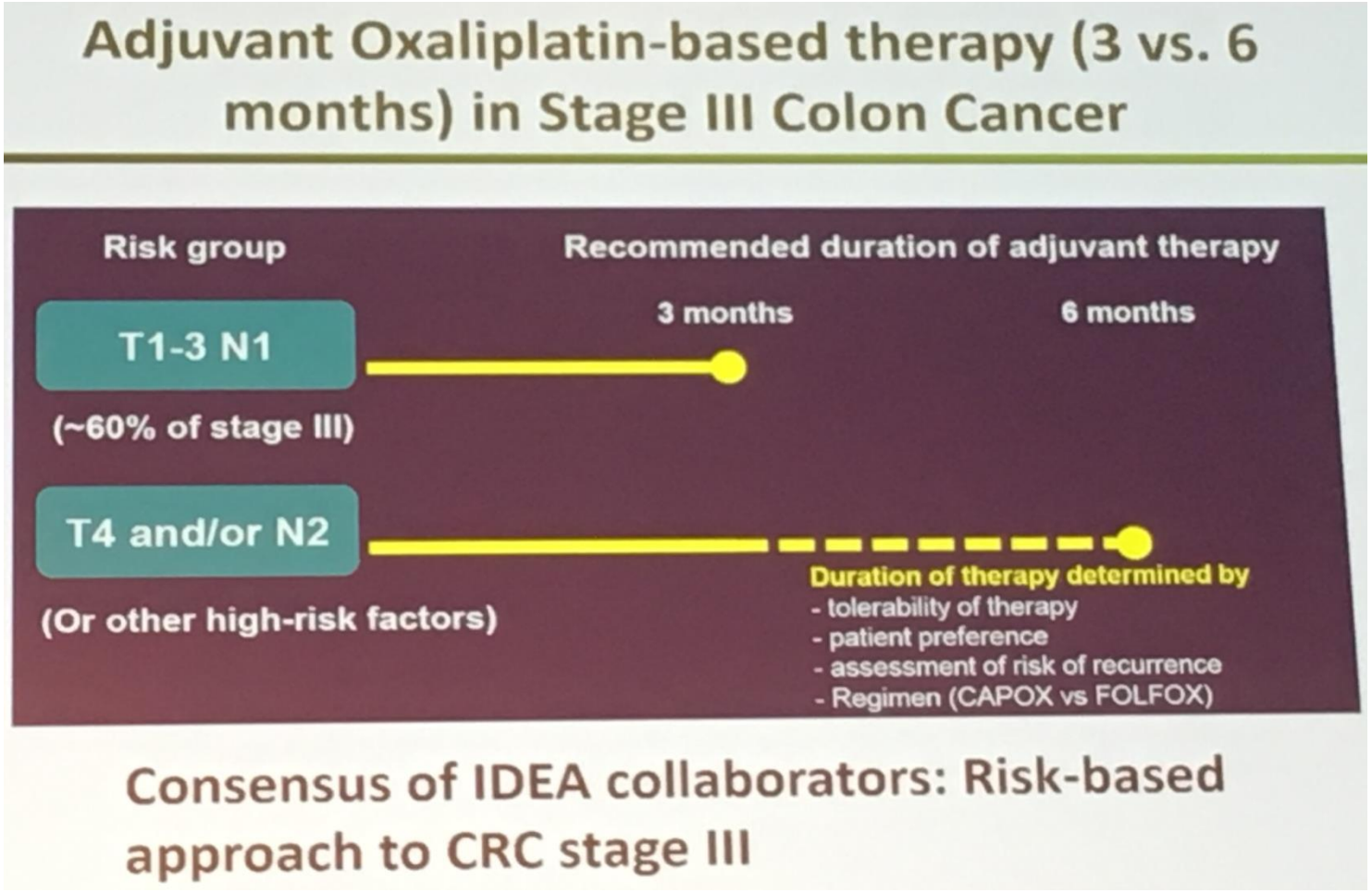
Kolonkarzinom - Adjuvante Therapie

Adjuvant Oxaliplatin-based therapy (3 vs. 6 months) in Stage III Colon Cancer

	FOLFOX			CAPOX		
Adverse Events	3m Arm	6m Arm	p-value[1]	3m Arm	6m Arm	p-value[1]
Overall						
G2	32%	32%	<.0001	41%	48%	<.0001
G3-4	38%	57%		24%	37%	
Neurotoxicity						
G2	14%	32%	<.0001	12%	36%	<.0001
G3-4	3%	16%		3%	9%	
Diarrhea						
G2	11%	13%	<.0001	10%	13%	0.0117
G3-4	5%	7%		7%	9%	

Kolonkarzinom - Adjuvante Therapie



Kolonkarzinom - Palliative Therapie

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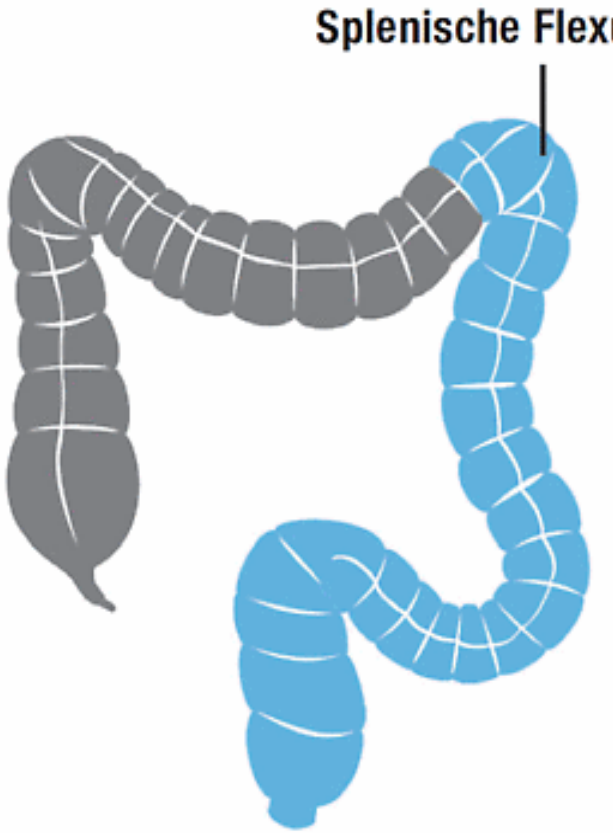
Lokalisation von Darmtumoren und deren Häufigkeit



