2° THE PITER MEETING

Uno strumento per produrre evidenze *"real-life"*
nell'ambito delle epatiti virali croniche in Italia

LO STUDIO PROSPETTICO DI HCC DI TUTTE LE EZIOLOGIE

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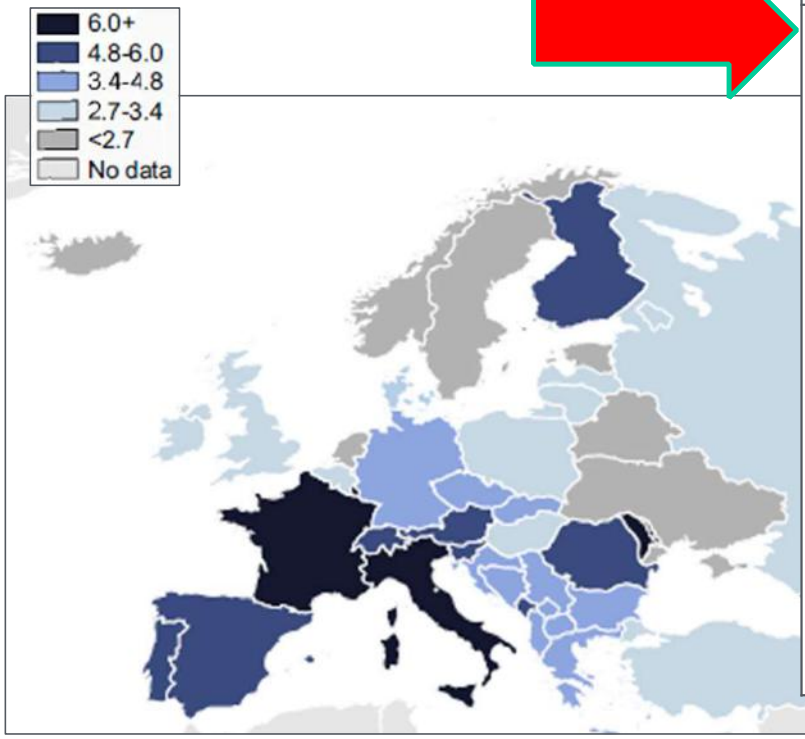
Hepatocellular carcinoma (HCC): Introduction

- high rate of mortality;
- strictly associated with chronic liver disease, mainly cirrhosis;
- biological and clinical heterogeneity and wide prognosis.

Incidence of primary liver cancer in Europe

Incidence rates per 100,000



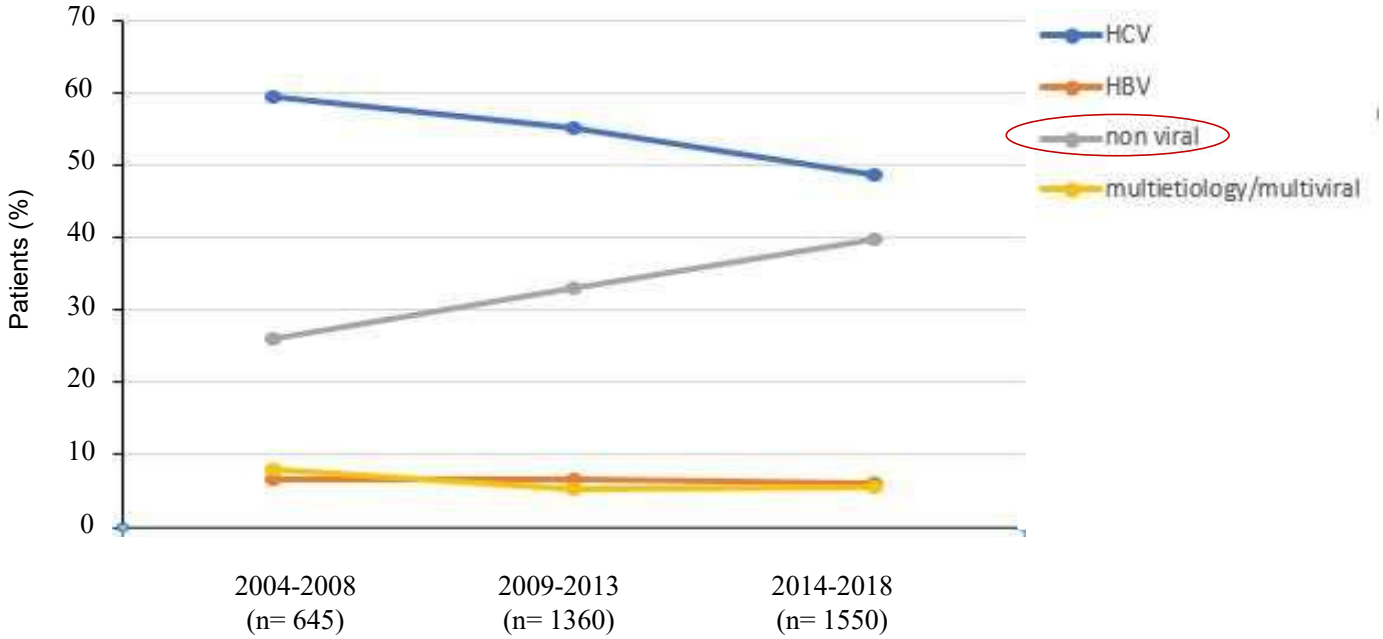
Total number per country	
Italy 10,733	**The Netherlands** 475
Germany 9,202	**Croatia** 466
France (metropolitan) 8,332	**Republic of Moldova** 448
Russian Federation 6,812	**Slovakia** 398
Spain 5,522	**Belarus** 327
United Kingdom 4,186	**Bosnia Herzegovina** 314
Romania 2,214	**Denmark** 311
Poland 1,998	**Ireland** 239
Ukraine 1,567	**Slovenia** 216
Greece 1,054	**Norway** 190
Portugal 1,004	**Lithuania** 175
Austria 955	**Albania** 171
Czech Republic, 919	**Latvia** 154
Switzerland 811	**FYR Macedonia** 135
Serbia 799	**Luxembourg** 68
Belgium 645	**Estonia** 64
Bulgaria 640	**Cyprus** 56
Hungary 630	**Montenegro** 51
Finland 620	**Malta** 19
Sweden 490	**Iceland** 10

