«New theapies for HCC: a methodological approach»

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Pavia, 20 marzo 2024

Prof Calogero Cammà
University of Palermo

Il sottoscritto dichiara di aver avuto negli ultimi 12 mesi
conflitto d'interesse in relazione a questa presentazione
(EISAI, MSD, Roche, AstraZeneca, Gilead)
e
che la presentazione non contiene discussione
di farmaci in studio o ad uso off-label

«New theapies for HCC: a methodological approach»

Alvan R. Feinstein

CLINICAL

JUDGMENT

1967

RISK / BENEFIT

Probability

Safety
Efficacy/Effectiveness
Patient value (PRO)

Stephen Pauker & Jerome Kassirer

The Threshold Approach to Clinical Decision Making

NEJM 1980

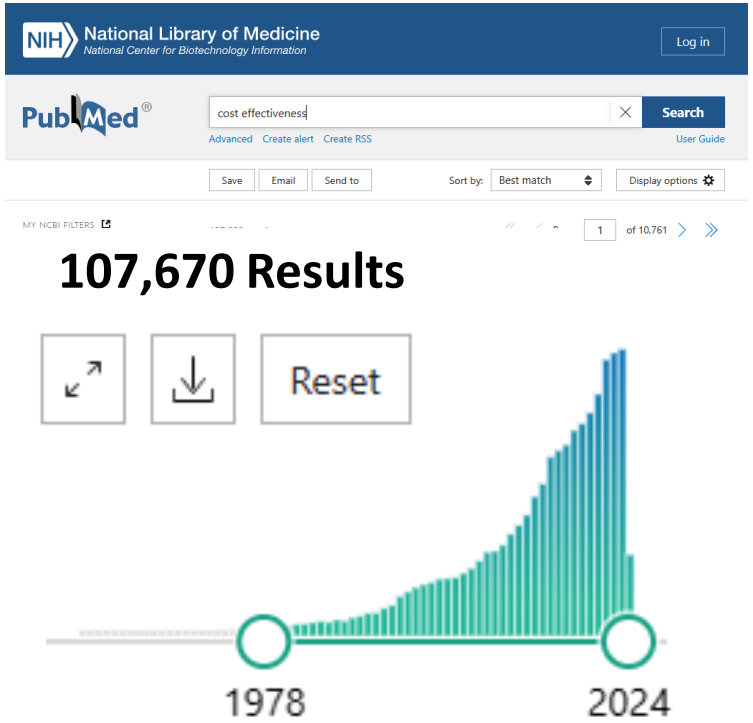
COST / RISK / BENEFIT

First Principles of Cost-Effectiveness Analysis in Health

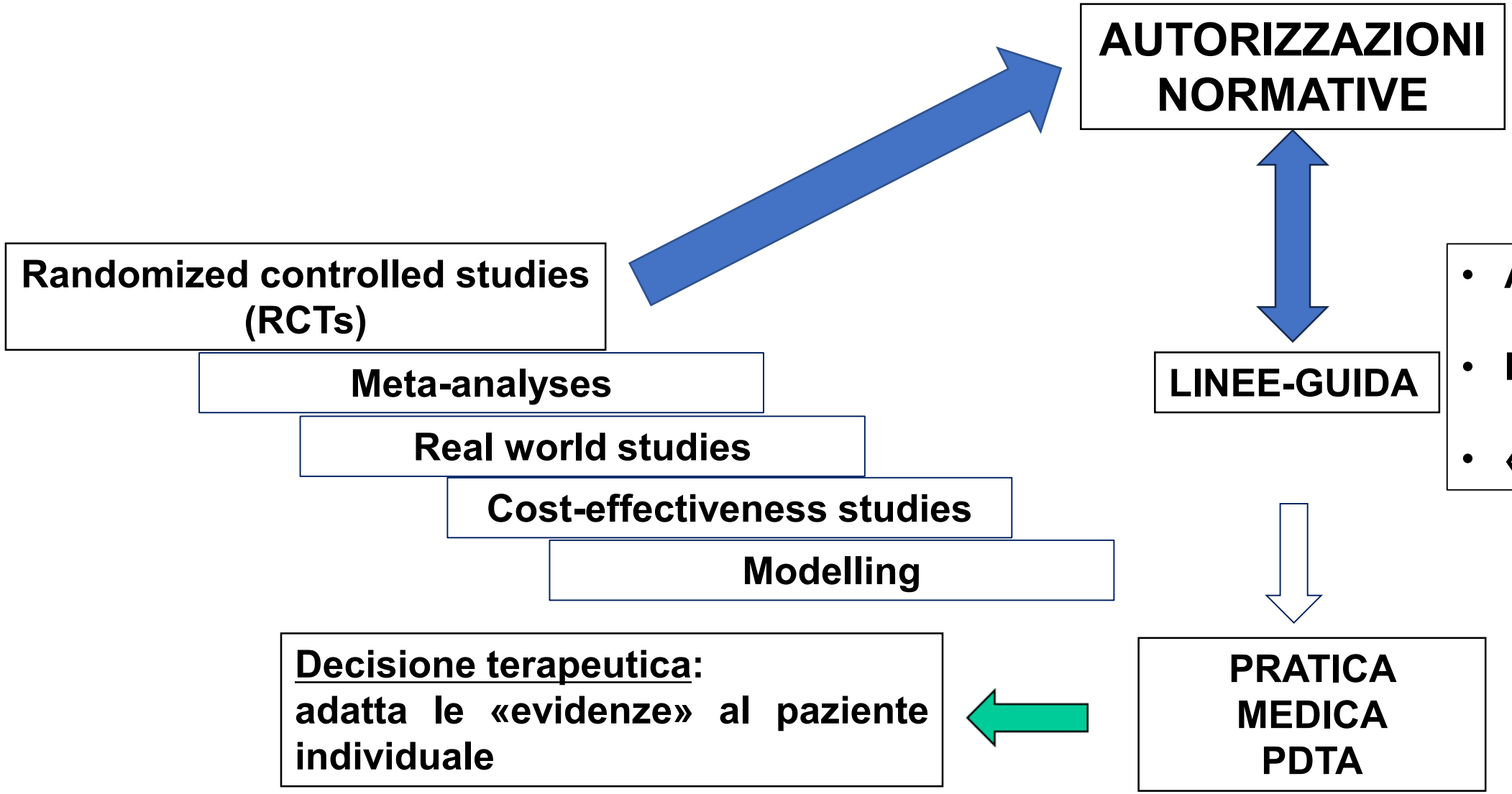
DONALD S. SHEPARD, PhD
MARK S. THOMPSON, PhD

1979 Harvard University

COST-EFFECTIVENESS



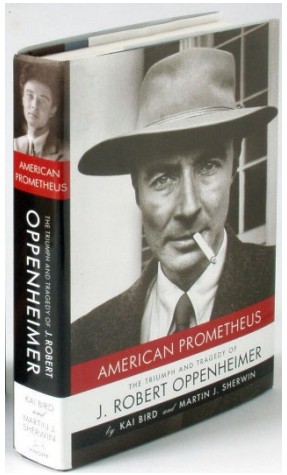
Clinical value



AUTORIZZAZIONI NORMATIVE

FDA → EMA → AIFA

- **Industry**
- **Finance**
- **Politics**



COVID-19

Independent research

- **Patients and families**
- **Physicians**
- **Scientific societies**

AI

1 L **Lenva**
AtezoBeva
Durva+Treme

2 L **Sorafenib**

AI simbolica

Expert system

AI non simbolica

ChatGPT

Reasoning

Prediction

A performance evaluation of the expert system ‘Jaundice’ in comparison with that of three hepatologists 1991

Calogero Cammà • Germana Garofalo • Piero Almasio • Fabio Tinè • Antonio Craxì • Ugo Palazzo • GiovanBattista Pinzello • Felice Fiorello • Paolo M. Angelo • Luigi Pagliaro • Show less

Prediction is not reasoning

Agenda

- Systemic therapies for early stage HCC
- Systemic therapies for intermediate stage HCC and combination with locoregional treatments
- Systemic therapies for advanced stage HCC
- Flaws of systemic therapies RCTs

Systemic therapies for HCC 2024

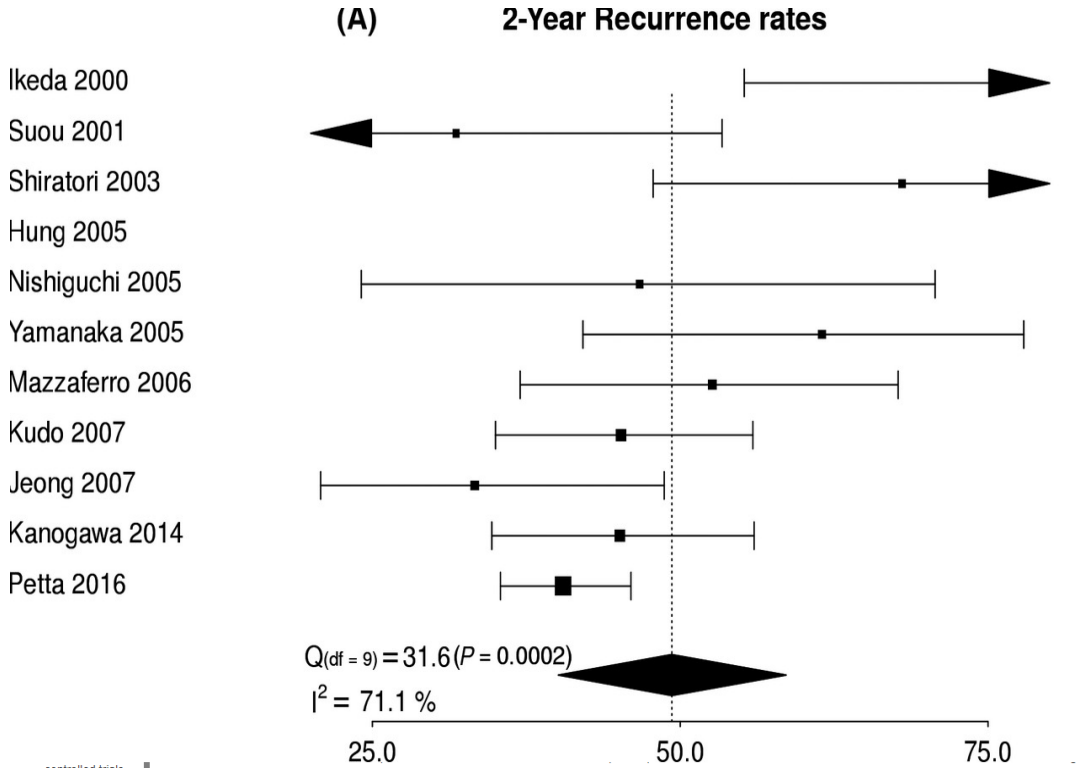
Target population	EARLY STAGE WITH HIGH RISK OF RECURRENCE	HCC ELIGIBLE TO TACE	ADVANCED HCC
Treatments	Adjuvant AtezoBeva after resection or ablation	Durva+Beva with TACE	AtezoBeva DurvaTreme Durvalumab (?) Lenvatinib AtezoBevaTira (?)
Primary endpoint	Recurrence-free survival **++**	Progression-free survival **+/- ?**	Overall survival **+++**

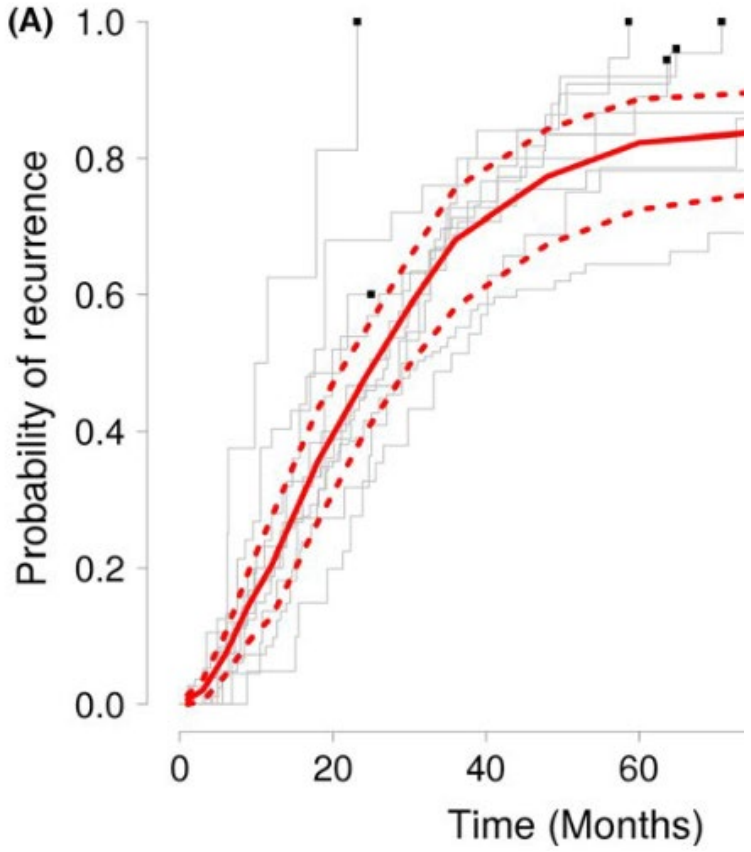
Agenda

- Systemic therapies for early stage HCC
- Systemic therapies for intermediate stage HCC and combination with locoregional treatments
- Systemic therapies for advanced stage HCC
- Flaws of systemic therapies RCTs

Natural history after «curative treatments»

Meta-analysis of 11 studies (701 pts)





- 1-year recurrence rate **20%** (range, 4.9-62.5%)
- 2-year recurrence rate **47%** (range, 31.8-100%)

High heterogeneity I^2=71.1%

Range: 37.2-100%

Cabibbo G et al. Liver Int 2016

Natural history after «curative treatments»

Risk of recurrence is higher in pts with

- large and/or multiple tumours,
- poor differentiation,
- high AFP,
- vascular invasion

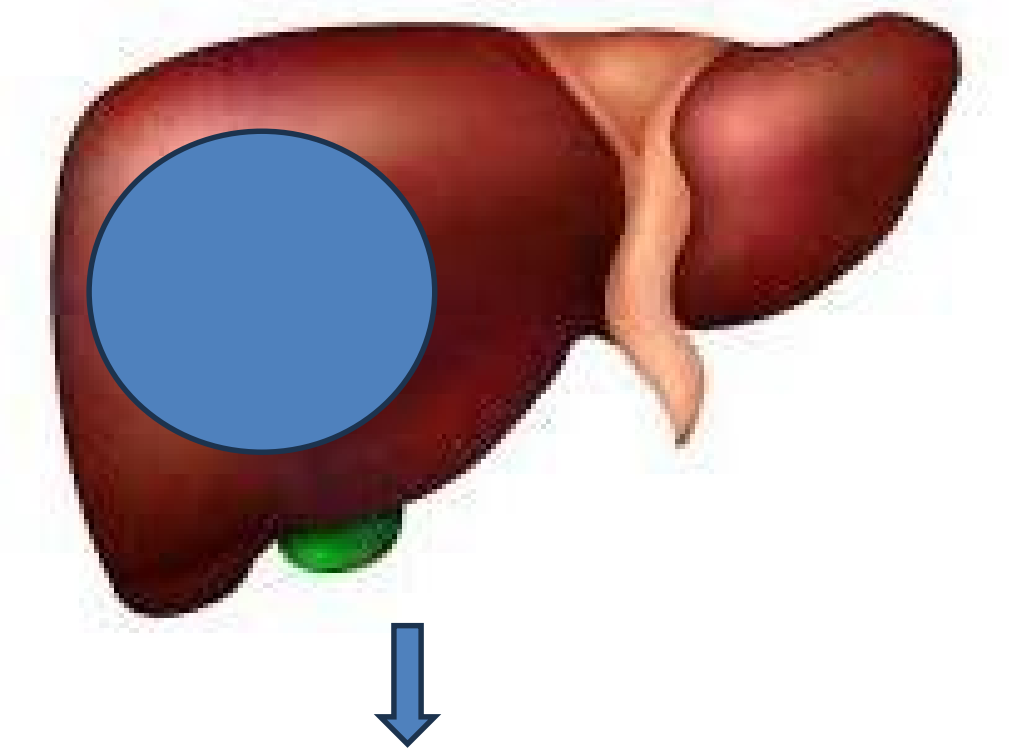
but…

Retrospective study[1] with low discrimination (AUC 0.71)

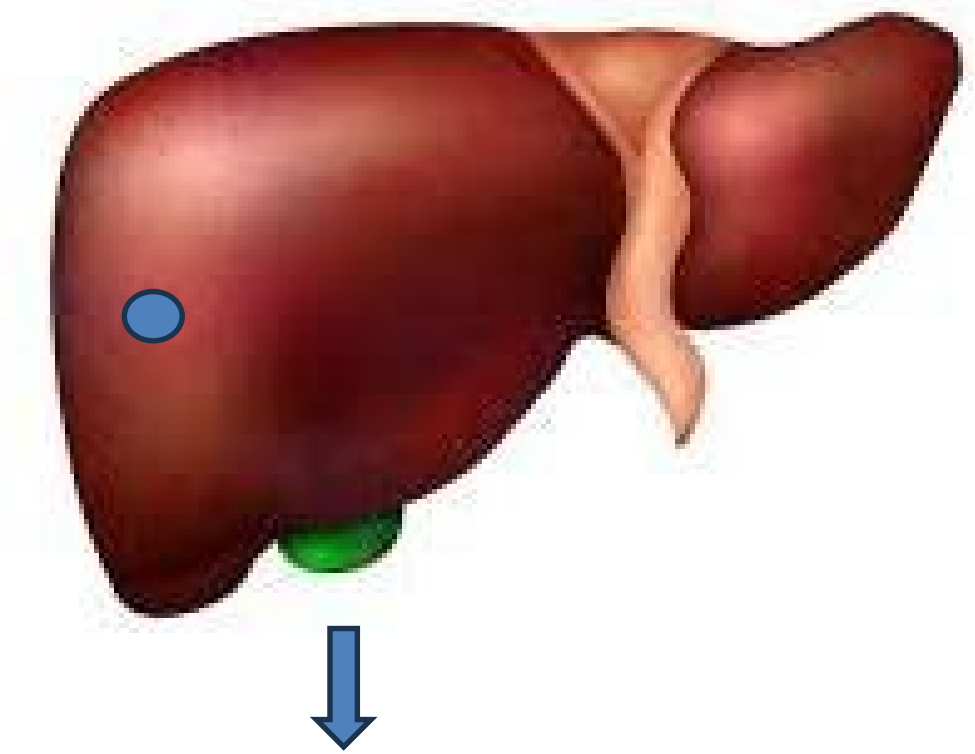
- Lack of worldwide accepted definition of recurrence
- Early potential for multifocality vs indolent course

1. Chan et al. J Hep 2018

Is HCC recurrence risk predictable?

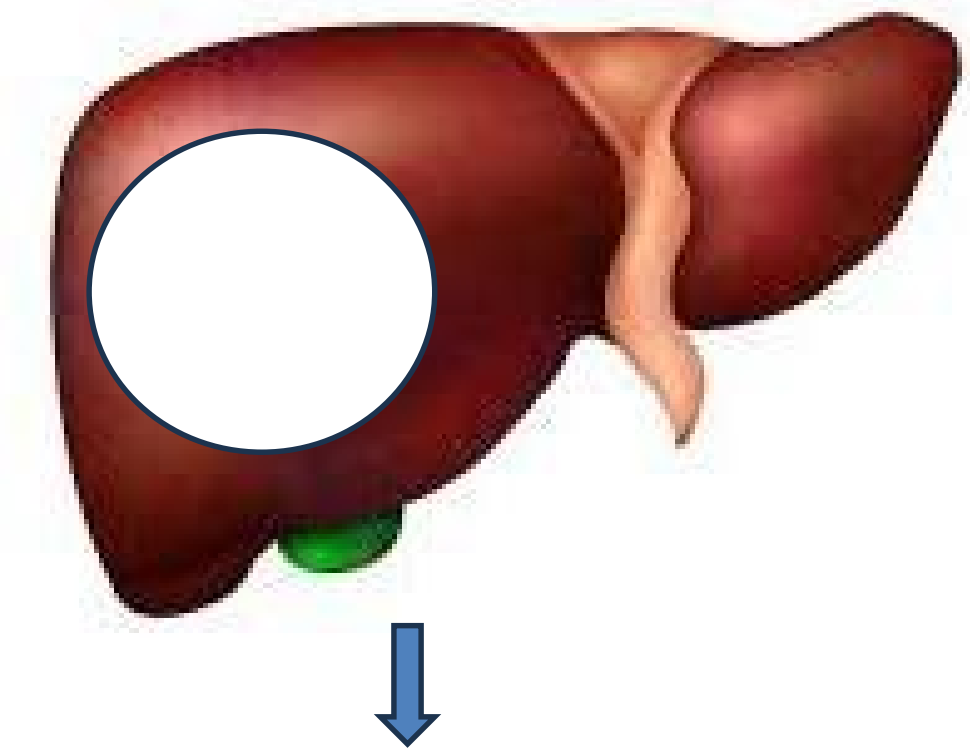


Large unifocal
Probability of recurrence?

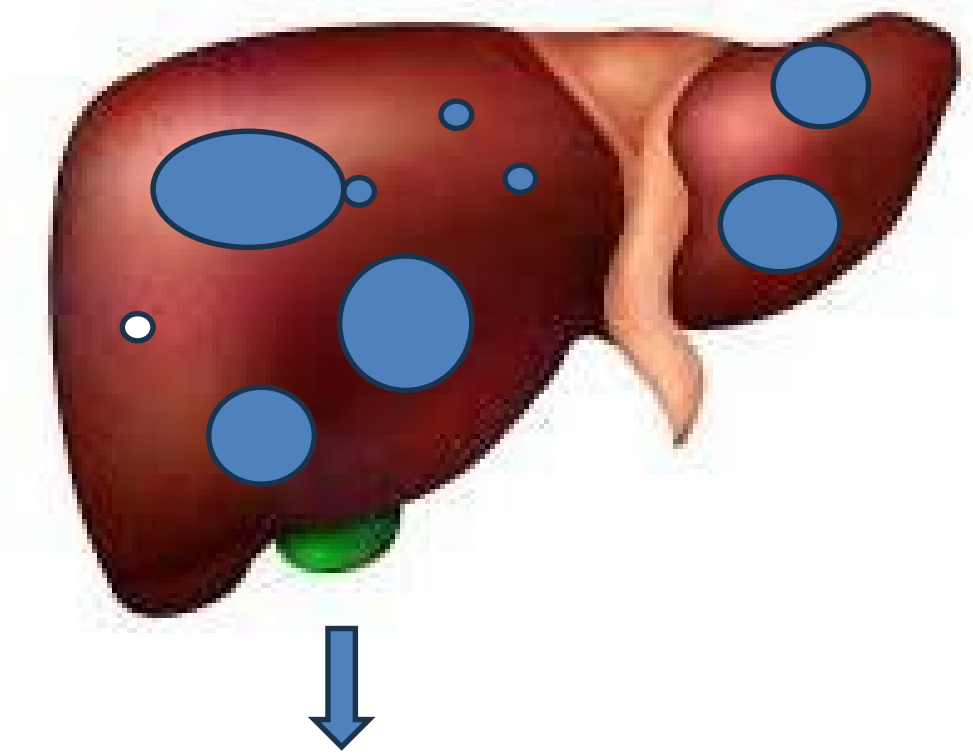


Born to be bad?