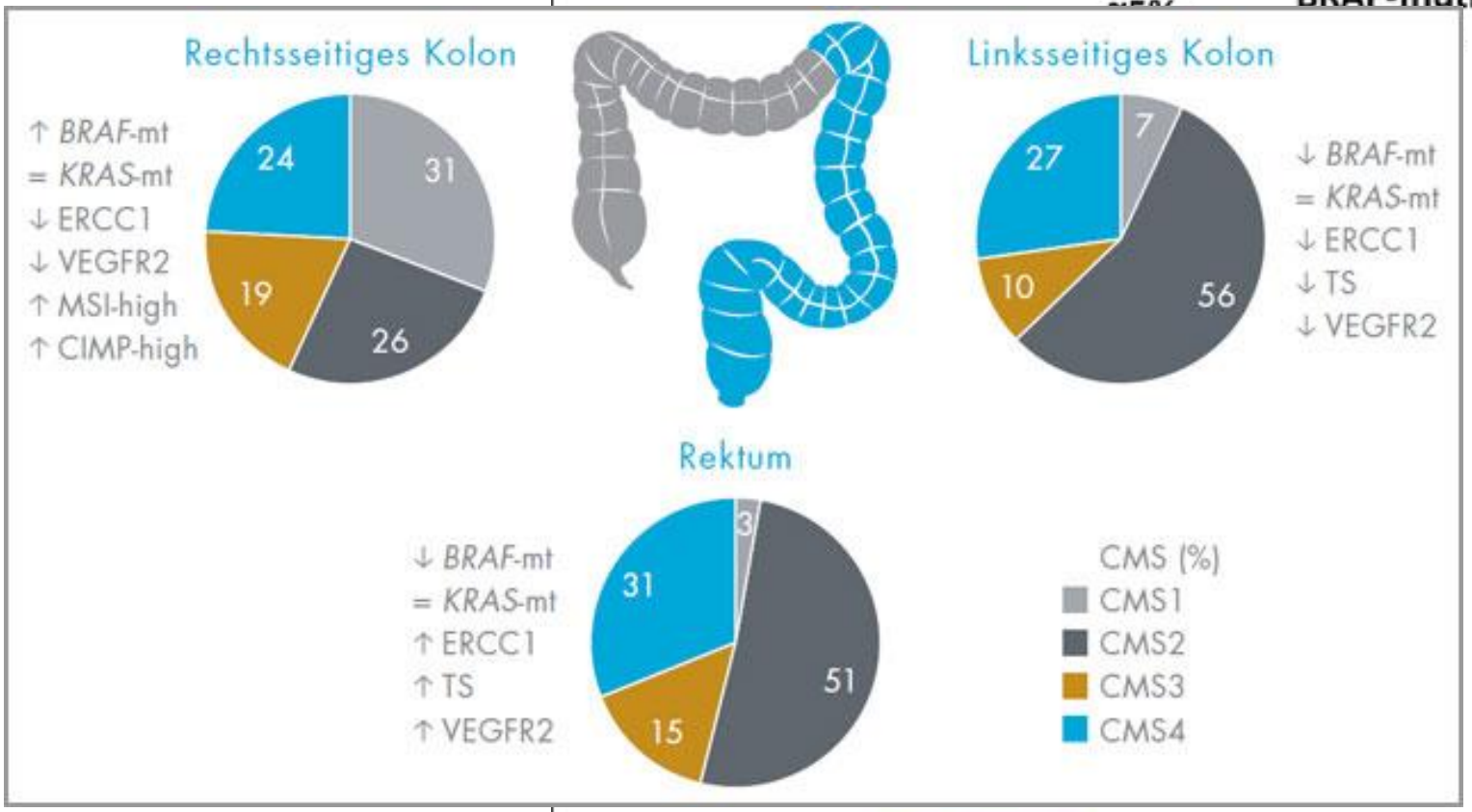
Rechtes Kolon 20–25 %

- Niedrigere Inzidenz
- Häufiger bei Frauen
- Höheres TNM, größere Tumoren, häufiger muzinös
- Stärker immunogen
- Vorwiegend CIMP, MSI, BRAF
- Kürzeres Überleben

Linkes Kolon 75–80 %

- Häufiger
- Häufiger bei Männern
- Niedriges TNM, kleinere Tumoren
- Weniger immunogen
- Vorwiegend chromosomal instabil
- Längeres Überleben

Kolonkarzinom - Palliative Therapie



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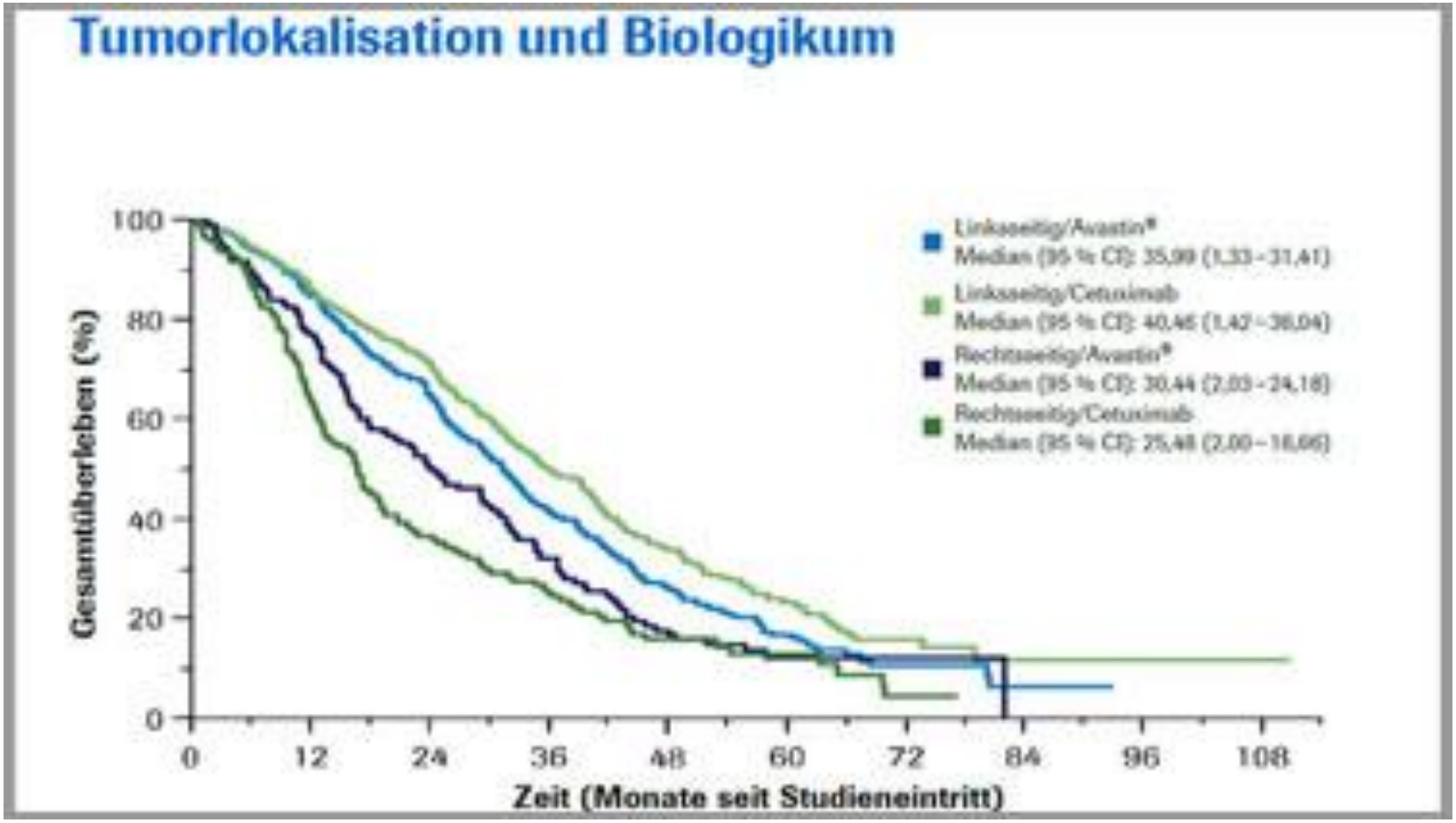
Kolonkarzinom - Palliative Therapie