EASL CPG HCC. J Hep 2018

Evolving aetiology of HCC

(ITA.LI.CA database 2018)

Patients aged ≤65 years (n. 2260)



Garuti F et al., for ITA.LI.CA, Liver Int 2021; 41: 585-597

EASL CPG: Management of hepatocellular carcinoma

Table 3. Recommendations for HCC surveillance: Categories of adult patients in whom surveillance is recommended.

- Cirrhotic patients, Child-Pugh stage A and B (**evidence low; recommendation strong**)
- Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation (**evidence low; recommendation strong**)
- Non-cirrhotic HBV patients at intermediate or high risk of HCC* (according to PAGE-B† classes for Caucasian subjects, respectively 10–17 and ≥18 score points) (**evidence low; recommendation weak**)
- Non-cirrhotic F3 patients, regardless of aetiology may be considered for surveillance based on an individual risk assessment (**evidence low; recommendation weak**)

J Hep 2018

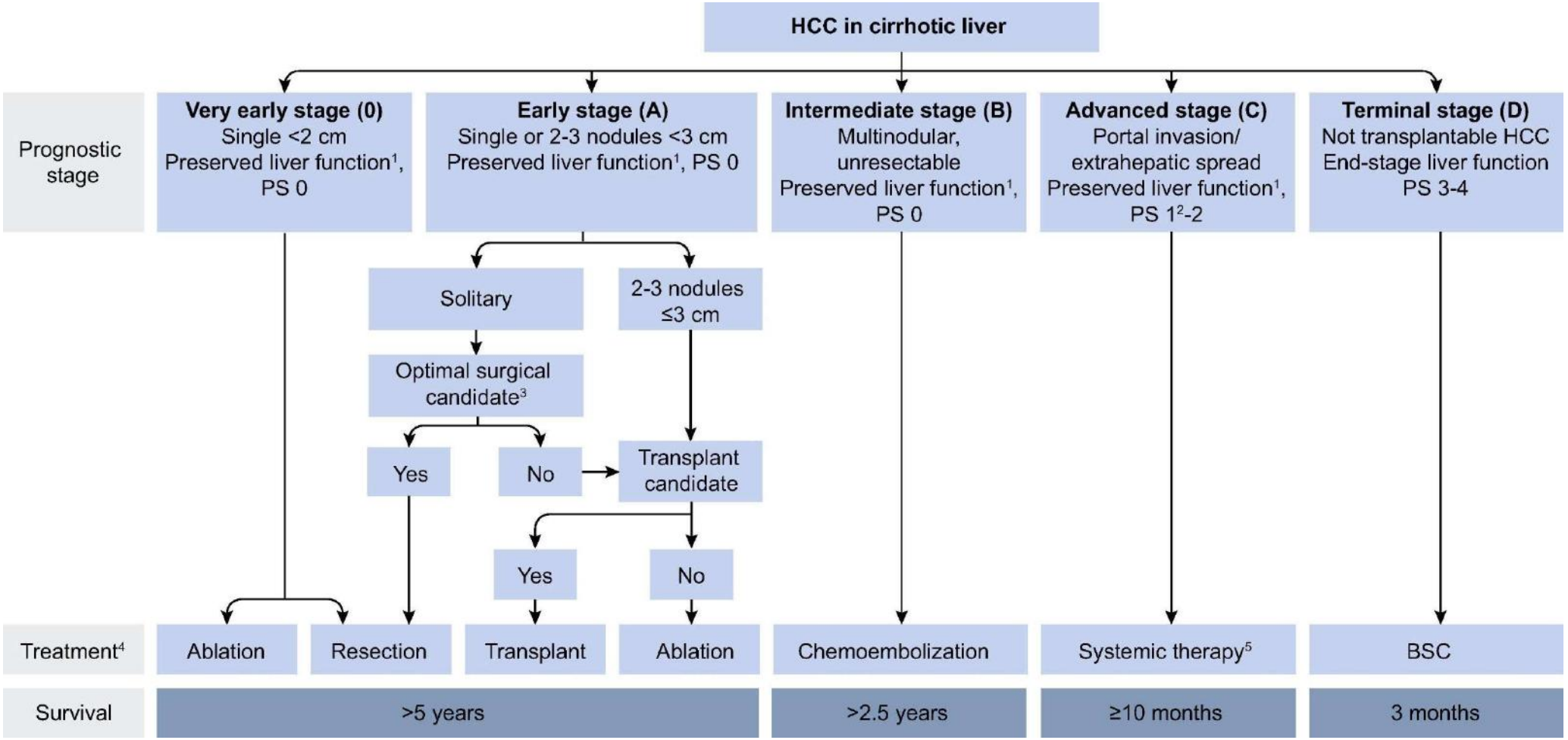