Is HCC recurrence risk predictable?

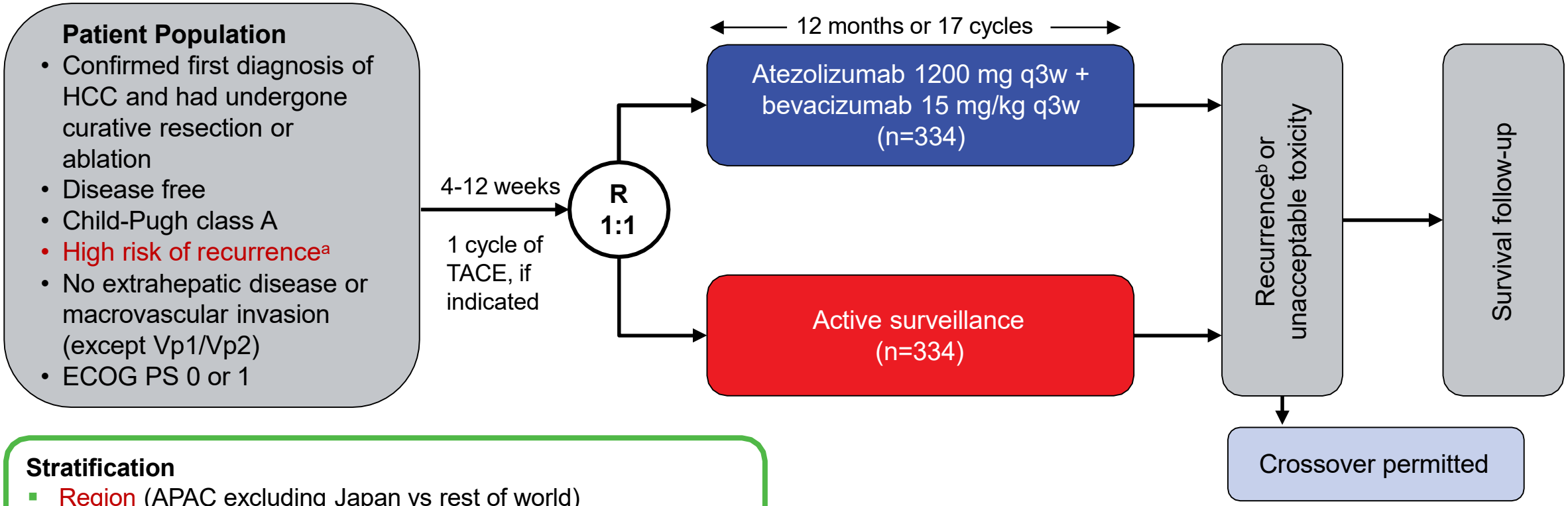


Large unifocal
No recurrence



Born to be bad

IMbrave050 study design



Stratification
- Region (APAC excluding Japan vs rest of world)
- High-risk features and procedures:
  - Ablation
  - Resection, 1 risk feature, adjuvant TACE (yes vs no)
  - Resection, ≥2 risk features, adjuvant TACE (yes vs no)

Primary endpoint
- Recurrence-free survival assessed by the independent review facility[b]

ClinicalTrials.gov, NCT04102098. ECOG PS; Eastern Cooperative Oncology Group performance status; Q3W, every three weeks; R, randomization; TACE, transarterial chemoembolization.

[a] **High-risk features** include: tumor >5 cm, >3 tumors, microvascular invasion, minor macrovascular invasion Vp1/Vp2, or Grade 3/4 pathology.

[b] Intrahepatic recurrence defined by EASL criteria. Extrahepatic recurrence defined by RECIST 1.1.

Is HCC recurrence risk predictable?

EASL | JOURNAL OF HEPATOLOGY

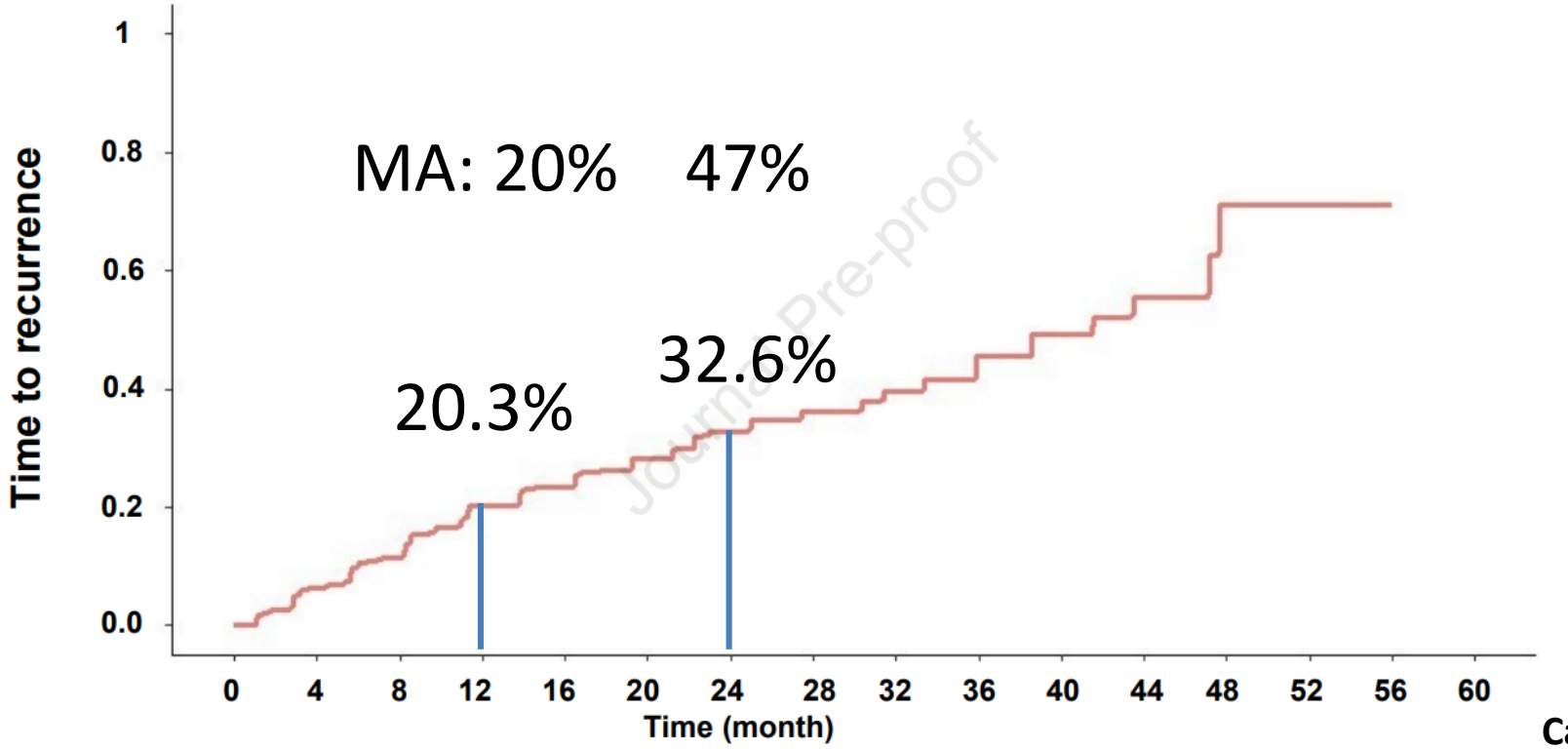
REVIEW | ARTICLES IN PRESS

Navigating the Landscape of Liver Cancer Management: Study Designs in Clinical Trials and Clinical Practices

Giuseppe Cabibbo • Ciro Celsa • Lorenza Rimassa • Ferran Torres • Jordi Rimola • Roman Kloeckner • Jordi Bruix • Calogero Cammà • Maria Reig • Show less

Reconstructed Pooled data from STORM and IMbrave 050 RCT control harms

Time to recurrence



Cabibbo G et al. J Hep 2024

Is HCC recurrence risk predictable?

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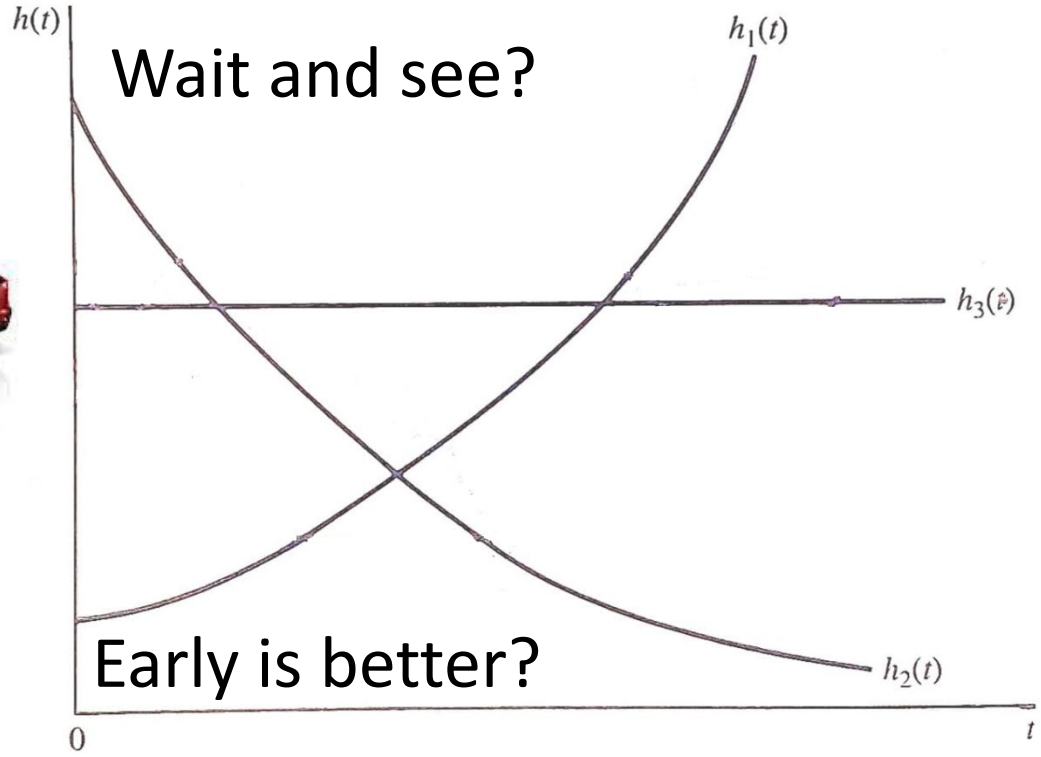
TIMING ADJUVANT ?



RISCHIO ISTANTANEO (HAZARD FUNCTION)

Is HCC recurrence risk predictable?

EASL | JOURNAL OF HEPATOLOGY

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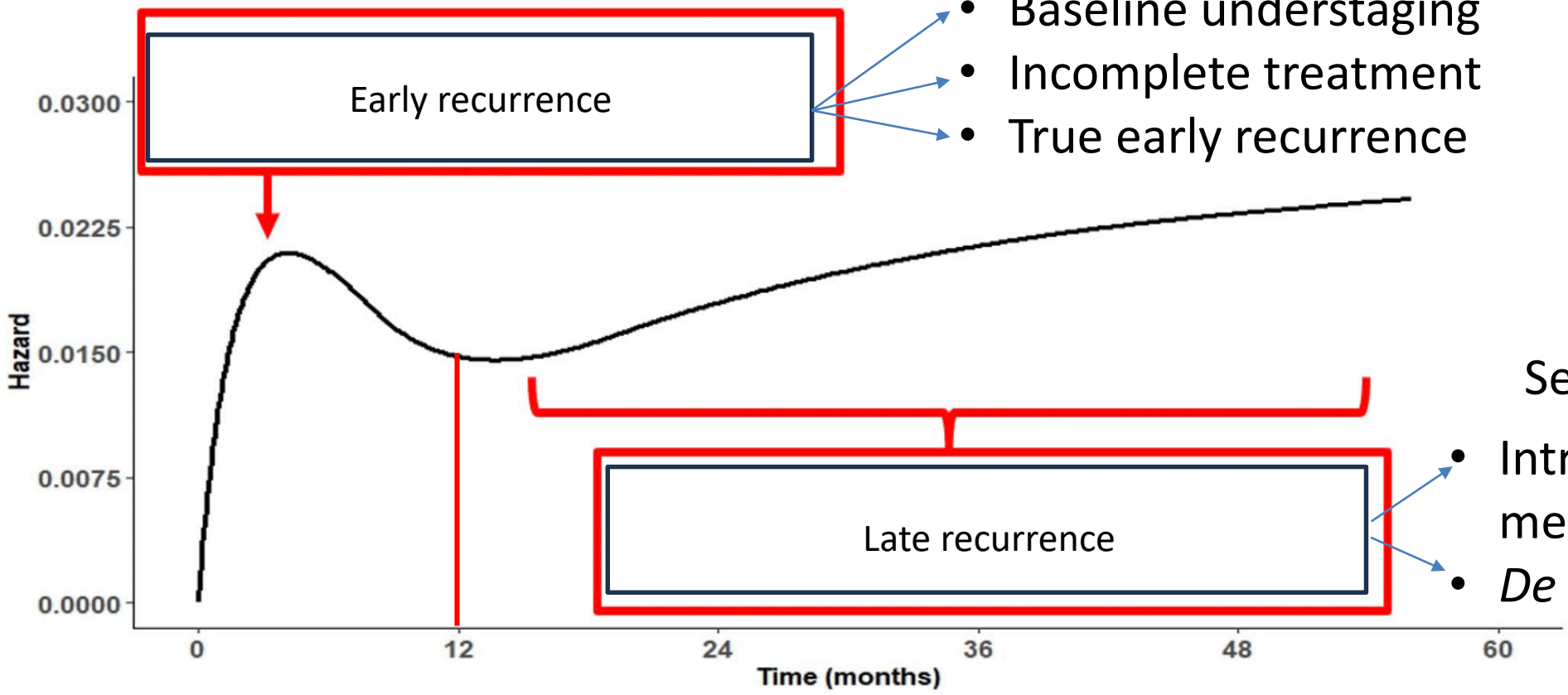
Reconstructed Pooled data from STORM and IMbrave 050 trial control curves



- Baseline understaging
- Incomplete treatment
- True early recurrence

Second tumor

- Intrahepatic metastases
- *De novo* recurrence

Estimated hazard function of hepatocellular carcinoma recurrence

Cabibbo G et al. J Hep 2024

IMbrave050 study design

Patient Population
- Confirmed first diagnosis of HCC and had undergone curative resection or ablation
- Disease free
- Child-Pugh class A
- High risk of recurrence[a]
- No extrahepatic disease or macrovascular invasion (except Vp1/Vp2)
- ECOG PS 0 or 1

4-12 weeks

1 cycle of TACE, if indicated

R 1:1

12 months or 17 cycles

Atezolizumab 1200 mg q3w + bevacizumab 15 mg/kg q3w (n=334)

Active surveillance (n=334)

Recurrence[b] or unacceptable toxicity

Survival follow-up

Crossover permitted

Stratification
- Region (APAC excluding Japan vs rest of world)
- High-risk features and procedures:
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IMbrave050 Inclusion Criteria

Patient Population

- Confirmed first diagnosis of HCC and had undergone curative resection or ablation
- Disease free
- Child-Pugh class A
- High risk of recurrence[a]
- No extrahepatic disease or macrovascular invasion (except Vp1/Vp2)
- ECOG PS 0 or 1

[a] **High-risk features** include:

- tumor >5 cm,
- >3 tumors, microvascular invasion,
- minor macrovascular invasion Vp1/Vp2,
- or Grade 3/4 pathology.

- 71% from Asia
- 63% HBV
- Cirrhosis pts n= ???

External validity??

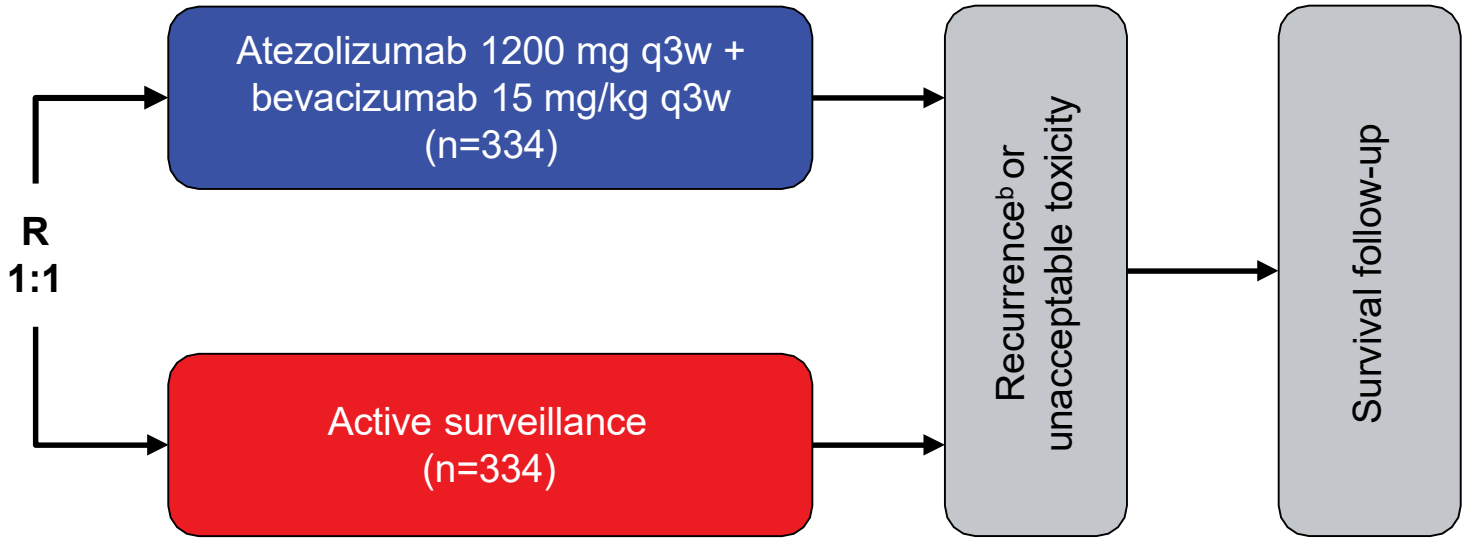
Chow et al IMbrave050
https://bit.ly/3ZPKzgM

IMbrave050 Stratification

Stratification

- Region (APAC excluding Japan vs rest of world)
- High-risk features and procedures:
  - Ablation
  - Resection, 1 risk feature, adjuvant TACE (yes vs no)
  - Resection, ≥2 risk features, adjuvant TACE (yes vs no)

Pre-planned analysis
(Robust evidence)
Practice Changing

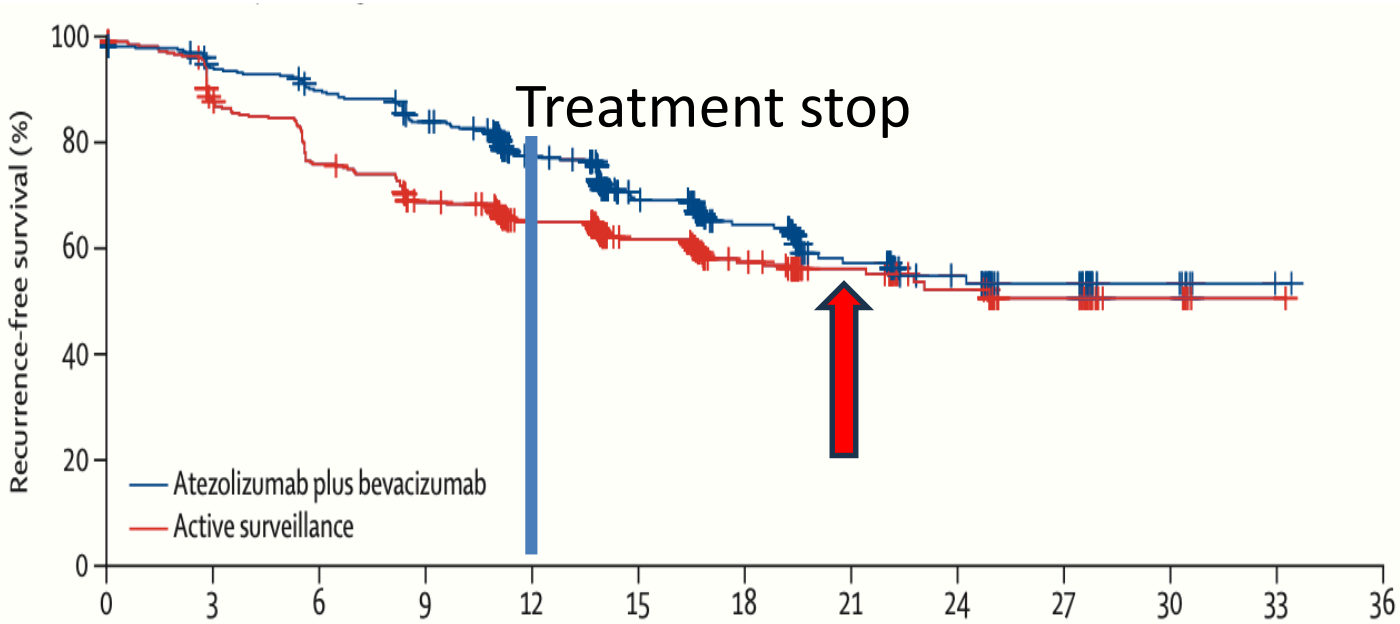


If no stratification:
post-hoc analysis
(only hypothesis generating)

Chow et al IMbrave050
https://bit.ly/3ZPKzgM

Imbrave 050 Recurrence free survival (RFS)

First positive trial in adjuvant setting



Number at risk (number censored)													
Atezolizumab plus bevacizumab	334 (0)	305 (10)	290 (12)	268 (15)	211 (53)	139 (105)	97 (139)	63 (164)	37 (188)	22 (202)	9 (215)	1 (223)	NE (NE)
Active surveillance	334 (0)	283 (12)	245 (12)	214 (20)	179 (44)	131 (84)	93 (114)	57 (148)	36 (166)	20 (181)	6 (195)	1 (200)	NE (NE)

HR: 0.72 (95%CI 0.53-0.98)