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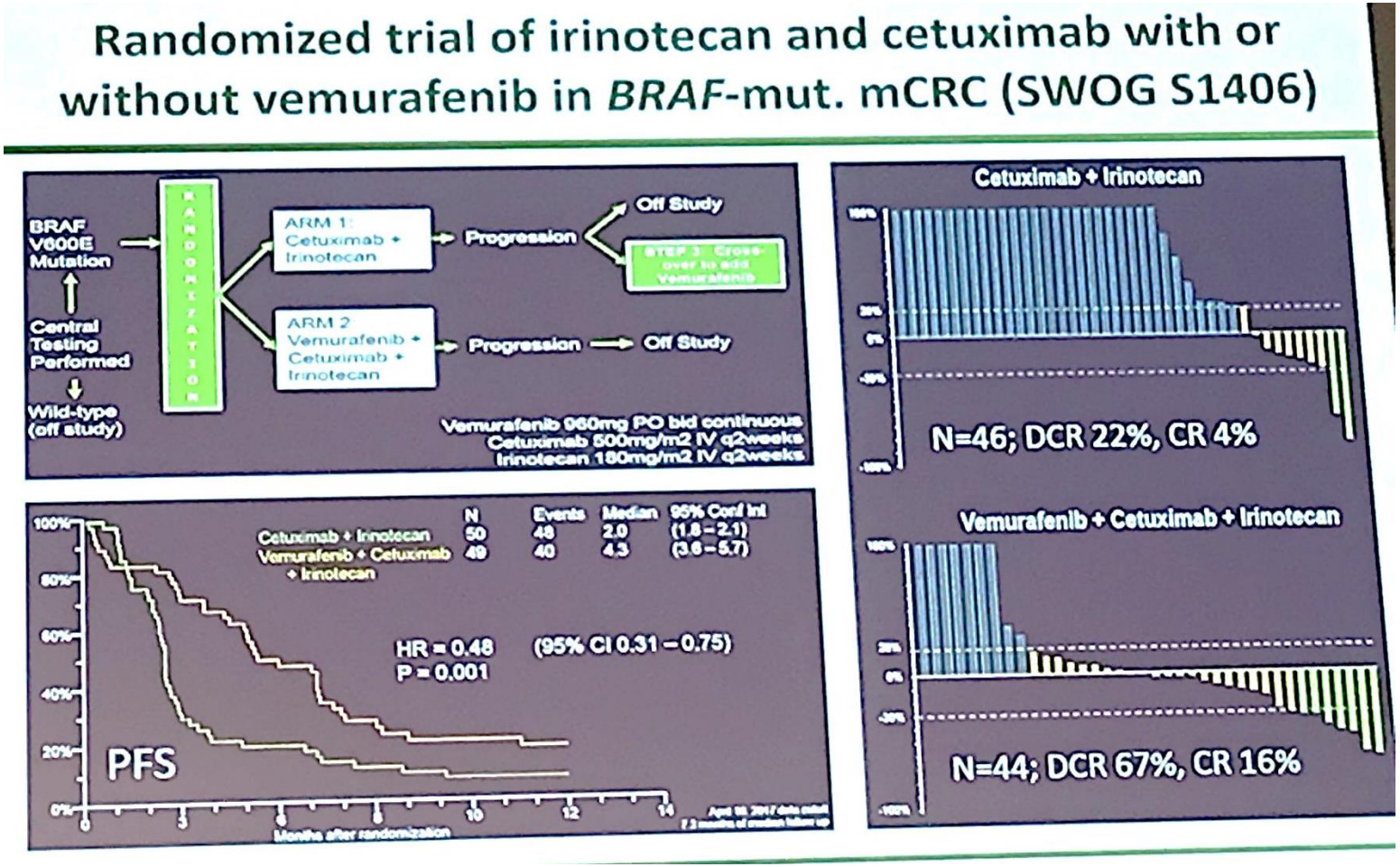
Kolonkarzinom - Palliative Therapie

TKI bei BRAF V600E mut.



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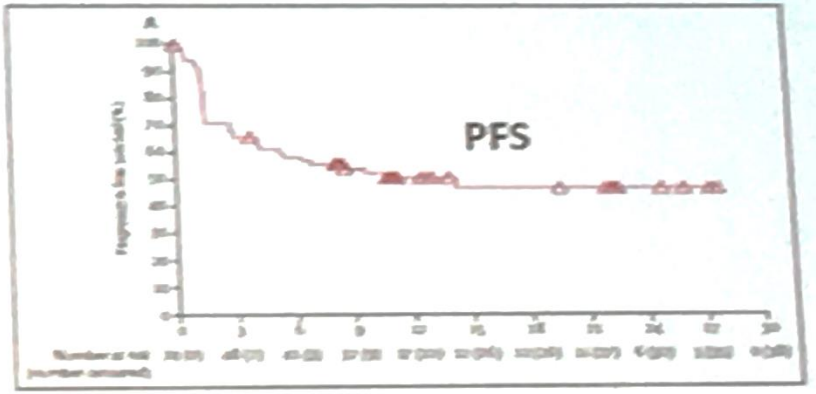
Kolonkarzinom - Palliative Therapie

Nivolumab – Checkpoint-Inhibition

Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study

Michael J Overman, Ray McDermott, Joseph L Leach, Sara Lonardi, Heinz-Josef Lenz, Michael A Morse, Joseph Desai, Andrew Hill, Michael Axelson, Rebecca A Moss, Monica V Goldberg, Z Alexander Cao, Jean-Marie Ledeine, Gregory A Maglinte, Scott Kopetz*, Thierry André*

- Phase 2 study; 74 pts dMMR/MSI-H metastatic pretreated CRC
- RR 31%, DCR 67%
- Duration of response not reached; --> long-term survival



DNA mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) metastatic CRC (about 5% of patients) are a distinct biomarker-defined population who benefit less from conventional chemotherapy and have a shorter OS than do patients with proficient MMR (pMMR), higher mutational burden and tumour neoantigen load, dense immune cell infiltration.

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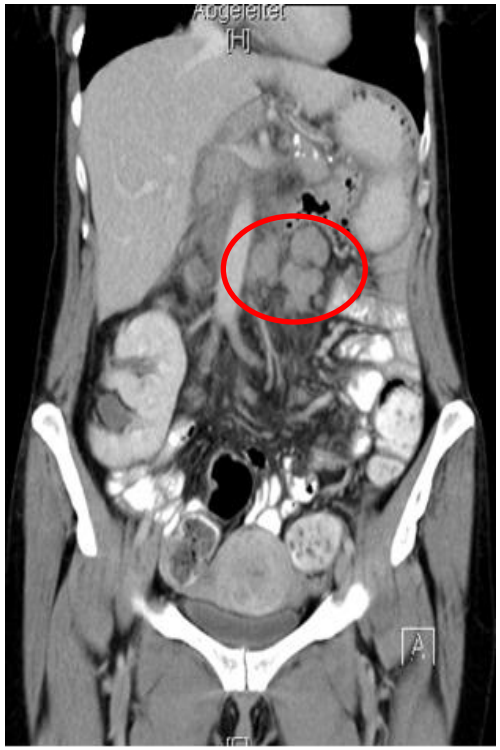
Kolonkarzinom - Palliative Therapie

