(Nieuwe) behandelingen van hepatocellulair carcinoom

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MDL-arts Amsterdam UMC, locatie AMC/VUMC
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Disclosures

Dr. Takkenberg:

- Speakersfee for Norgine, and Sobi
- Grants: ZonMw, Gastrostart, MLDS

Dr. Klümpen, all to institution

- Speakersfee for Medtalk, IPSEN
- Advisory board: IPSEN, Janssen, Astra-Zeneca
- Grants: KWF, BAYER

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Vraag 1: Ik behandel wel eens een patiënt met primair leverkanker

A. Ja, wekelijks

B. Ja, maandelijks

C. Nooit

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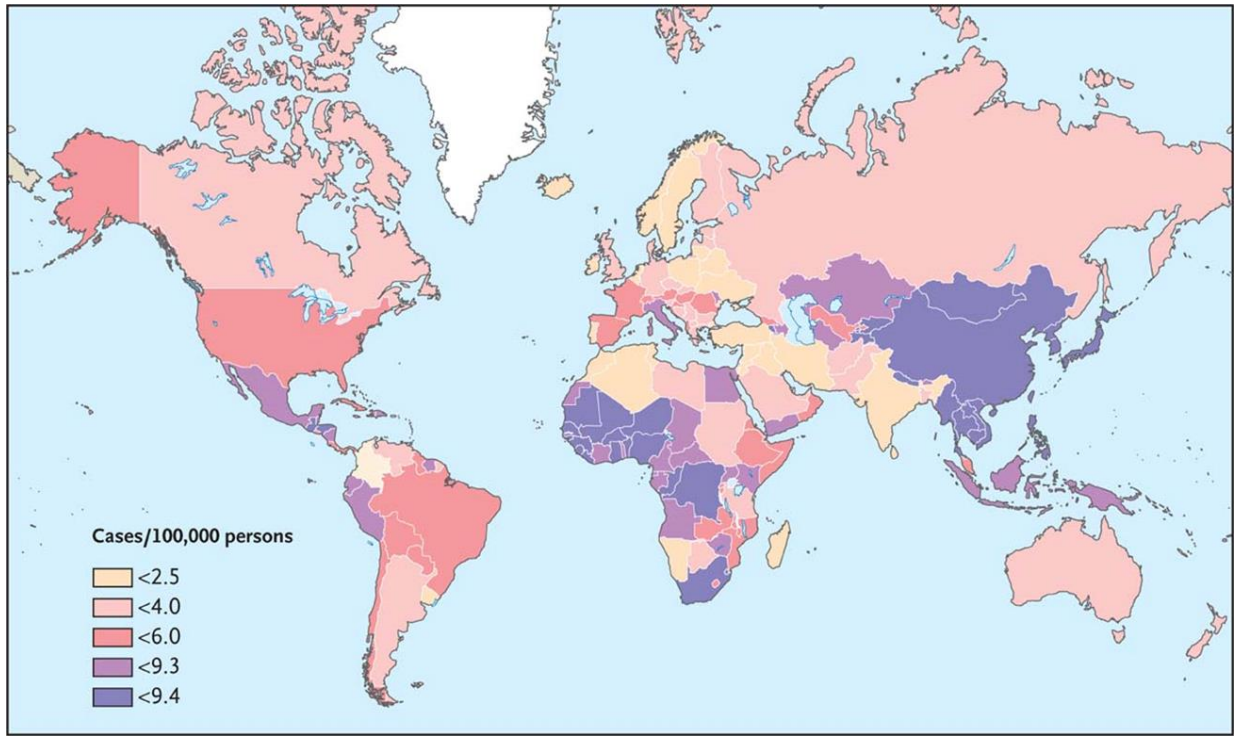
Introduction and Aims

Hepatocellular carcinoma

- Third leading cause of death worldwide

- Risk factors:
  - Liver cirrhosis
  - Non cirrhotic
    - (Non) Alcoholic liver disease
    - No underlying disease
    - Chronic hepatitis B
    - Hemochromatosis

- Incidence has increased



Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians 2018;68:394-424, El-Serag HB. N Engl J Med 2011;365:1118-1127

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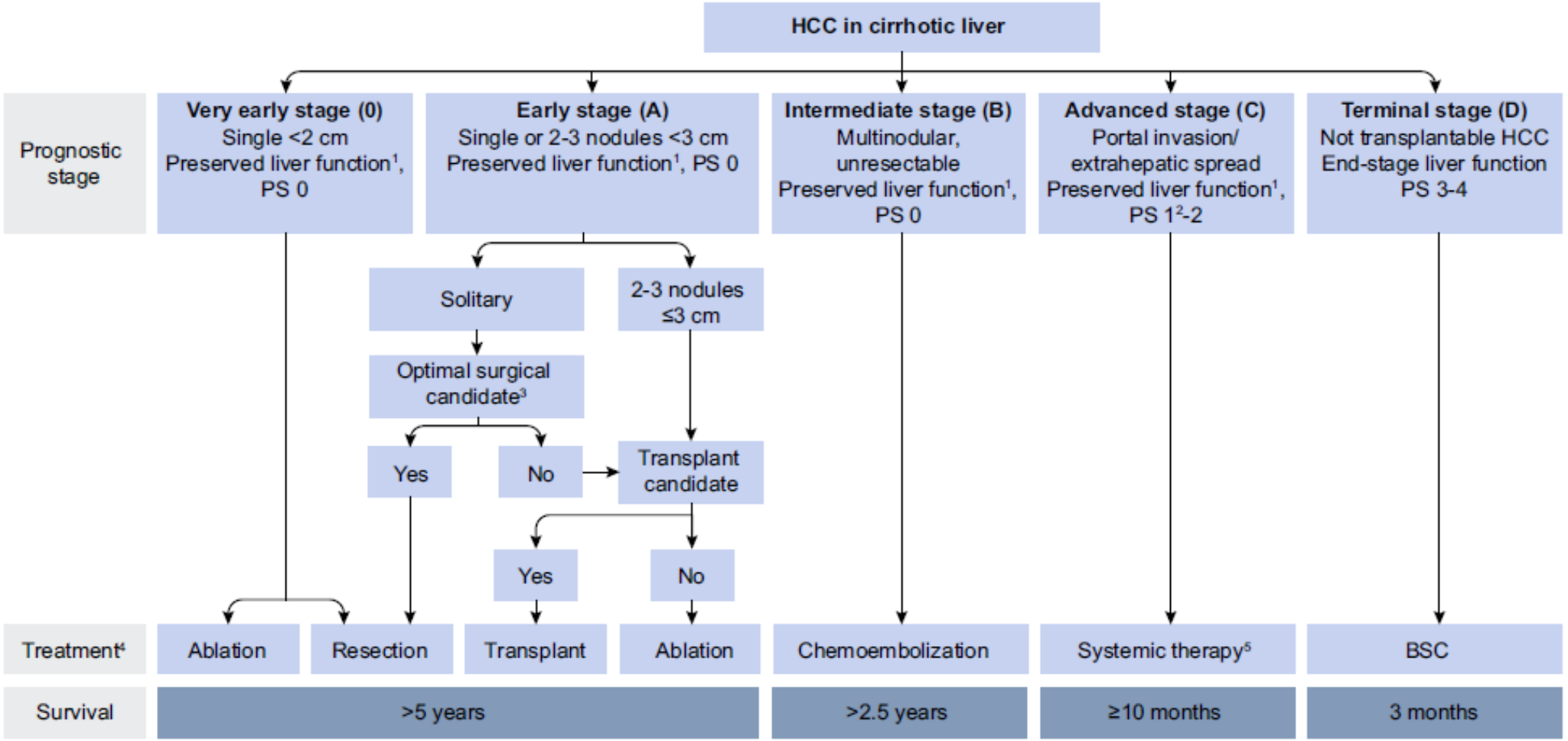
Barcelona Clinic Liver Cancer (BCLC) modified staging system (pre-2020)



EASL clin. Guidelines on HCC, Journal of Hepatology 2018(69):182–236

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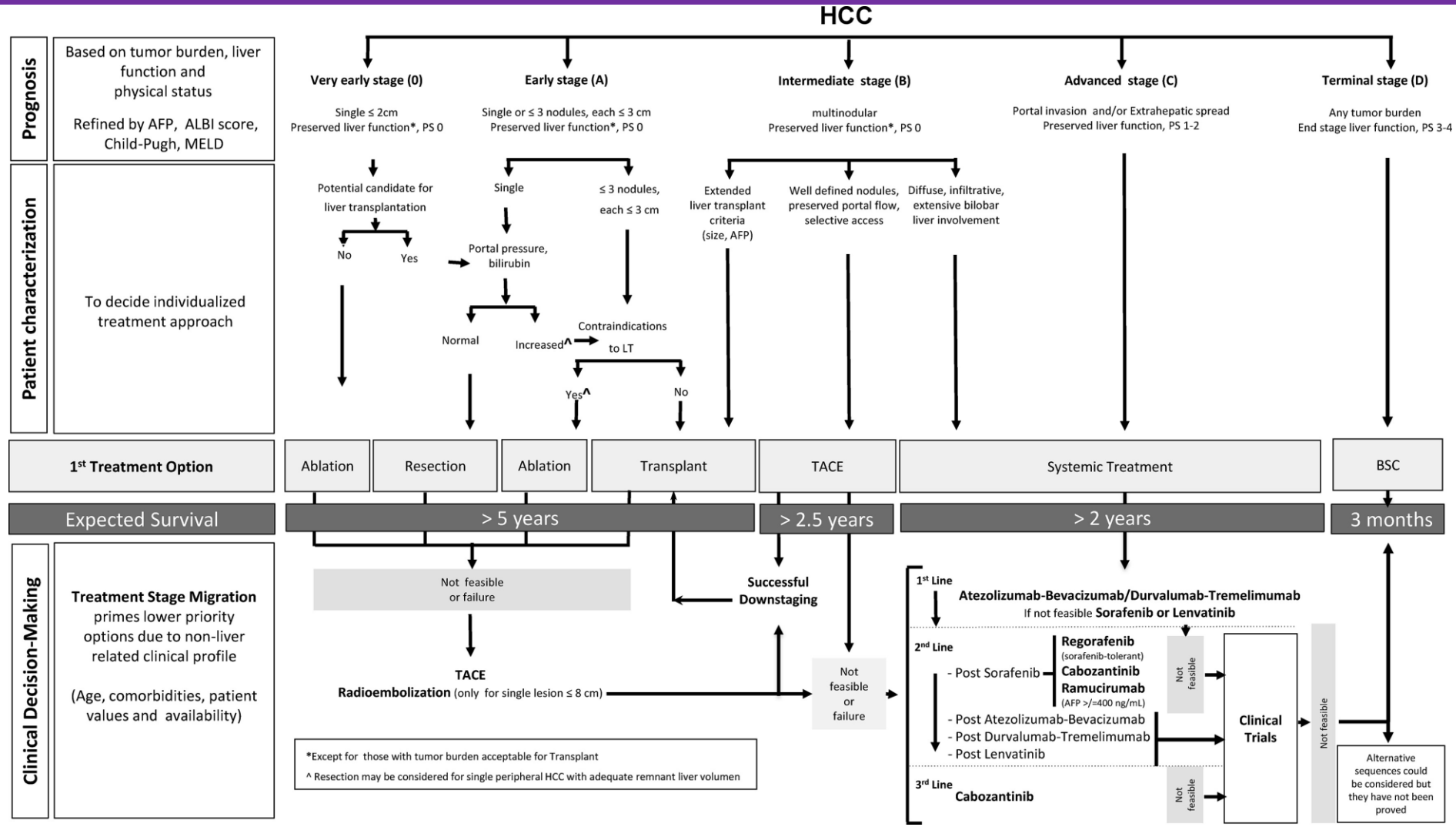
Barcelona Clinic Liver Cancer (BCLC) modified staging system (2022)



M.Reig et.al, Journal of Hepatology J Hepatol. 2021 Nov 18;S0168-8278(21)02223-6

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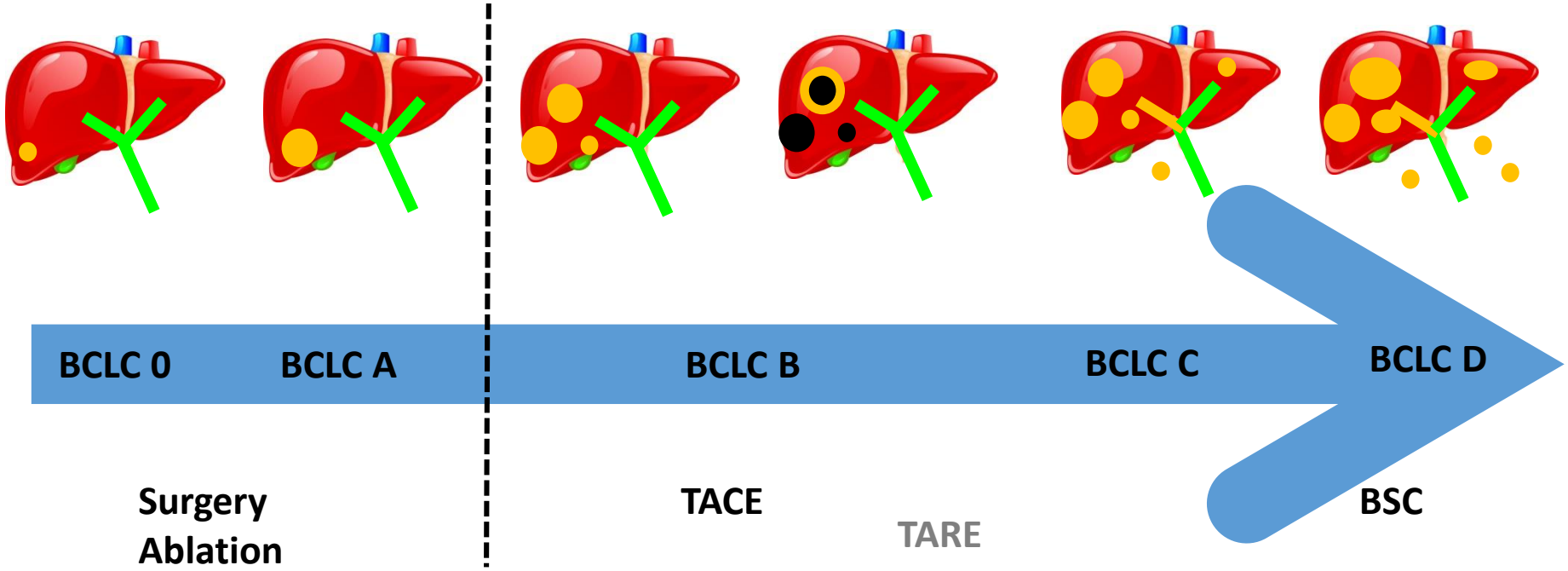
Hepatocellular carcinoma (2022)



Therapy based upon:

1. Tumor burden
2. Liver Function
3. Performance Status

- Atezolizumab + bevacizumab (2021)
- Sorafenib (2008)
- Regorafenib (2016)
- Lenvatinib (2016)
- Cabozantinib (2016)
- Ramucirumab (2016)

Reig et al, Semin Liver Dis 2014;34:444–455

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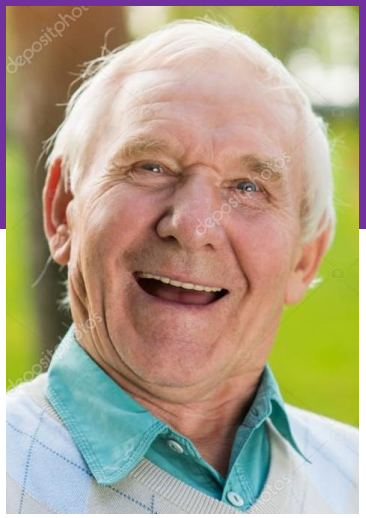
Aims

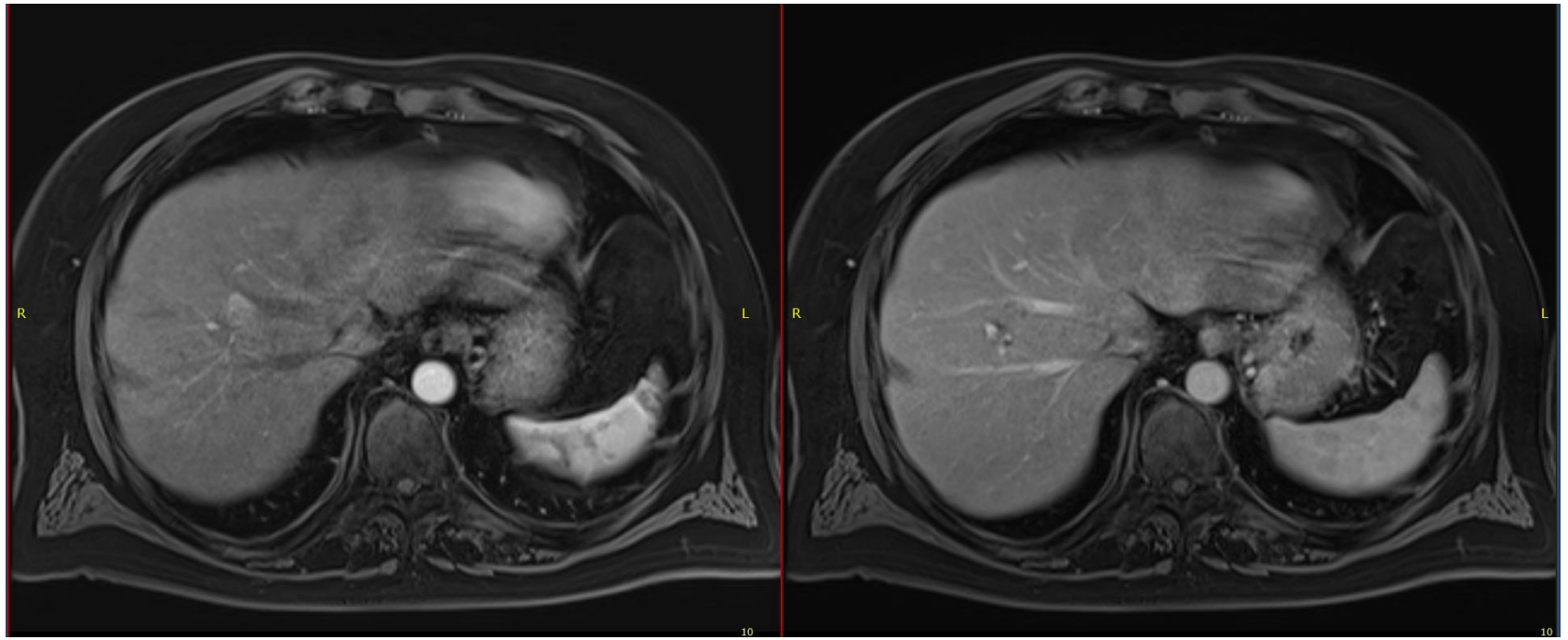
1. Current treatment options HCC (me)