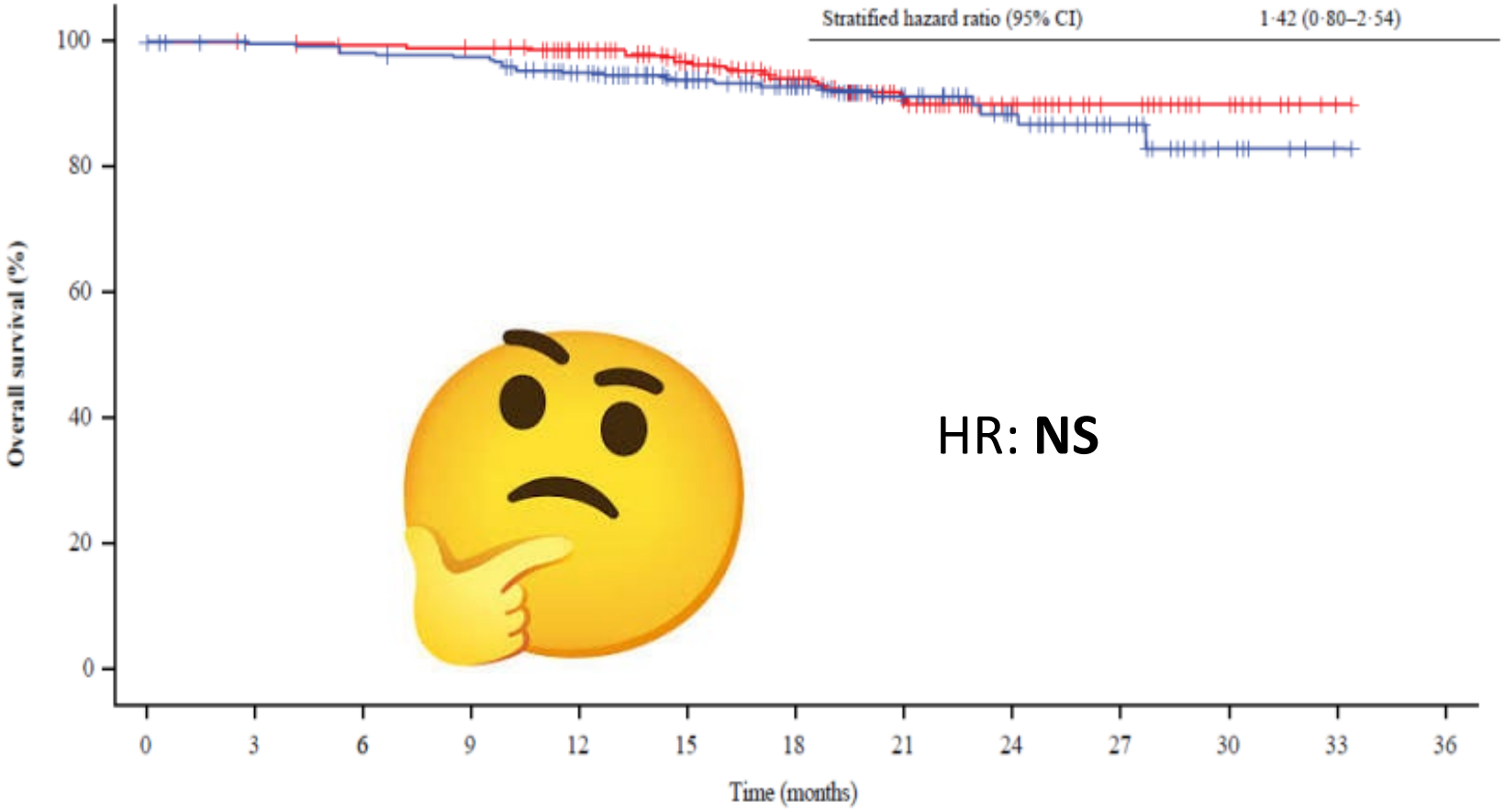
28% Risk Reduction

1 / 4 patients

Qin S. et al. The Lancet 2023

Imbrave 050 Overall survival (OS)

OS (immature?????)



HR: **NS**

Death n AB=27

Death n Control=20

Qin S. et al. The Lancet 2023

OS *or* RFS ?

FDA
DRUG INFO ROUNDS
ACCELERATED APPROVAL PROGRAM

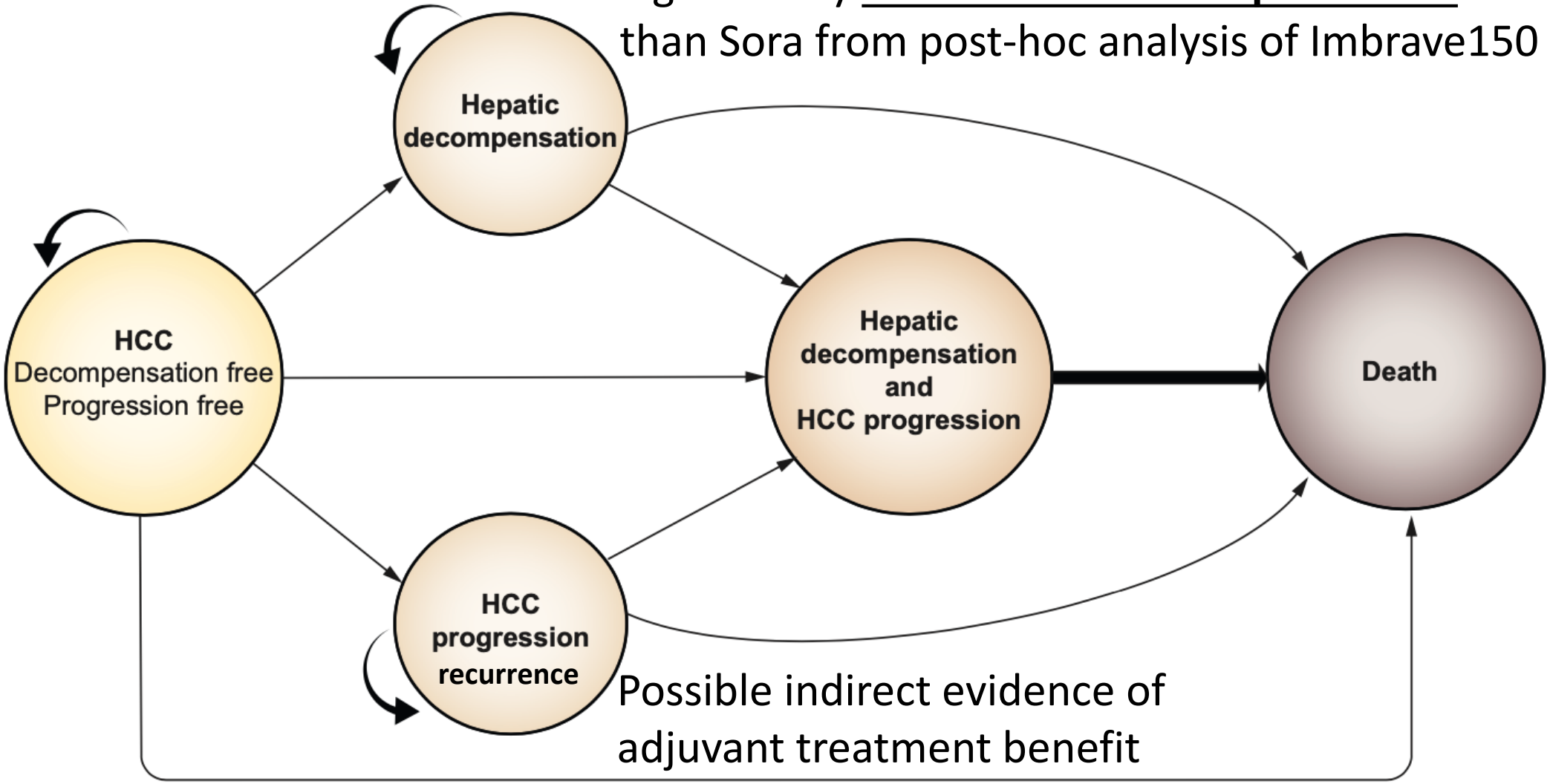
RFS as primary endpoint?

Is RFS a surrogate of OS?

OS as primary endpoint?

Cancer Recurrence / Progression significantly impact on survival

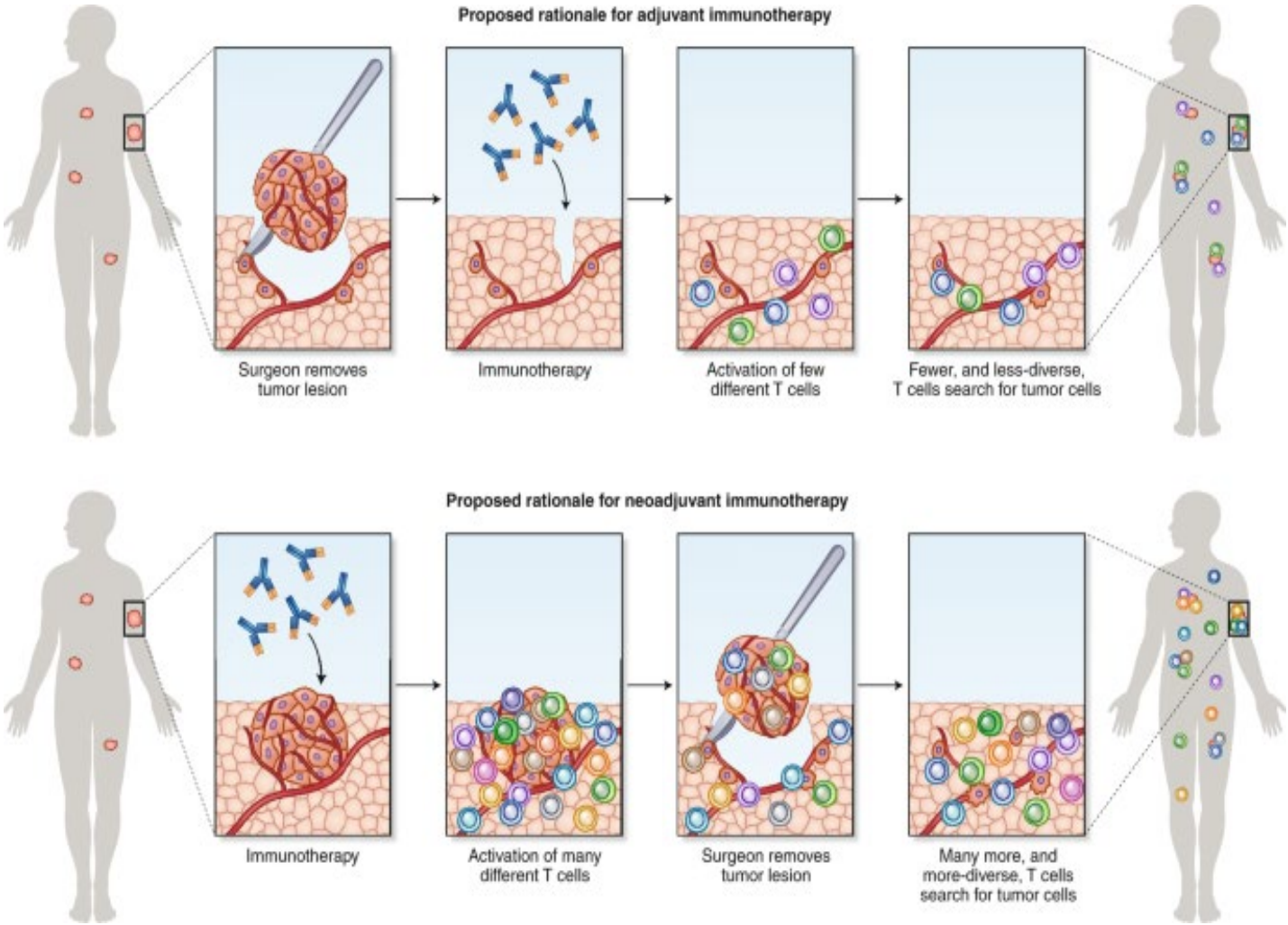
Significantly **lower risk of decompensation** for AtezoBev than Sora from post-hoc analysis of Imbrave150



Possible indirect evidence of adjuvant treatment benefit

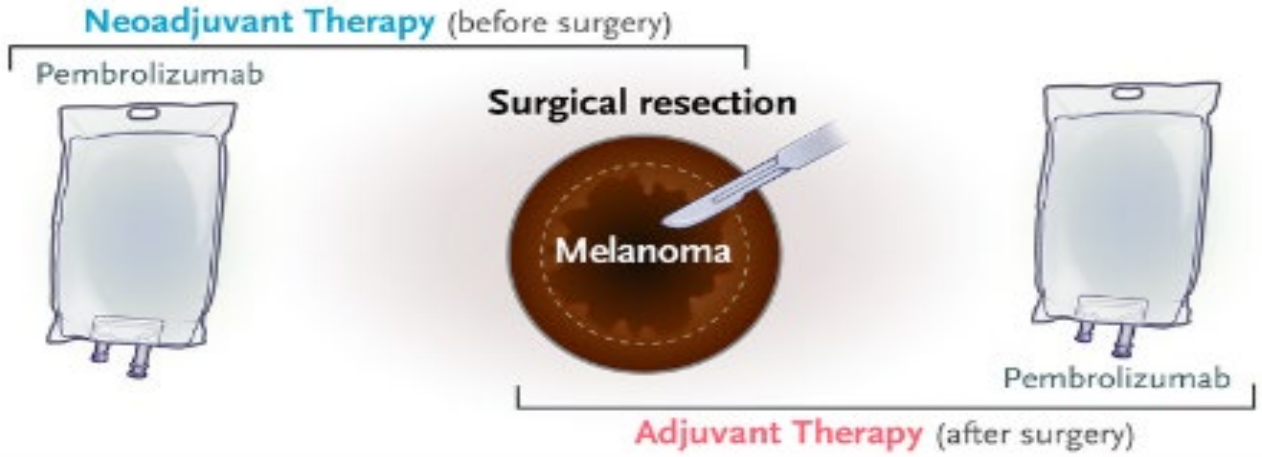
Reig & Cabibbo J Hep 2021

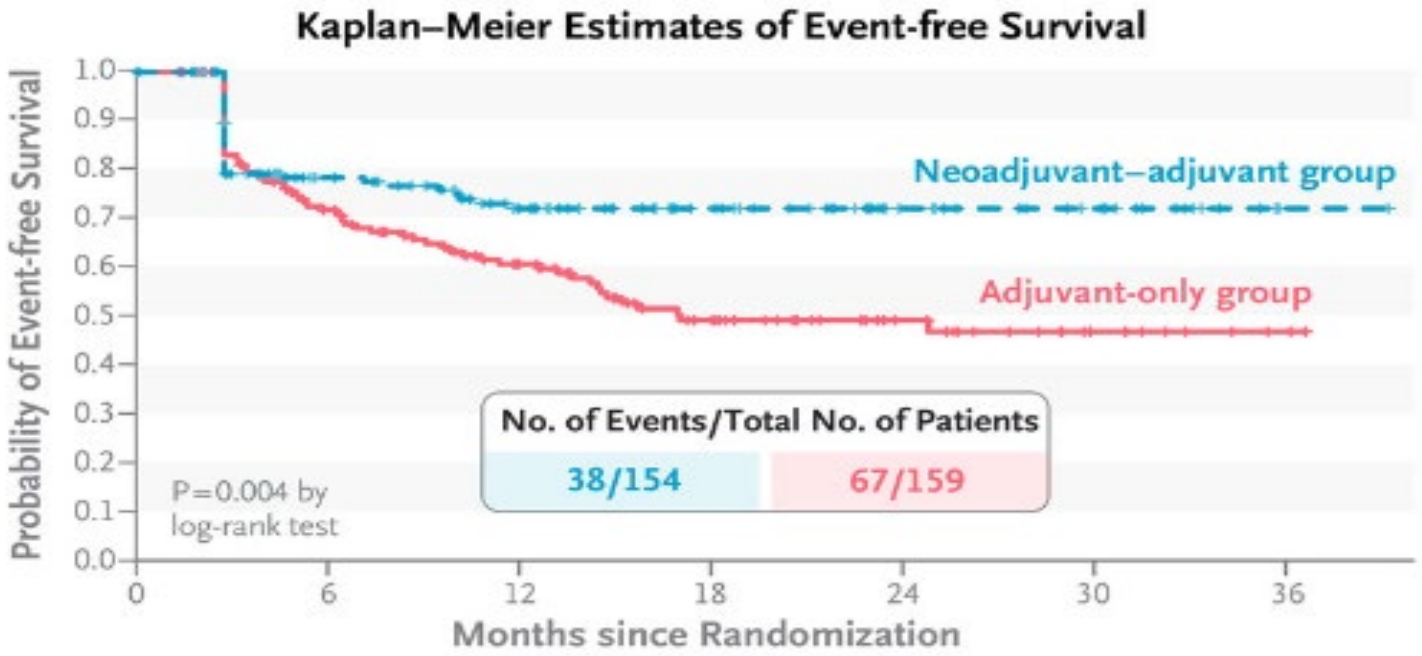
Is adjuvant enough?



Verslius et al. Nature Medicine, 2020

Is adjuvant enough?





3 doses of neoadjuvant Pembro + 15 infusions of adjuvant Pembro

Vs

18 doses of adjuvant Pembro

Ongoing trials in HCC: NCT05908786

Patel et al. NEJM, 2023

Conclusions (early stage)

- Lack of worldwide accepted definition of recurrence
- Prediction of recurrence risk cannot be adequately assess in individual patients
- How to assess net benefit in adjuvant setting?
- Is RFS a validated surrogate of OS?
- Is there a risk for over treatment with adjuvant treatment?
- Neo adjuvant → radical treatment → adjuvant (waiting for data)

Agenda

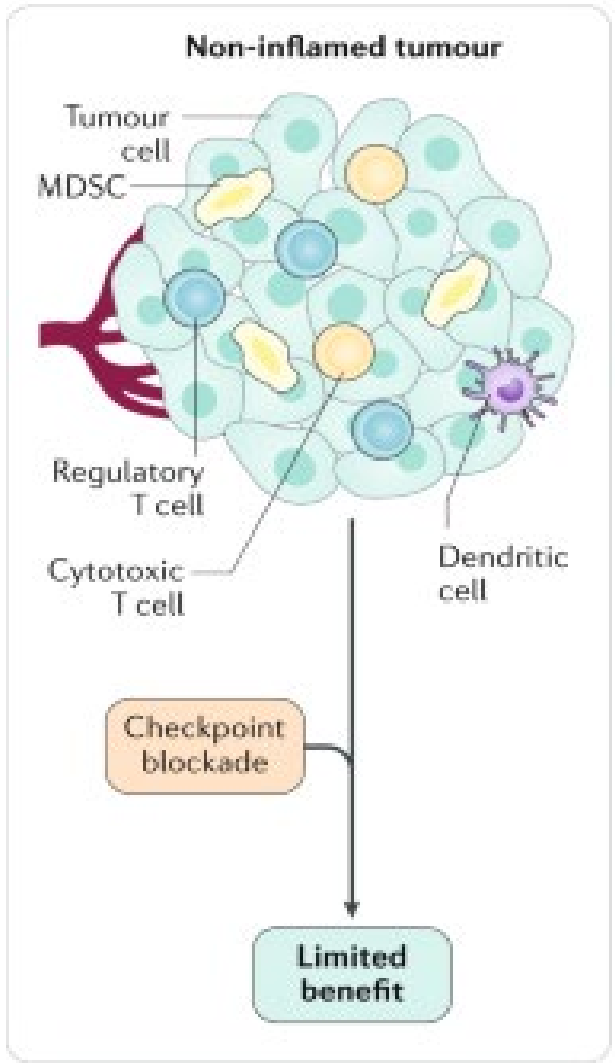
- Systemic therapies for early stage HCC
- Systemic therapies for intermediate stage HCC and combination with locoregional treatments
- Systemic therapies for advanced stage HCC
- Flaws of systemic therapies RCTs

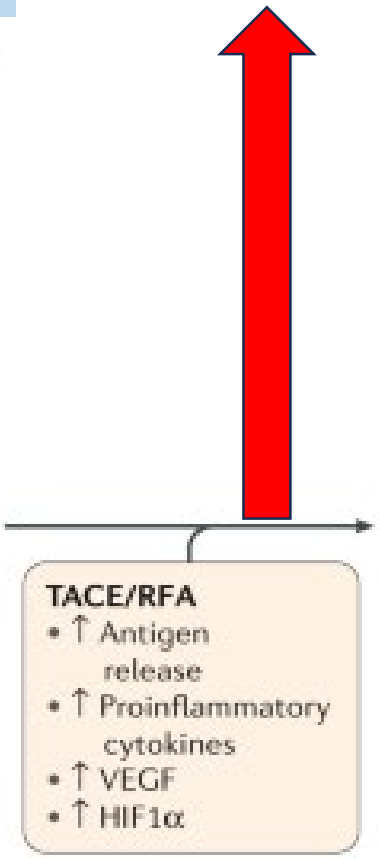
Systemic therapies for HCC 2024

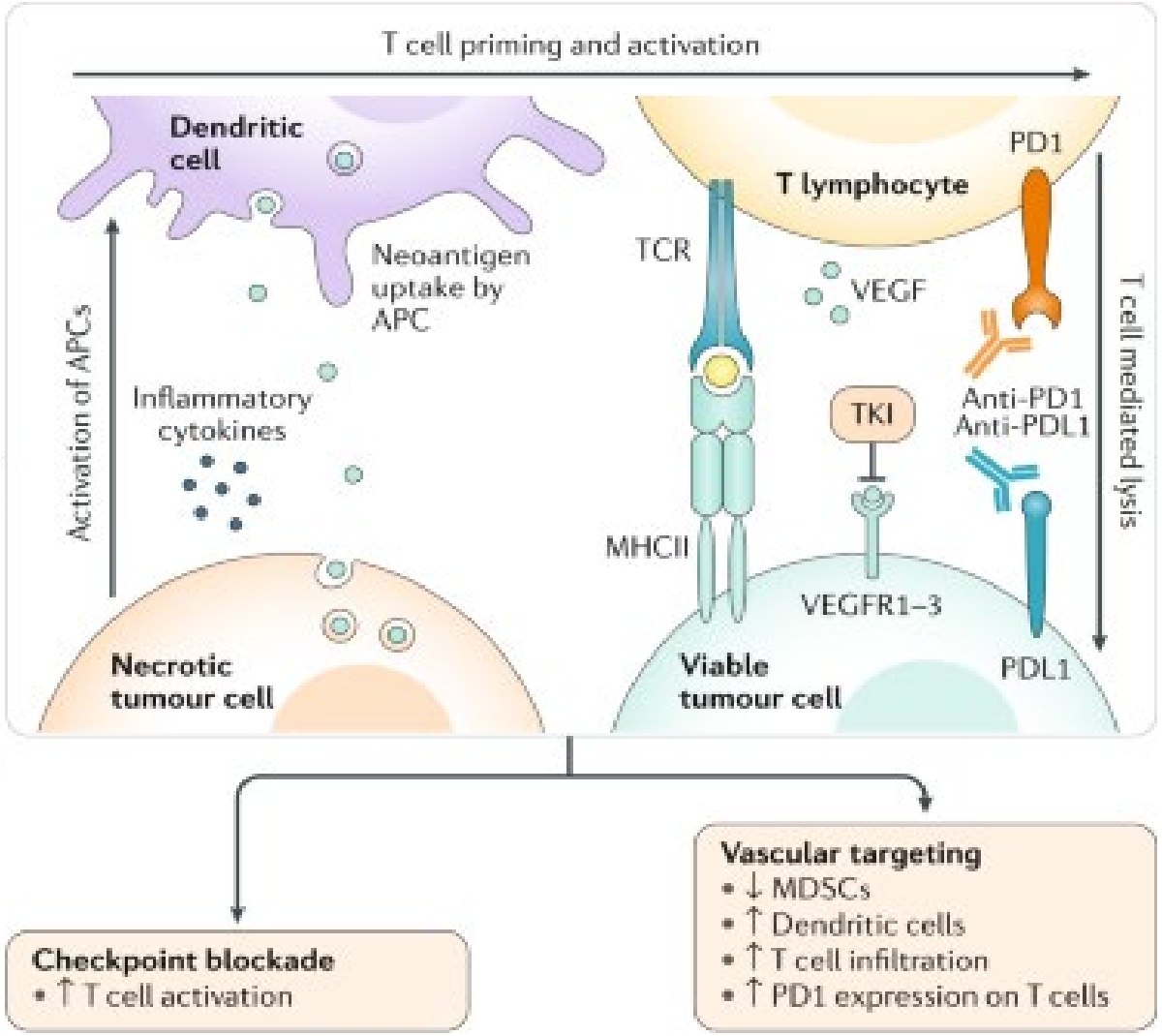
Target population	EARLY STAGE WITH HIGH RISK OF RECURRENCE	HCC ELIGIBLE TO TACE	ADVANCED HCC
Treatments	Adjuvant AtezoBeva after resection or ablation	Durva+Beva with TACE	AtezoBeva DurvaTreme Durvalumab (?) Lenvatinib AtezoBevaTira (?)
Primary endpoint	Recurrence-free survival **++**	Progression-free survival **+/- ?**	Overall survival **+++**