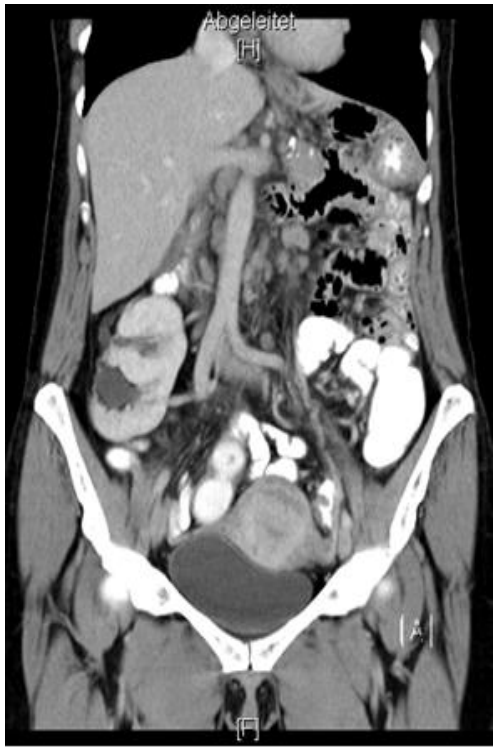
Immunologische Therapieansätze – Bedeutung für die onkolog. Reha

47j Patientin, Gymnasiallehrerin

- metastas. Colon-CA (ED 03/2016).
- nach OP Progress auf 2nd line CTX
- massive Nebenwirkungen (PNP, Schmerzen)
- individueller Heilversuch („off label“) mit Pembrolizumab seit 04/2017
- Gutes Ansprechen, keine Neben-wirkungen

→ Patient möchte nach Onkolog. Reha wieder ihre Lehrtätigkeit aufnehmen…





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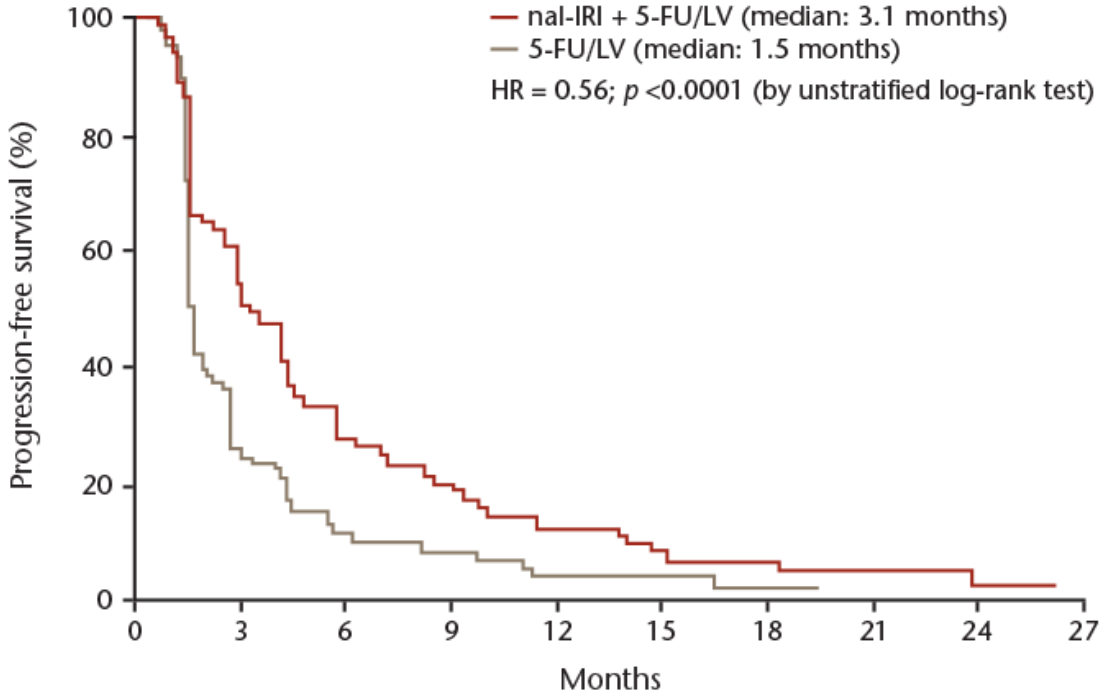
Therapie des Pankreas-CAs
Neuzulassung nab-Irinotecan



Number at risk									
nal-IRI + 5-FU/LV	117	50	26	17	10	5	4	2	1
5-FU/LV	119	23	10	6	3	3	1	0	0

5-FU/LV = 5-fluorouracil and leucovorin; HR = hazard ratio; nal-IRI = nanoliposomal irinotecan; PFS = progression-free survival

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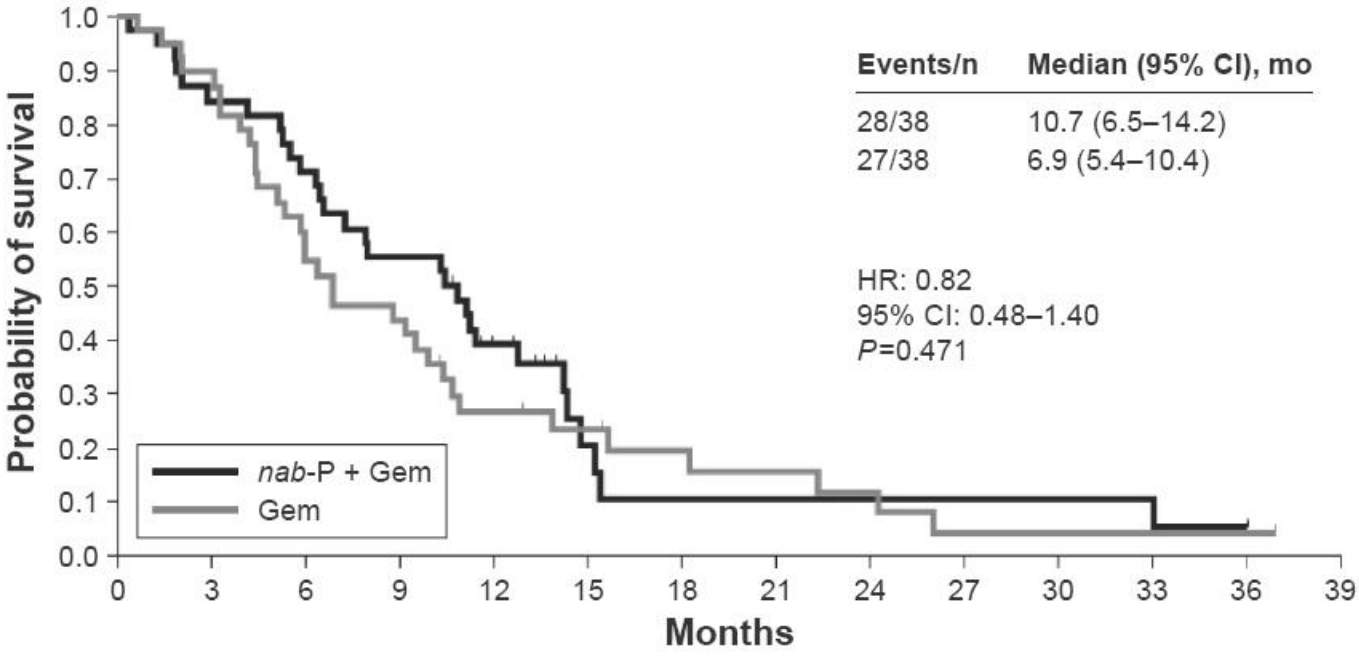
Therapie des Pankreas-CAs
Einsatz von nab-Paclitaxel



Patients at risk														
nab-P + Gem:	38	32	27	21	12	4	2	2	2	2	2	2	1	0
Gem:	38	34	21	16	9	7	5	4	3	1	1	1	1	0

Figure 1 Overall survival in the Western European cohort.
Abbreviations: CI, confidence interval; Gem, gemcitabine; HR, hazard ratio; mo, month; *nab*-P, *nab*-paclitaxel.