The Barcelona Clinic Liver Cancer (BCLC) Staging Classification for HCC

	BCLC stage	Performance status	Tumor volume, number and invasiveness	Child-Pugh
0	Very early	0	Single < 2 cm	A
A	Early	0	Single or 3 nodules < 3 cm	A – B
B	Intermediate	0	Large/Multinodular	A – B
C	Advanced	1 – 2	Portal invasion and/or Extrahepatic spread N1M1	A – B
D	Terminal	> 2	Any of above	C

Llovet JM et al. J Gastroenterol 2005; 40: 225-235

AFP (?!?!?)

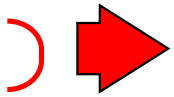
EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma 2018



European Association for the Study of the Liver, J Hepatol 2018

Surgical Resection

- **Optimal candidates:**
  - **BCLC stage 0 or A**
    - Child-Pugh A
    - Performance status 0
    - Single tumors
    - Normal portal pressure
    - Normal bilirubin
  - **Excellent functional reserve**



5-year survival 60-70%

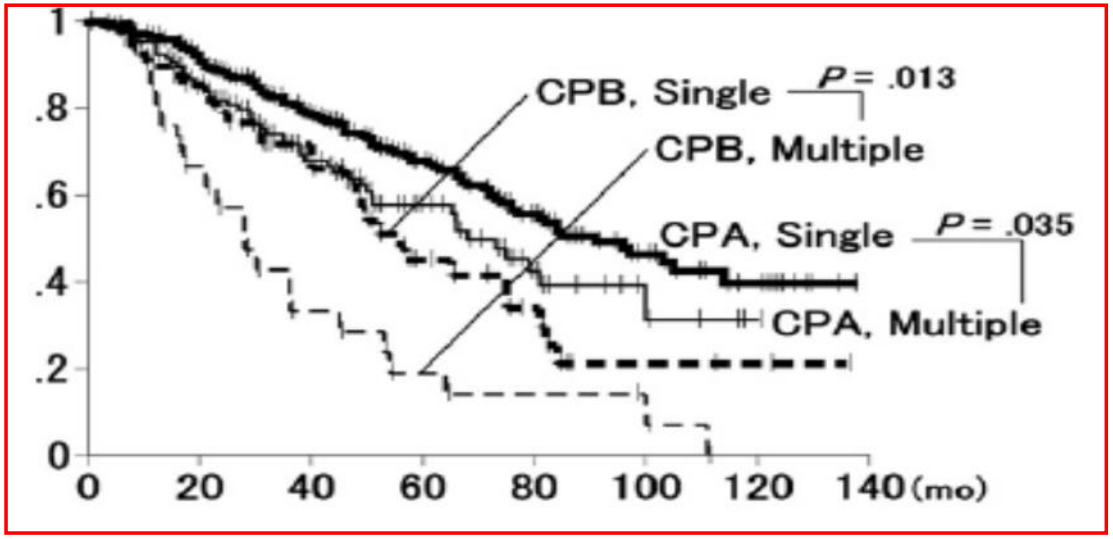
High recurrence rate
50% at 3 years
70% at 5 years