Rationale for combining locoregional therapies with systemic therapies for HCC

COLD TUMOUR → HOT TUMOUR





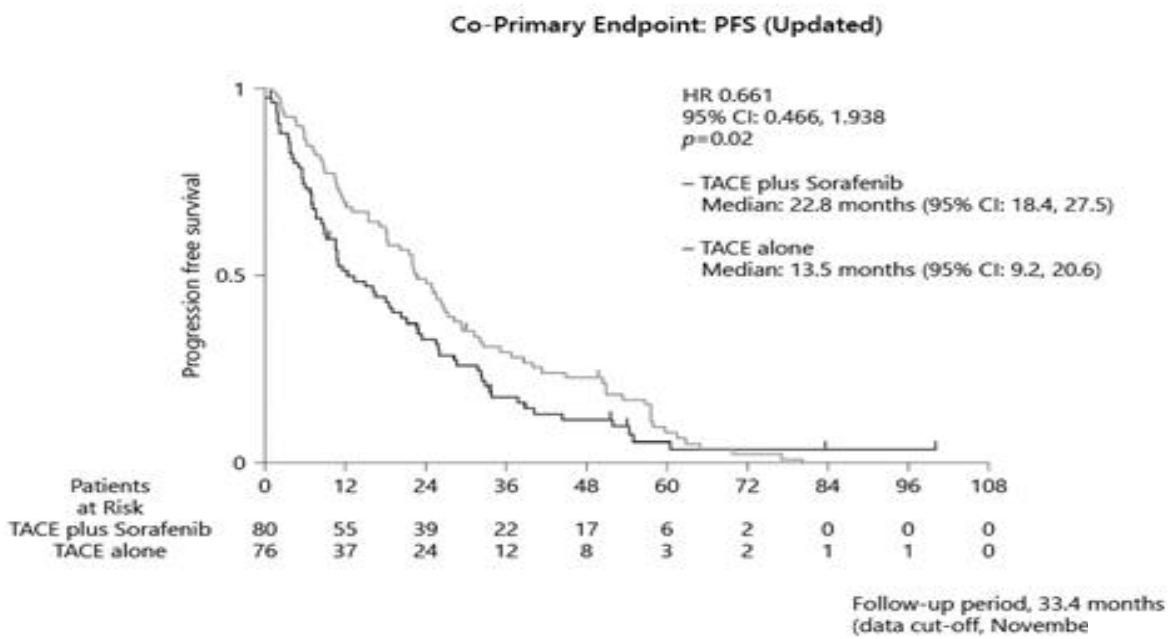


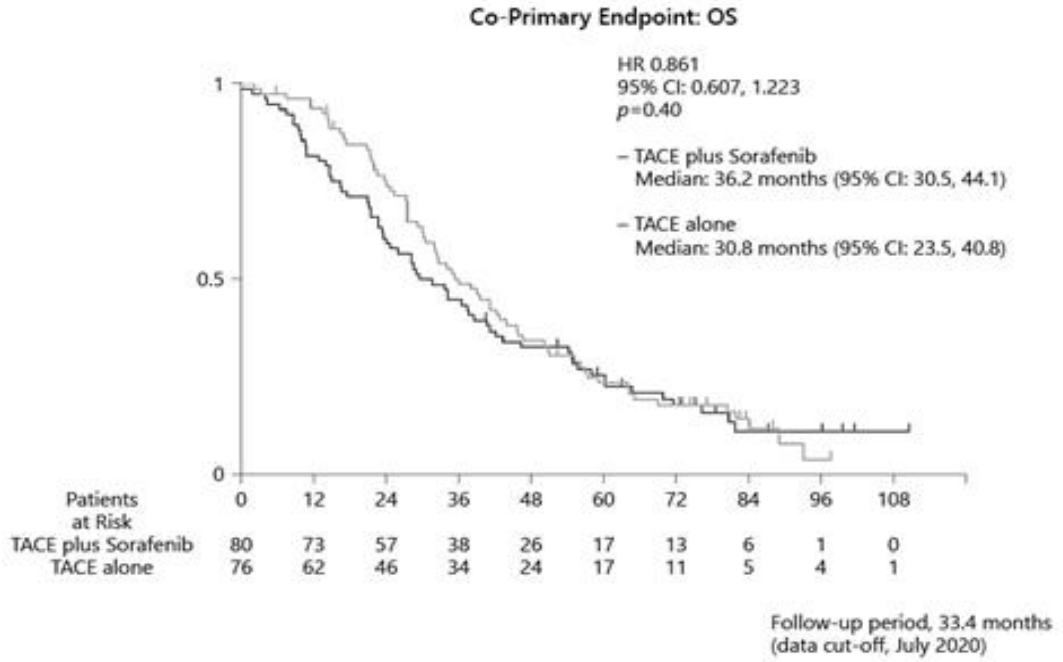
Llovet et al. Nat Rev Gastroenterol Hepatol. 2021

TACTICS trial
TACE+Sorafenib vs TACE alone

No vascular invasion or extrahepatic disease

Co-Primary endpoint: PFS/OS





Significant Benefit in PFS

No Benefit in OS

Kudo et al. Gut 2020
Kudo et al. Liver Cancer, 2022

Selected ongoing phase III RCTs of combination treatments

TACE + IO

Acronym (projected enrolment)	Experimental arm	Control arm	Disease stage	Primary end point	ClinicalTrials.gov registration
Primary treatment with locoregional therapies					
EMERALD-1 (600 patients)	Durvalumab plus bevacizumab plus TACE	TACE plus placebo	Intermediate/advanced stage	PFS	NCT03778957
TACE-3 (522 patients)	Nivolumab plus DEB-TACE	DEB-TACE	Intermediate stage	OS	NCT04268888
LEAP-012 (950 patients)	Lenvatinib plus pembrolizumab plus cTACE	cTACE	Intermediate stage	PFS–OS, co-primary end points	NCT04246177
CheckMate 74W (765 patients)	Arm 1: nivolumab plus ipilimumab plus cTACE Arm 2: nivolumab plus placebo plus cTACE	cTACE plus placebo	Intermediate stage	TTTP[a]–OS, co-primary end points	NCT04340193

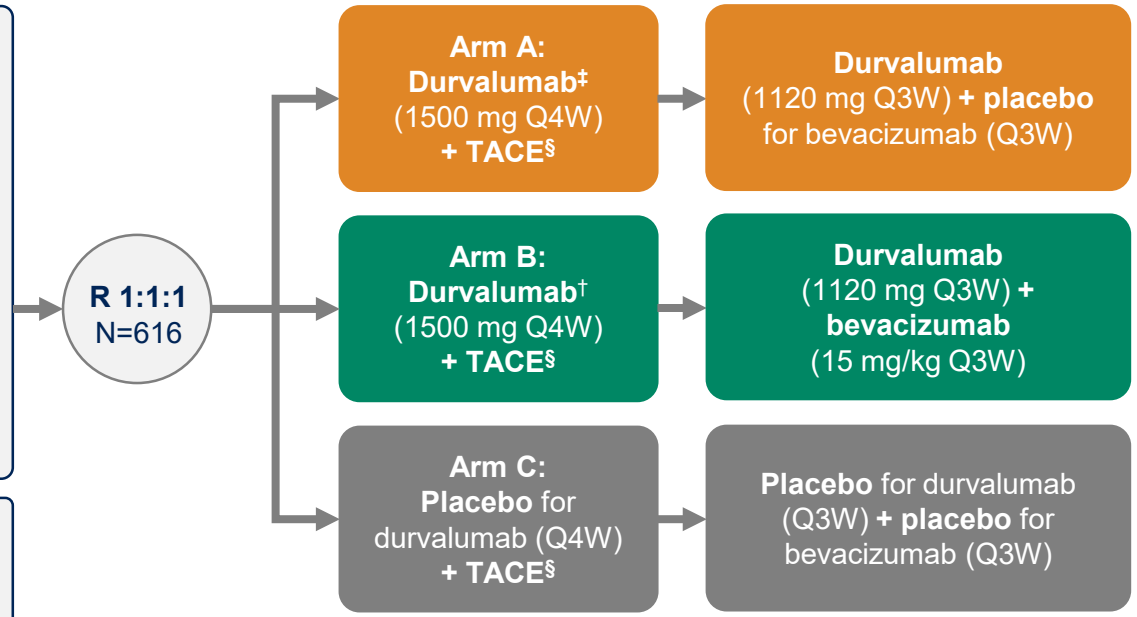
Llovet et al. Nat Rev Gastroenterol Hepatol. 2021

EMERALD-1 study design

EMERALD-1 was a global, double-blind, placebo-controlled Phase 3 study

Study population*
- Adults with confirmed HCC
- Not amenable to curative therapy, e.g. surgical resection, ablation, transplantation
- No extrahepatic disease
- Child-Pugh A to B7
- ECOG PS 0 or 1
- Measurable disease per mRECIST
- Excludes Vp3 and Vp4
- No prior systemic therapy or TACE†

Stratification factors
- TACE modality (DEB-TACE vs cTACE)
- Geographical region (Japan vs Asia [excluding Japan] vs other)
- Portal vein invasion (Vp1 or Vp2+ / -Vp1 vs none)



Primary endpoint:
- PFS‖ for Arm B vs Arm C using BICR per ***RECIST 1.1***

Key secondary endpoints:
- PFS for Arm A vs Arm C
- OS
- QoL

Other secondary endpoints:
- ORR and TTP using BICR per ***RECIST 1.1***
- Safety
- PFS, ORR, and TTP using investigator and BICR per ***mRECIST***

*Upper endoscopy to evaluate varices and risk of bleeding was required within 6 months of randomization. †Prior use of TACE or TAE is acceptable if it was used as part of therapy with curative intent, but not if it was used as the sole modality in curative therapy. ‡Durvalumab / placebo started ≥7 days after TACE. §DEB-TACE or cTACE. Participants will receive up to 4 TACE procedures within the 16 weeks following Day 1 of their first TACE procedure. ‖Only new lesions consistent with progression that were not eligible for TACE occurring prior to the first on study imaging at 12 weeks were considered progression events; standard mRECIST progression criteria were used after the 12-week imaging.

BICR, blinded independent central review; cTACE, conventional transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; DEB-TACE, drug-eluting bead-transarterial chemoembolization; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q3W / Q4W, every 3 / 4 weeks; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization; TAE, transarterial embolization; TTP, time to progression.

EMERALD-1 study population

Study population*
- Adults with confirmed HCC
- Not amenable to curative therapy, e.g. surgical resection, ablation, transplantation
- No extrahepatic disease
- Child-Pugh A to B7
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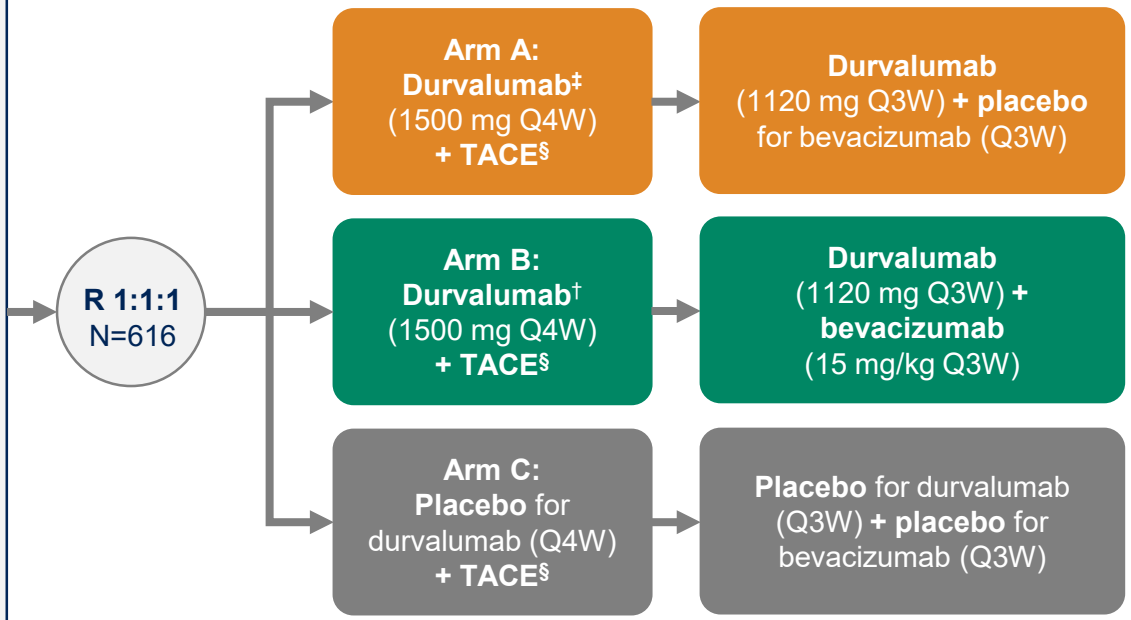

EMERALD-1 stratification

- TACE modality (DEB-TACE vs cTACE)
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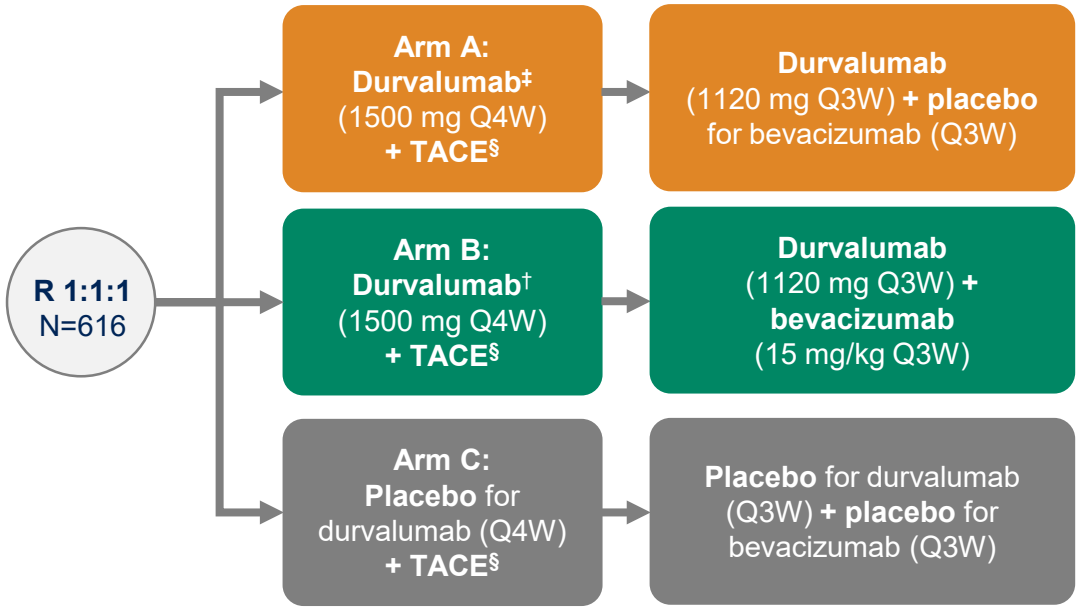
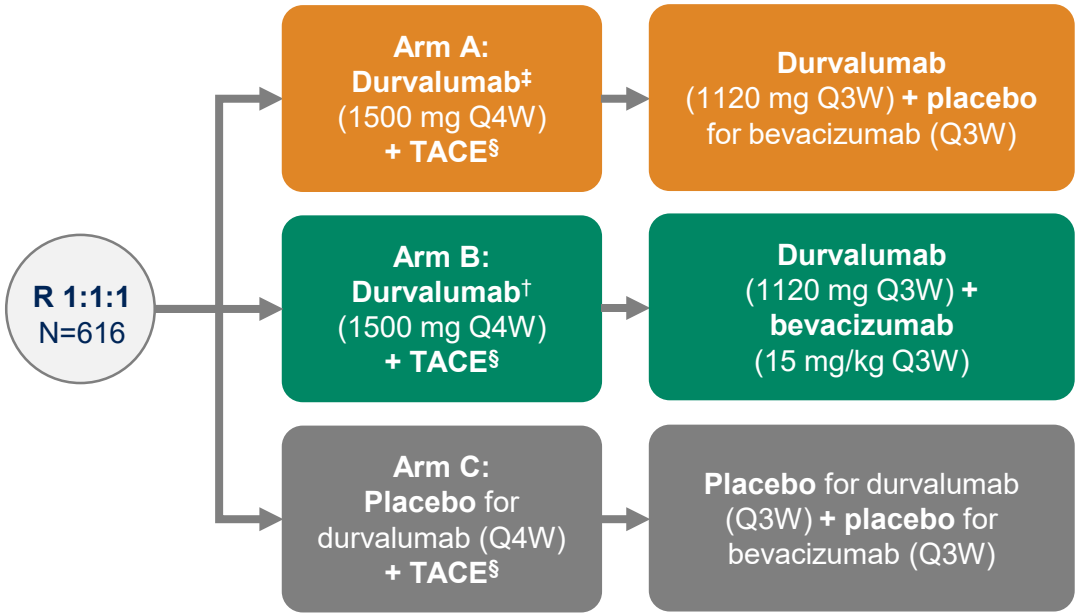


EMERALD-1 endpoints



Primary endpoint:

- PFS‖ for Arm B vs Arm C using BICR per ***RECIST 1.1***

Key secondary endpoints:

- PFS for Arm A vs Arm C
- OS
- QoL

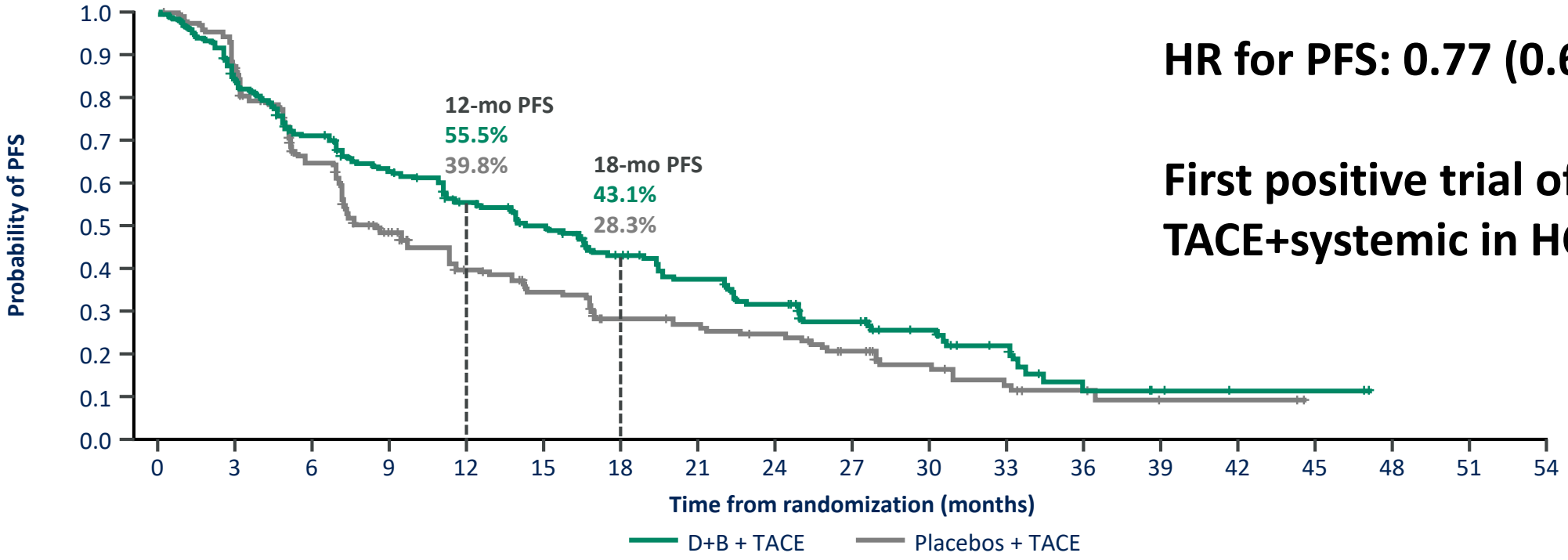
Other secondary endpoints:

- ORR and TTP using BICR per ***RECIST 1.1***
- Safety
- PFS, ORR, and TTP using investigator and BICR per ***mRECIST***

INTERMEDIATE STAGE

EMERALD-1 trial

Median PFS was improved by 6.8 months with D+B + TACE versus placebos + TACE



HR for PFS: 0.77 (0.61–0.98)

First positive trial of TACE+systemic in HCC

When comparing DURVA+TACE vs PLACEBO+TACE: HR for PFS 0.94 (0.75–1.19)