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Therapie des Pankreas-CAs

Aktuelle Therapie-Optionen:

- Gemzitabin -/+ Erlotinib
- nab-Paclitaxel + Genzitabin
- nab-Irinotecan + 5-FU
- FOLFIRINOX
- (FolFOx, FolfIri, 5-FU, Capezitabin, etc.)

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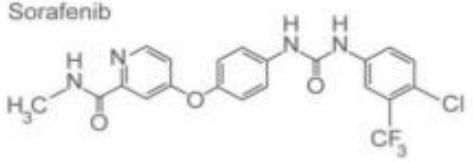
Palliative Systemtherapie des HCCs
Regorafenib (Zulassung Herbst 2017)

Regorafenib a Mutikinase Inhibitor

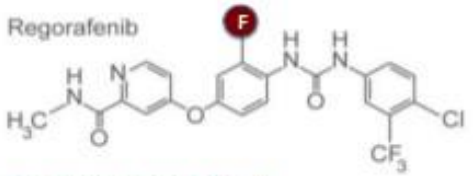
Sorafenib

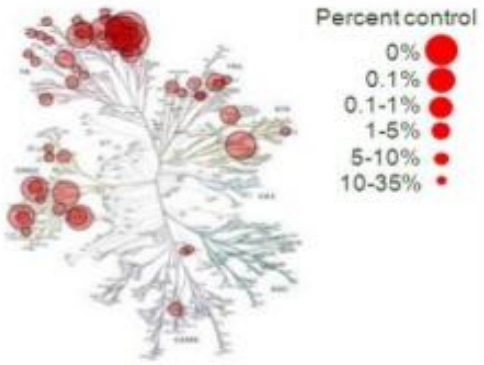
a)



Regorafenib

b)





phase III RESORCE trial

Stratify by:
- Geographic region
- ECOG PS
- Alpha-fetoprotein level
- Extrahepatic disease
- Macrovascular invasion

RANDOMIZE
2 : 1
(Target N=530)

Regorafenib
160 mg orally once daily
3 weeks on, 1 week off
plus best supportive care (4 weeks/cycle)

Placebo
Matching tablets orally once daily
3 weeks on, 1 week off
plus best supportive care (4 weeks/cycle)

ECOG PS, Eastern Cooperative Oncology Group performance status

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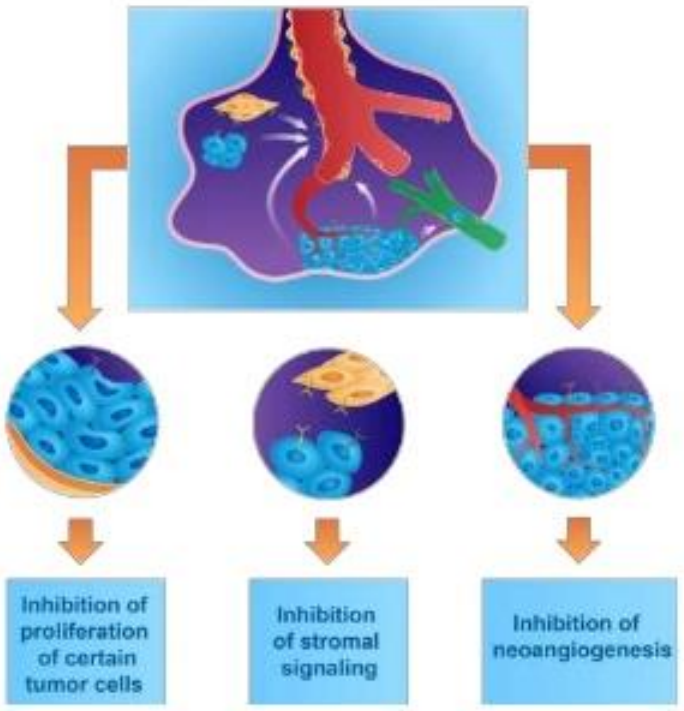
Palliative Systemtherapie des HCCs
Regorafenib (Zulassung Herbst 2017)

Mode of Action of Regorafenib

- **Regorafenib inhibits multiple cell-signaling kinases:**
  - Angiogenic
    - VEGFR1–3, TIE2
  - Stromal
    - PDGFR-β, FGFR
  - Oncogenic
    - KIT, PDGFR, RET
- **$T_{1/2}$ in man: approx. 26-28 hrs**
  - **Two major metabolites (M2, M5) are pharmacologically active**



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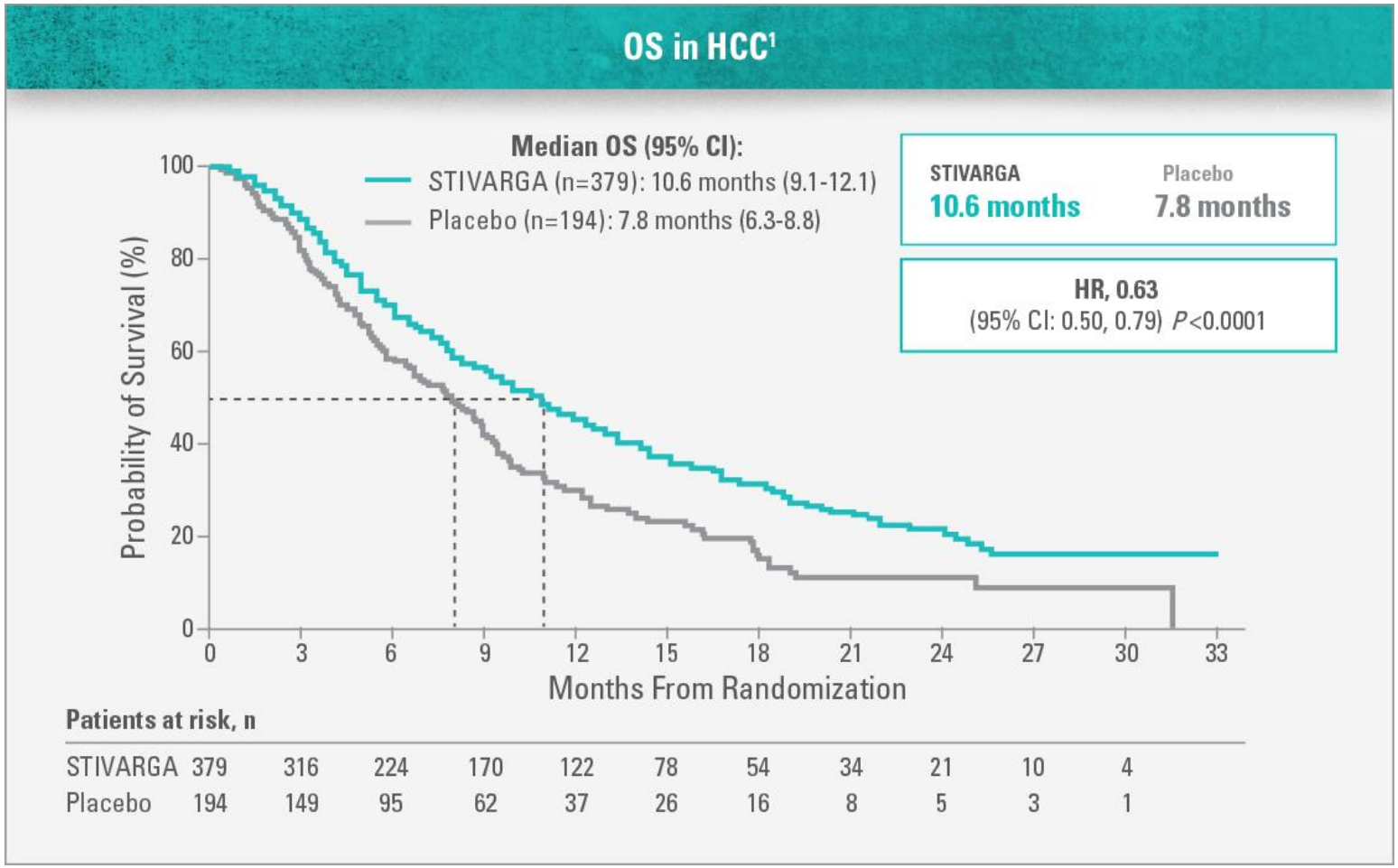
Palliative Systemtherapie des HCCs
Regorafenib (Zulassung Herbst 2017)