2. Future treatment options (HJ)

Case: Mr B, 74 years



- Child Pugh A (5 points) liver cirrhosis
- PSO 0
- Surveillance US: 1 lesion 17 mm right hemi liver
- MRI:



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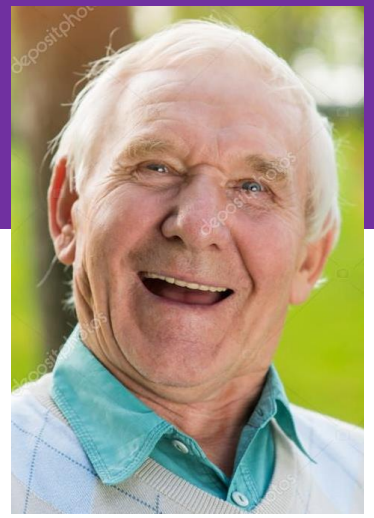
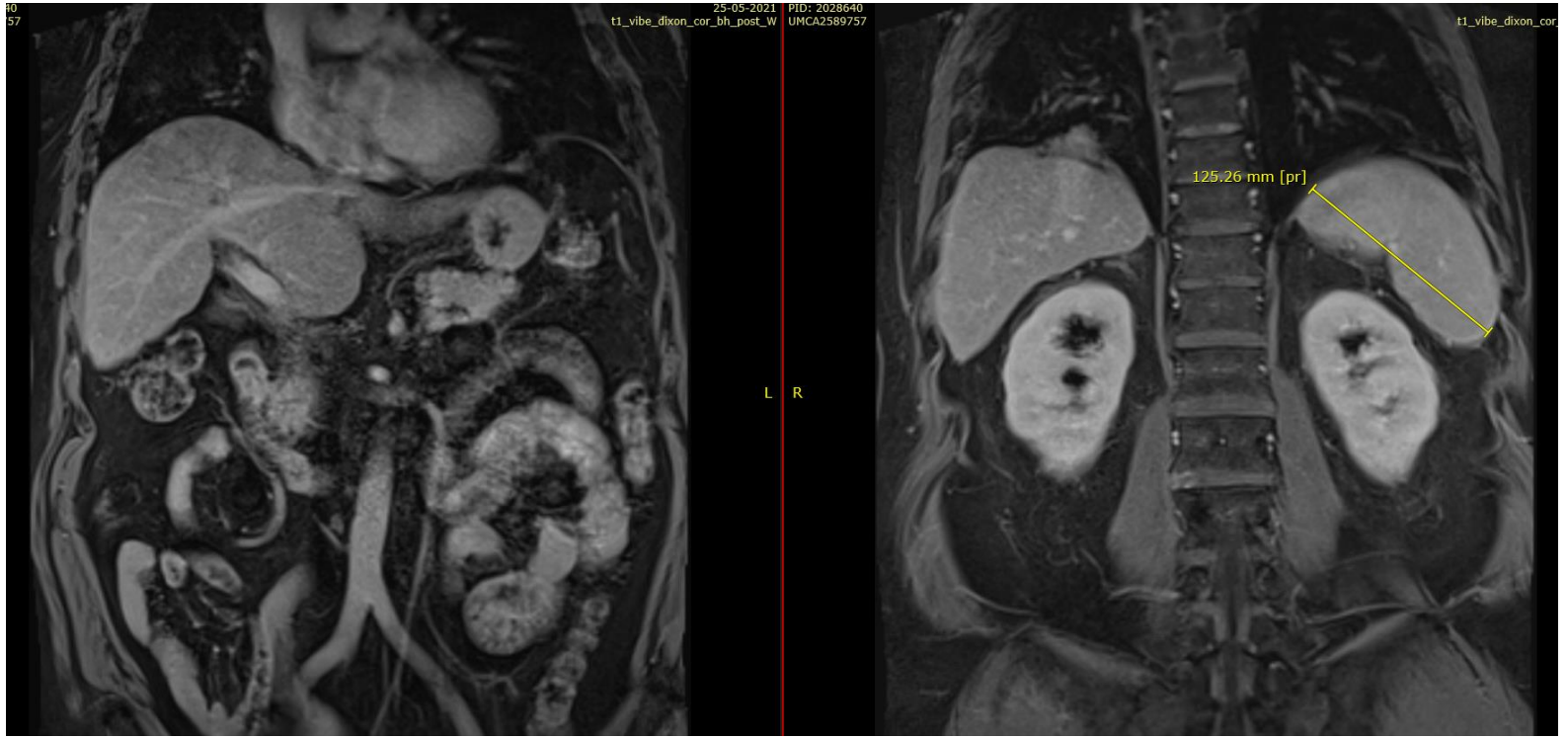


- **Conclusion:**
  - HCC segment 8 (17 mm)
  - CP-A cirrhosis, no PH
  - **<u>BCLC stage ?</u>**



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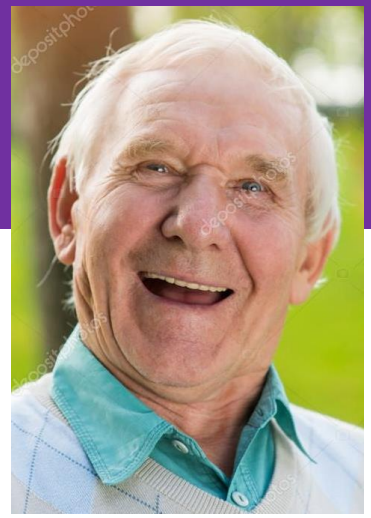
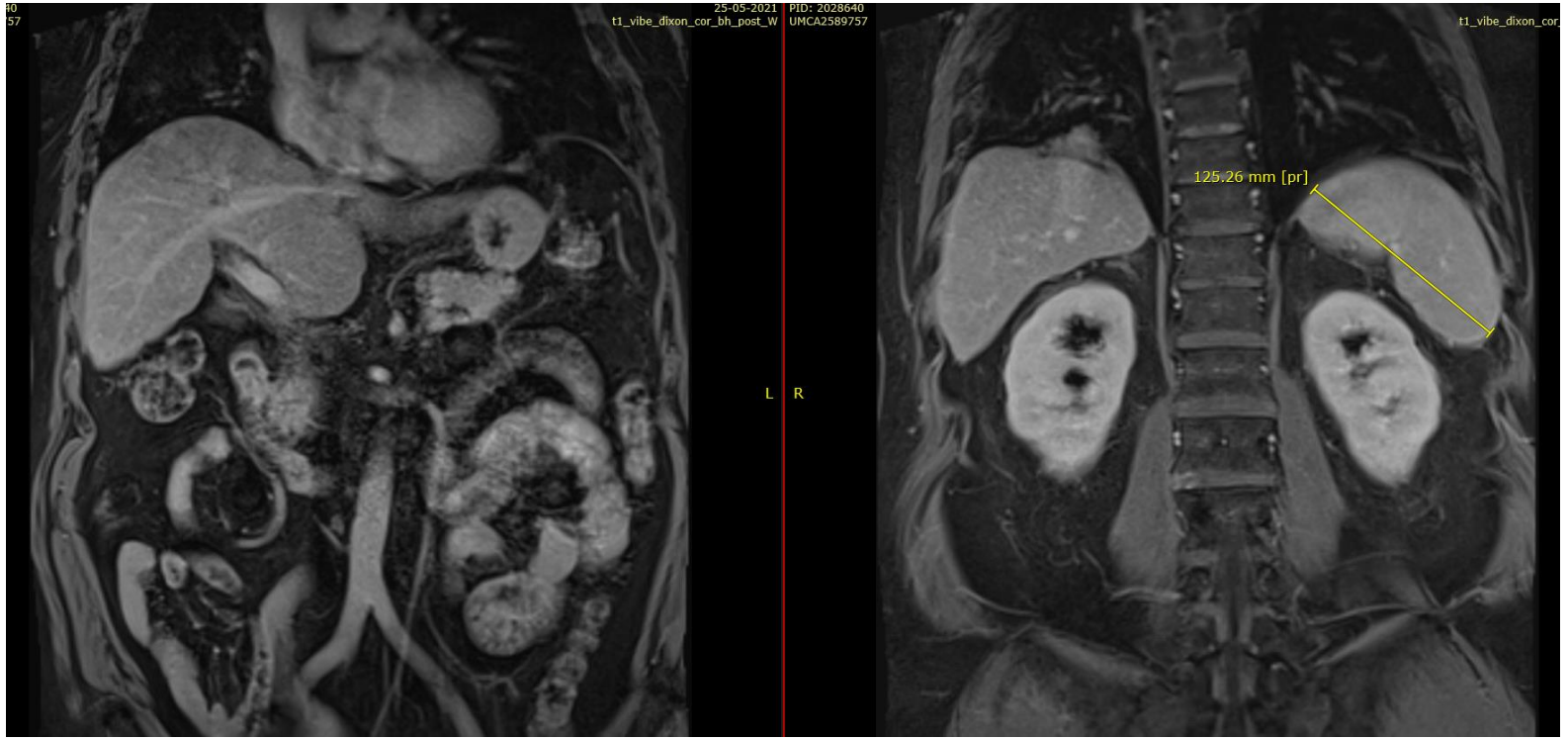


- **Conclusion:**
  - HCC segment 8 (17 mm)
  - CP-A cirrhosis, no PH
  - **<u>BCLC stage: 0</u>**

- **Questions:**
  - Treatment option?



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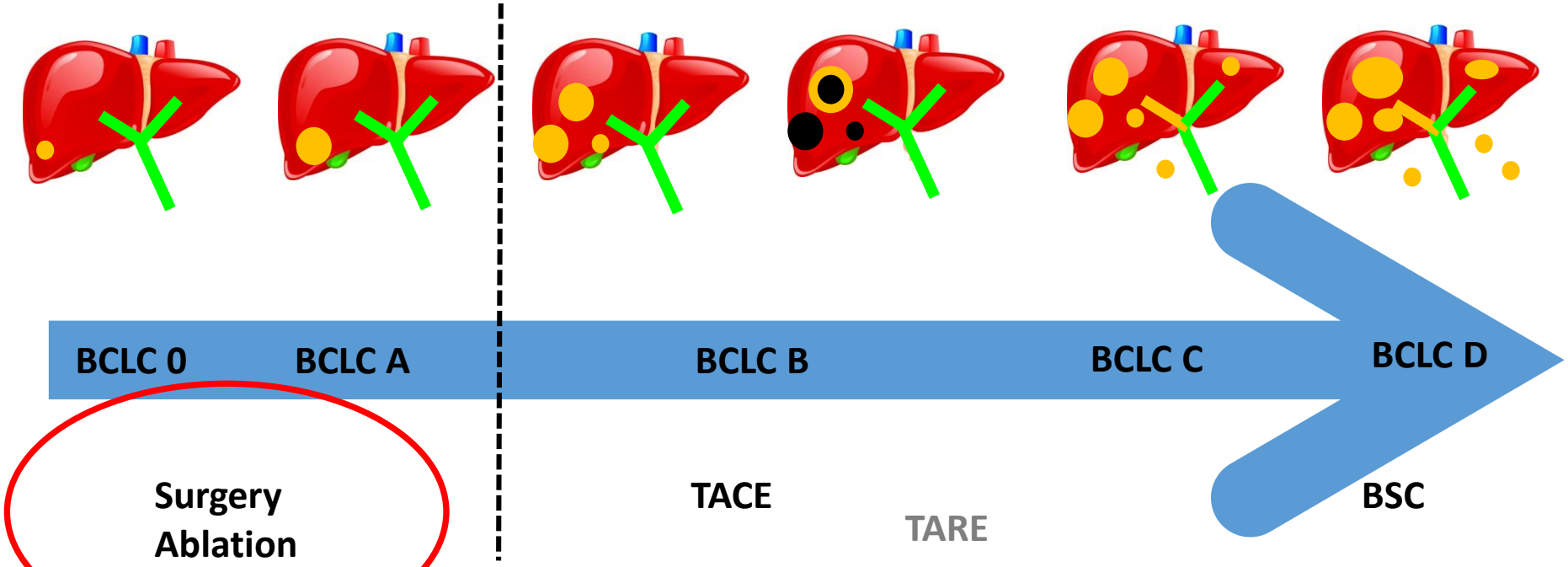

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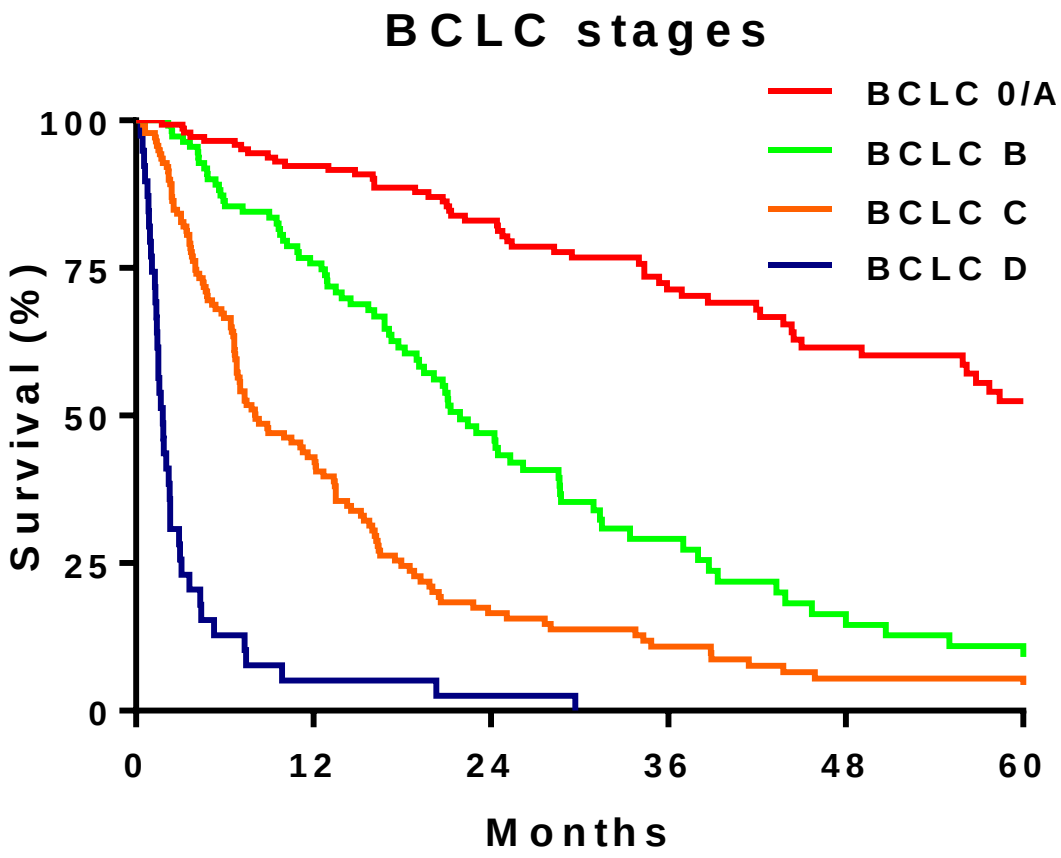
Real time data



BCLC 0/A	63 months	(38-88 months)
BCLC B	19 months	(17-22 months)
BCLC C	7 months	(6-9 months)
BCLC D	2 months	(1-2 months)

Labeur et al. CVIR 2018

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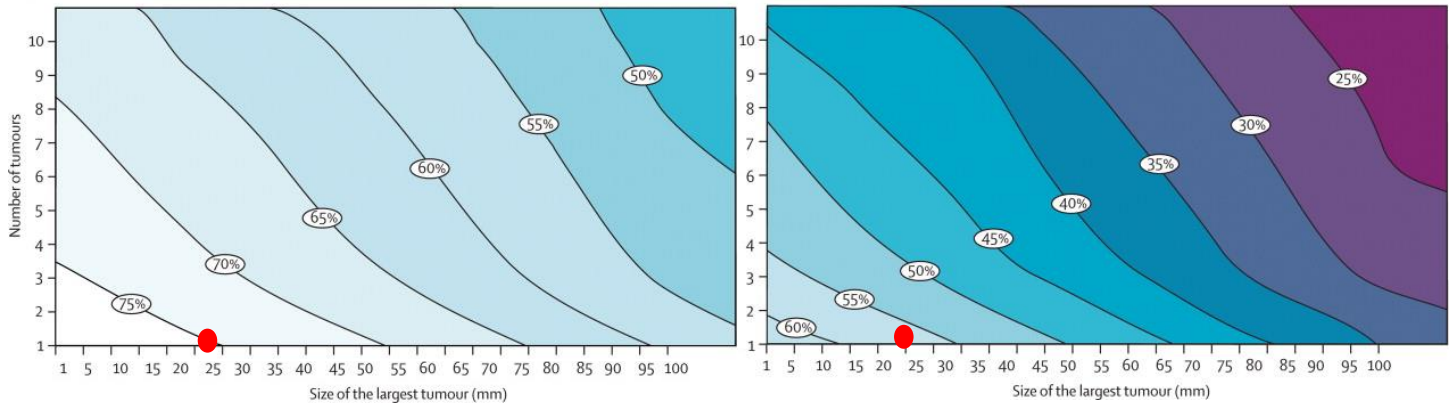
Macro vascular invasion (MVI)

- (Micro-)vascular invasion is highly predictive for survival [1].



- MVI is considered BCLC stage C [2,3]
  - Again this is a very heterogeneous group
  - Representing 10-60% of new HCC cases

(1) Mazzaferro et al, Lancet Oncology 2009; 10 35-43 (2) EASL clinical guidelines 2018, J. Hepatol 2018 (69): 182-236
(3) Chan SI et al, World J Gastroenterol 2016; 22 (32):7289–7300

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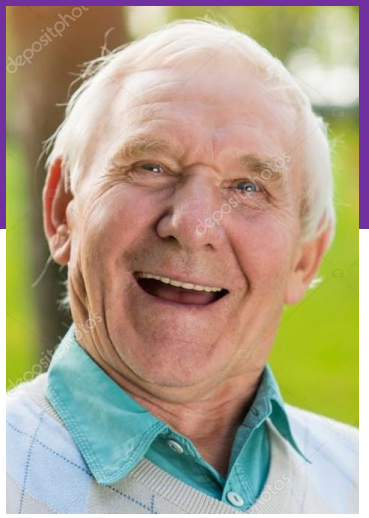
Alternative studies?