Lencioni et al. Presented at ASCO GI 2024

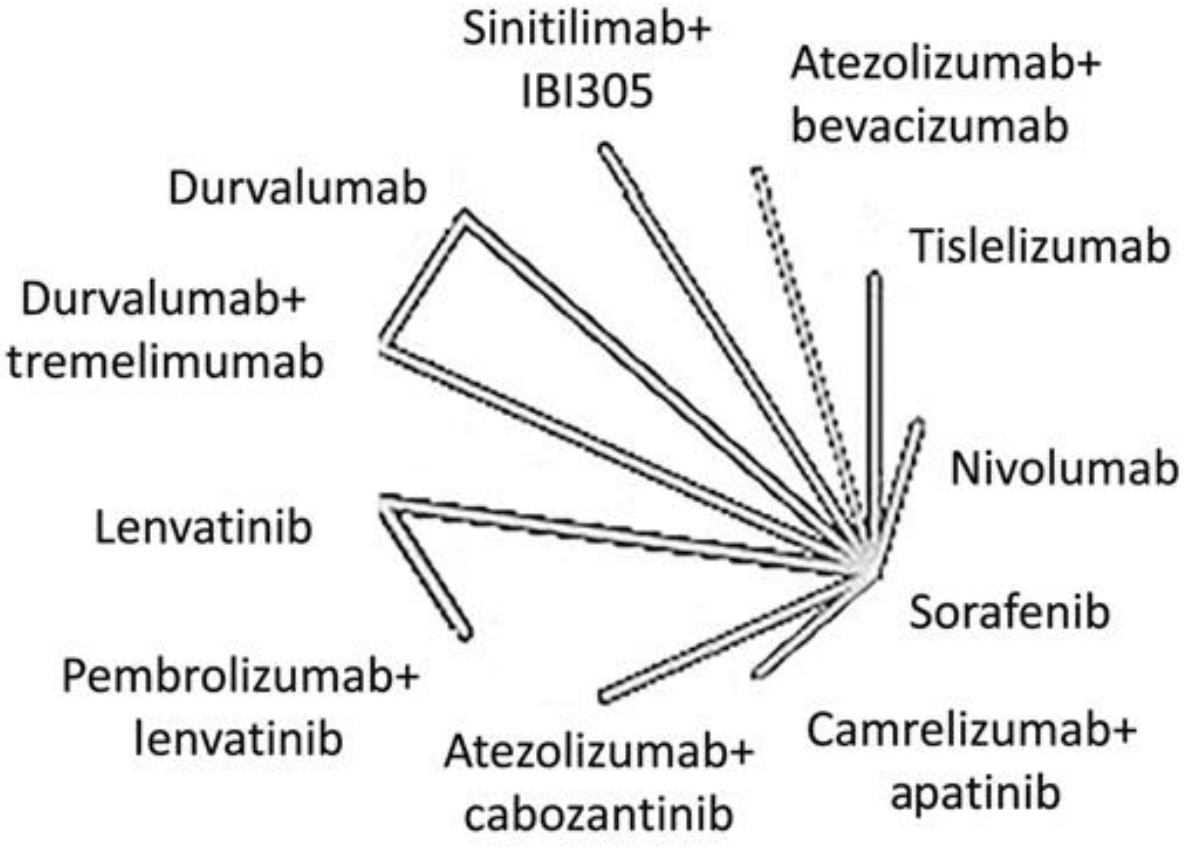
Agenda

- Systemic therapies for early stage HCC
- Systemic therapies for intermediate stage HCC and combination with locoregional treatments
- Systemic therapies for advanced stage HCC
- Flaws of systemic therapies RCTs

Systemic therapies for HCC 2024

Target population	EARLY STAGE WITH HIGH RISK OF RECURRENCE	HCC ELIGIBLE TO TACE	ADVANCED HCC
Treatments	Adjuvant AtezoBeva after resection or ablation	Durva+Beva with TACE	AtezoBeva DurvaTreme Durvalumab (?) Lenvatinib AtezoBevaTira (?)
Primary endpoint	Recurrence-free survival **++**	Progression-free survival **+/- ?**	Overall survival **+++**

ADVANCED STAGE
Efficacy



Celsa et al. Liver Cancer, 2023

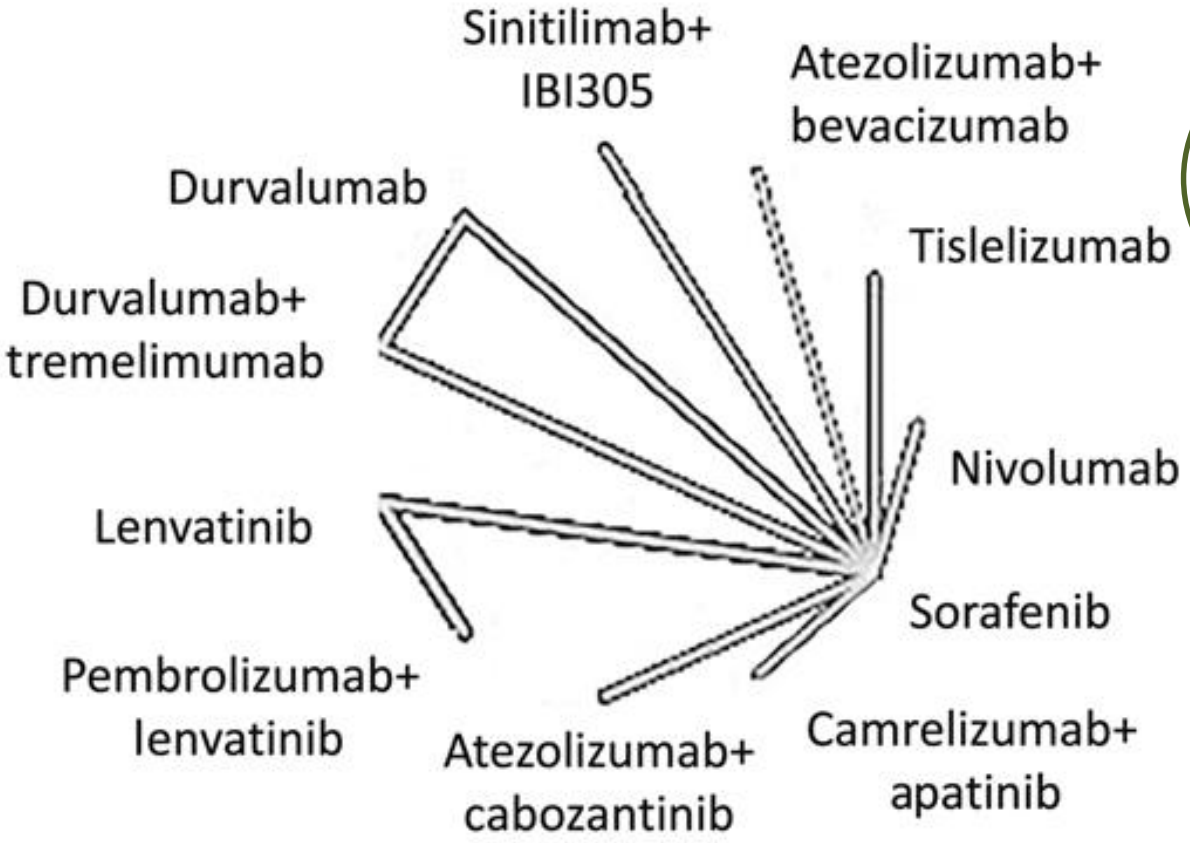
OS

treatment	SUCRA
Atezolizumab + bevacizumab	0.883
Camrelizumab + apatinib	0.865
Pembrolizumab + lenvatinib	0.722
Durvalumab + tremelimumab	0.626
Nivolumab	0.506
Lenvatinib	0.466
Tislelizumab	0.352
Durvalumab	0.342
Atezolizumab + cabozantinib	0.120
Sorafenib	0.114
-	-

PFS

treatment	SUCRA
Pembrolizumab + lenvatinib	0.926
Lenvatinib	0.858
Camrelizumab + apatinib	0.786
Sintilimab + IBI305	0.712
Atezolizumab + cabozantinib	0.695
Atezolizumab + bevacizumab	0.518
Sorafenib	0.347
Durvalumab + tremelimumab	0.324
Nivolumab	0.153
Durvalumab	0.107
Tislelizumab	0.070

ADVANCED STAGE
Safety



Celsa et al. Liver Cancer, 2023

Grade≥3 adverse events

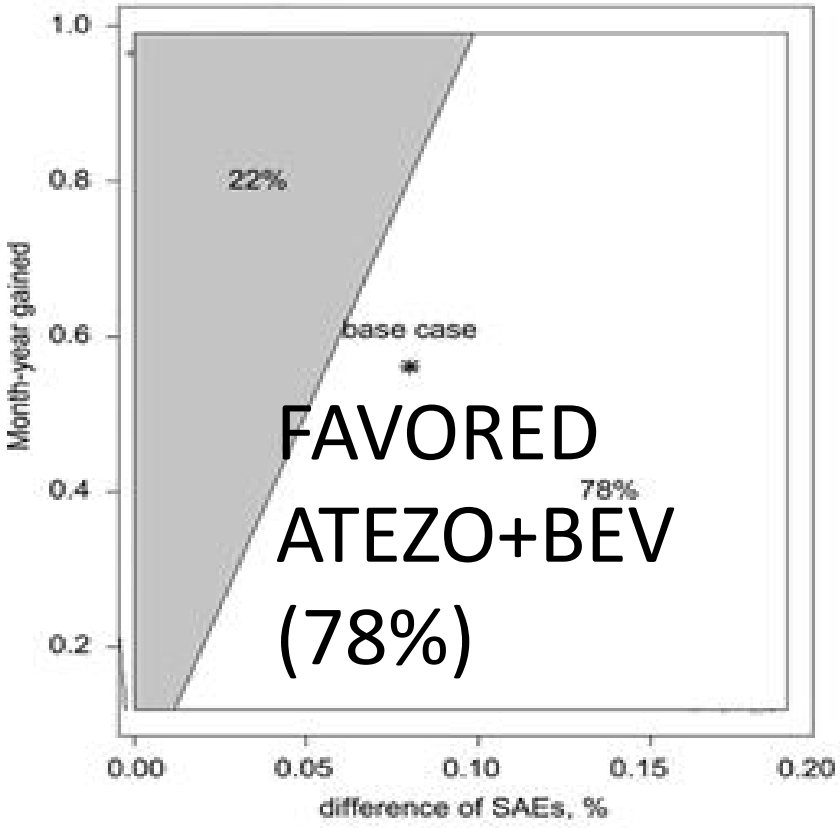
Treatment	SUCRA
Tislelizumab	0.972
Nivolumab	0.895
Durvalumab	0.833
Durvalumab plus Tremelimumab	0.686
Sintilimab plus IBI305	0.504
Sorafenib	0.497
Atezolizumab plus Bevacizumab	0.493
Lenvatinib	0.373
Pembrolizumab plus Lenvatinib	0.203
Atezolizumab plus Cabozantinib	0.091
Camrelizumab plus Apatinib	0.015

Systemic therapy “net benefit”

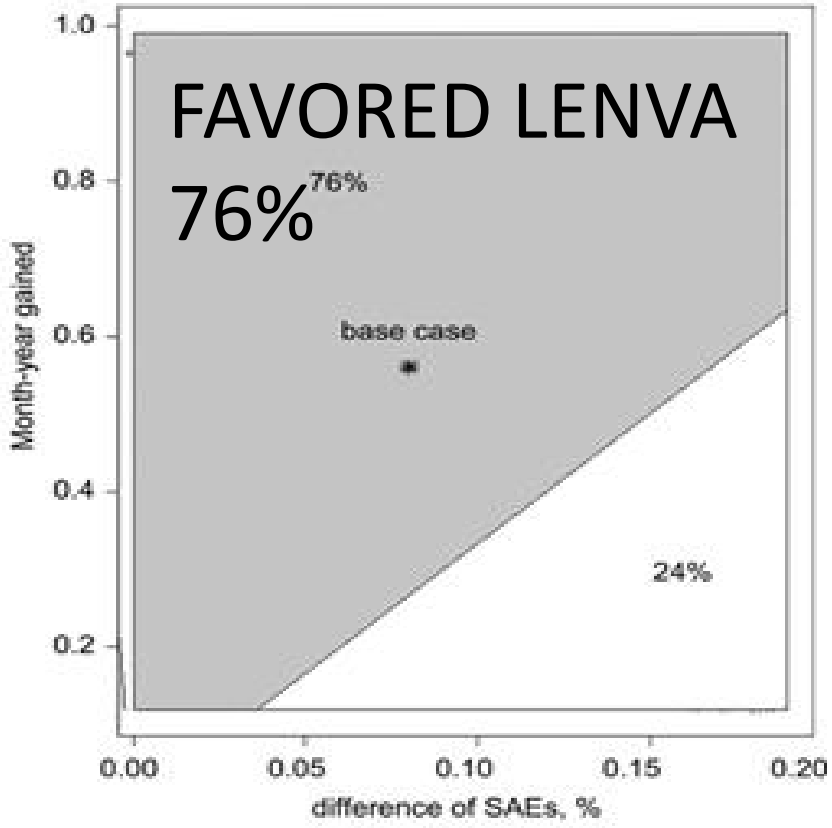
Incremental safety-effectiveness ratio (ISER)

$$\text{ISER} = \frac{\text{Delta SAEs\%}}{\text{LYG}}$$

10% SAEs/month



30% SAEs/month



Lenva favored over AtezoBeva only for higher willingness to risk SAEs

Atezolizumab plus bevacizumab
Lenvatinib

Celsa et al. Liver Cancer, 2023

Agenda

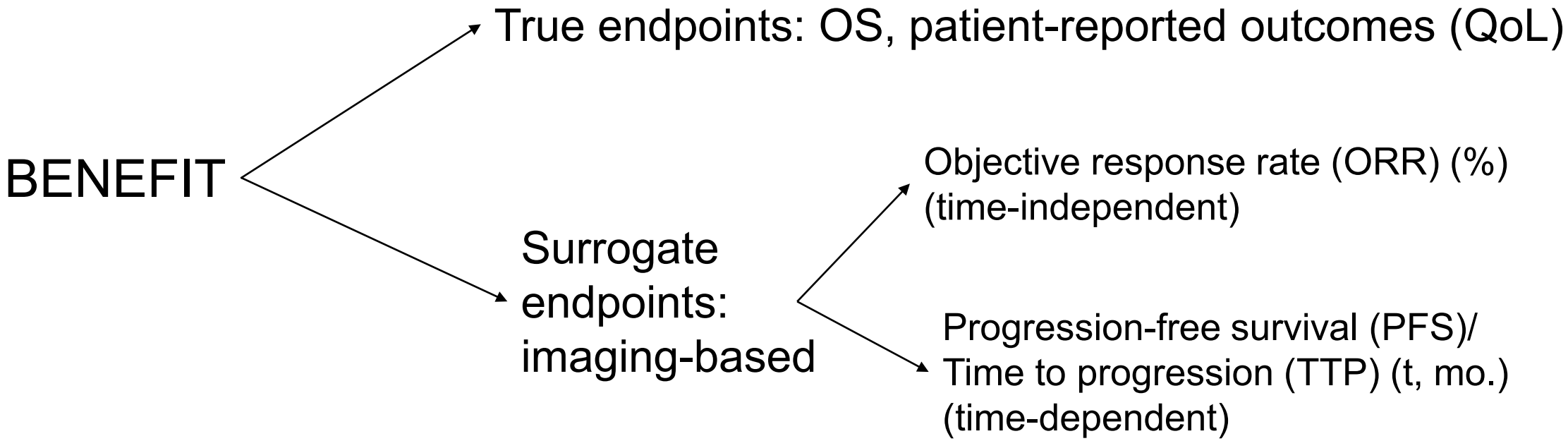
- Systemic therapies for early stage HCC
- Systemic therapies for intermediate stage HCC and combination with locoregional treatments
- Systemic therapies for advanced stage HCC
- Flaws of systemic therapies RCTs

Flaws of ICI treatment RCTs

- **Surrogate endpoints**
- **Competing risks in HCC setting**
- **Sequential treatments: 1°L → 2°L**
- **Hazards of Hazard Ratio**

Which goal when treating HCC?

- **True endpoint**: The goal of any cancer treatment (true endpoint) is to improve the duration and/or quality (QoL) of patient's survival (OS)
  - **Surrogate endpoint** (FDA): "a marker (such as radiographic image) that is thought to predict clinical benefit, but is not itself a measure of clinical benefit"



Surrogate endpoints

JAMA Internal Medicine | Original Investigation

Estimation of Study Time Reduction Using Surrogate End Points Rather Than Overall Survival in Oncology Clinical Trials

Emerson Y. Chen, MD; Sunil K. Joshi, BA; Audrey Tran, BA; Vinay Prasad, MD, MPH

- **Surrogate endpoint needs to be VALIDATED**
- **Smaller sample size needed for RCTs**
- **Shorter trials duration and earlier results**
- **Lower costs of RCTs, but unfortunately not for drug**

Time-independent
Objective Response Rate, ORR (%)

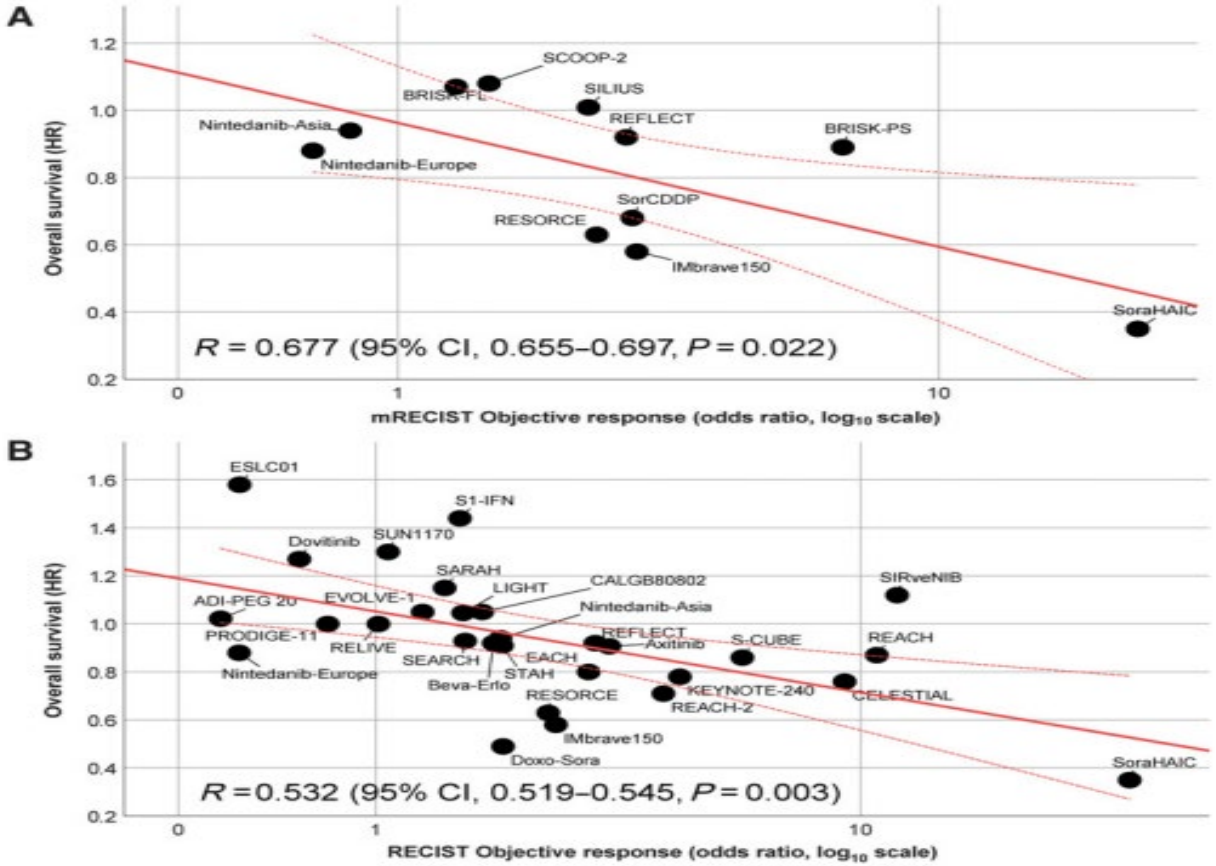
Objective Response Predicts Survival in Advanced Hepatocellular Carcinoma Treated with Systemic Therapies

Masatoshi Kudo[1], Robert Montal[2,3], Richard S. Finn[4], Florian Castet[3], Kazuomi Ueshima[1], Naoshi Nishida[1], Philipp K. Haber[5], Youyou Hu[6], Yasutaka Chiba[7], Myron Schwartz[5], Tim Meyer[8,9], Riccardo Lencioni[10,11], and Josep M. Llovet[3,5,12]

ORR

OS

Weak surrogacy



mRECIST

R=0.677

RECIST

R=0.532

Clinical Cancer Research, **2022**

Time-independent
Objective Response Rate, ORR (%)

- Reproducibility of radiology-based outcome→ Impact on clinical decision making?
- High ORR → Patient benefit in downstaging ???
- Drug activity → Implications in phase II (pre-registration) trials

FDA Panel Opposes Nivolumab for Second-line Advanced HCC

April 30, 2021

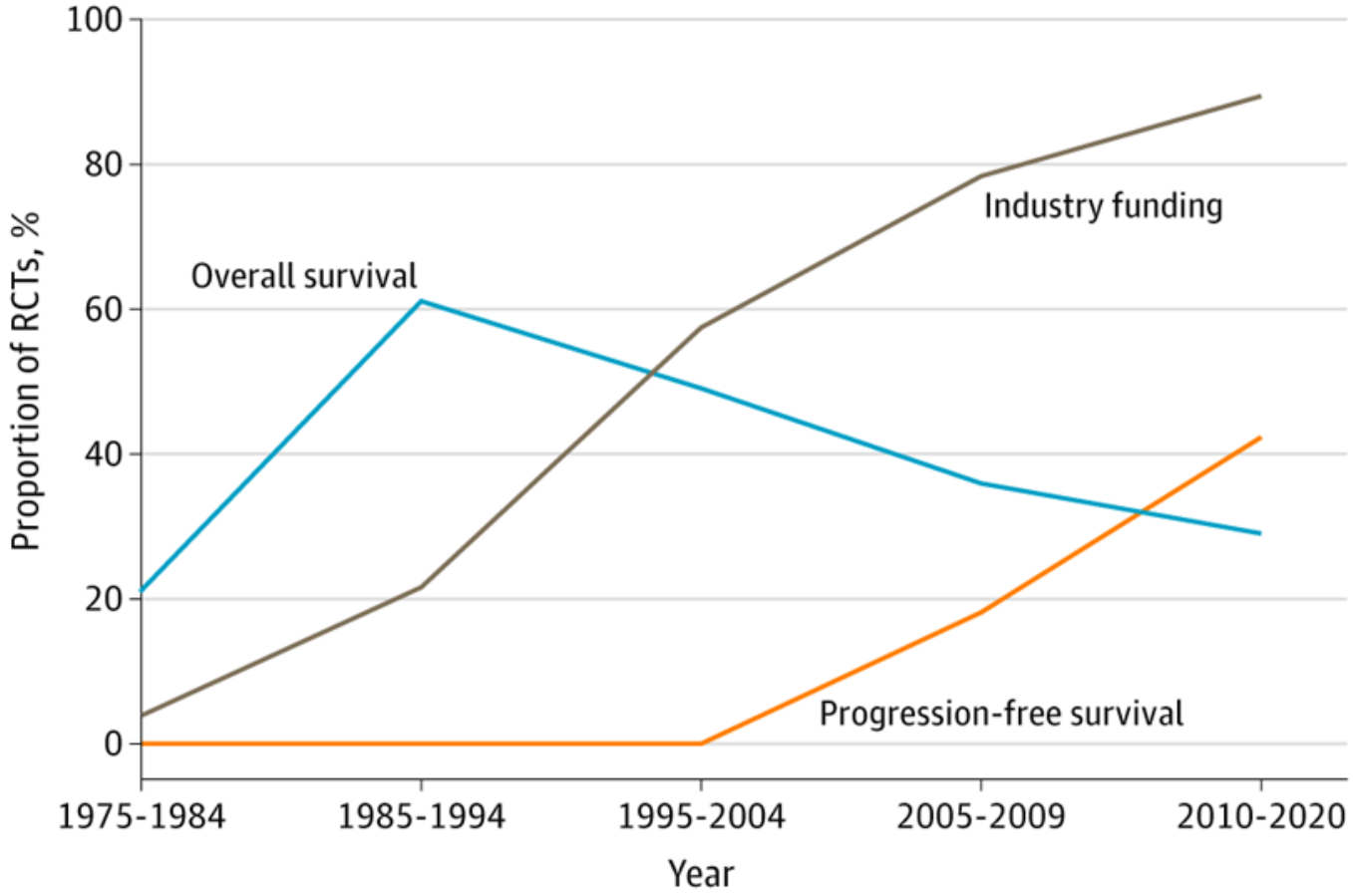
FDA's Oncologic Drugs Advisory Committee voted to oppose maintaining the accelerated approval of 2-L Nivolumab (advantage in ORR, but not in OS)

Time-dependent
Progression-Free Survival, PFS (t, mo)

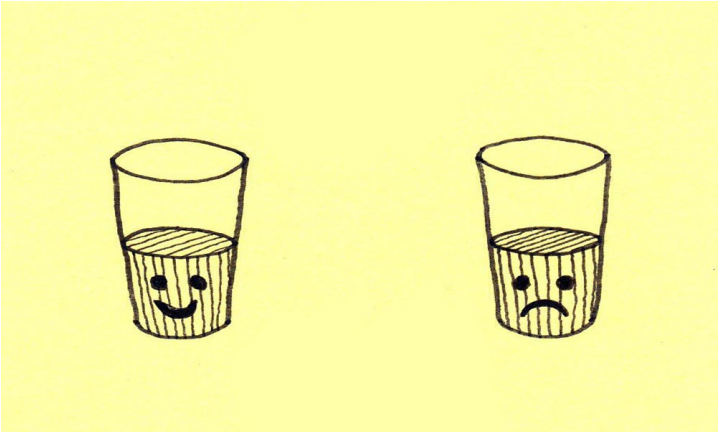
1) Is PFS accepted by regulatory agencies (FDA, EMA) as the **only primary outcome** for drug approval ?