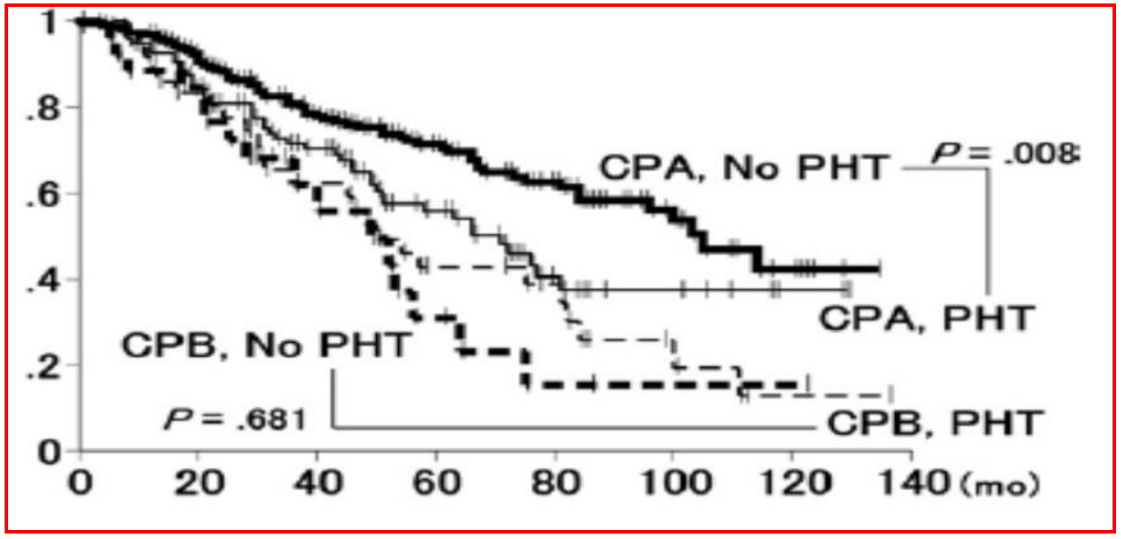
- **Too restrictive in real life: > 50% are above….**

Bruix J et al. Hepatology 2005; Llovet JM. J Gastroenterol 2005; Forner A et al Nat Rev Clin Oncol 2014

Neither Multiple Tumors Nor Portal Hypertension Are Surgical Contraindications for Hepatocellular Carcinoma

GASTROENTEROLOGY 2008





Child A patients		5-yr survival
Multiple	(126)	58%
Single	(308)	68%

Child A patients		5-yr survival
PTH	(136)	56%
No PTH	(250)	71%

Ishizawa T, et al. Gastroenterology 2008

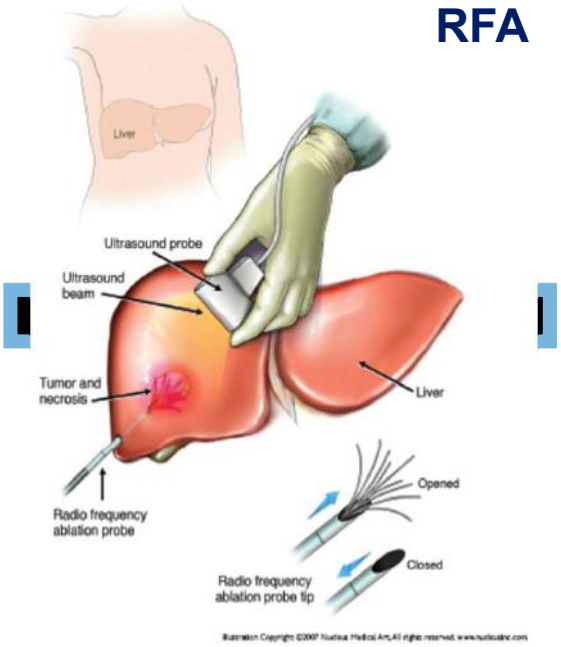
Ablation Therapies

Therapeutic Options

Advantage	Minimally invasive, easily repeatable
Disadvantage	Higher recurrence risk with respect to resection