- HORA EST, PROMETHEUS, IMBRAVE

Back to the case: Mr B, 74 years



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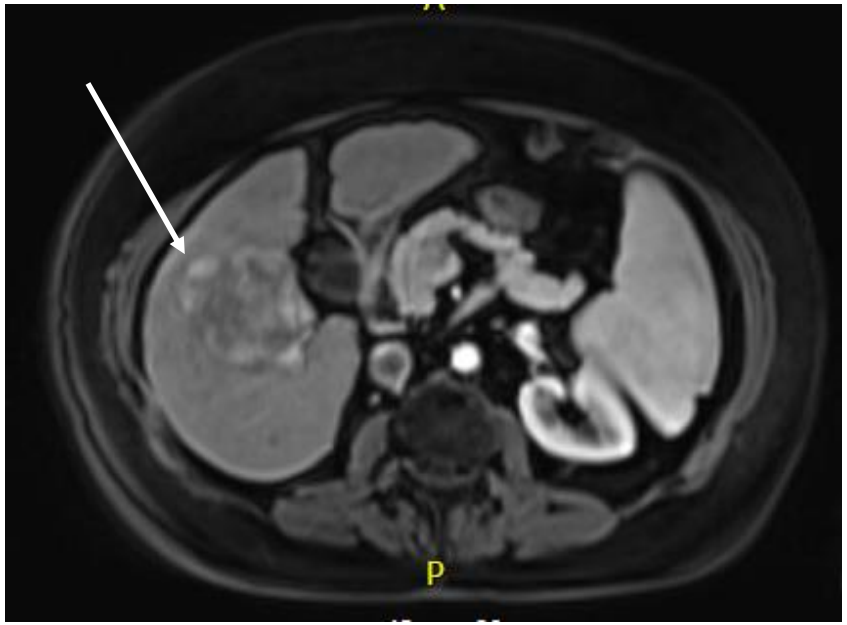

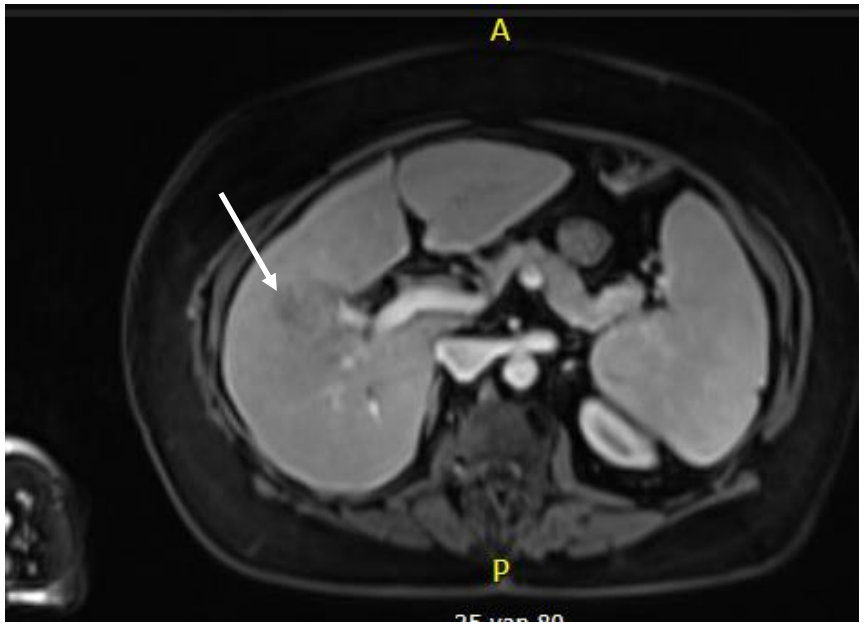

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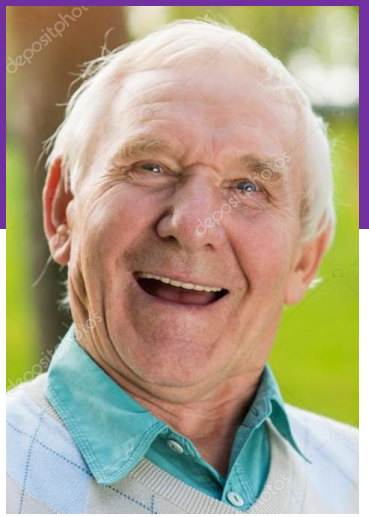

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  - Satellite lesion segment 5/6 (1.5 cm)
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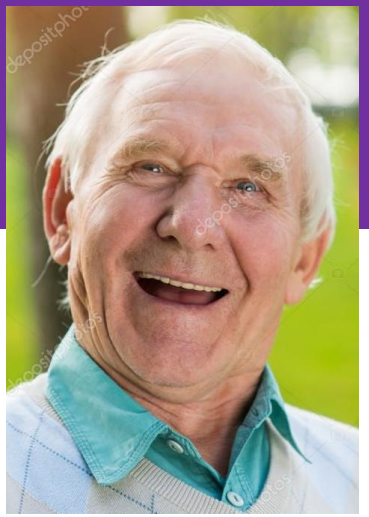

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- **Treatment options: ?**

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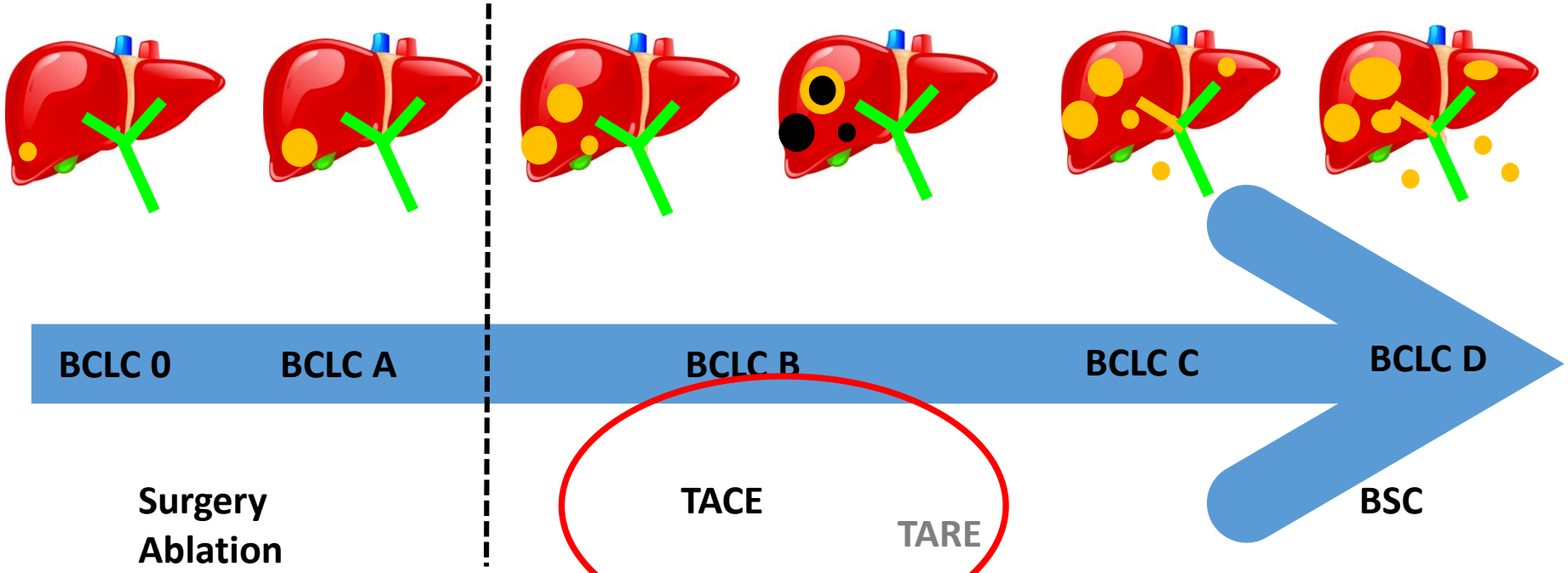
Hepatocellular carcinoma (2022)



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Reig et al, Semin Liver Dis 2014;34:444–455

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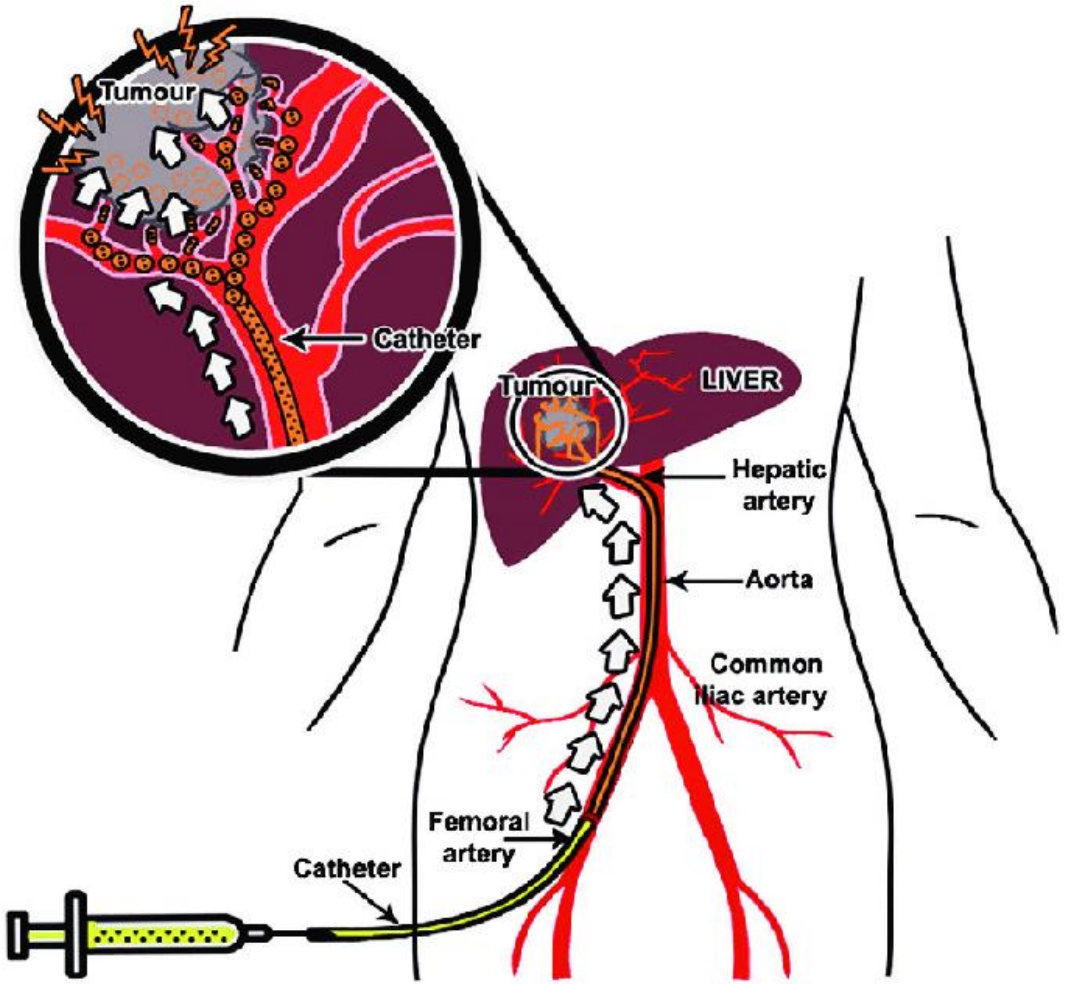
TACE for intermediate stage disease



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TACE for intermediate stage disease

- 2 positive RCT's

Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, Fan ST, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:11641171. 33.

Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, Ayuso C, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellual carcinoma: a randomised controlled trial. Lancet 2002;359:1734-1739.

- 1 systematic review

Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology 2003; 37: 429-42. 62.

Lo et.al, Hepatology 2002;35:11641171. 33, Llovet et al. Lancet 2002; 359:1734-1739, Llovet et al Hepatology 2003;37:429-42

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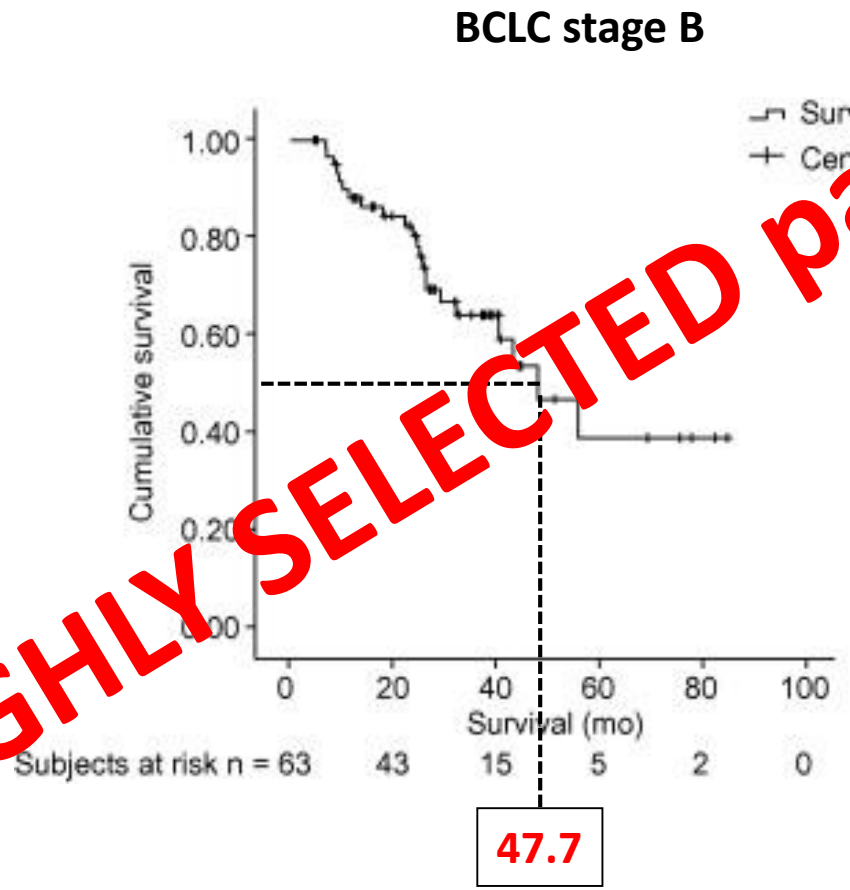
What is the prognosis?
Studies



HIGHLY SELECTED patients

Burrel et al, J. Hepatol 2012; 56(6):1330-1335

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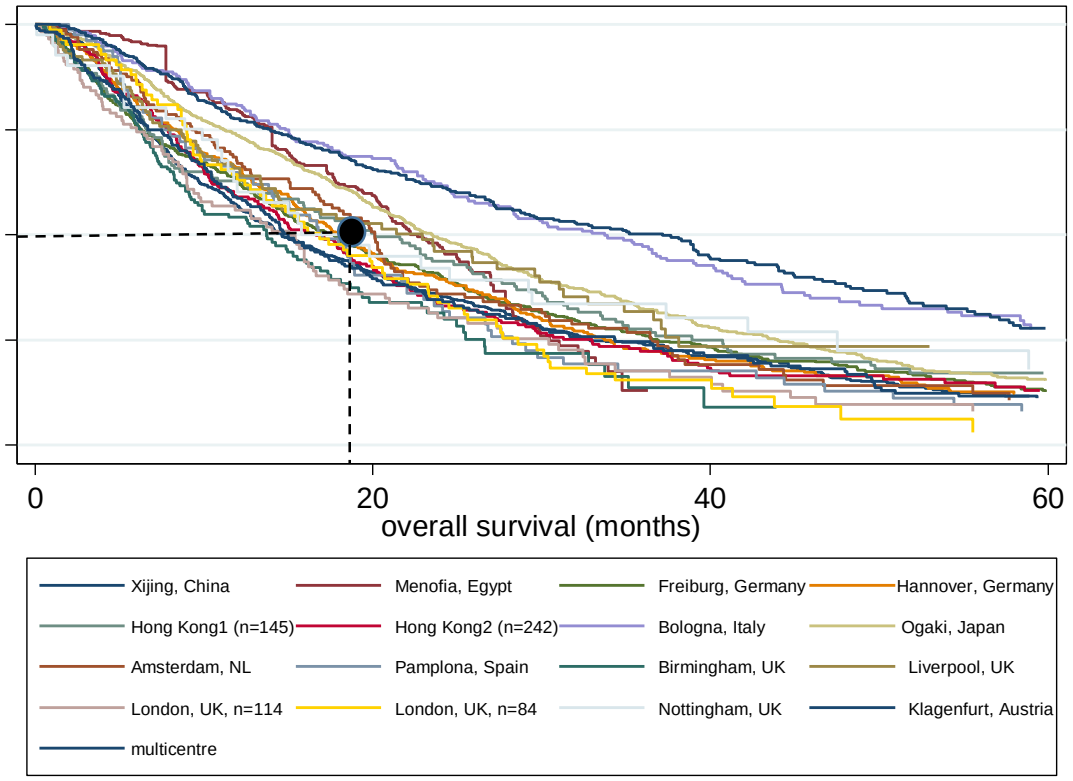
TACE for intermediate stage disease….. HOWEVER

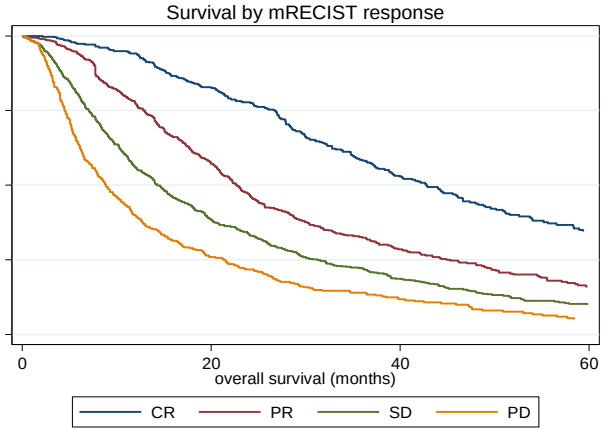
- Very heterogeous
- Tumor size and tumor load
- Location
- Biology

What is the prognosis?
Real life



- Retrospective cohort study
- 4,621 patients
- 17 centers, 9 countries
- Median survival was **<u>19.9 months</u>**

- <u>Survival depended on:</u>
  - Tumor response
  - Vascular invasion
    - 0-31%
    - Amsterdam 6%



- Does vascular invasion has impact on survival?