2) Can improvement in **PFS itself** indicate patient benefit ? (surrogacy PFS→OS)

Time-dependent Progression-Free Survival, PFS (t, mo)



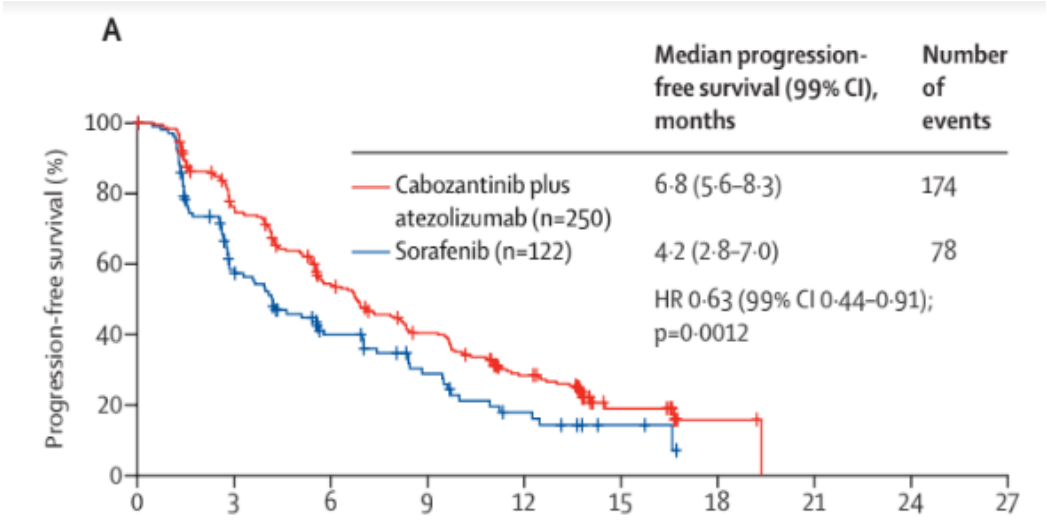
- 50% of cancer drugs approved by FDA and EMA according to PFS benefit, were shown to improve OS

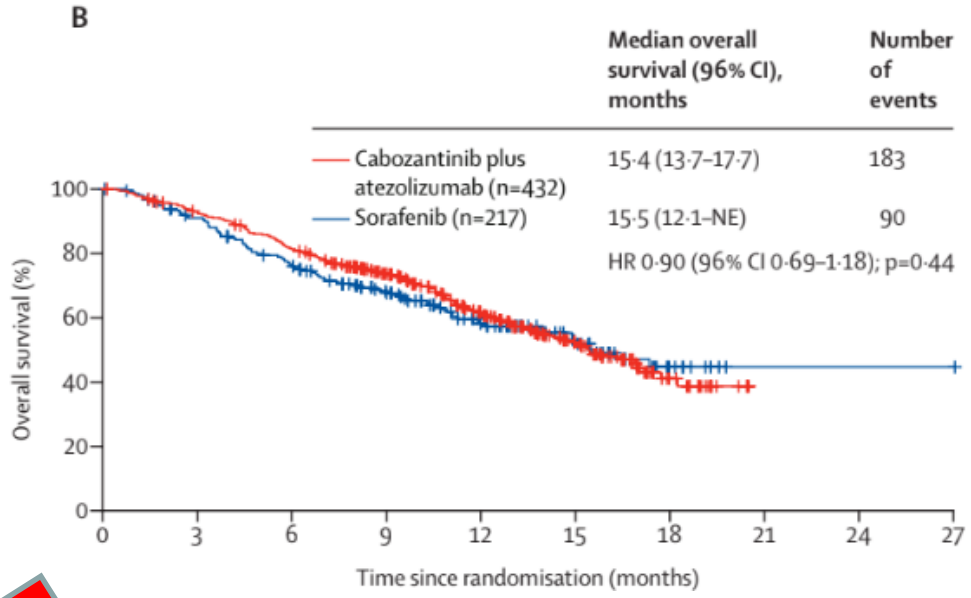


HCC setting ???

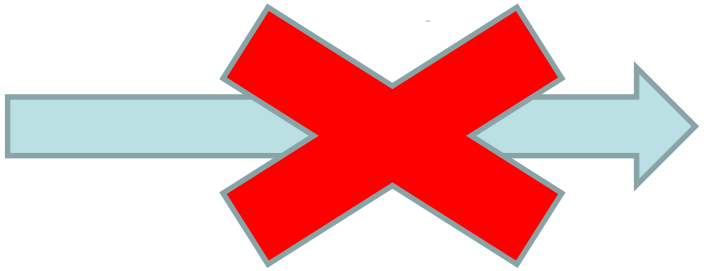
Del Paggio et al. JAMA oncology 2022

Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): a multicentre, open-label, randomised, phase 3 trial





PFS



OS

Kelley et al. Lancet Oncology 2022

Time-dependent Progression-Free Survival, PFS (t, mo)

PFS may be accepted by regulatory agencies, but…

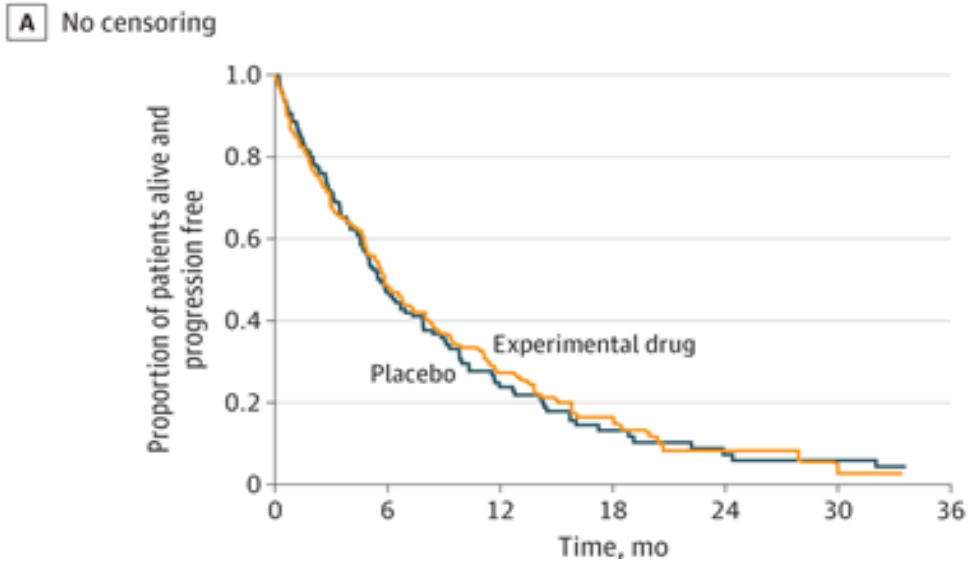
Methodological issues

1) Possible biases in evaluation of PFS

2) Competing risks (HCC setting)

1. Biased evaluation of PFS

Biased Evaluation in Cancer Drug Trials—
How Use of Progression-Free Survival as the Primary
End Point Can Mislead



SIMILAR PFS, LOW TOXICITY

Low drop-out rate for toxicity

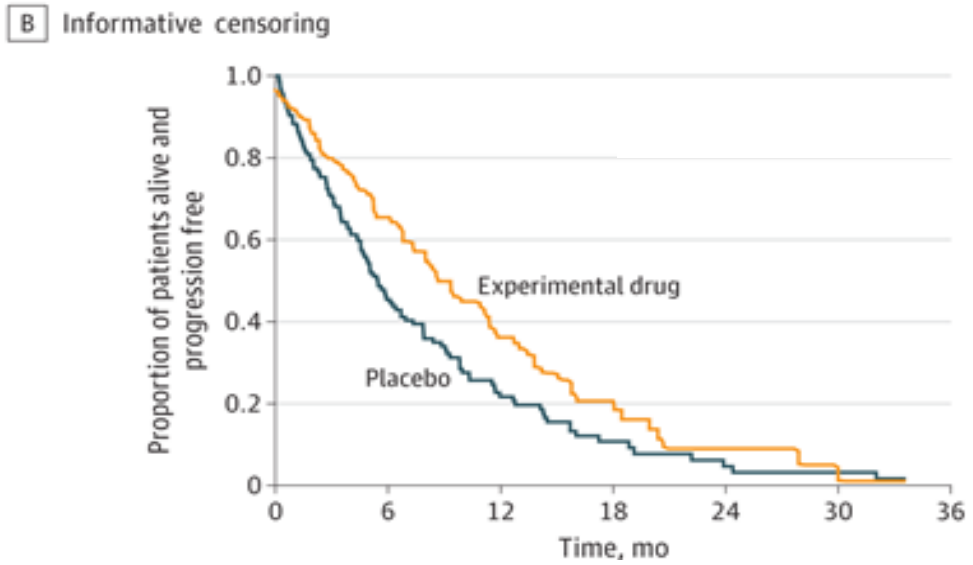
What happens with higher toxicity ?

Tannock et al. JAMA oncology 2022

1. Biased evaluation of PFS

Biased Evaluation in Cancer Drug Trials—
How Use of Progression-Free Survival as the Primary End Point Can Mislead

Toxicity but also
hepatic decompensation
in HCC setting

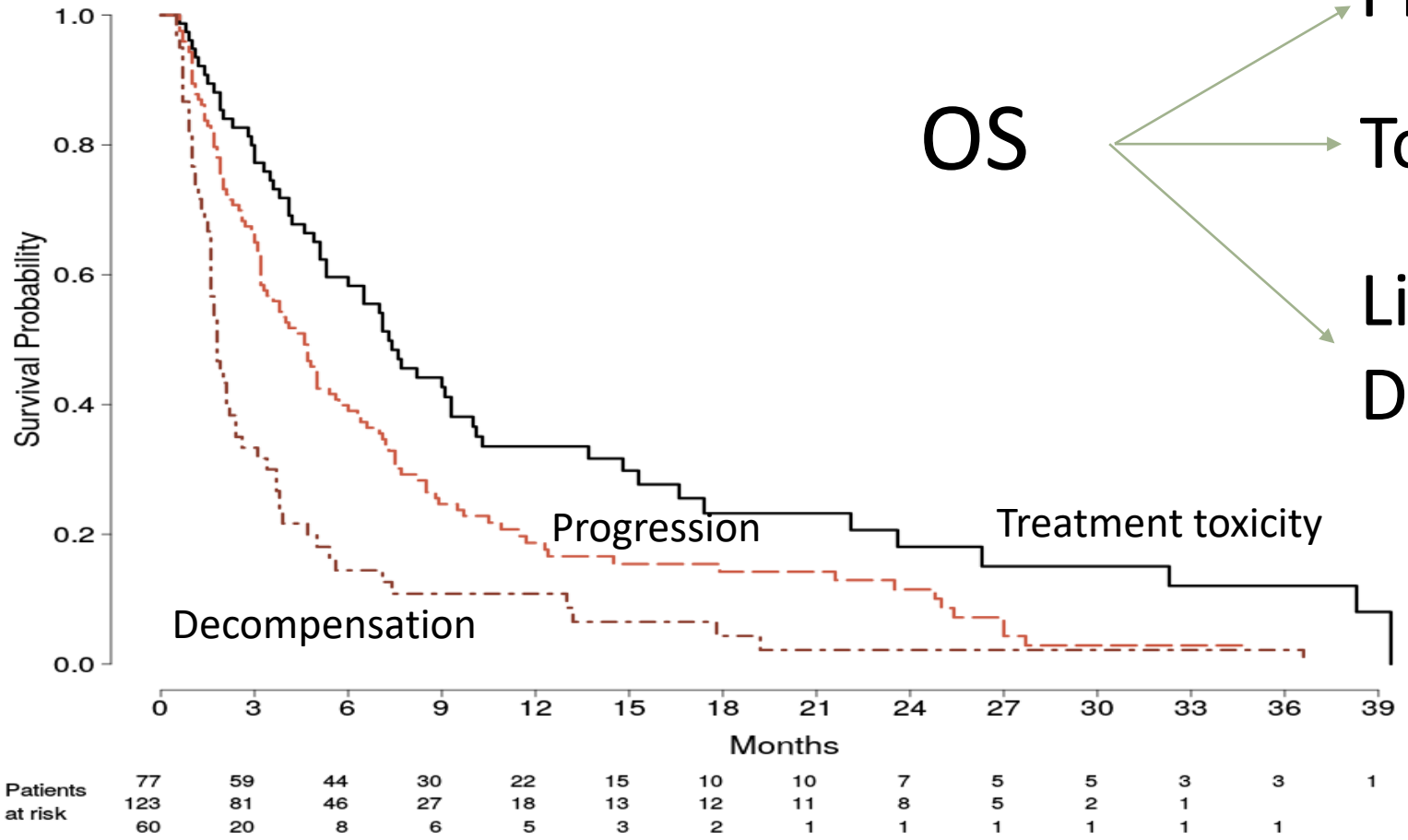


APPARENT HIGHER PFS (EFFICACY)

High drop-out rate for toxicity
before progression

Tannock et al. JAMA oncology 2022

Competing risks for overall survival



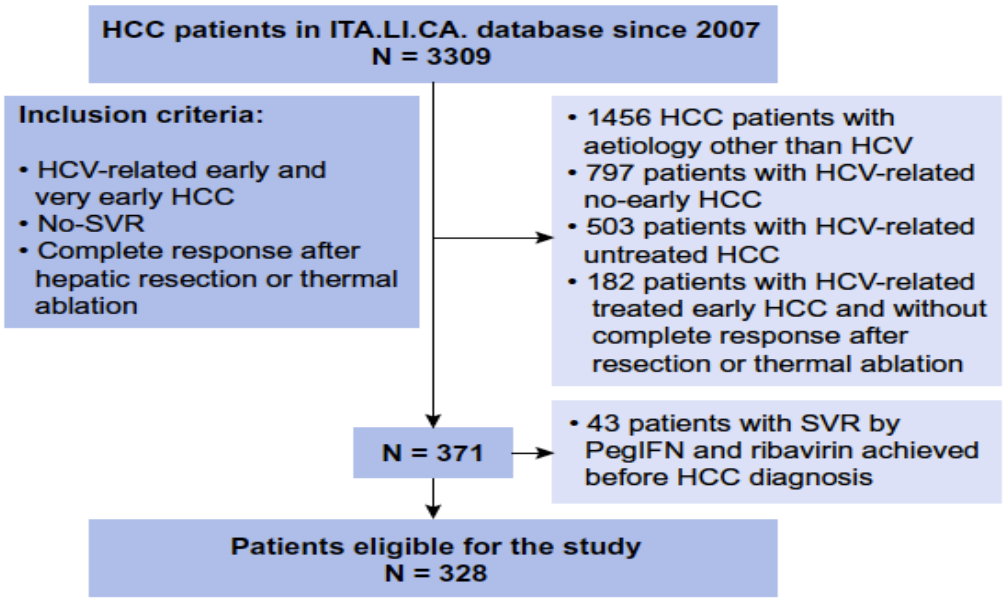
OS

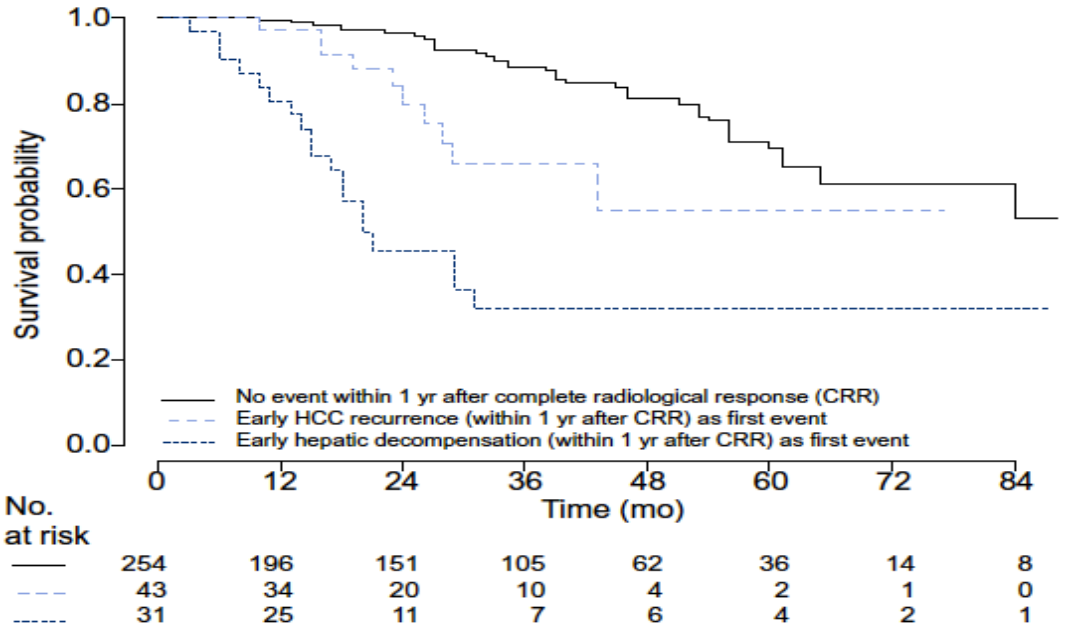
- Progression
- Toxicity
- Liver Decompensation

Iavarone, Cabibbo et al. Hepatology 2015

EASL JOURNAL OF HEPATOLOGY

Hepatic decompensation is the major driver of death in HCV-infected cirrhotic patients with successfully treated early hepatocellular carcinoma





Time dependent Cox model (MV analysis)

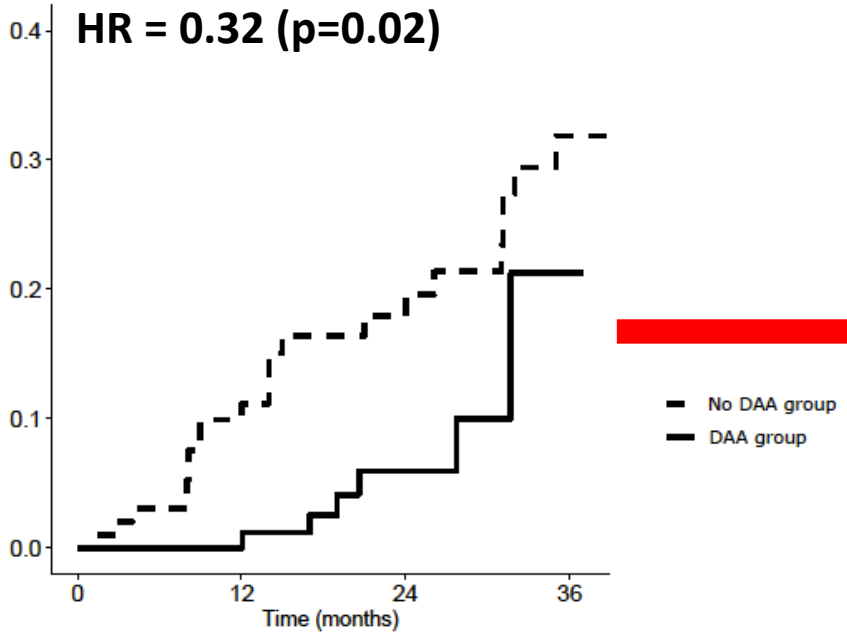
Predictor of Survival	HR	95%CI	P-value
Early recurrence	**2.5**	1.2-5.1	0.01
Early hepatic decompensation	**7.5**	4.2-13.5	<0.0001

Cabibbo G. et al, on behalf ITA.LI.CA. Group. J Hep 2017

DAAs as First Adjuvant Therapy for HCC!