- Radiofrequency ablation (RFA); MW ablation
- Percutaneous ethanol injection (PEI)

RFA



Optimal candidates:

- BCLC Stage A disease (No vascular invasion or metastases)
- Child-Pugh A or B
- **Single nodule < 2 cm** (feasible also for solitary tumor < 5 cm or ≤ 3 nodules < 3 cm

RFA or PEI
5-year survival 40-50%

High recurrence rate
50% at 3 years
70% at 5 years

•Llovet JM. J Gastroenterol 2005; 40 : 225-235; Bruix J, Sherman M. Hepatology 2005; 42: 1208-1236; Bruix J et al. J Hepatol 2001; 35: 421-430

Terapia HCC singolo

- Tutti i pazienti con HCC singolo e funzione epatica preservata vanno considerati per un trattamento curativo (chirurgia o ablazione), scegliendolo in base alle dimensioni della lesione:

  - **HCC ≤2 cm**: se approcciabile in sicurezza con trattamenti interstiziali percutanei o laparoscopici, la termoablazione va considerata il trattamento di prima linea, se eseguita in centri esperti.

  - **HCC di 2.1–3 cm**: la scelta tra chirurgia e termoablazione deve essere fatta caso per caso e multidisciplinarmente, *anche se la resezione (anatomica) è il trattamento preferibile per radicalità*.

  - **HCC >3 cm**: la resezione epatica è il trattamento di prima scelta.

Liver Transplantation

Advantage	Removal of the diseased liver together with the tumor
Disadvantage	Long waiting lists

Optimal candidates:

- BCLC Stage A disease
- No vascular invasion
- No metastases
- Fulfill the Milan criteria
  - Solitary tumor < 5 cm or
  - ≤ 3 nodules < 3 cm

5-year survival 70% Recurrence rate < 15%

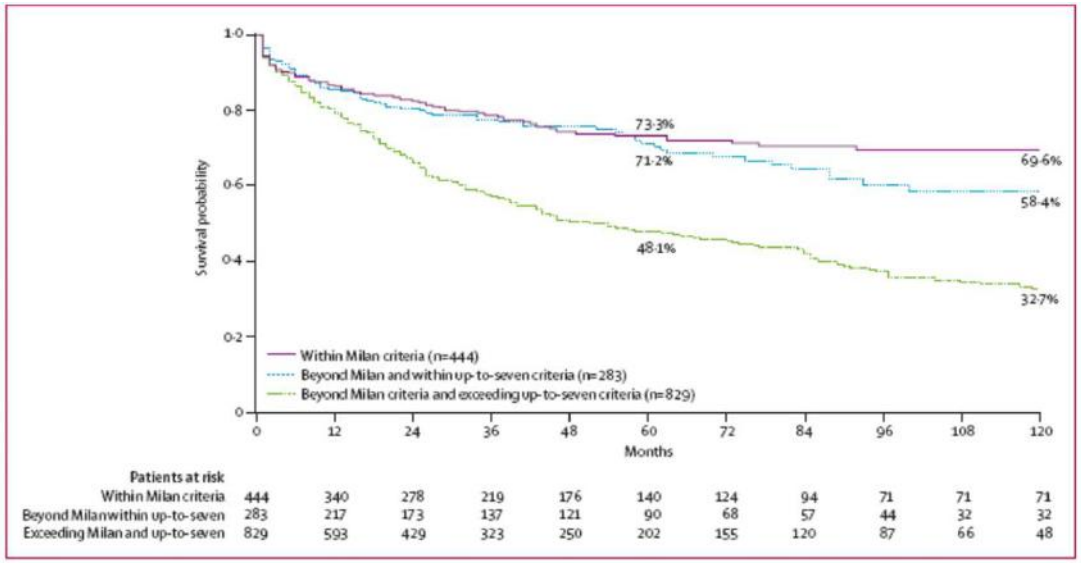


Figure 3: Up-to-seven criteria

… but organ shortage and too strict criteria (UCSF, up-to-seven AFP, …)

- **Bruix J, Sherman M. Hepatology 2005; Llovet JM. J Gastroenterol 2005;**
- **Mazzaferro V et al. N Engl J Med 1996; Mazzaferro V. et al. Lancet 2009**