Han, Labeur et al Hepatology. 2020 Jul;72(1):198-212

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When TACE is not possible

- Locoregional therapy
  - TARE/SIRT

- Systemic therapy
  - Atezolizumab + bevacizumab
  - 2^{e} line treatment

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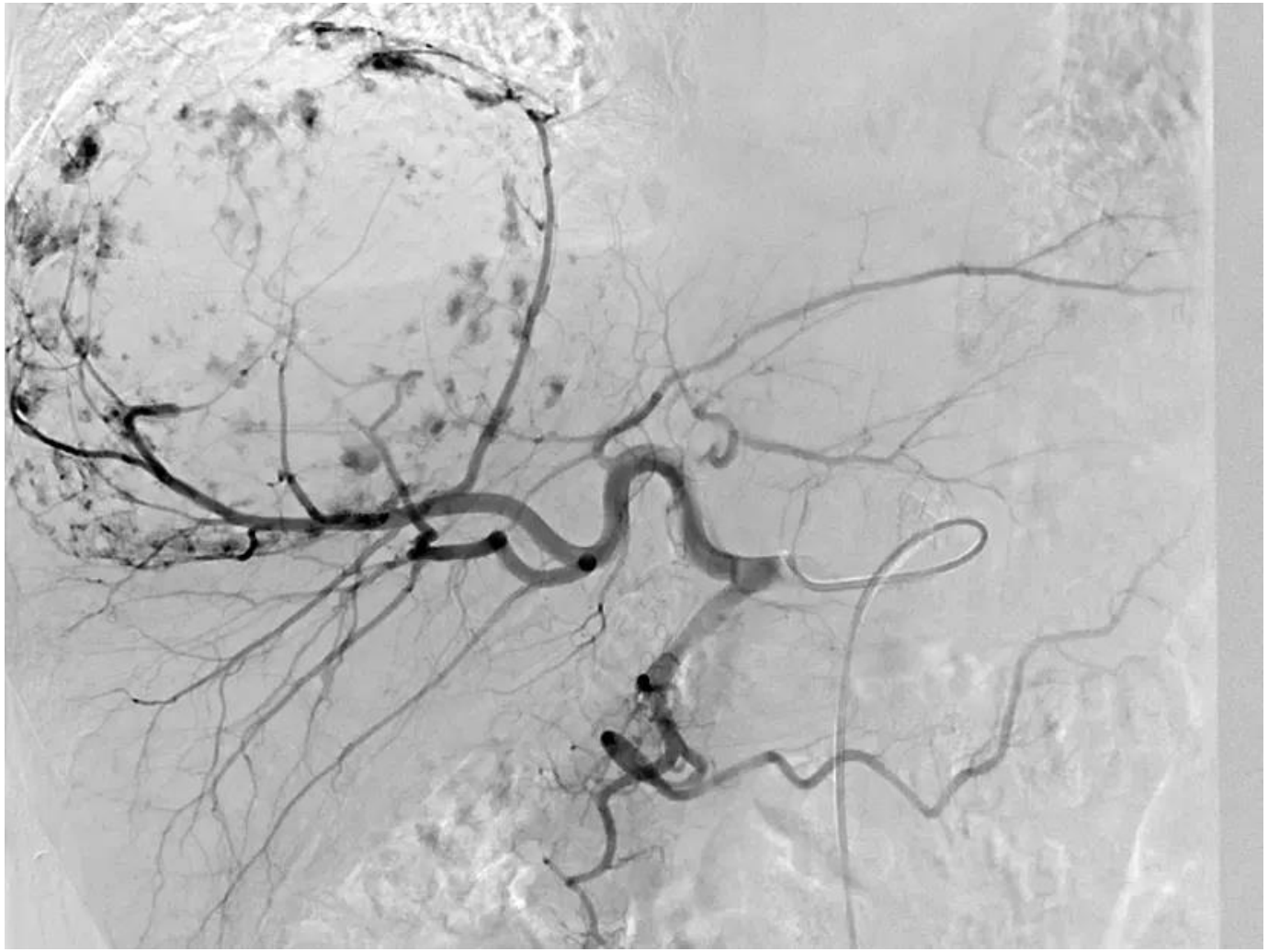
Selective Internal Radiaton Therapy (SIRT)



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SIRT for intermediate stage disease

- Systemic review SIRT vs TACE

Yttrium-90 transarterial radioembolization versus conventional transarterial chemoembolization for patients with hepatocellular carcinoma: a systematic review and meta-analysis. Yang Y, Si T. Cancer Biol Med. 2018 Aug;15(3):299-310

- 9 observational studies, 3 RCT's
  - SIRT better OS in observational subgroups
  - SIRT better objective response (OR) rate (mRECIST)

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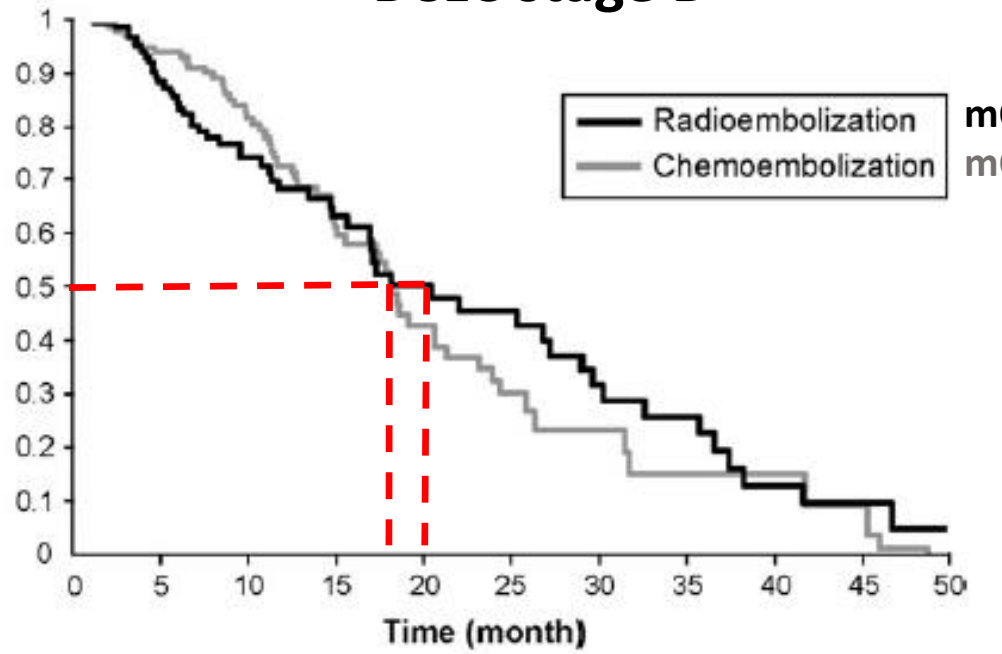
SIRT for patients with HCC

"The story of her life"

BCLC stage B



mOS 20.5 months

mOS 17.4 months

Number at risk											
Chemoem.	122	79	56	31	18	11	8	5	5	3	0
Radioem.	123	84	54	37	24	19	14	10	5	3	2

Riad Salem, Gastroenterology 2011;140:497-507

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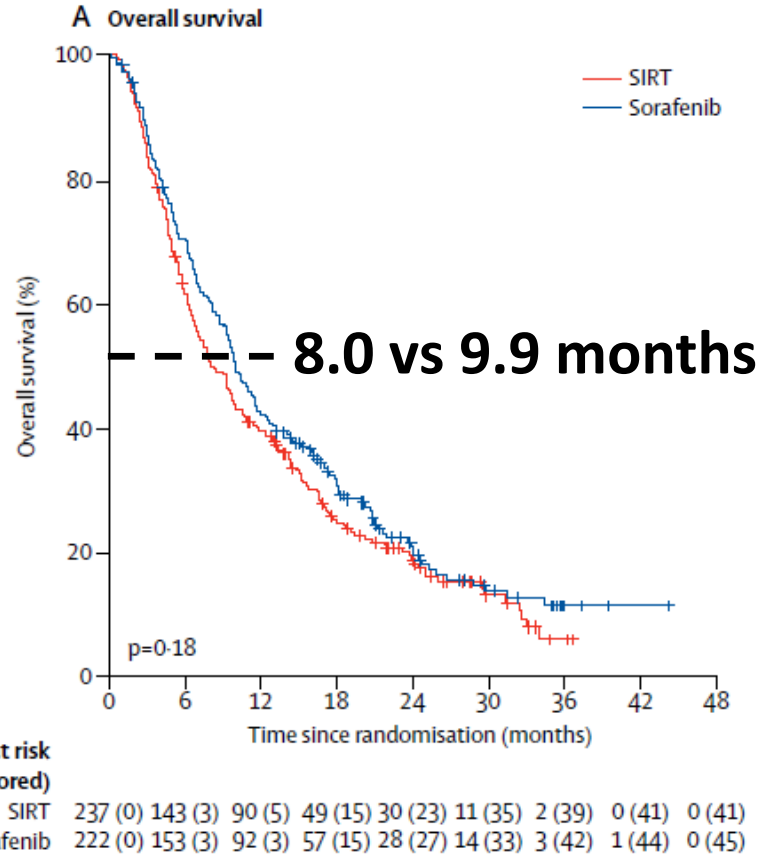
SIRT for patients with HCC

"The story of her life"

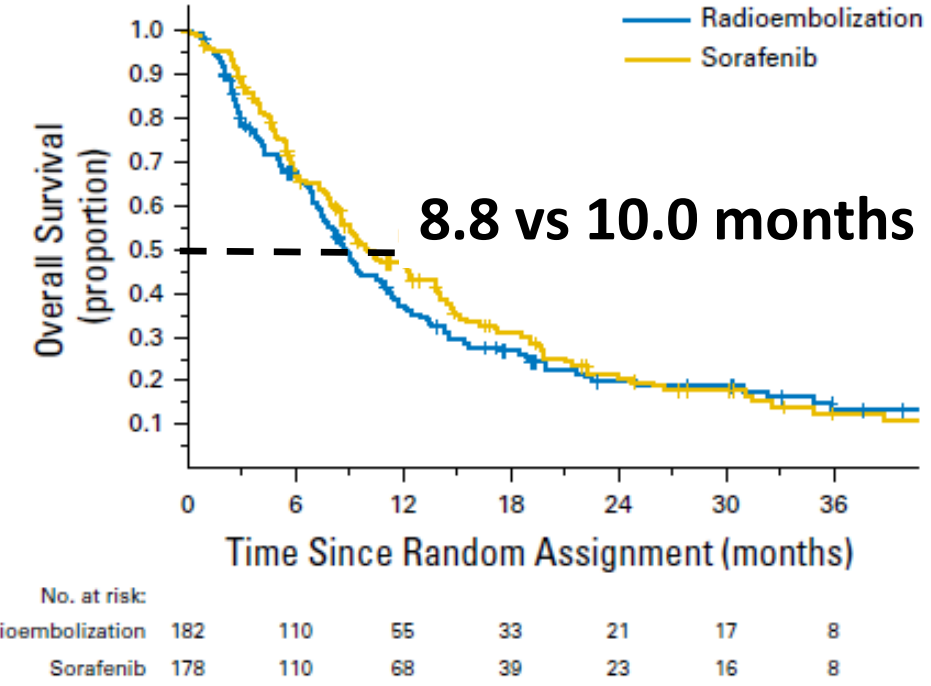
Europe

MVI 63% vs 58%



Asia-Pacific

MVI 31% vs 30%



Valérie Vilgrain et al, Lancet oncol 2017; 18:1624-36, Chow P.K.H. et. al. J Clin Oncol. 2018 Jul 1;36(19):1913-1921

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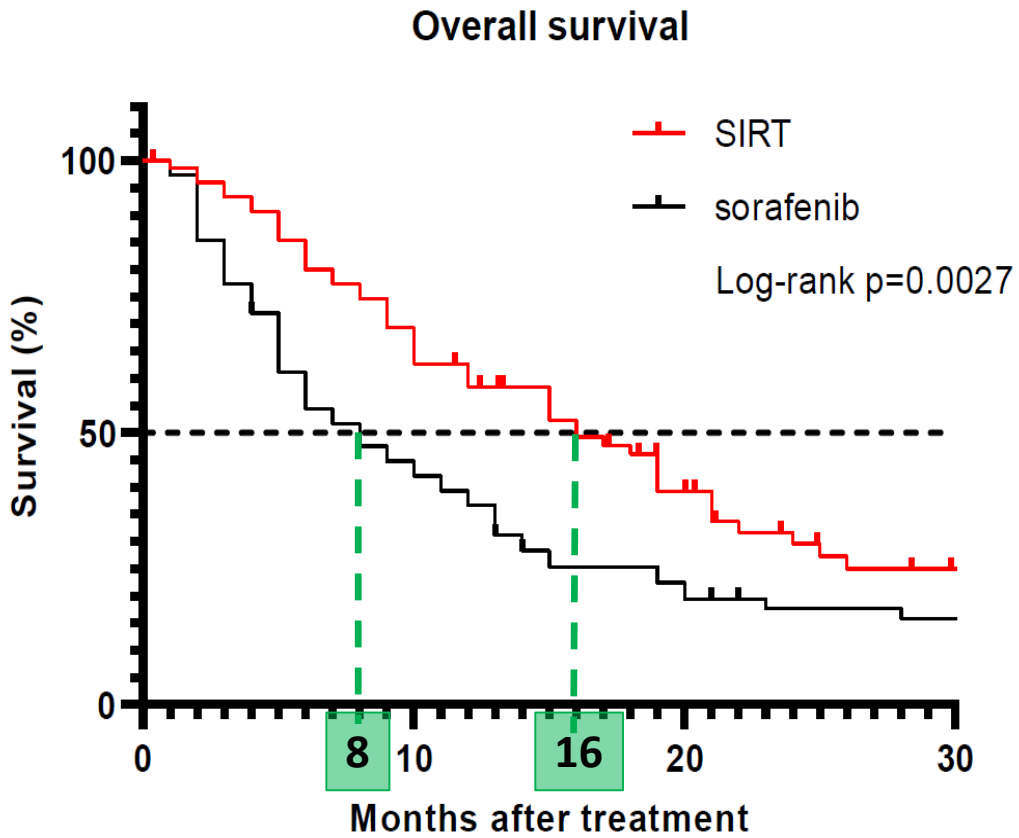
SIRT in The Netherlands

retrospective data of long-term responders (> 4 months)



Number at risk				
SIRT	76	52	23	9
sorafenib	76	33	15	9

Van Doorn, Takkenberg et al Cancer 2021

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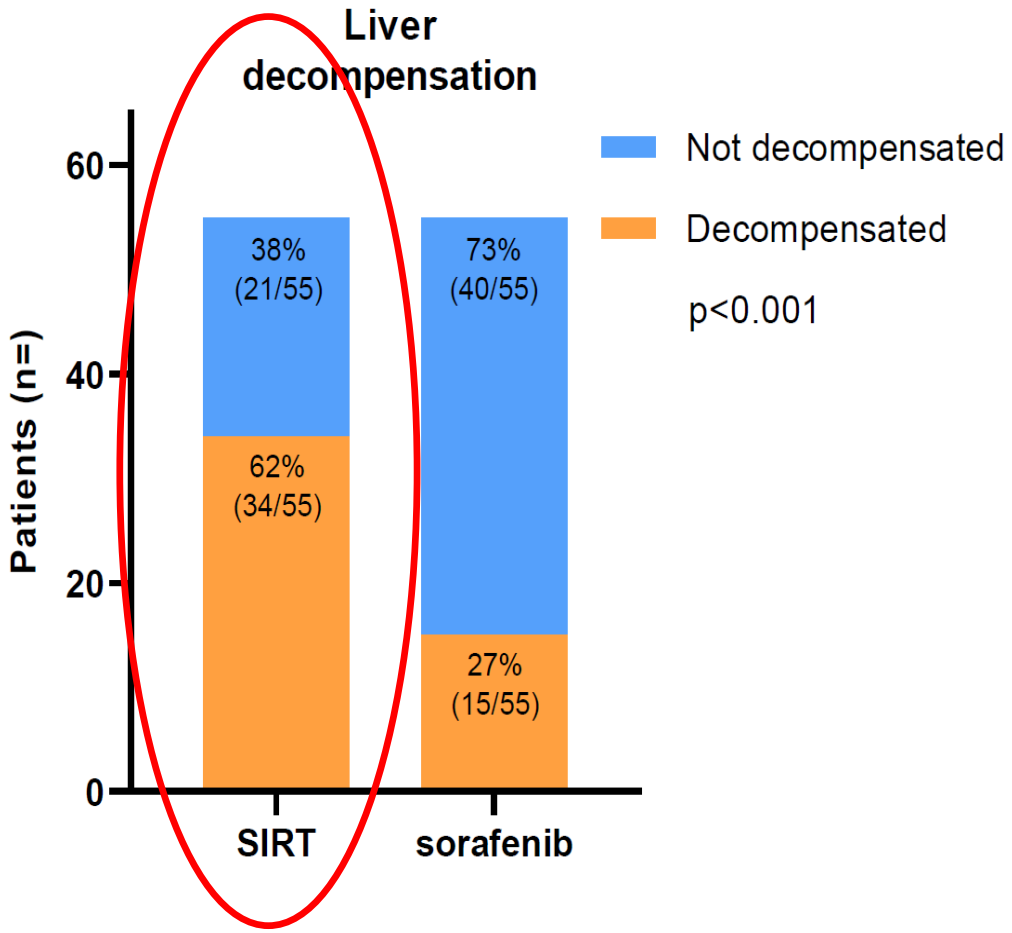