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Palliative Systemtherapie des HCCs
Lenvatinib

A Phase 3 Trial of Lenvatinib vs Sorafenib in First-line Treatment of Patients With Unresectable Hepatocellular Carcinoma (REFLECT Study)

Ann-Lii Cheng,[1] Richard S. Finn,[2] Shukui Qin,[3] Kwang-Hyub Han,[4] Kenji Ikeda,[5] Fabio Piscaglia,[6] Ari Baron,[7] Joong-Won Park,[8] Guohong Han,[9] Jacek Jassem,[10] Jean Frederic Blanc,[11] Arndt Vogel,[12] Dmitry Komov,[13] TR Jeffry Evans,[14] Carlos Lopez,[15] Corina Dutcus,[16] Min Ren,[16] Silvija Kraljevic,[17] Toshiyuki Tamai,[16] Masatoshi Kudo[18]

Patients with unresectable HCC (N = 954)
No prior systemic therapy for unresectable HCC; Child-Pugh A, ECOG PS ≤ 1

Lenvatinib (n = 478)
8 mg (BW < 60 kg) or 12 mg (BW ≥ 60 kg) once daily

Sorafenib (n = 476)
400 mg twice daily

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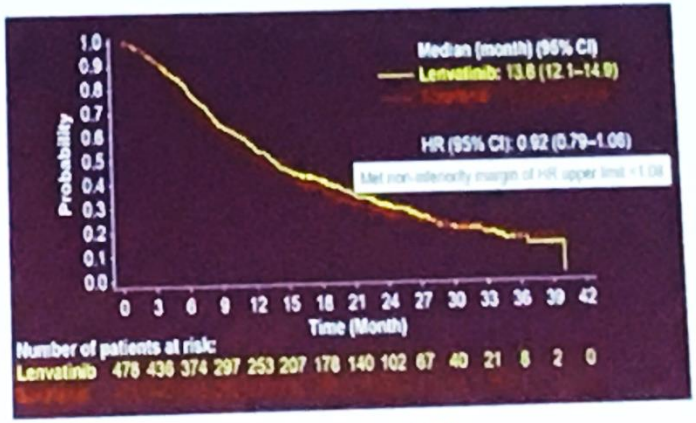
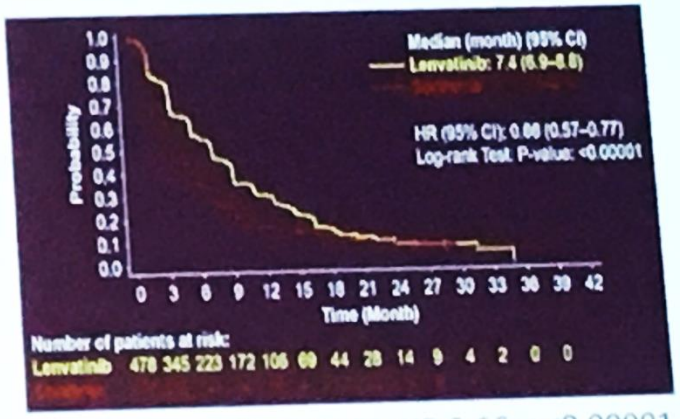
Palliative Systemtherapie des HCCs
Lenvatinib

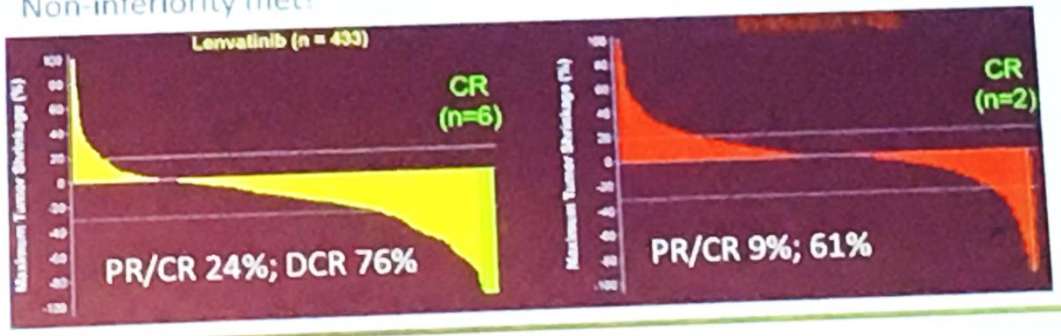
Lenvantinib vs. Sorafenib in HCC



Primary Endpoint OS: HR 0.92;
Non-inferiority met!



Secondary Endpoint PFS: HR 0.66; p<0.00001



Treatment related serious SAE: Len. 18 vs. Sor. 10%

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Palliative Systemtherapie des HCCs
Lenvatinib

Lenvantinib vs. Sorafenib in HCC

- Lenvatinib has demonstrated noninferiority versus sorafenib in overall survival as first line systemic therapy and represents and alternative first line option in advanced HCC.
- Lenvatinib demonstrates statistically significant improvement in PFS, TTP, and ORR versus sorafenib in this population
- Acceptable safety profiles of lenvatinib, although slightly higher grade 3 AEs and treatment related SAEs (L:18% vs S:10%). Less hand foot syndrome, more hypertension noted