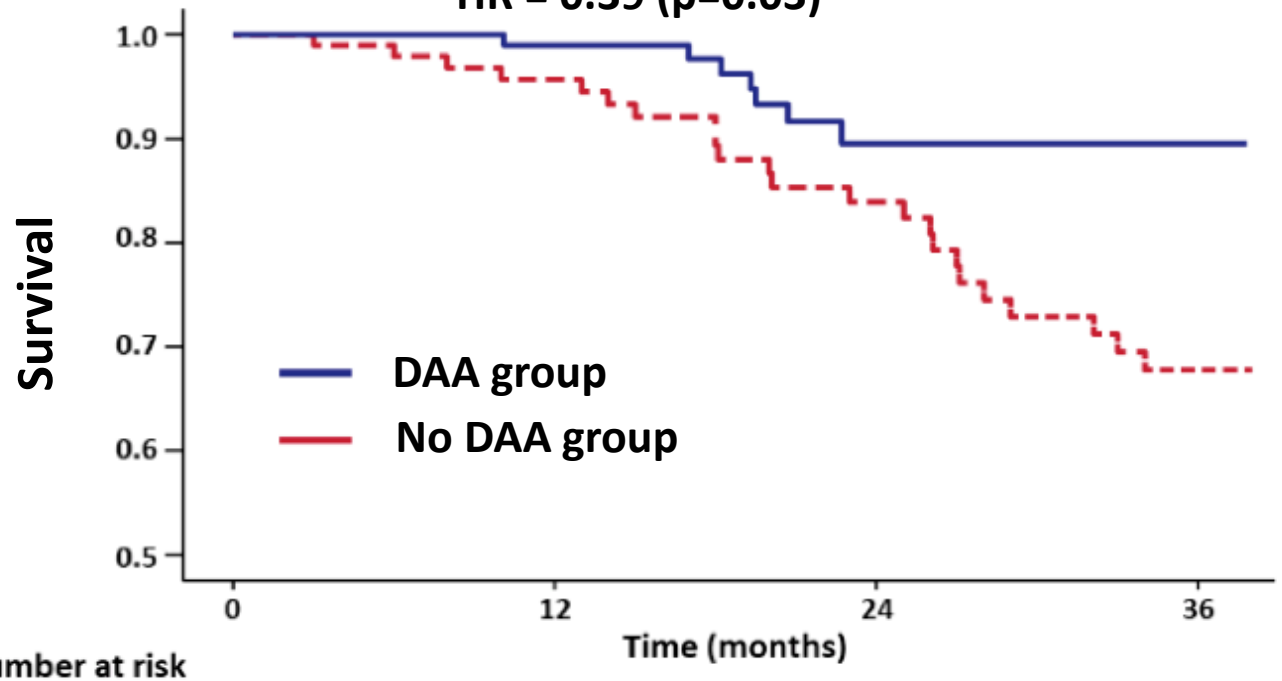
EASL | JOURNAL OF HEPATOLOGY

DAA group vs no DAA group
HR = 0.32 (p=0.02)



Number at risk				
No DAA group	102	72	50	27
DAA group	102	86	36	1

DAA group vs no DAA group
HR = 0.39 (p=0.03)

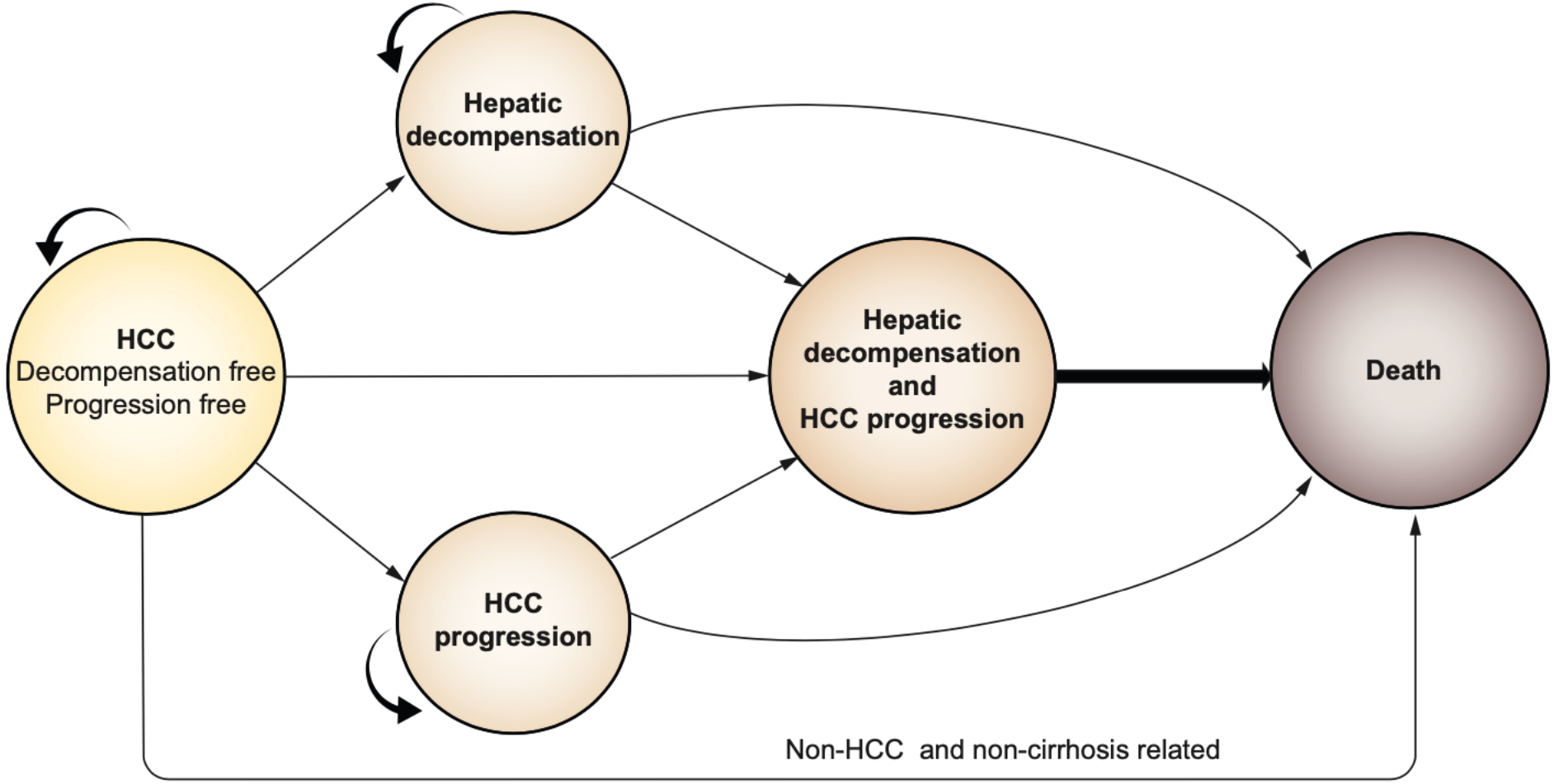


Number at risk				
DAA group	102	88	39	1
No DAA group	102	81	59	34

Improvement in overall survival seems due to significant reduction in hepatic decompensation

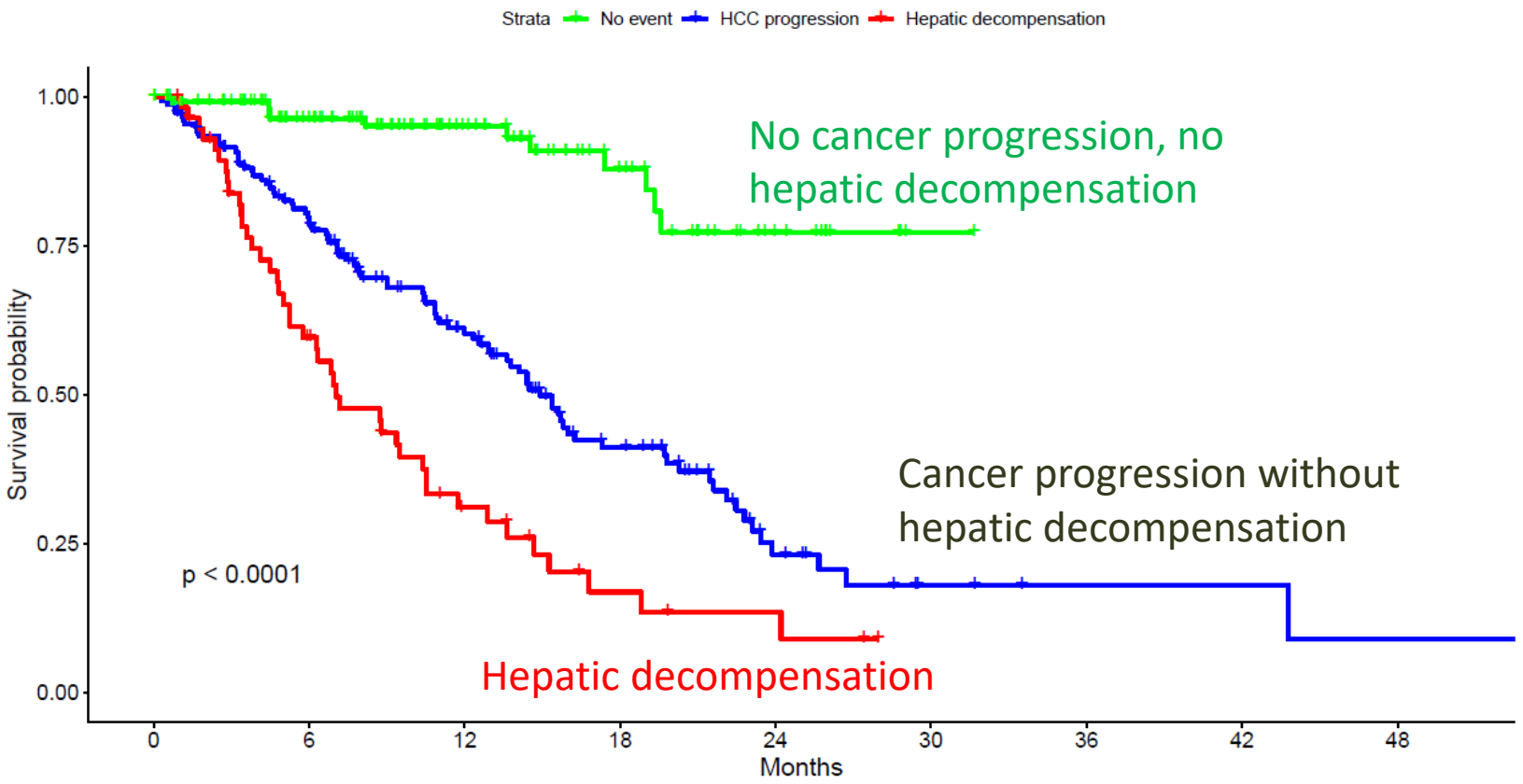
Cabibbo, Celsa et al, on behalf RESIST-HCV & ITA.LI.CA. J Hep 2019

Competing risks for overall survival



Reig M & Cabibbo G, J Hep 2021
Cabibbo, Celsa et al. Lancet Oncology, 2022

Competing risks for overall survival



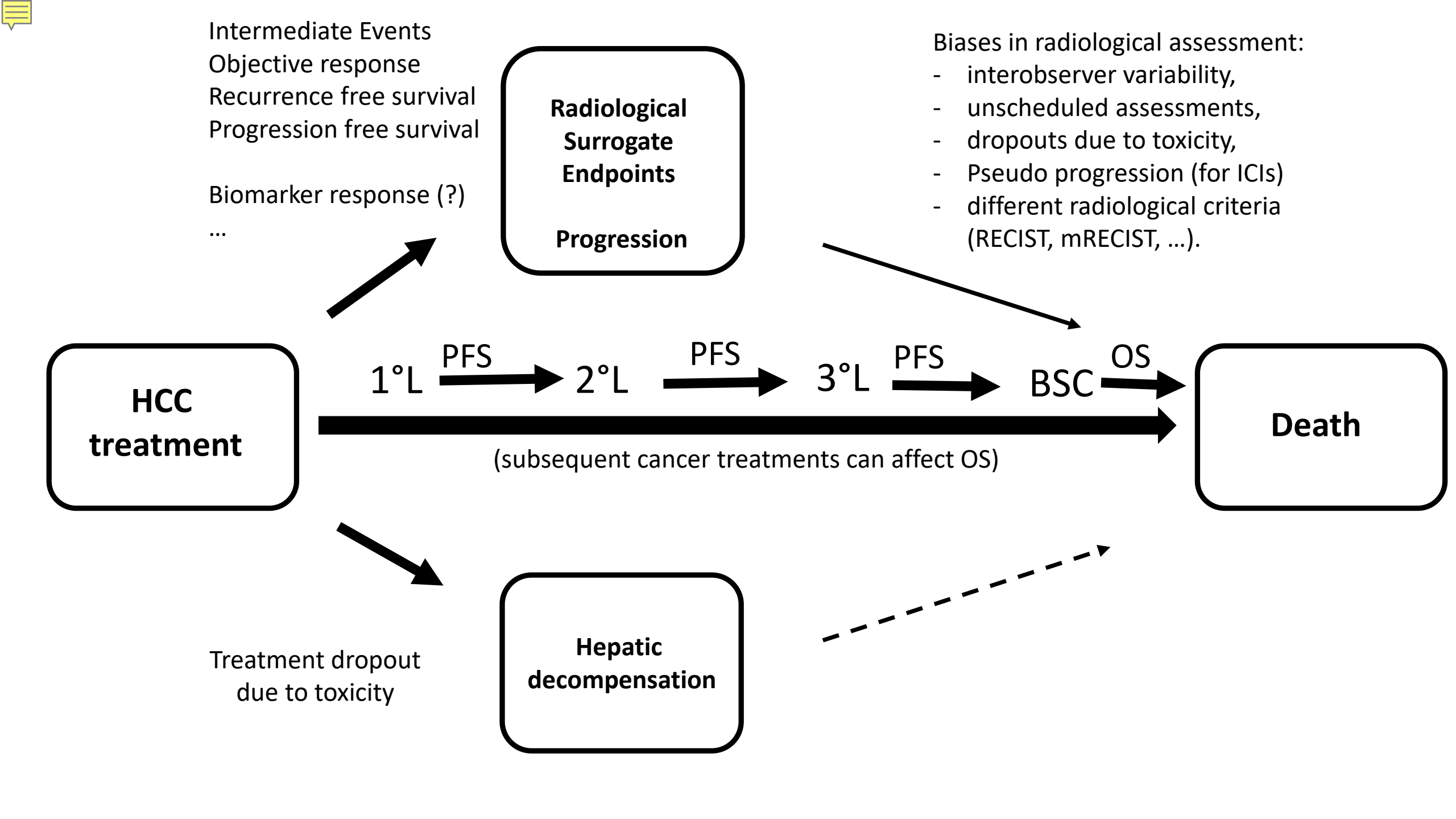
Hepatic decompensation is the main driver of death also in advanced stage, although is completely neglected in clinical trials

346 patients with HCC and Child-Pugh A cirrhosis treated with AtezoBeva in clinical practice setting

Celsa, Cabibbo, et al. Under review

Systemic therapies for HCC 2024

Target population	EARLY STAGE WITH HIGH RISK OF RECURRENCE	HCC ELIGIBLE TO TACE	ADVANCED HCC
Treatments	Adjuvant AtezoBeva after resection or ablation	Durva+Beva with TACE	AtezoBeva DurvaTreme Durvalumab (?) Lenvatinib AtezoBevaTira (?)
Primary endpoint	Recurrence-free survival **++**	Progression-free survival **+/- ?**	Overall survival **+++**


Intermediate Events
Objective response
Recurrence free survival
Progression free survival
Biomarker response (?)
…
Radiological Surrogate Endpoints
Progression
Biases in radiological assessment:
- interobserver variability,
- unscheduled assessments,
- dropouts due to toxicity,
- Pseudo progression (for ICIs)
- different radiological criteria (RECIST, mRECIST, …).
HCC treatment
1°L
PFS
2°L
PFS
3°L
PFS
BSC
OS
Death
(subsequent cancer treatments can affect OS)
Treatment dropout due to toxicity
Hepatic decompensation

Sequential treatments

Optimizing Sequential Systemic Therapies for Advanced Hepatocellular Carcinoma: A Decision Analysis

Giuseppe Cabibbo [1,†], Ciro Celsa [1,2,†], Marco Enea [3], Salvatore Battaglia [4], Giacomo Emanuele Maria Rizzo [1], Stefania Grimaudo [1], Domenica Matranga [3], Massimo Attanasio [4], Paolo Bruzzi [5], Antonio Craxì [1] and Calogero Cammà [1,*]

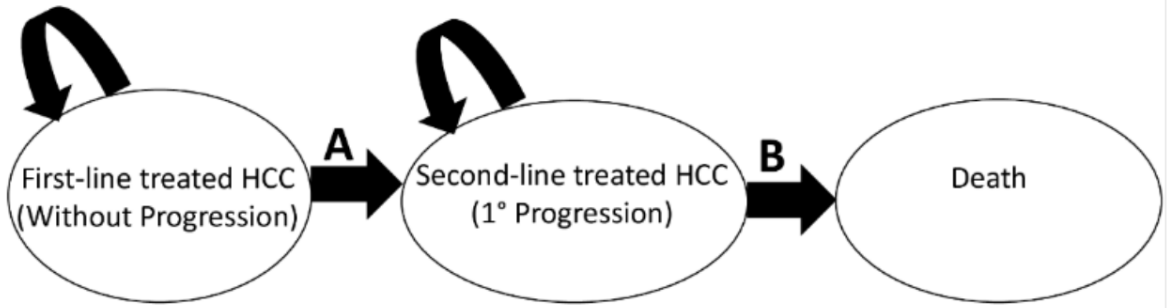
First-line agents

- Sorafenib
- Lenvatinib
- Atezolizumab + Bevacizumab

Second-line agents

- Regorafenib
- Cabozantinib
- Ramucirumab
- Nivolumab
- Pembrolizumab

Structure of Markov Model



A: Progression Free Survival of first-line. B: Overall survival of second-line.

TKI 1L → ICI 2L

Treatment Sequence	Median OS (mo)
Lenvatinib-Nivolumab	27
Lenvatinib-Pembrolizumab	25
Atezolizumab plus Bevacizumab-Nivolumab	24
Sorafenib-Nivolumab	23
Atezolizumab plus Bevacizumab-Pembrolizumab	23
Lenvatinib-Ramucirumab	22
Lenvatinib-Regorafenib	22
Lenvatinib-Cabozantinib	22
Sorafenib-Pembrolizumab	20
Atezolizumab plus Bevacizumab-Ramucirumab	20
Atezolizumab plus Bevacizumab-Regorafenib	20
Atezolizumab plus Bevacizumab-Cabozantinib	20
Sorafenib-Cabozantinib	18
Sorafenib-Regorafenib	18
Sorafenib-Ramucirumab	18

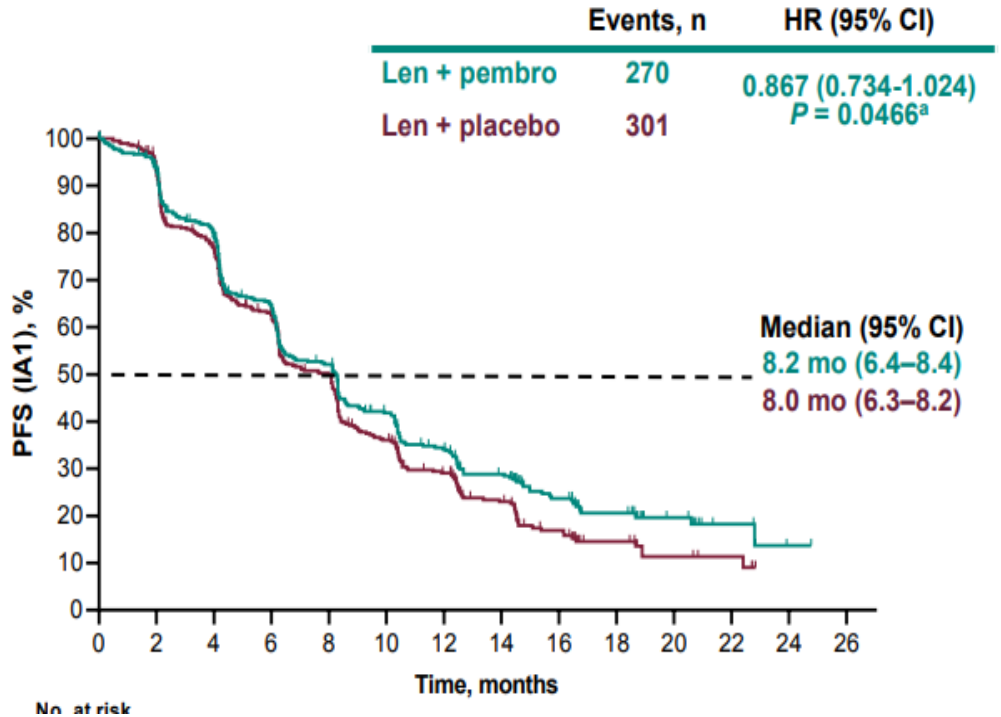
CHANGE THE CLASS!