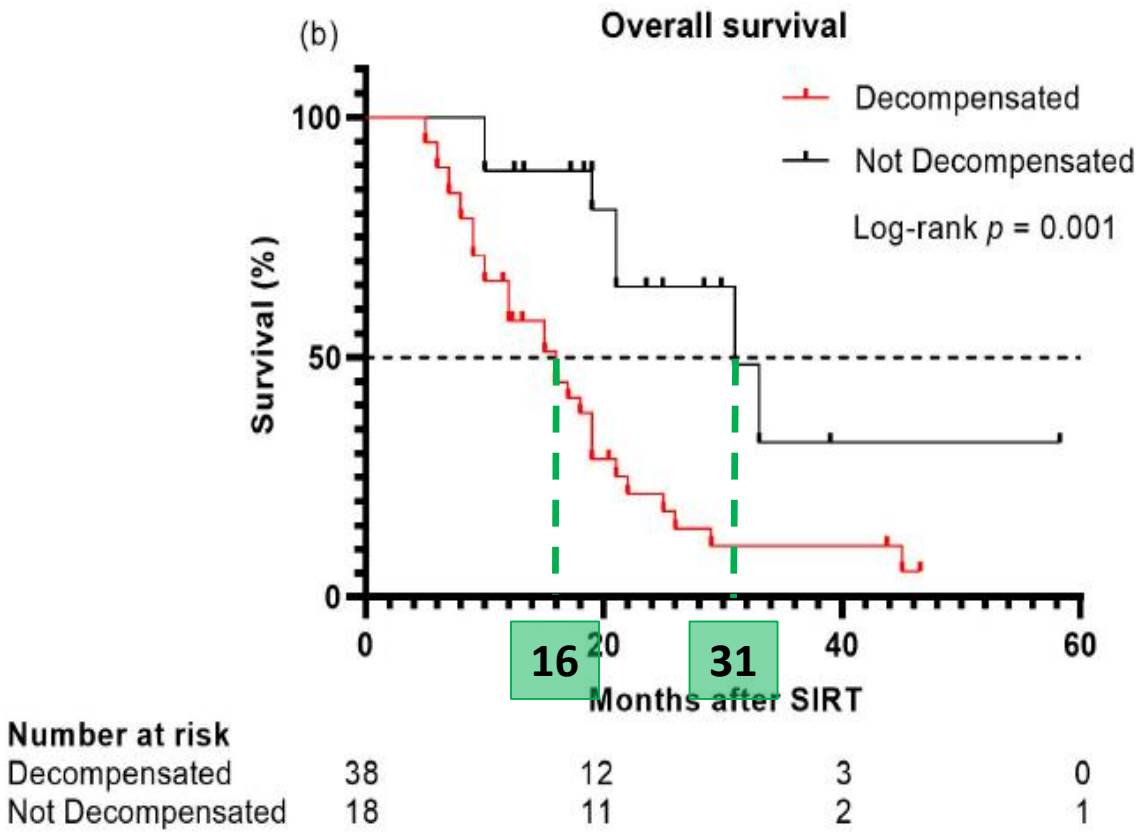

Van Doorn, Takkenberg et al Cancer 2021

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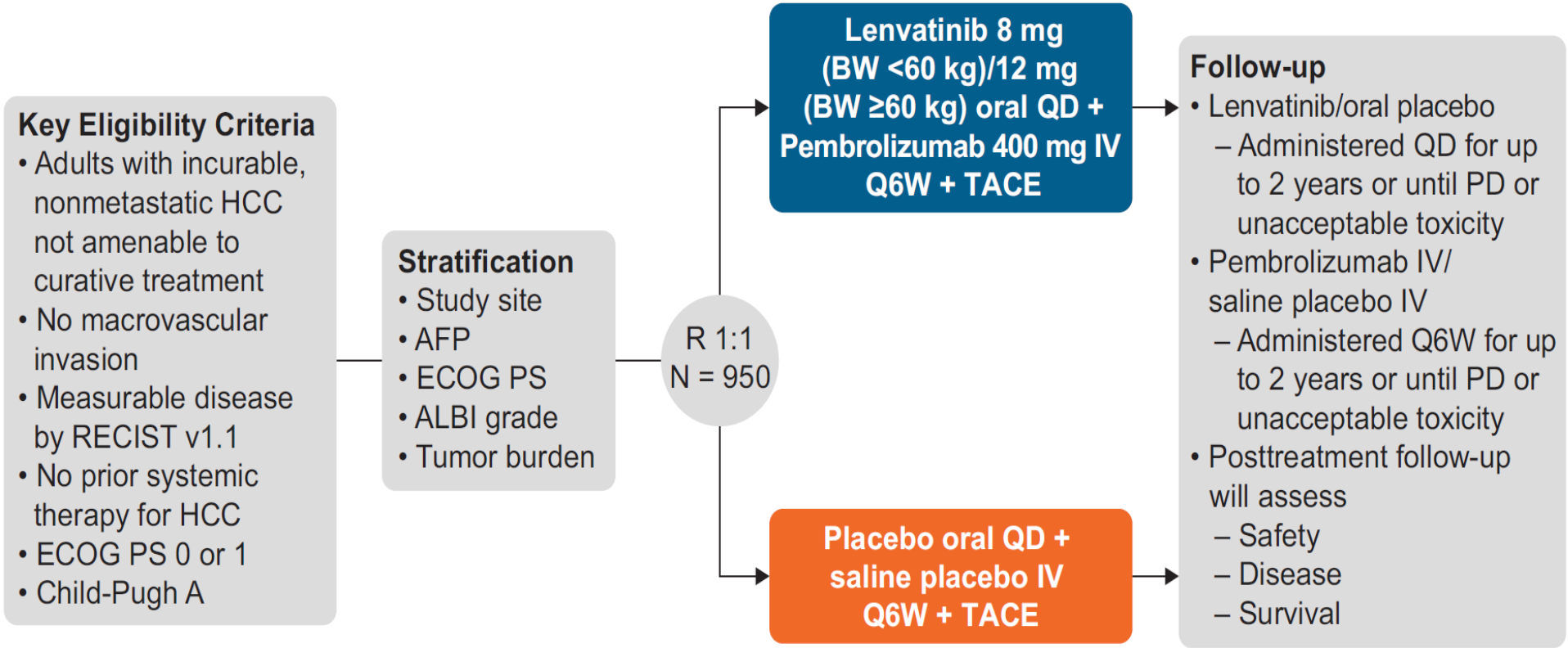
Alternative: TACE + ICI?

- LEAP 012 studie ongoing



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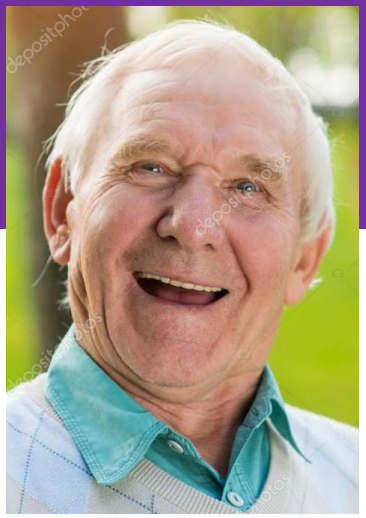

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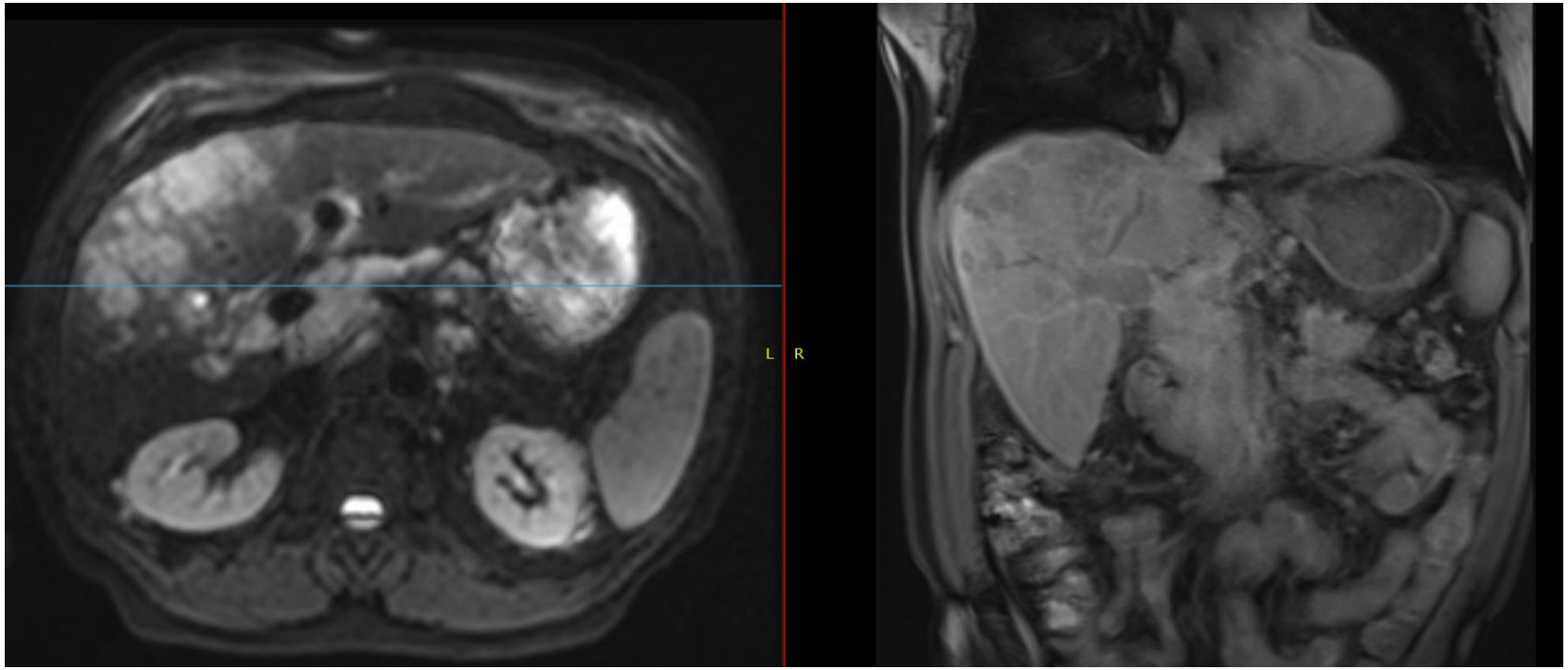

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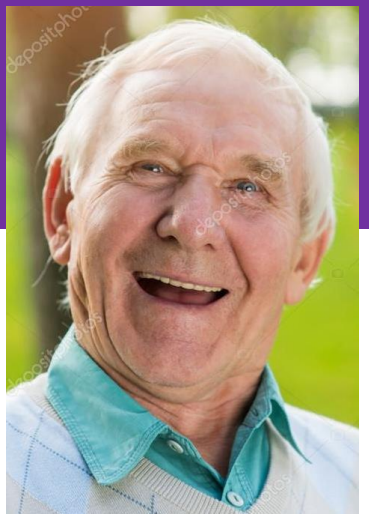

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  - Invasion in portal vein
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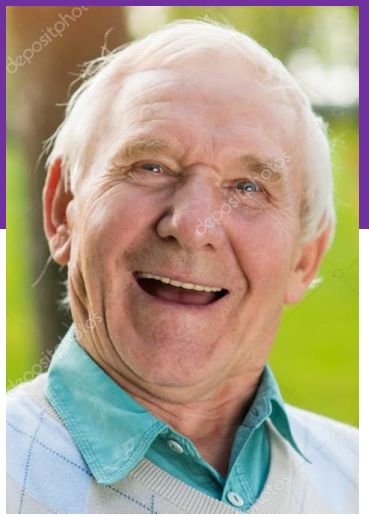

- **Conclusion:**
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  - Invasion in portal vein
  - CP-A cirrhosis, no PH
  - **<u>BCLC stage C</u>**

- **Treatment options: ?**

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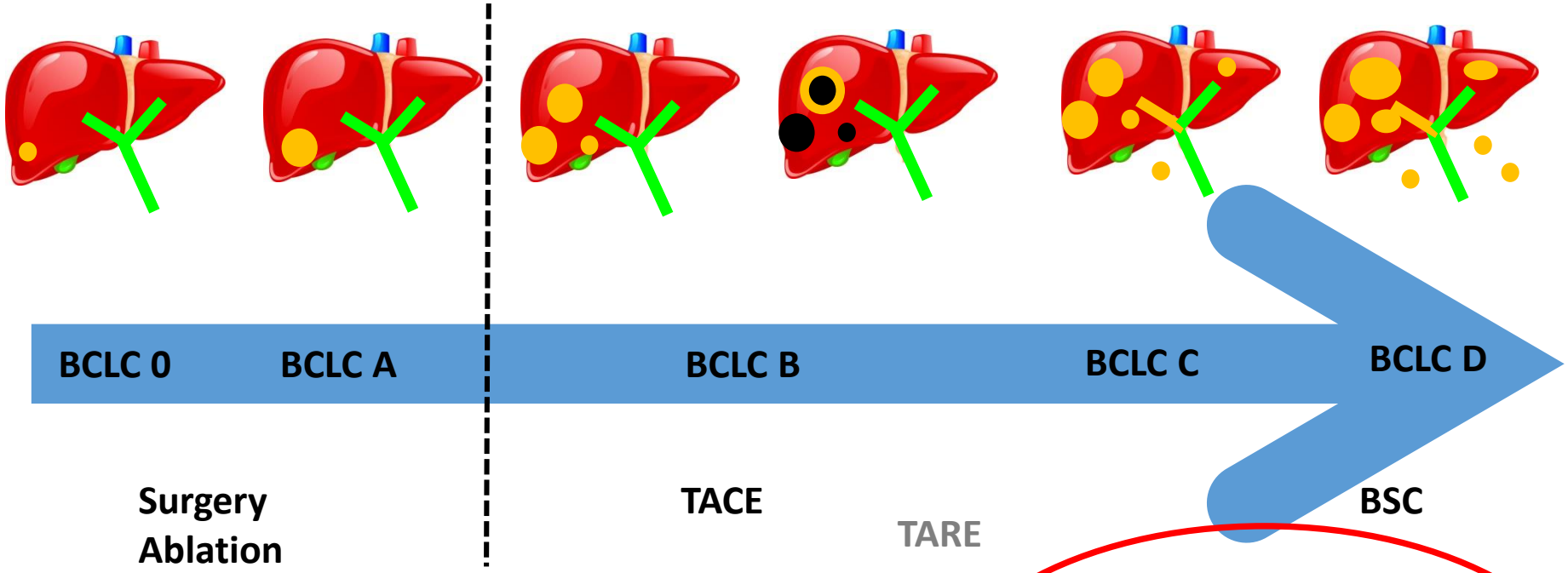
Hepatocellular carcinoma (2022)



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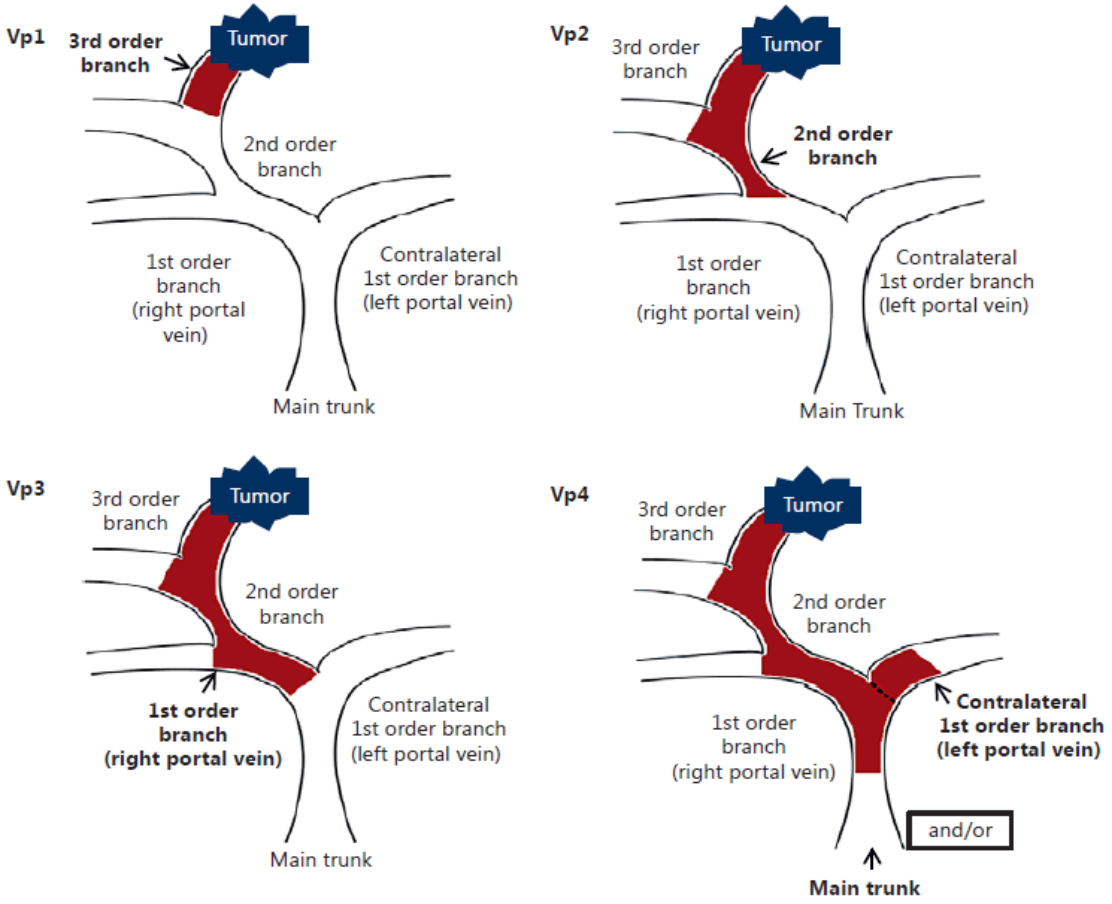
Classification of macro vascular invasion

Types of MVI	Description
Vp0	No invasion
Vp1	Distal to but not in second-order branches
Vp2	In second-order branches
Vp3	In first-order branches
Vp4	In main trunk or contralateral or both



Ikai I et al, Hepatol Res 2010;40:1043-1059

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Sorafenib for advanced HCC (BCLC C)

- **2 registration trials**
  - SHARP [1] 602 patients (299/303) 82/83% BCLC stage C
  - Asia-Pacific[2] 226 patients (150/ 76) 96/95% BCLC stage C
- Median overall survival (mOS)
  - SHARP **10.7 months** vs 7.9 mothns
  - Asia-Pacific **6.5 months** vs 4.2 months
- **Subgroup analysis for MVI**
  - SAHRP[3]:
    - Sorafenib 108/299 (36%) mOS: **8.1 months**
    - Placebo 123/303 (41%) mOS: 4.9 months
  - Asia-Pasific[4]:
    - Sorafenib 118/150 (79%) mOS: **5.6 months**
    - Placebo 61/ 76 (80%) mOS: 4.1 months

[1]Llovet, J.m. et al N Engl J Med 2008;359:378-390. [2]Cheng A.L. et al Lancet Oncol 2009;10:25-34.
[3]Bruix J. et al; J Hepatol 2012;57:821-829. , [4]Cheng A.L. et al; Eur J Cancer. 2012 Jul;48(10):1452-65

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PROSASH-II survival Calculator sorafenib

Inputs:
AFP

Albumin

Total Bilirubin

Macrovascular Invasion

Extra-hepatic spread

Largest Tumor Size

https://jscalc.io/calc/qXgkZNB1h6B1jEfq

Alternatives for Sorafenib?