Trapianto

Considerazione organizzativa generale

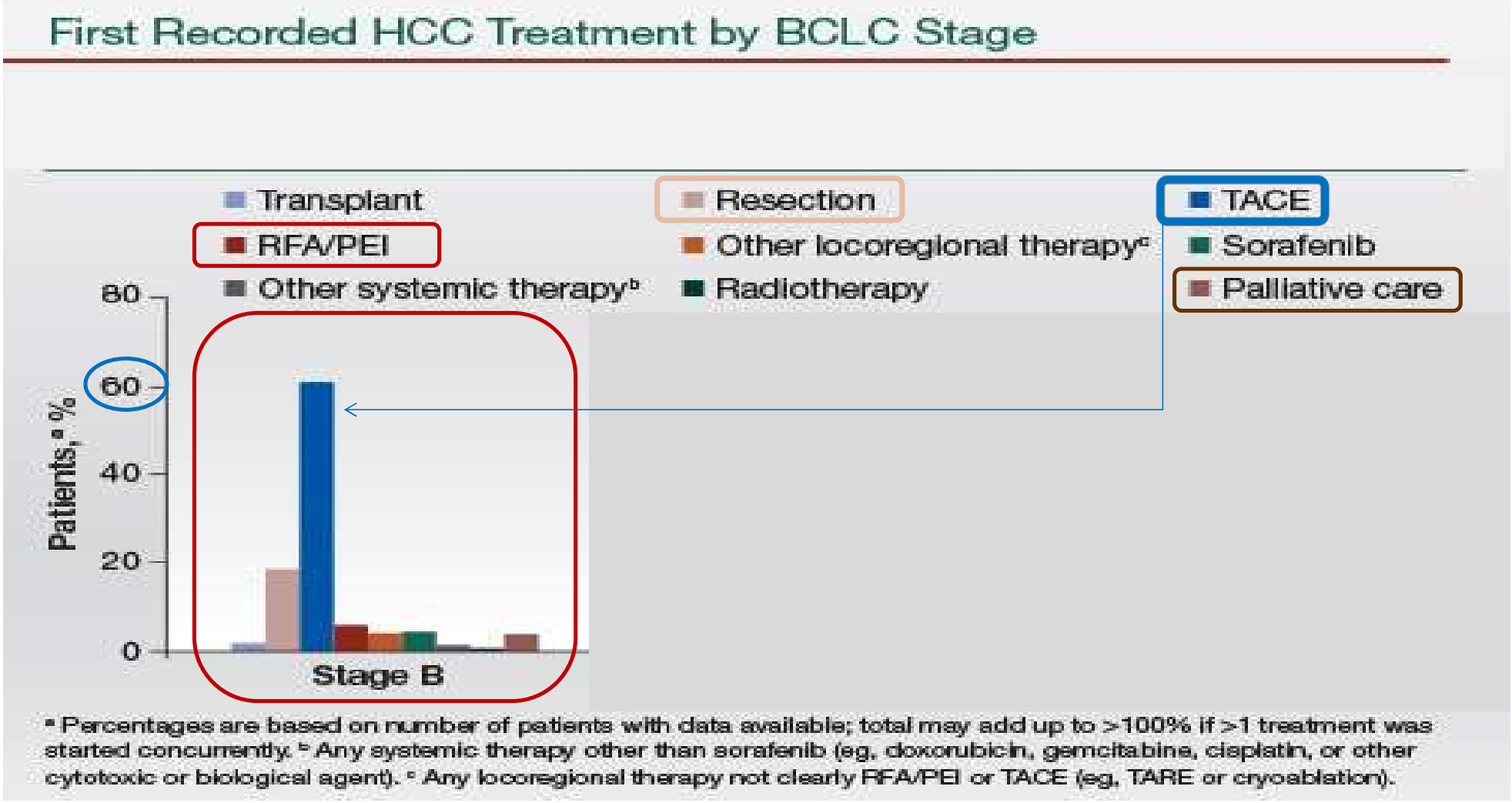
Per **tutti** i pazienti in età trapiantologica e ad alto potenziale di beneficio da trapianto, la strategia terapeutica dovrebbe

essere condivisa **precocemente** (anche in rete)

con un centro trapianti, al fine di ottimizzare l'iter terapeutico.