Cabibbo, Celsa et al. Cancers 2020

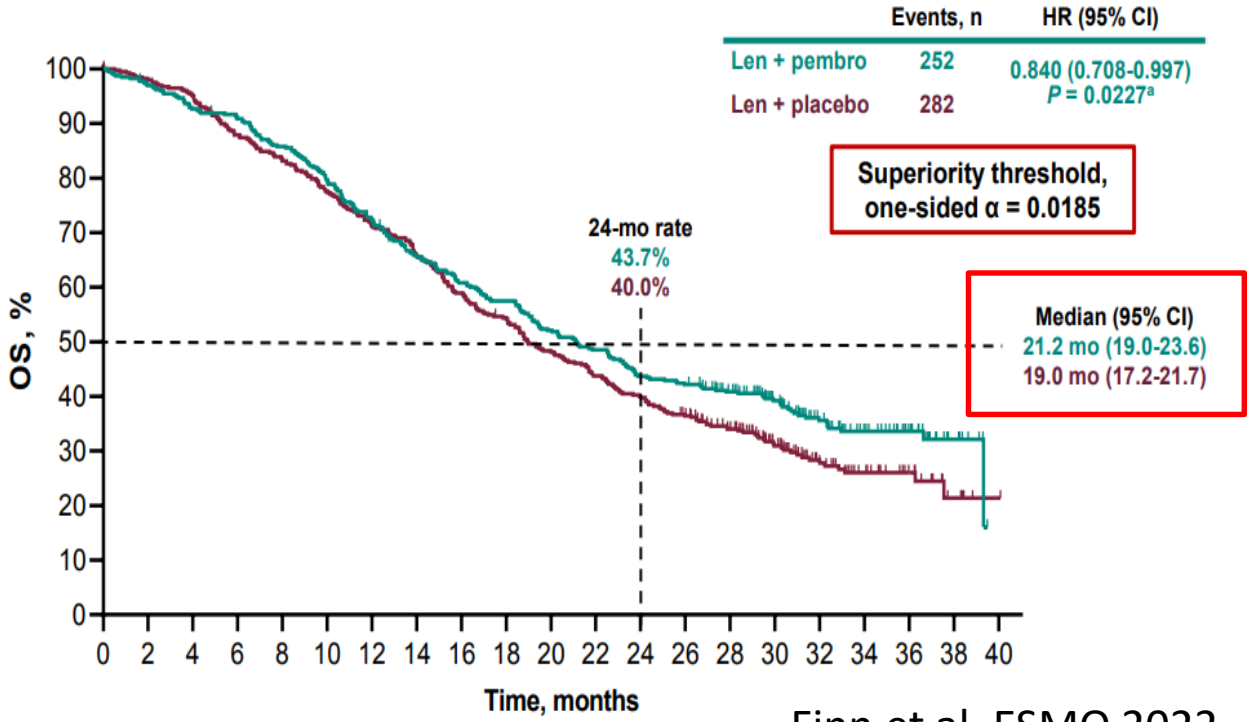
Sequential treatments

Primary Results From the Phase 3 LEAP-002 Study: Lenvatinib Plus Pembrolizumab Versus Lenvatinib as First-line Therapy for Advanced Hepatocellular Carcinoma

PFS



OS



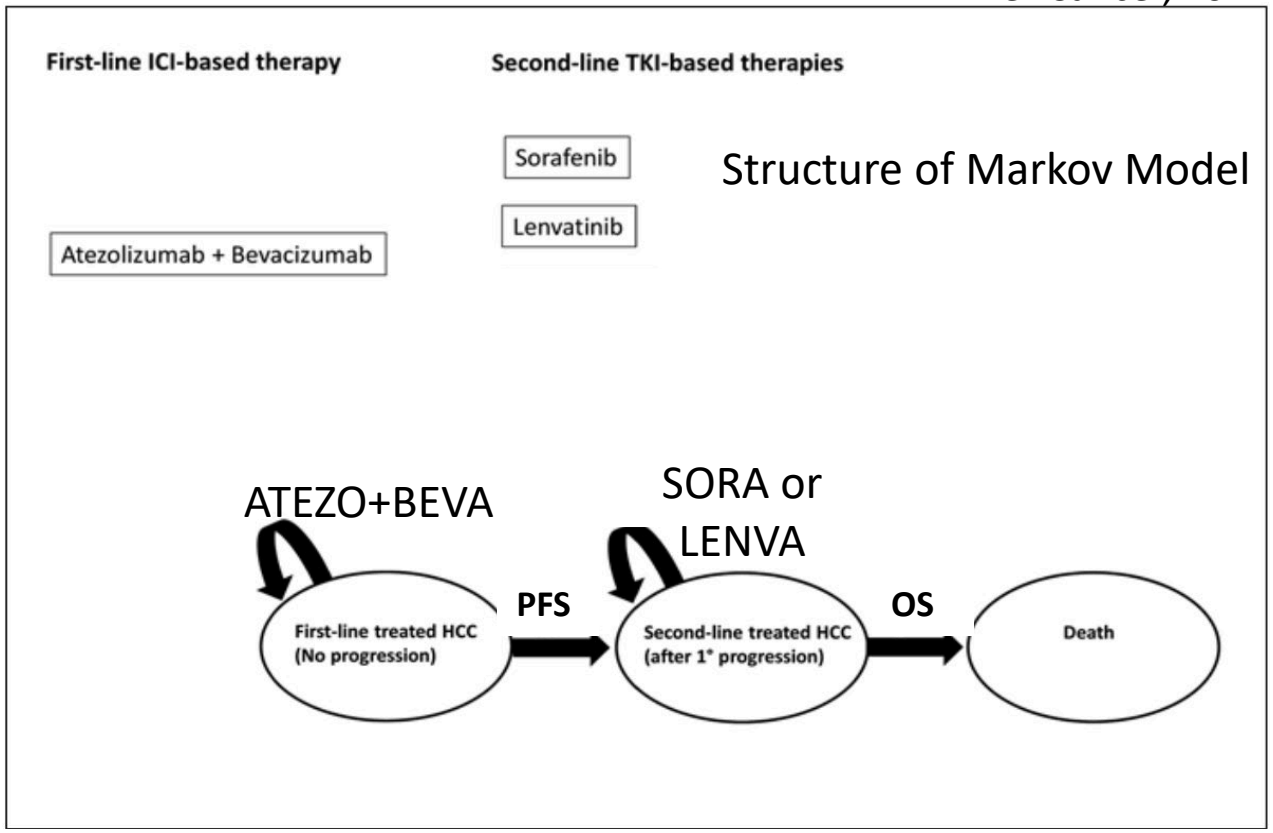
Finn et al. ESMO 2022

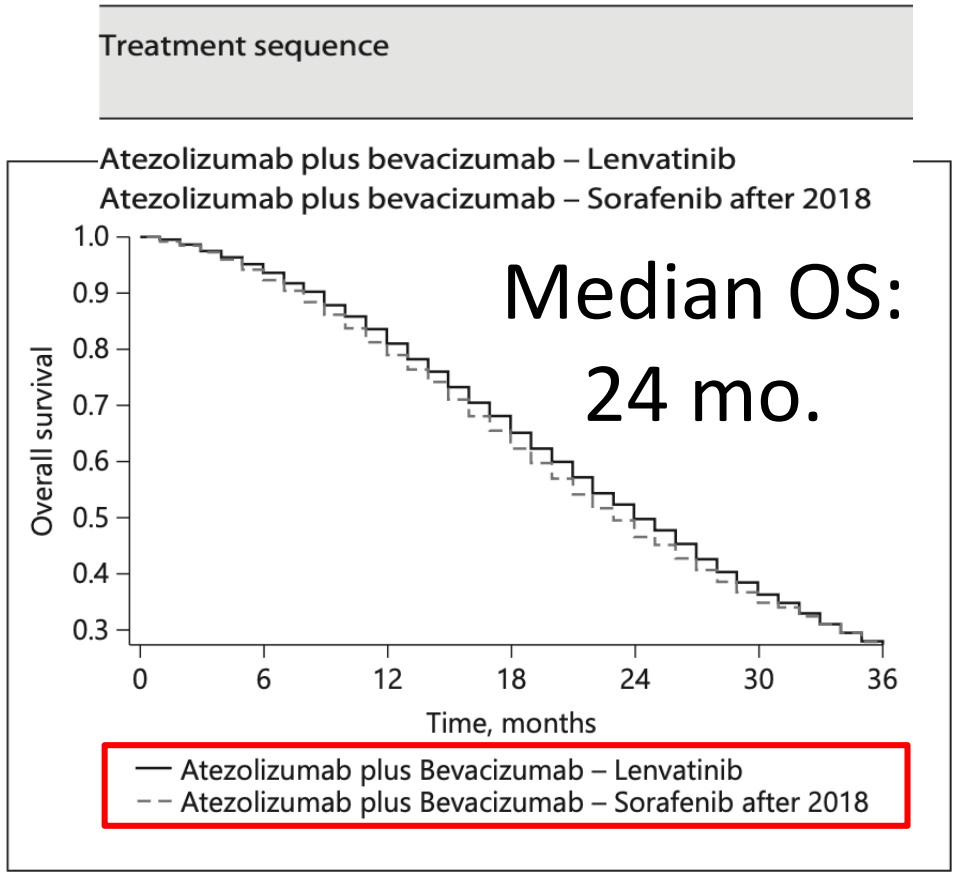
Sequential treatments

First-Line Immune Checkpoint Inhibitor-Based Sequential Therapies for Advanced Hepatocellular Carcinoma: Rationale for Future Trials

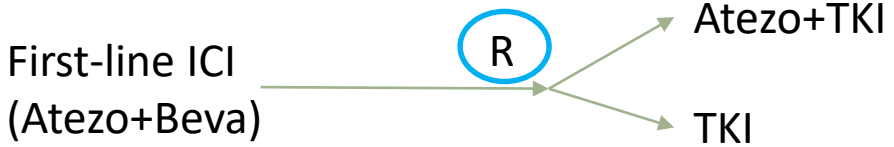
Giuseppe Cabibbo[a] Maria Reig[b] Ciro Celsa[a,c] Ferran Torres[d,e]
Salvatore Battaglia[f] Marco Enea[g] Giacomo Emanuele Maria Rizzo[a]
Salvatore Petta[a] Vincenza Calvaruso[a] Vito Di Marco[a] Antonio Craxì[a]
Amit G. Singal[h] Jordi Bruix[b] Calogero Cammà[a]

Liver Cancer, 2021





IMBrave 251 (NCT04770896)

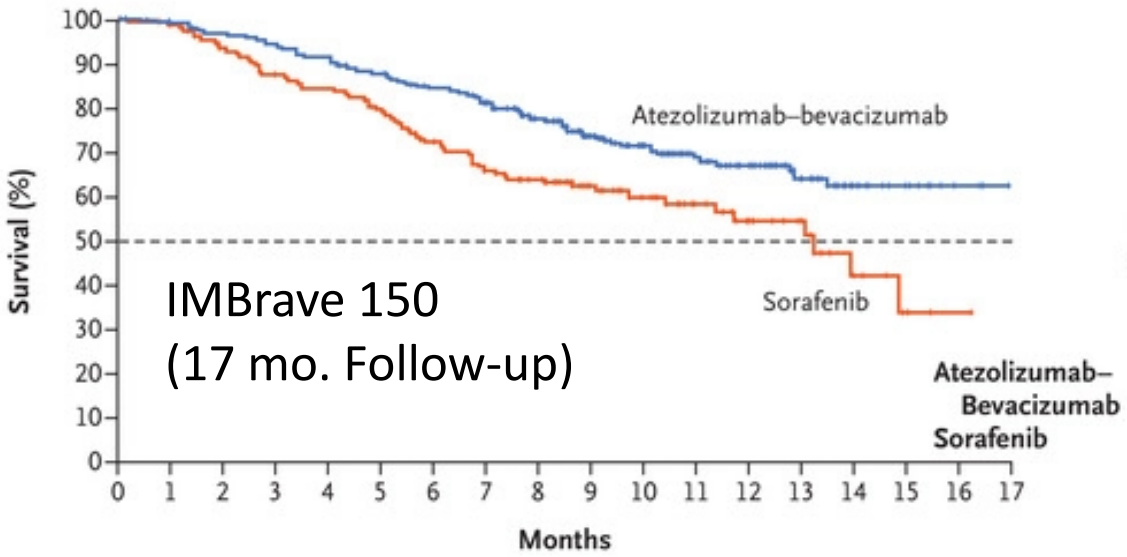


Sequential treatments

Failure of first-line for:

- HCC progression (w/preserved liver function) → CHANGE THE CLASS!
- Adverse events (w/good ECOG-PS) → CHANGE THE CLASS!
- Liver decompensation →

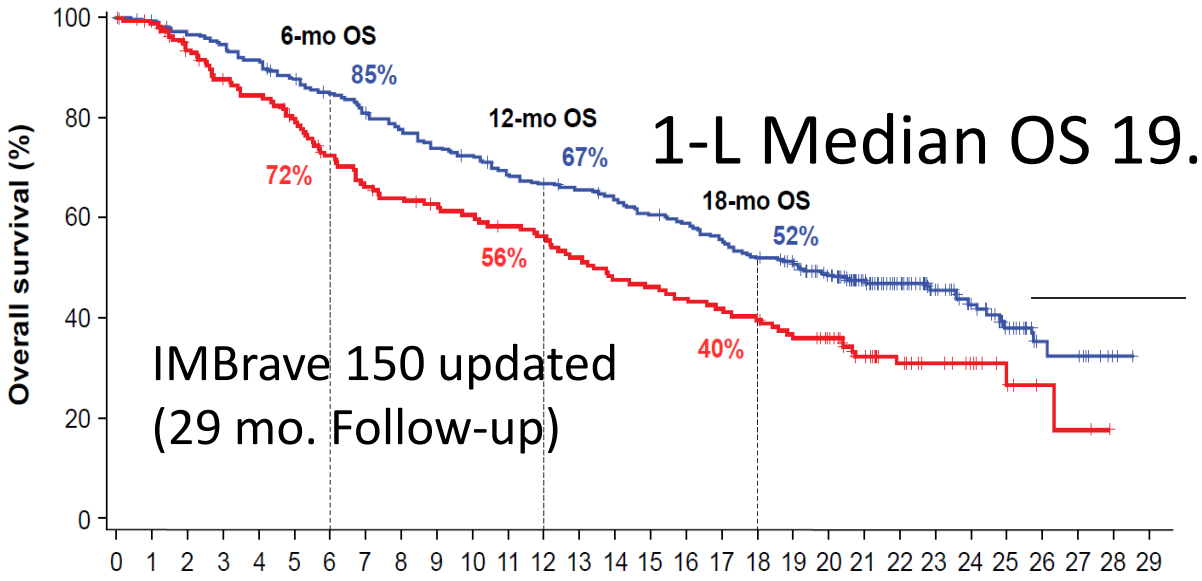
Hazard Ratio
Proportional HR



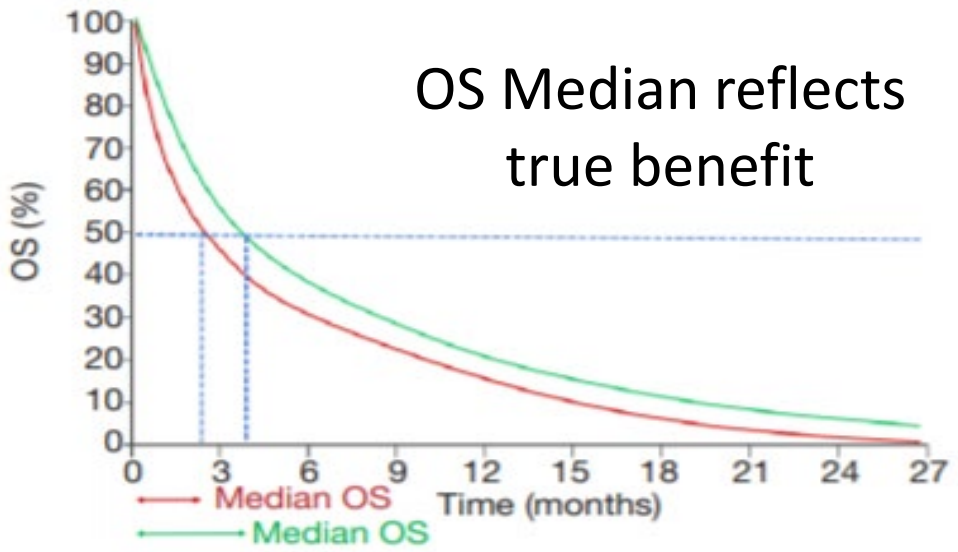
Constant efficacy over time

↓

True benefit



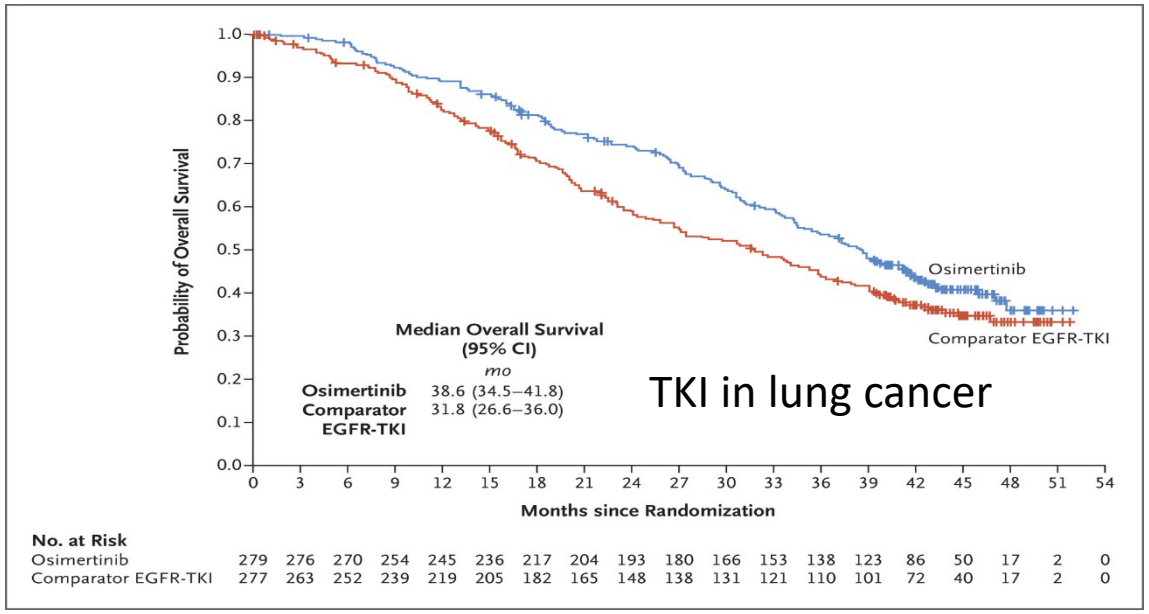
1-L Median OS 19.2 mo.



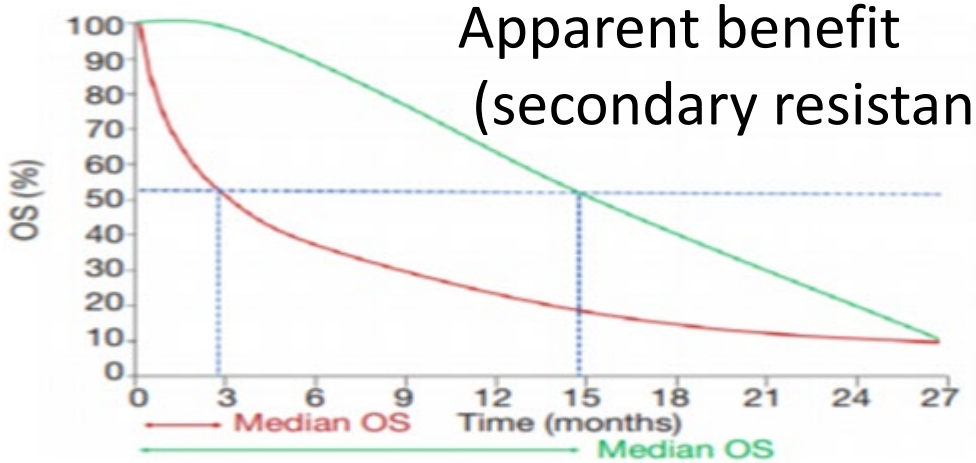
OS Median reflects true benefit

Finn et al. NEJM 2020, Cheng et al. JHep, 2021. Ferrara et al. J Thorac Dis 2018

Hazard Ratio
Non Proportional HR

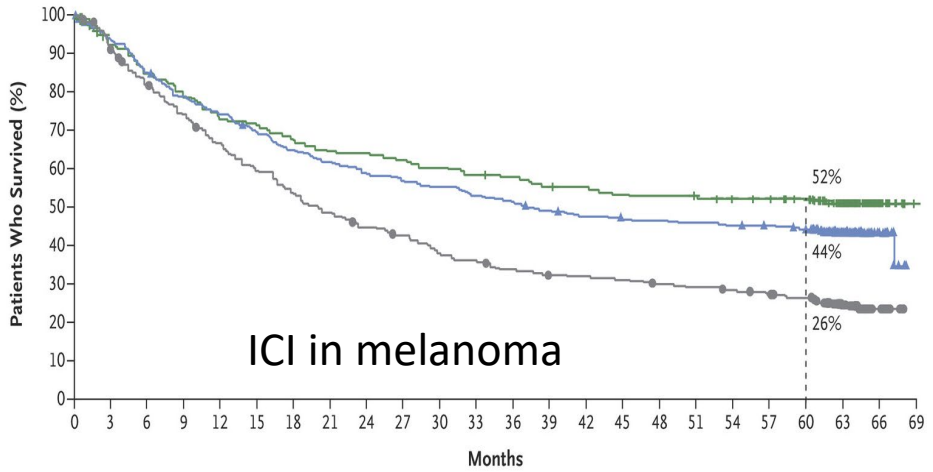


TKI in lung cancer

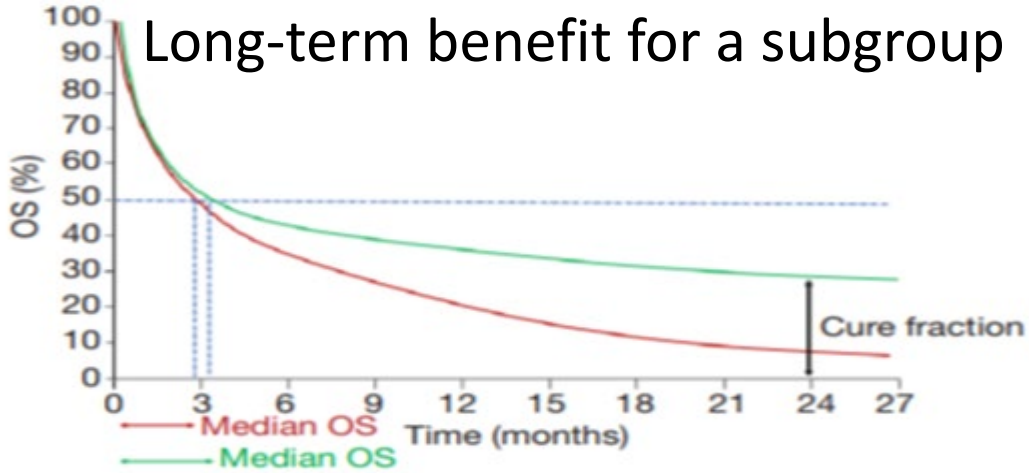


Apparent benefit
(secondary resistance?)

A Overall Survival



ICI in melanoma



Long-term benefit for a subgroup

Ramalingam et al. NEJM 2020, Larkin et al. NEJM 2019 Ferrara et al. J Thorac Dis 2018

Hazard of Hazard Ratio

Nonproportional Hazards for Time-to-Event Outcomes in Clinical Trials

JACC Review Topic of the Week

John Gregson, PhD,[a] Linda Sharples, PhD,[a] Gregg W. Stone, MD, PhD,[b,c] Carl-Fredrik Burman, PhD,[d] Fredrik Öhrn, PhD,[d] Stuart Pocock, PhD[a]

ABSTRACT

Most major clinical trials in cardiology report time-to-event outcomes using the Cox proportional hazards model so that a treatment effect is estimated as the hazard ratio between groups, accompanied by its 95% confidence interval and a log-rank p value. But nonproportionality of hazards (non-PH) over time occurs quite often, making alternative analysis strategies appropriate. This review presents real examples of cardiology trials with different types of non-PH: an early treatment effect, a late treatment effect, and a diminishing treatment effect. In such scenarios, the relative merits of a Cox model, an accelerated failure time model, a milestone analysis, and restricted mean survival time are examined. Some post hoc analyses for exploring any specific pattern of non-PH are also presented. Recommendations are made, particularly regarding how to handle non-PH in pre-defined Statistical Analysis Plans, trial publications, and regulatory submissions. (J Am Coll Cardiol 2019;74:2102–12) © 2019 by the American College of Cardiology Foundation.

- Nonproportionality of hazard occurs often
- Alternative methodologies

Take home messages

ORR

- ORR is useful to assess drug activity and for downstaging

PFS

- Surrogacy between PFS and OS is heterogeneous, depending on type of cancer and class of drug
- PFS may be useful when sequential treatments are available
- A rigorous interpretation of PFS needs new studies methodology and radiological standard (radiomics?)

Take home messages

OS

- OS is the hardest primary endpoint, but associating PFS and OS as co-primary endpoints may support evidence of treatment effect

- Innovative measures of net benefit capturing death, cancer progression, liver decompensation, drug toxicity and patient-reported outcomes should be **routinely collected** both in registrative trials and clinical practice

Principio di complementarietà

Possiamo dire davvero che **culture umane diverse** sono **complementari** le une rispetto alle altre.

Oggi che i destini di tutti i popoli sono così **inseparabilmente connessi** una collaborazione svolta nella fiducia reciproca, basata sulla piena valutazione di ogni aspetto della condizione umana, è più necessaria di quanto non lo sia mai stata nella storia dell'umanità.

Niels Bohr, 1927