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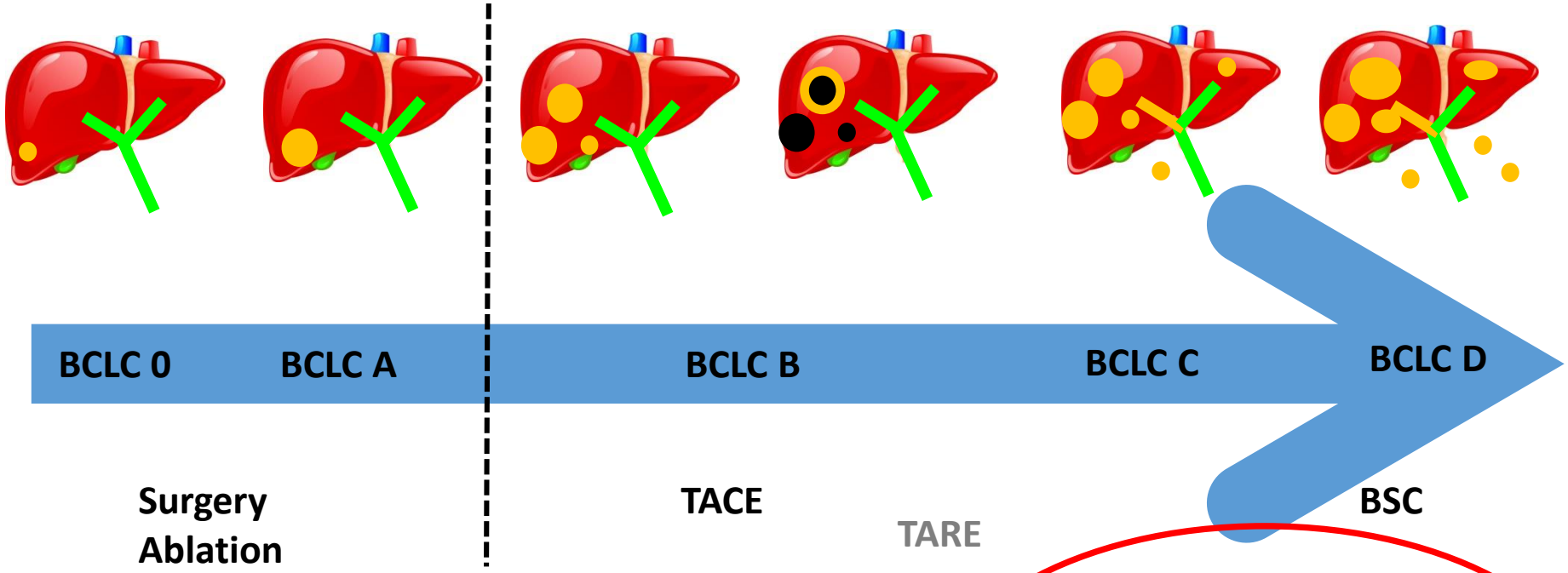
Hepatocellular carcinoma (2022)



Therapy based upon:

1. Tumor burden
2. Liver Function
3. Performance Status

- Atezolizumab + bevacizumab (2021)
- Sorafenib (2008)
- Regorafenib (2016)
- Lenvatinib (2016)
- Cabozantinib (2016)
- Ramucirumab (2016)

Reig et al, Semin Liver Dis 2014;34:444–455

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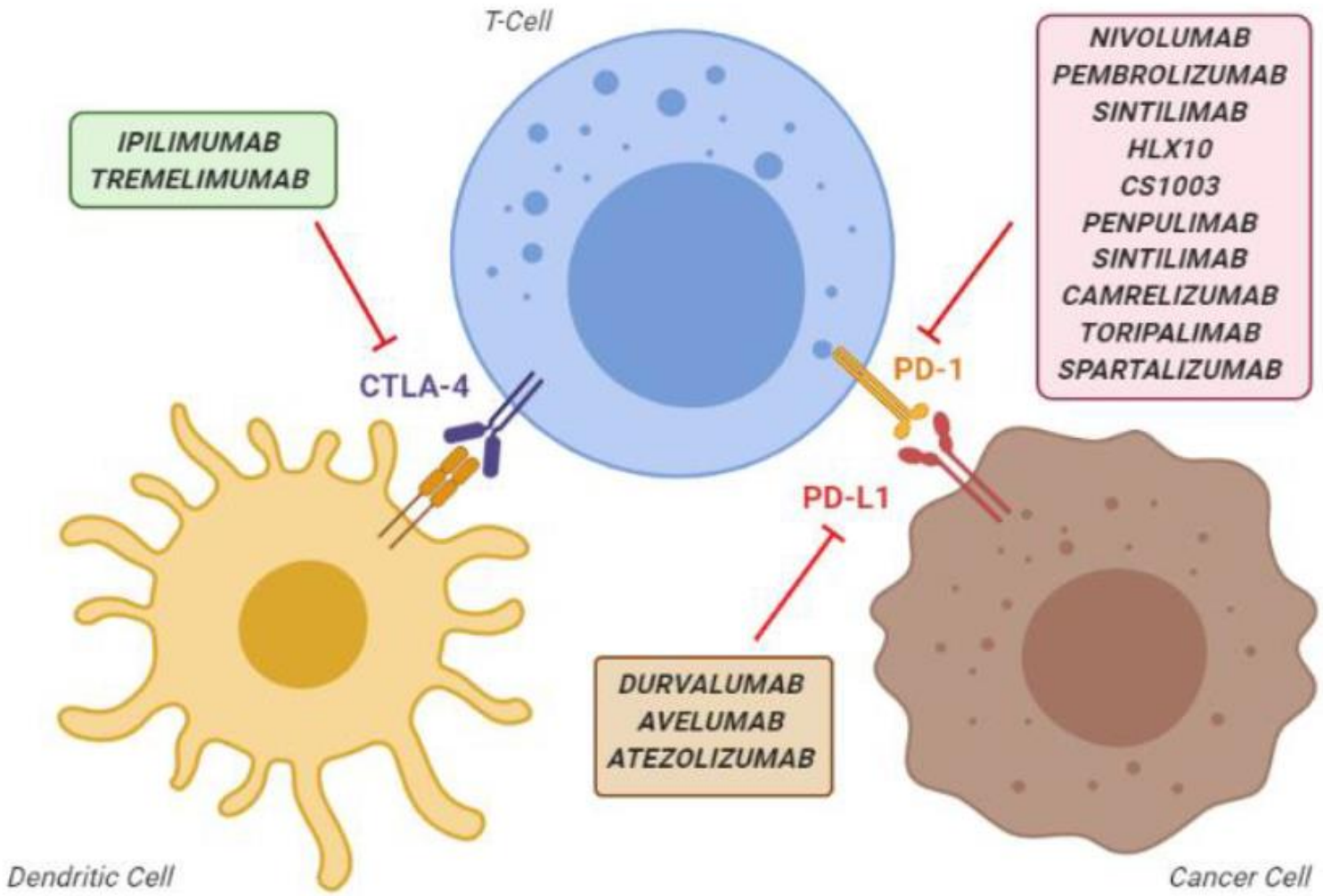
Immune checkpoint inhibitors



Tovoli et al, Vaccines 2020; 8: 578-598

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2020: Atezoluzimab + bevacizaumb (IMBrave150)

- 501 patients
- Randomized 2:1
- H_0: Synergistic effect VEGF-blockade + anti-PD-L1.
- Enrolment stopped after interim analysis
- mFollow-up: 8.6 months

	Atezolizum + bevacizumab (326)	Sorafenib (165)	p
Confirmed objective response	89 (27.3)	19 (11.9)	< 0.001
Complete response	18 (5.5)	0	
Partial Response	71 (21.8)	19 (11.9)	
Stable disease	151 (46.3)	69 (43.4)	
Progressive Disease	64 (19.6)	39 (24.5)	

Finn et. al. N Engl J Med. 2020 May 14;382(20):1894-1905.

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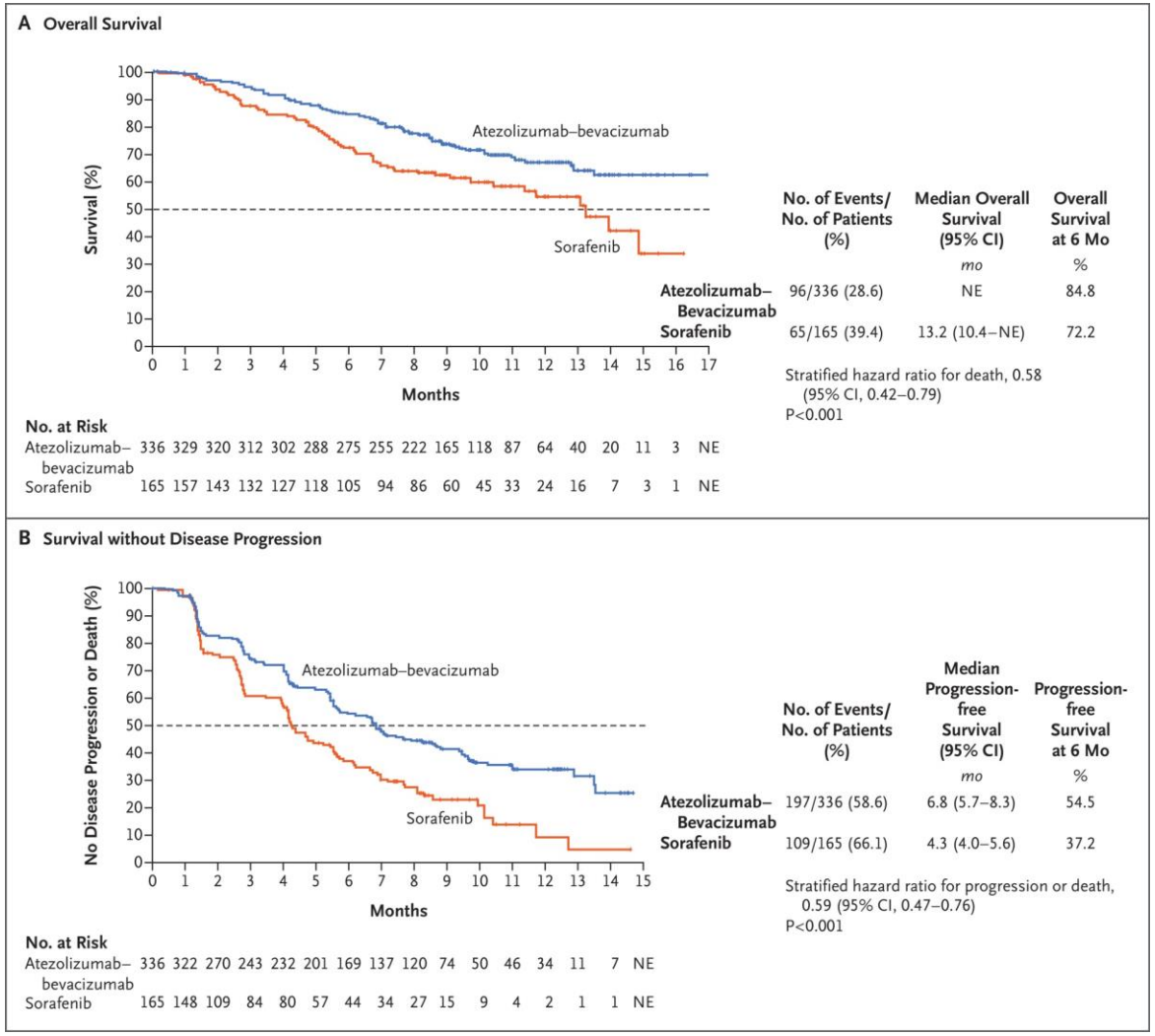
2020: Atezoluzimab + bevacizaumb (IMbrave150)



Overall survival (OS)

- Med. OS: not reached vs 13.2 months
- Estimated:
  - 6-months survival 84.8% vs 72.2%
  - 12-months survival 6.2% vs 54.6%

Progression-free survival (PFS)

- Med. PFS: 6.8 vs 4.3 months

Toxicity

- 15% hypertension
- SAE´s 15.5% vs 10.3%
- Liver enzyme abnormalities simular

Finn et. al. N Engl J Med. 2020 May 14;382(20):1894-1905.

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Advies commissie BOM dd 20-11-2020

Actuele adviezen

Oncologische middelen

Tumortypen

Beleidsdocumenten

Vergoede zorg

Over de adviezen

ADVIEZEN COMMISSIE BOM

Adviezen commissie BOM

TERUG NAAR LIJST

Auteur
NVMO-commissie BOM

Printdatum
20-11-2020

E-pubdatum
20-11-2020

Bron
Medische Oncologie

Atezolizumab en bevacizumab als eerstelijnsbehandeling bij gevorderd of gemetastaseerd hepatocellulair carcinoom

LEES ONLINE DOWNLOAD PDF

In de hier besproken interim-analyse van de IMbrave150-studie wordt bij hoog geselecteerde patiënten (zonder antistolling in therapeutische doseringen, zonder hypertensie en met vooraf behandelde varices) met een lokaal gevorderd of gemetastaseerd HCC na een follow-up van mediaan 8,6 maanden een statistisch significant langere OS gezien na palliatieve behandeling met atezolizumab en bevacizumab dan na behandeling met sorafenib (HR: 0,58 [95%-BI: 0,42-0,79]; P < 0,001). Ook de PFS is met

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Niews van ESMO dec. 2021 (Kelley et al. VP10-2021) COSMIC-312 studie

- Fase III, atezolizumab + cabozantinib vs sorafenib in 1e lijn HCC
  - Primary Endpoint: PFS P = 0.0012

	Atezo/cabozantinib	Cabozantinib	sorafenib
N	432	217	188
PFS	6.8 m	5.8 m	4.2 m
OS	15.4 m		15.5 m
RR	11 %	6.4%	3.7%
Grade 3/4 tox	54%	54%	32%

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Nieuws van ASCO GI januari 2022
Himalaya studie (Abou Alfa et al. abstr 379)

- Fase III Durvalumab + Tremelilumab vs sorafenib in 1e lijn HCC, Primary endpoint: OS

	STRIDE (n=393)	D (n=389)	S (n=389)
Median follow-up, mo	16.1	16.5	13.3
Deaths at DCO, %	66.7	72.0	75.3
Median OS (95% CI), mo	16.4 (14.2–19.6)	16.6 (14.1–19.1)	13.8 (12.3–16.1)
24/36-mo OS rate, %	40.5/30.7	39.6/24.7	32.6/20.2
Median PFS (95% CI), mo	3.8 (3.7–5.3)	3.7 (3.2–3.8)	4.1 (3.8–5.5)
ORR, %	20.1	17.0	5.1
Median DoR, mo	22.3	16.8	18.4
Grade 3/4 TRAE, %	25.8	12.9	36.9
Serious TRAE, %	17.5	8.2	9.4
Grade 5 TRAE, %	2.3	0	0.8
TRAE leading to discontinuation, %	8.2	4.1	11.0

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HCC behandeling gevorderde ziekte in NL 2022

- 1e lijn
  - Atezolizumab/bevacizumab
  - Sorafenib
  - Lenvatinib
- 2e lijn
  - Sorafenib
  - Regorafenib
- 3e lijn
  - Regorafenib

  - Rol van recente studies onduidelijk, daarom registry

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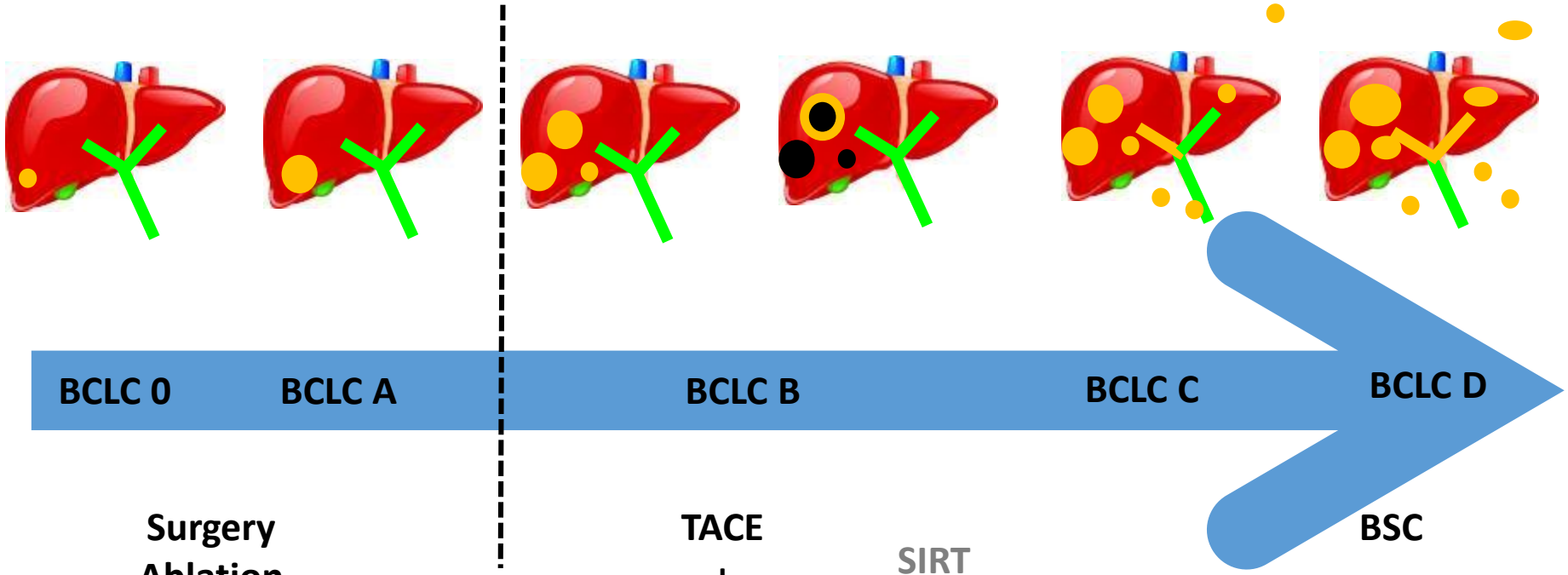
What does the future looks like……