HCC BRIDGE study

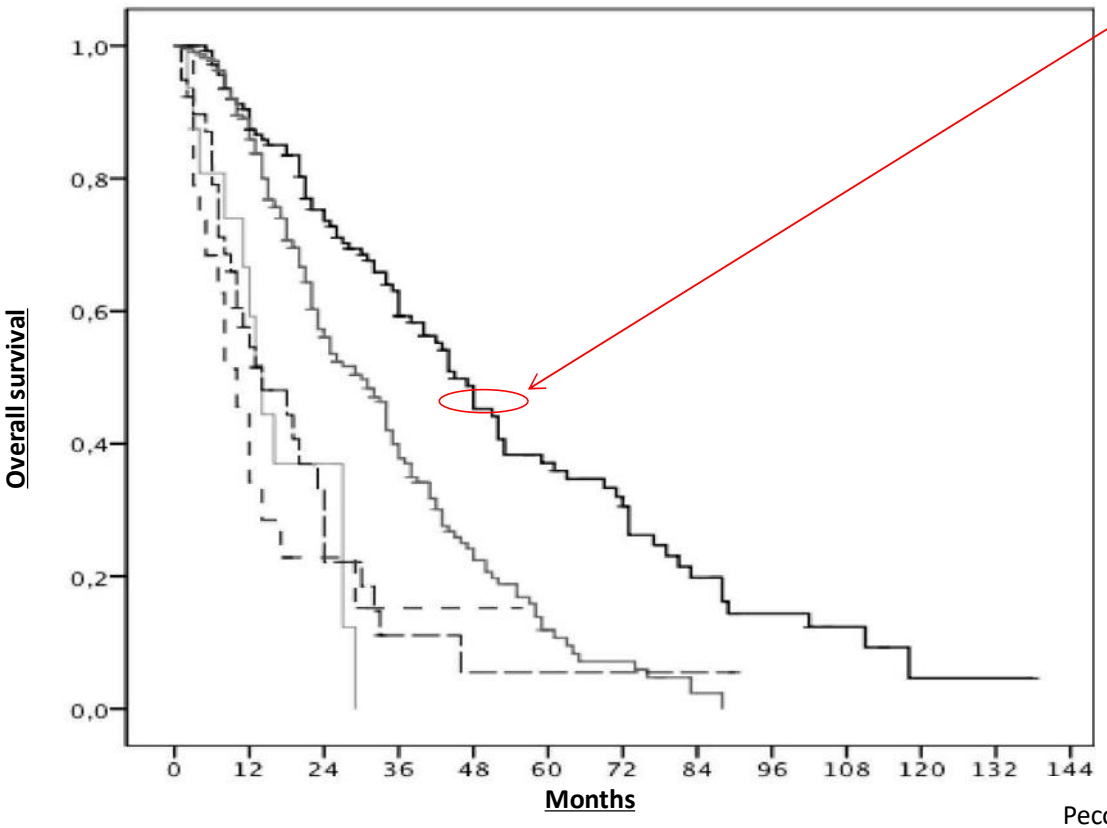
18,031 pts (67% from Asia, 20% from Europe and 13% from North America)



Liver Int. 2015

Curative therapies are superior to standard of care (TACE) for intermediate stage hepatocellular carcinoma