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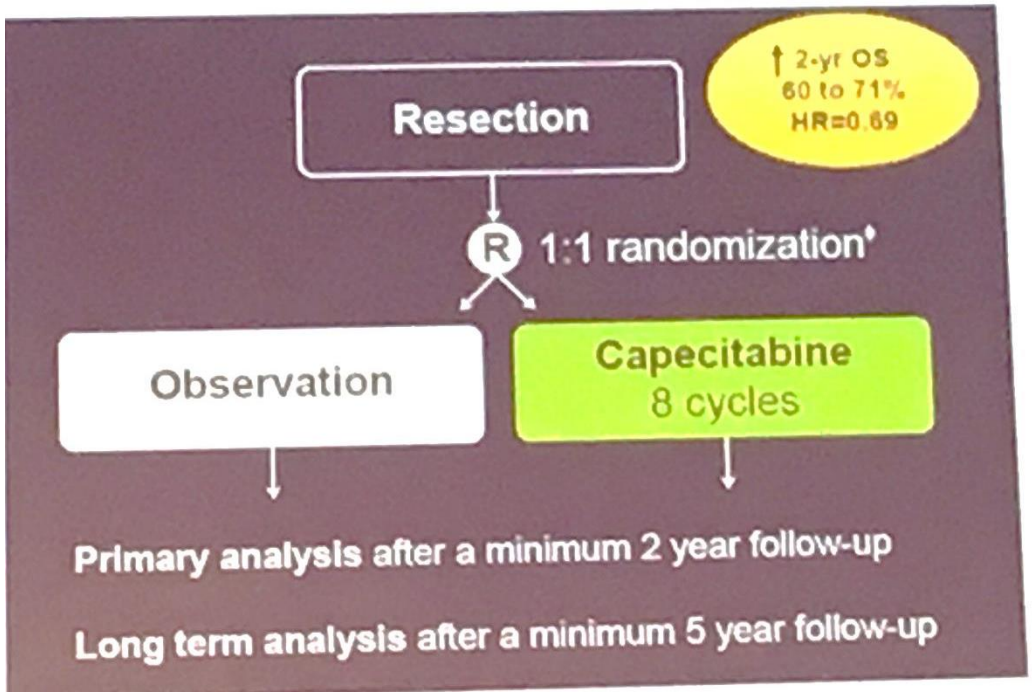
Adjuvante Therapie von Gallenwegstumoren

Adjuvant capecitabine for biliary tract cancer: The BILCAP randomized study



Capecitabine (1250mg/m2) twice a day on day 1 to 14 of a 3 weekly cycle for 24 weeks (8 cycles)

Intrahepatic cholangiocarcinoma (CC), Hilar CC, Muscle invasive gallbladder cancer, Lower common bile duct CC

- Radical & macroscopically complete surgery
- ECOG 0-2

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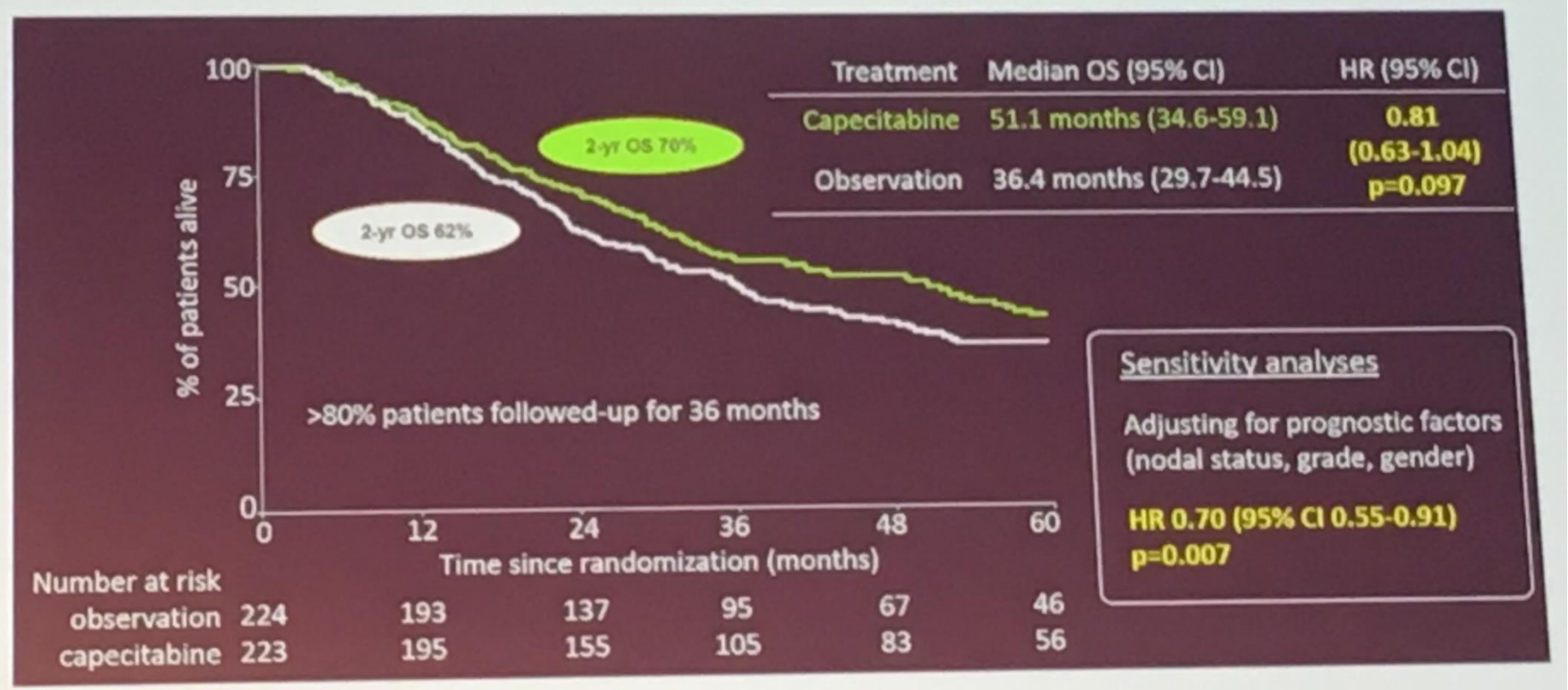
Adjuvante Therapie von Gallenwegstumoren



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Adjuvante Therapie von Gallenwegstumoren

	BILCAP			PRODIGE		
	Capecitabine N=223	Observation N=224	p	GEMOX N=94	Observation N=99	p
Median RFS	24.6 mo	17.6 mo	0.039	30.4 mo	22 mo	0.31
Median OS	51.1 mo	36.4 mo	0.097	Not available	Not available	

Adjuvant Capecitabine improved median OS by 15 months in resected biliary tract cancers and should become the standard of care: Clinically meaningful, acceptable toxicity profile.

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Perioperative Therapie des Magen-CAs

Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4): A multicenter, randomized phase 3 trial

Al-Batran SE, Homann N, Schmalenberg H, Kopp HG, Haag GM, Luley KB, Schmiegel WH, Folprecht G, Probst S, Prasnikar N, Thuss-Patience P, Fischbach W, Trojan J, Koenigsmann M, Pauligk C, Goetze TO, Jaeger E, Lindig U, Kasper S, Hozaeel W, Meiler J, Schuler MH, Hofheinz RD for the German Gastric Study Group at AIO