- **ICI + TKI**
  - 2 phase 3 studies ongoing
  - 14 phase 2 studies ongoing

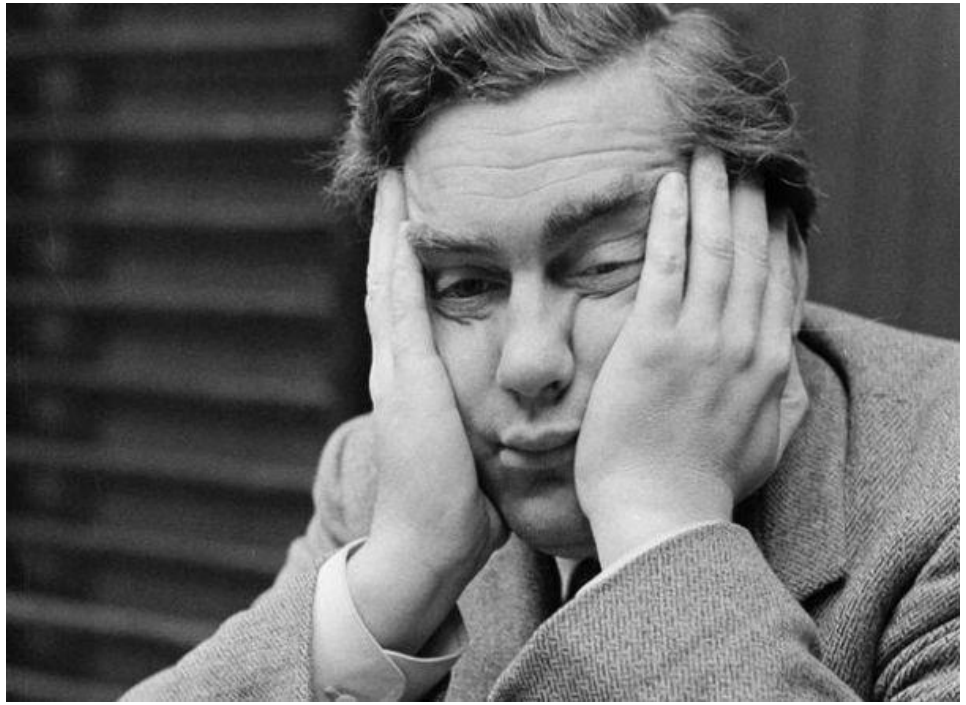
- **ICI + CTLA-4 inhibitors**
  - 1 phase 3 study ongoing
    → studie resultaat volgt 12-2021 (Camrelizumab + FOLFOX vs Sorafenib + FOLFOX4)
  - 10 phase 2 studies ongoing

What does the future looks like……



Reig et al, Semin Liver Dis 2014;34:444–455

Questions?



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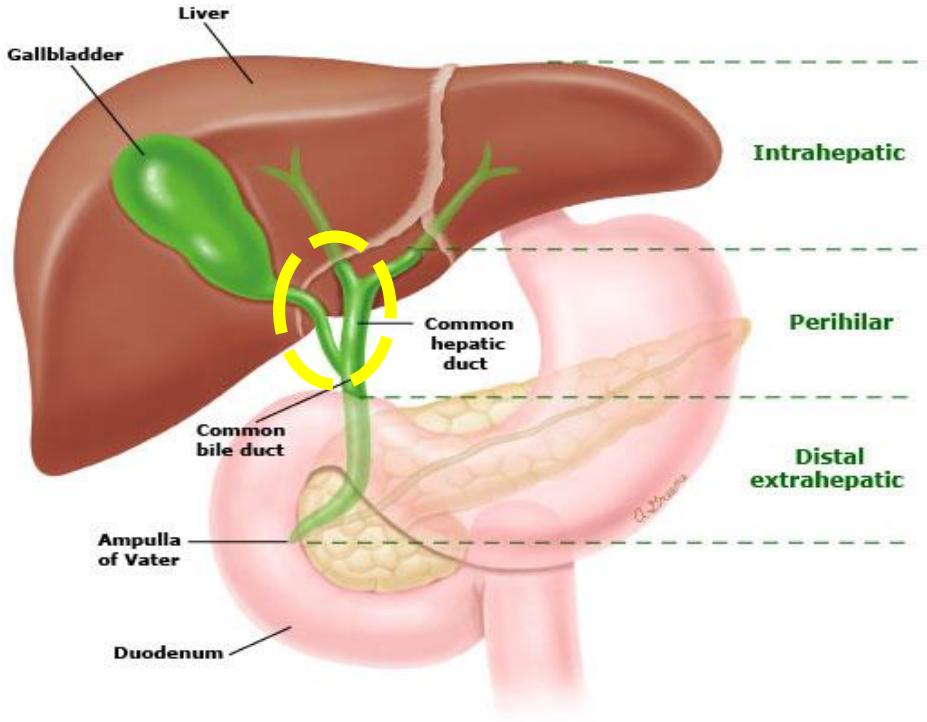
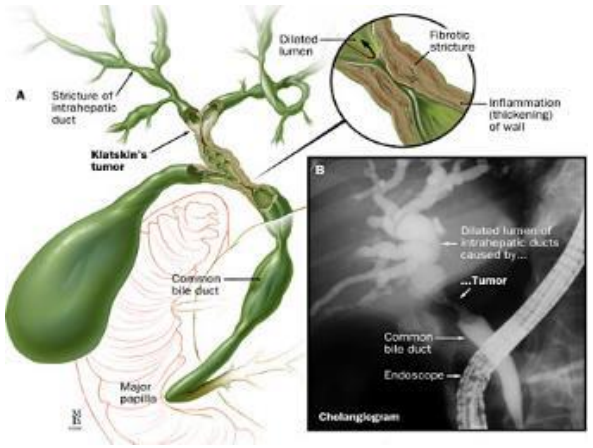
Mutatie gestuurde zorg galwegkanker

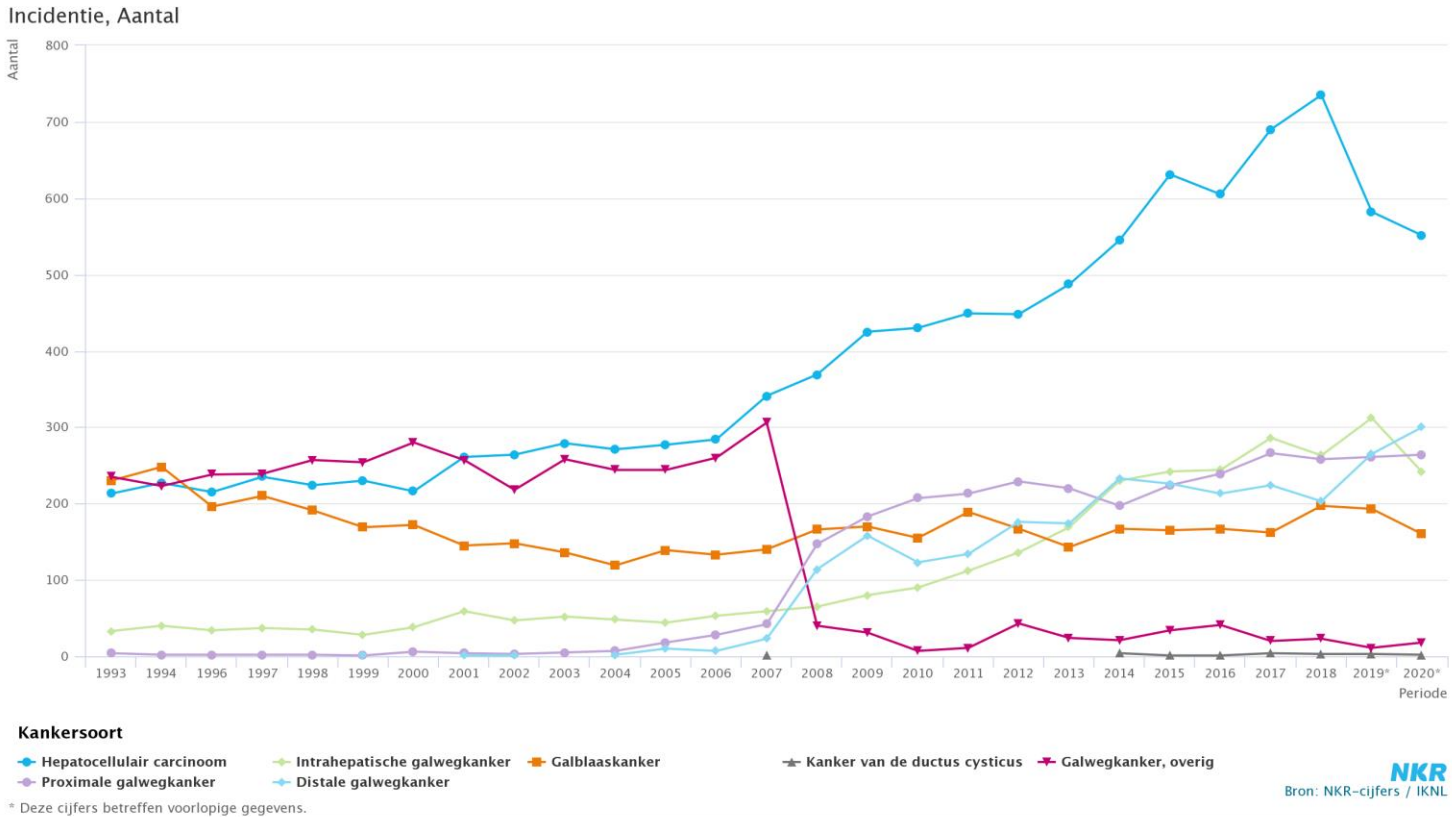
Dr. Heinz-Josef Klümpen
Internist-Oncoloog, Amsterdam UMC

Introductie galwegkanker





Introductie/ Incidentie



Galwegca.

1000/jaar

HCC

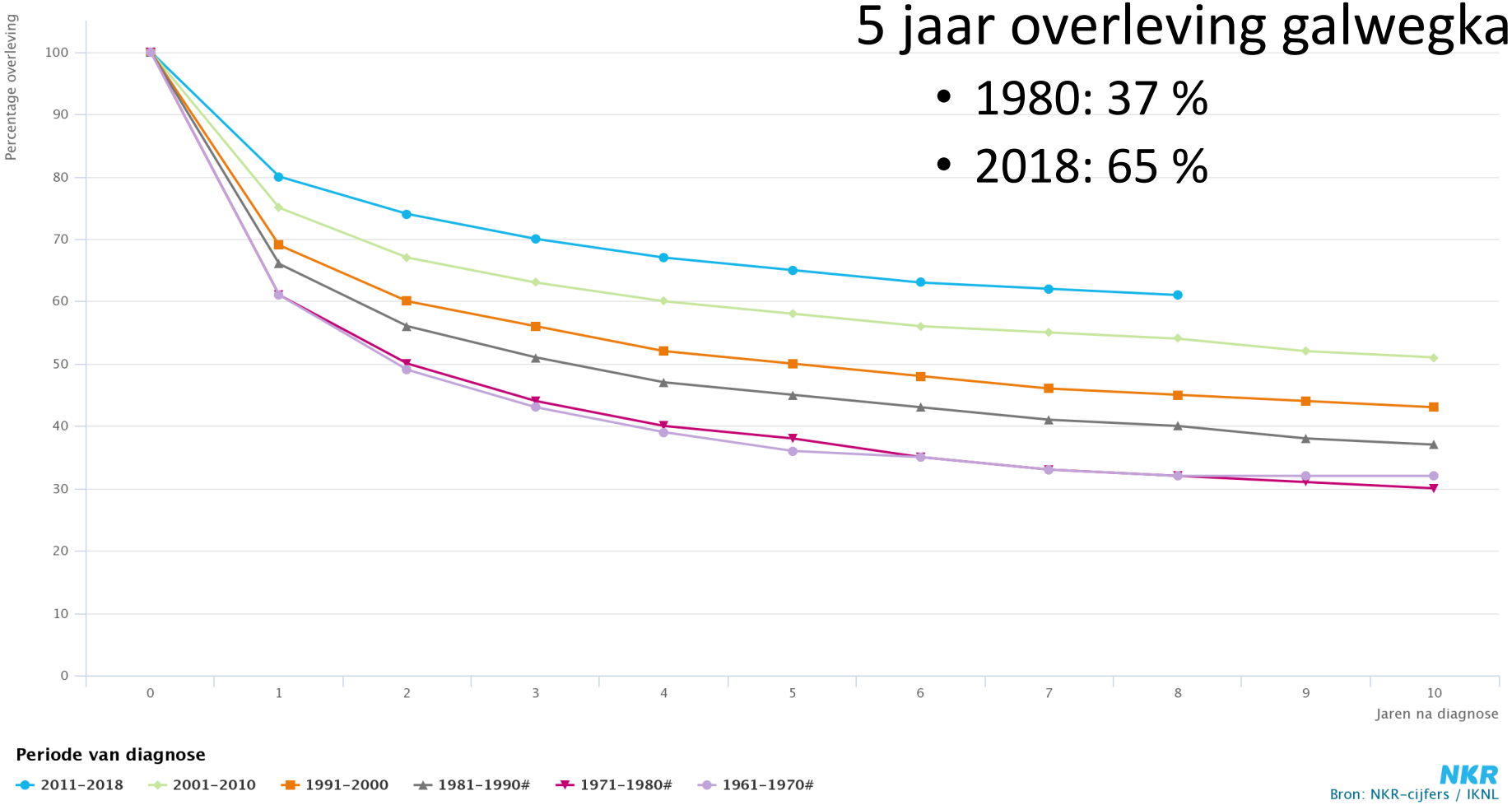
800/jaar

Nederlandse kankerregistratie:www.cijfersoverkanker.nl: geraadpleegd op 12-10-2021

Introductie/Survival

5 jaar overleving galwegkanker

- 1980: 37 %
- 2018: 65 %



NKR
Bron: NKR-cijfers / IKNL

Behandeling

Curatief

- Operatie (20%)
- Lever transplantatie (strikte criteria, Mayo Clinic) (< 2%)

Palliatief

- Palliatieve chemotherapie (gegeven in 20%)
- Palliatieve radiotherapie (zelden)

Symptoombestrijding

Drainage galwegsysteem ERCP/PTC (in alle fases noodzakelijk!)

→ 77% Best-supportive care

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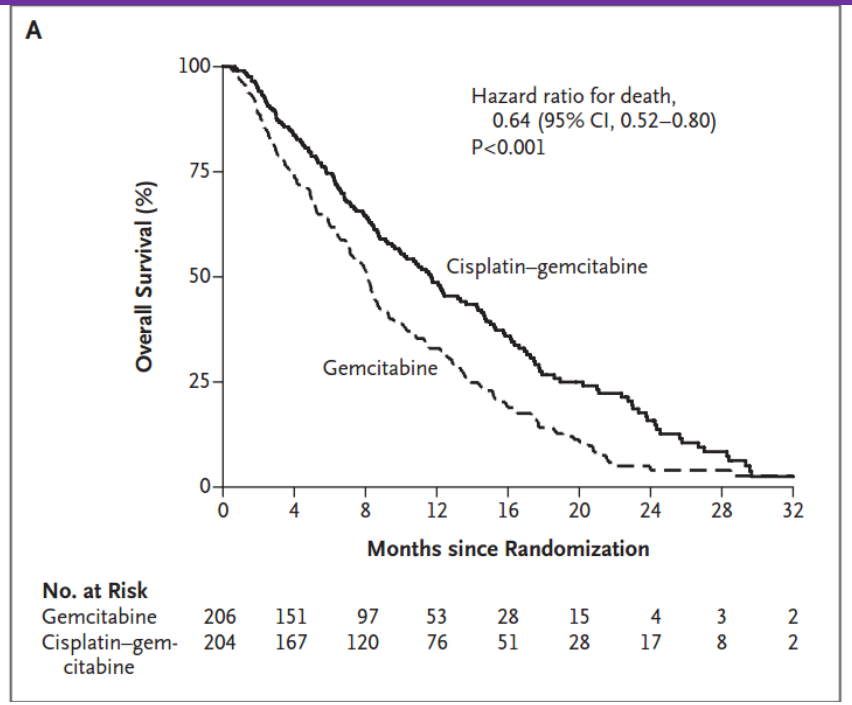
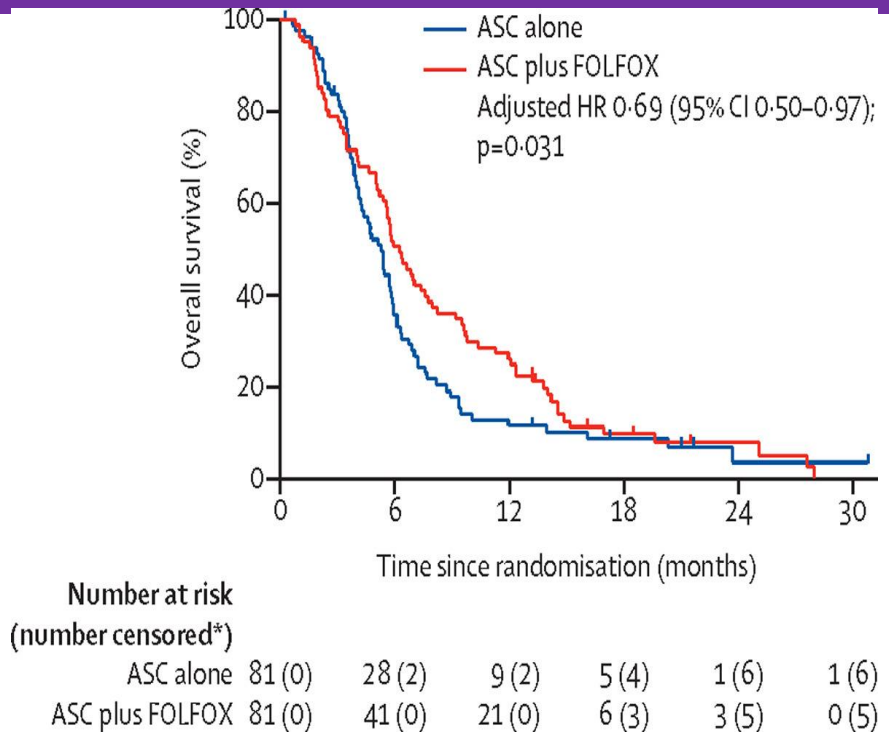
ABC02 studie



- 1e lijn, goede tolerantie
- M. OS: 11 vs 8 maanden
- Internationale standaard sinds 2010
- bij nierfunctiestoornissen: GEMOX of Gem alleen

N ENGL J MED 362;14

ABC06 studie



- 2e lijn, goede tolerantie
- M. OS: 6.2 vs 5.3 maanden
- BOM goedkeuring okt 2021 (obv HR)

Lamarca et al. Lancet 2021

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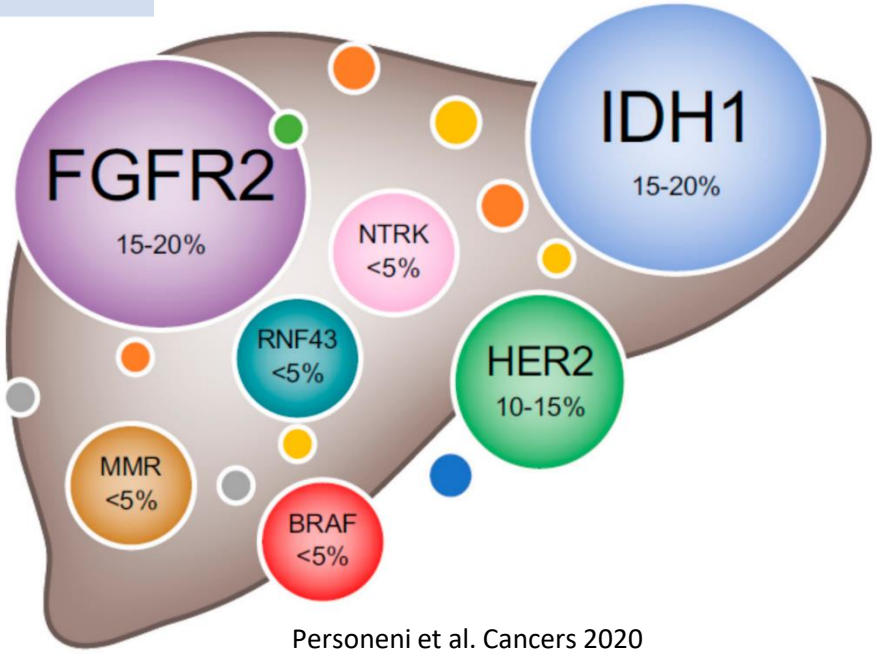
Prognose en prognostische factoren

Gevorderde ziekte OS na gem/cis	
ICC	15.4 m
ECC	?
Galblaas	7.1

Actionable mutaties/ amplificaties



Lamarca et al. JNCI 2020
De Savornin Lohman et al. Cancers 2020

Personeni et al. Cancers 2020

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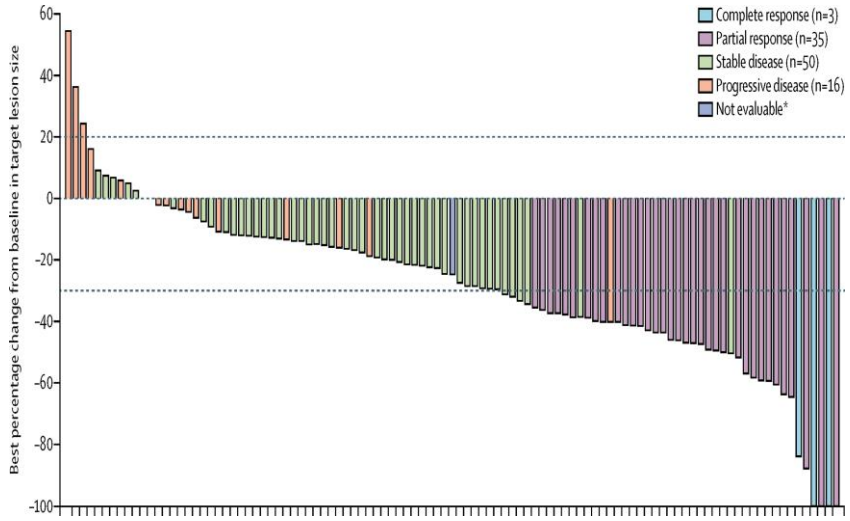
Mutation in BTC
N = 3634

FOUNDATION MEDICINE

- MSI high: 1%
- PD-L1 mutation: 0.2%, expression: 9%
- Most common gene amplifications:
  - *TP53* (31%), *CDKN2A* (29%), *KRAS* (20%) and *ARID1A* (17%).
  - Potentially targetable
    - *FGFR2* (11%, 85% fusions)
    - *BRAF* (5%, 50% V600E)
    - *ERBB2* (5%, 72% AMP)
    - *MET* (2%, 90% AMP)

Javle et al. ASCO abstract # 4078, 2019

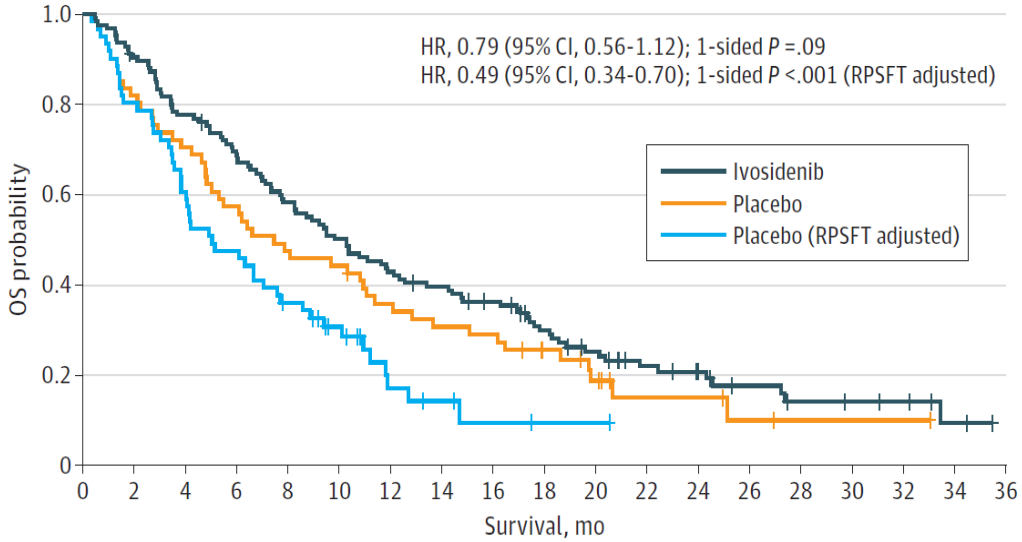
Pemigatinib



- FGFR 2 fusie
- Fase II, single arm
- 2e lijn, N = 146
- PFS 6.9 m, OS volgt

Abou-Alfa et al. The Lancet Oncology 2020

Ivosidenib



- IDH 1
- Fase III, RCT, cross-over design
- N=187
- mOS 10.3 vs 7.5 m

Rank-preserving structural failure time (RPSFT)

Zhu et al. JAMA 2021

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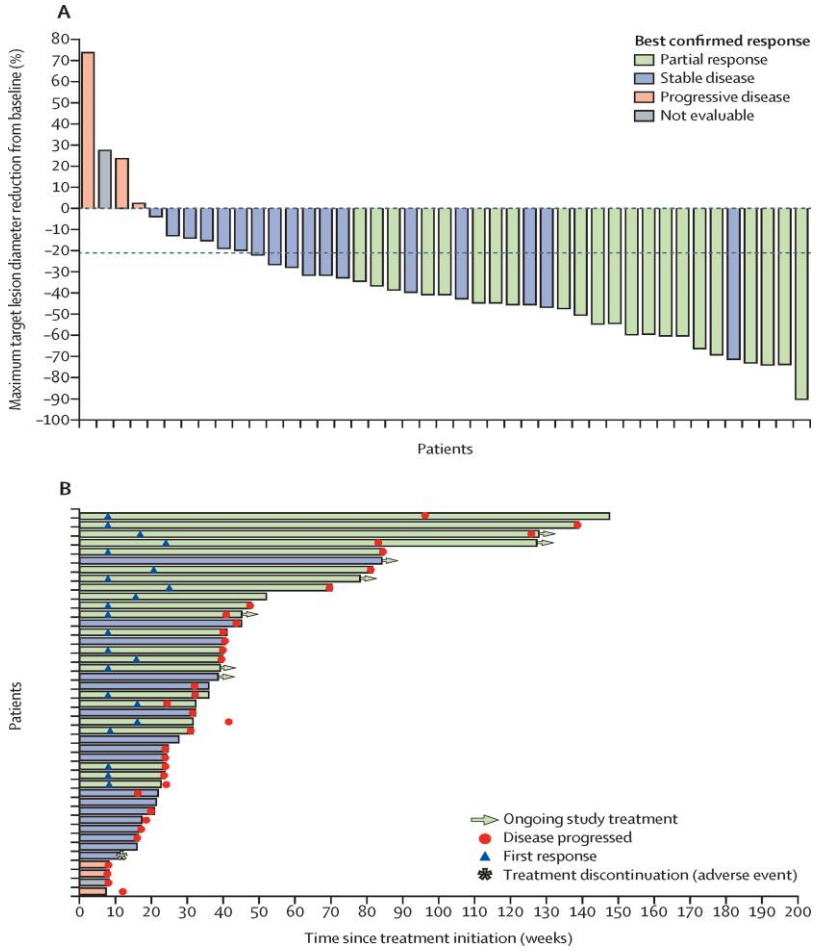
HER2+

- Zanidatamab
  - Fase I
  - RR 40 %
  - 25 % vooraf Her2 behandeling
  - 57% galblaasca.
  - Mediane duur van response 7.4 m

Meric-Bernstam et al. ASCO GI 2021

BRAF

- Phase II
- Single arm
- $BRAF^{V600E}$
- N= 43
- RR 51%
- PFS 9 m
- OS 14m



Subbiah et al. Lancet 2020

Nieuws van ASCO GI
TOPAZ-1

TOPAZ-1 is a double-blind, multicenter, global, Phase 3 study

Key eligibility
- Locally advanced or metastatic BTC (ICC, ECC, GBC)
- Previously untreated if unresectable or metastatic at initial diagnosis
- Recurrent disease >6 months after curative surgery or adjuvant therapy
- ECOG PS 0 or 1

Stratification factors
- Disease status
  - (initially unresectable versus recurrent)
- Primary tumor location
  - (ICC versus ECC versus GBC)

R (1:1) (N=685)

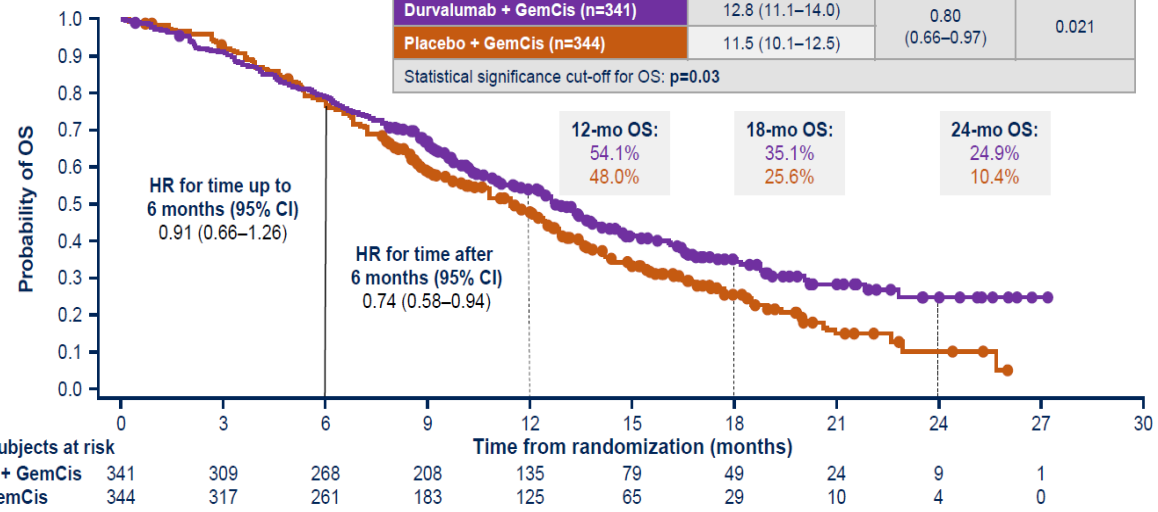
- Durvalumab 1500 mg Q3W + GemCis (up to 8 cycles) → Durvalumab 1500 mg Q4W until PD
- Placebo Q3W + GemCis (up to 8 cycles) → Placebo Q4W until PD

Primary objective
- Overall survival

Secondary objectives
- Progression-free survival
- Objective response rate
- Duration of response
- Efficacy by PD-L1 status
- Safety

Primary endpoint: OS

	Median OS (95% CI), months	Hazard ratio (95% CI)	p-value
Durvalumab + GemCis (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + GemCis (n=344)	11.5 (10.1–12.5)		
Statistical significance cut-off for OS: p=0.03			



Oh et al. ASCO GI 2022

Nieuwe ontwikkelingen

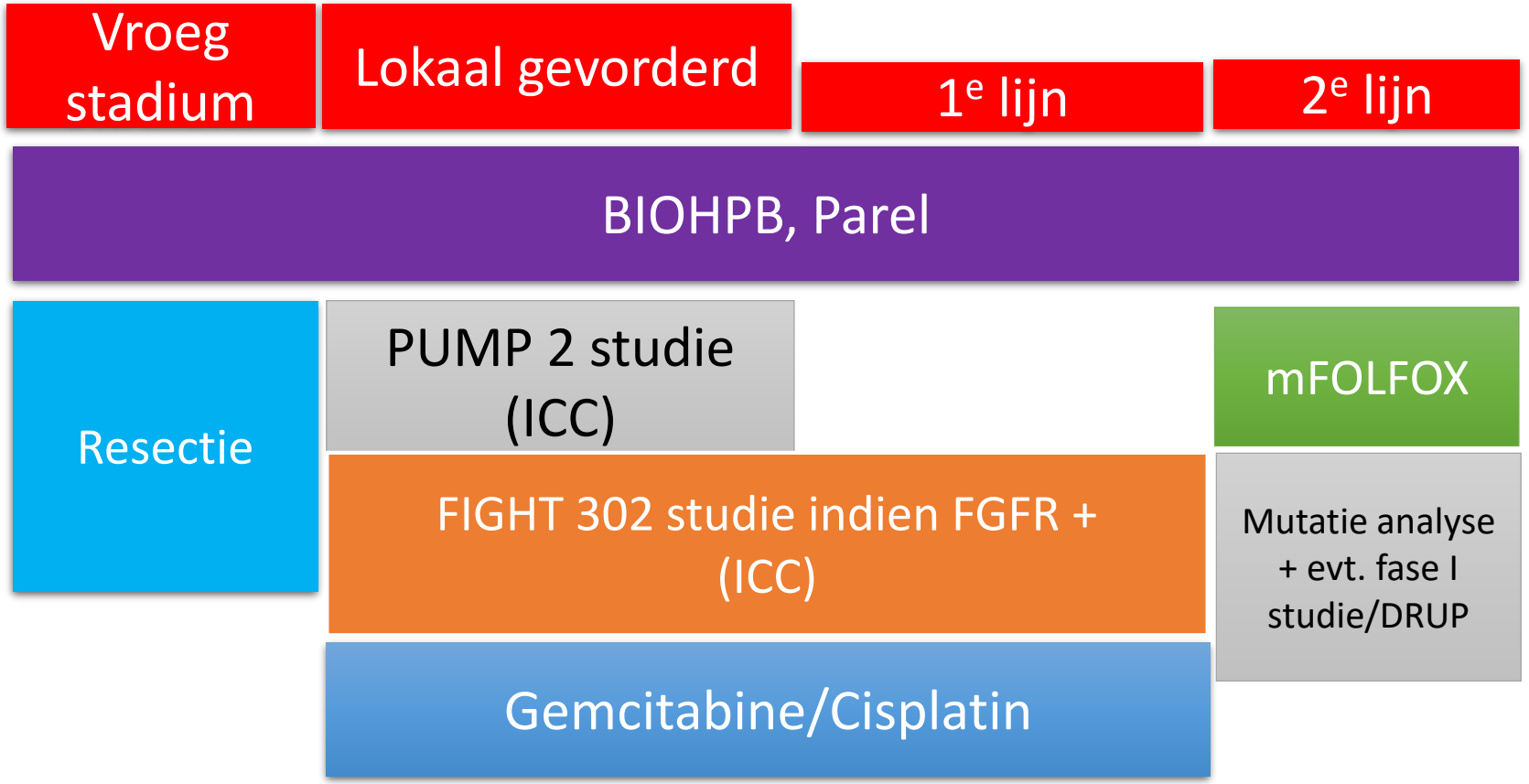
- **Intra-arteriele** chemo (PUMP-2)
- Stereotactische **RT** (STRONG-2)
- **Her2**, fase III, 1e lijn Zanidatamab
- **FGFR 2 fusie**, fase III, 1e lijn (5 RCTs!!!)
- **BRAF**
- Consensus resectie criteria
- **Inductie** therapie
- Drainage (RFA)
- Implementatie NGS

Nieuwe ontwikkelingen

Resultaten van Fase III studies te verwachten

- ACTICCA 1
  - Adjuvant gem/cis vs capecitabine
- KEYNOTE 966
  - Pall. gem/cis +/- pembrolizumab

Behandeling
voorbeeld Amsterdam UMC



ICC = intrahepatisch cholangioca

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Nationale en internationale samenwerking

DHCG

Dutch Hepato & Cholangio Carcinoma Group

cholangiocarcinoma FOUNDATION

AMMF THE CHOLANGIOCARCINOMA CHARITY

nfk

ENS-CCA

European Cholangiocarcinoma Network
COST ACTION CA18122

IBTCC | International Biliary Tract Cancer Collaborators

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Conclusie

- Meeste patienten met galwegkanker hebben een ongunstige prognose
- Wij hebben 2 lijnen van palliatieve chemotherapie met aangetoond effect
- Positieve studie met immo/chemotherapie
- Behandelbare mutaties komen voor bij 20-30 % van de patienten
- Positief in klinische studies geteste fouten in DNA van tumor zijn :
  - FGFR 2 fusion, IDH 1, BRAF
- Veelbelovend: Her 2
- Advies: NGS voor alle patienten met galwegkanker

Vragen?