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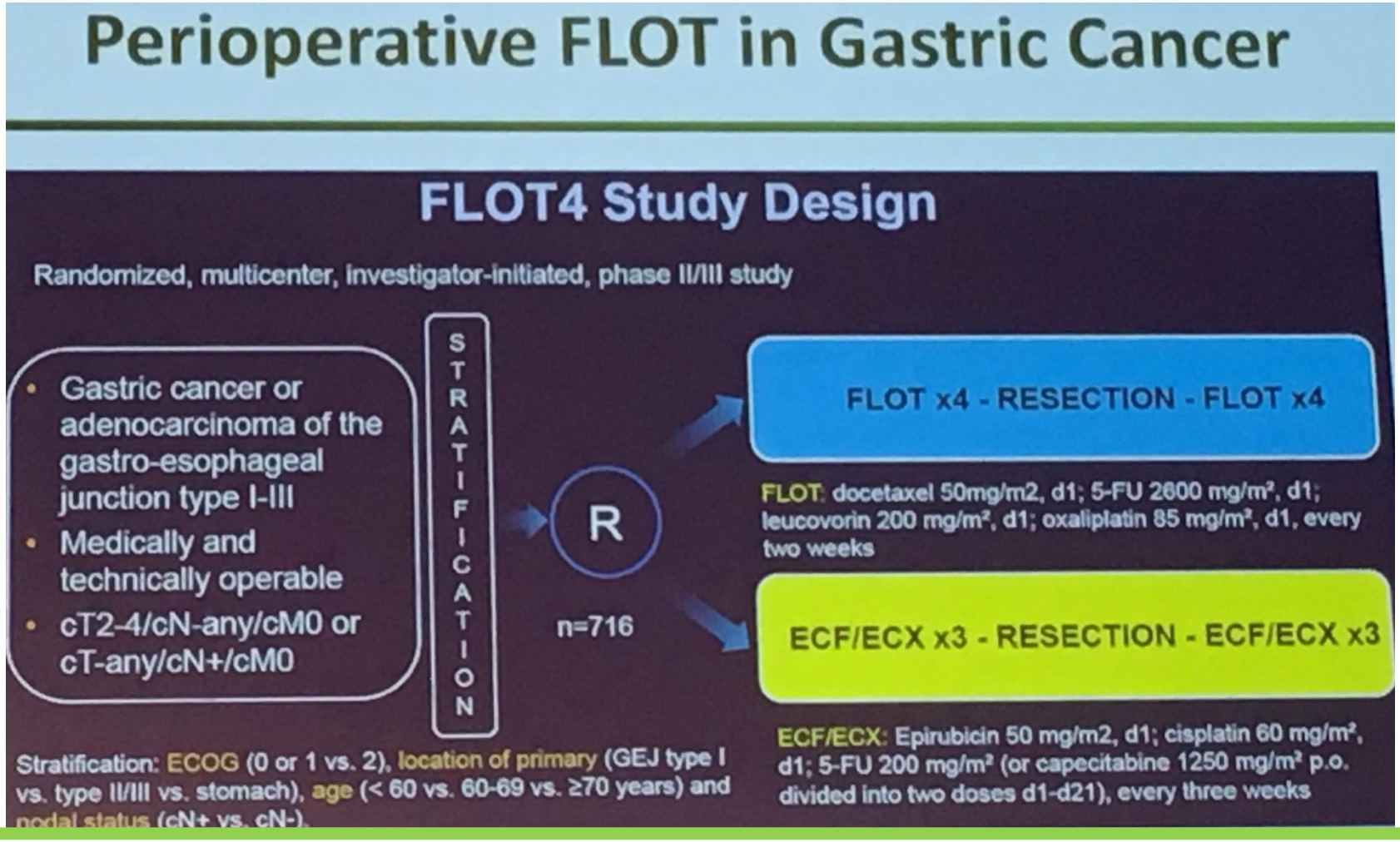
Perioperative Therapie des Magen-CAs



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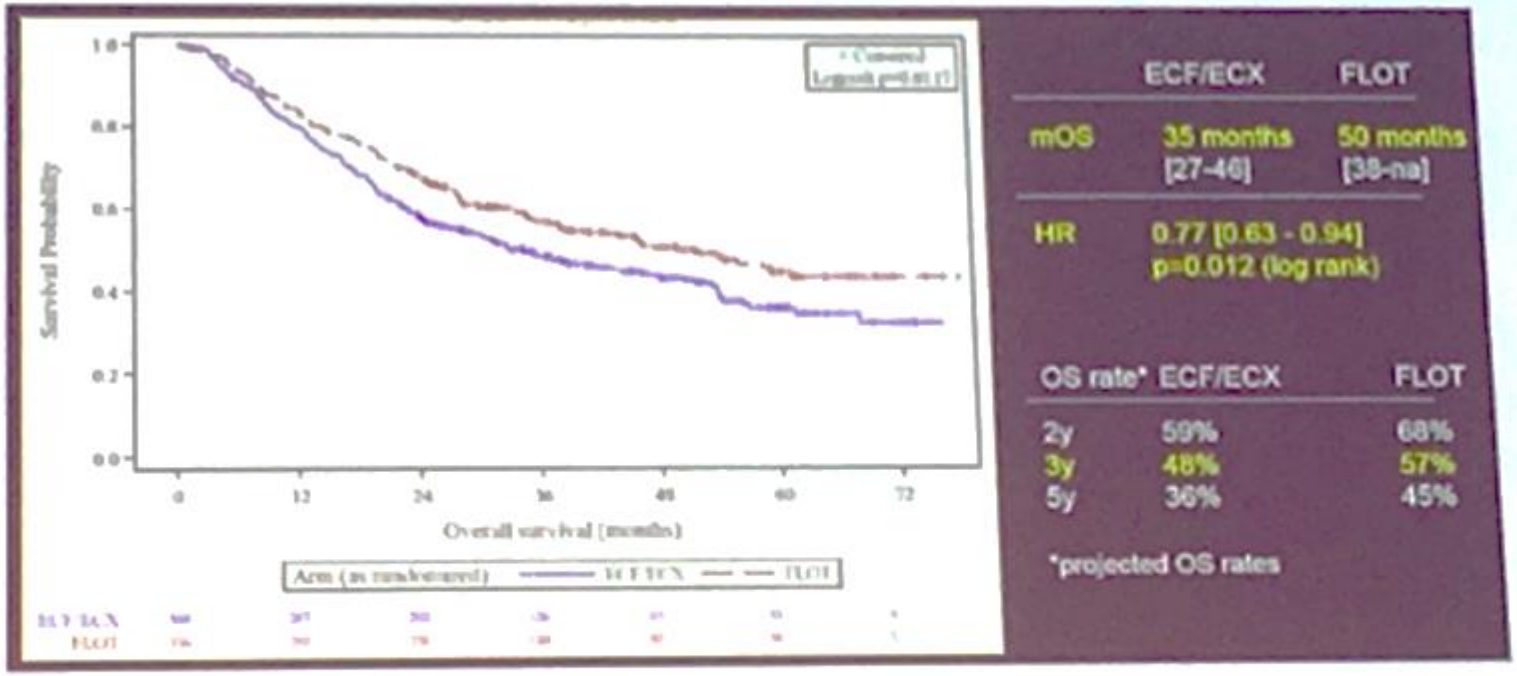
Perioperative Therapie des Magen-CAs



- FLOT increases rates of curative surgery and prolonged PFS and OS as compare to ECF/ECX
- Toxicity was manageable ; no increase in surgical morbidity and mortality
- Perioperative FLOT should replace ECX/ECF , complete neoadjuvant applicatic

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Zusammenfassung

- Zukünftig „individuelle“ adjuvante Therapiedauer beim KRK
- „target therapy“ des mKRK in Erprobung (TKI/Checkpoint-Inhibitoren) sowie Einsatz in Abhängigkeit von TU-Lokalisation
- Neue Therapieoptionen beim Pankreas-CA
- Erstmals seit 15 Jahren dokumentierter Fortschritt in der systemischen Therapie des HCCs
- Adjuvante Therapie von Gallenwegstumoren als Therapie-Standard etabliert
- FLOT neuer Therapie-Standard bei der perioperativen Therapie von Magenkarzinomen

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Vielen Dank für Ihre Aufmerksamkeit !

Fragen ??