Survival by treatment of 456 BCLC-B patients



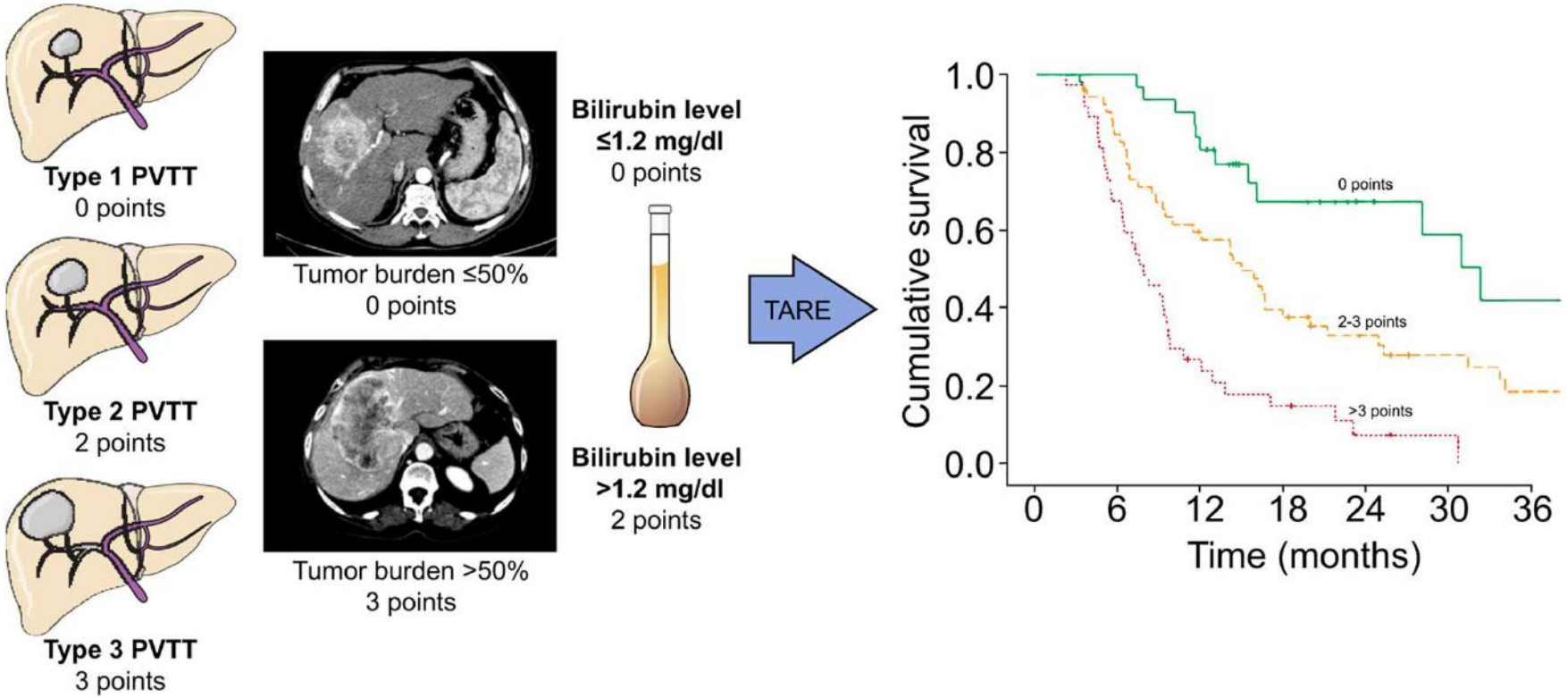
Curative treatments n. 145
TACE n. 233
Sorafenib n. 18
Other treatments n. 39
BSC n. 21

Treatment choice was an **independent prognostic factor** for BCLC B pts after adjustment for other predictors.

Pecorelli A et al., for ITA.L.ICA, Liver Int 2016 Aug 27. doi: 10.1111/liv.13242 [Epub ahead of print]

EASL | JOURNAL OF HEPATOLOGY

Development of a prognostic score to predict response to Yttrium-90 radioembolization for hepatocellular carcinoma with portal vein invasion



Spreafico et al. J Hep 2018

Approved Systemic Therapies for HCC

First line systemic therapy

- **Sorafenib (2008)**
- **Lenvatinib (2018)**
- **Atezolizumab-bevacizumab (2020)**

Drug	Target
Sorafenib	RAF/MEK/ERK pathway VEGFR/PDGFR
Lenvatinib	VEGFR; PDGFR; FGFR
Atezolizumab-Bevacizumab	PD-L1 (Atezo); VEGFR-1 e VEGFR-2 (Beva)

Second line systemic therapy

- **Regorafenib (2017)**
- **Cabozantinib (2018)**
- **Ramucirumab (2019)**
- **Nivolumab (2017) [FDA]**
- **Pembrolizumab (2018) [FDA]**
- **Nivolumab-Ipilimumab (2020) [FDA]**

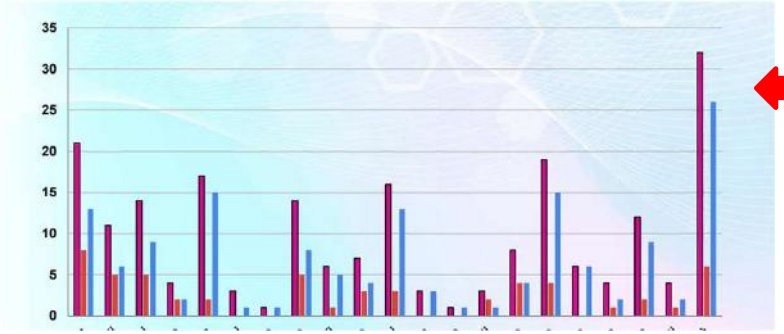
Drug	Target
Regorafenib	VEGF1/VEGF2/VEGF3/ PDGFR/FGFR/KIT/RET/RAF-1/ BRAF
Cabozantinib	MET/VEGFR2/FLT3/c-KIT/ RET
Ramucirumab	VEGFR-2
Nivolumab	PD-1
Pembrolizumab	PD-1
Nivolumab-Ipilimumab	PD-1 (Nivo); CTLA-4 (IPI)

Atezolizumab plus bevacizumab in **MET**astatic

Hepatocellular carcinoma **I**talian **S**afety **Tri**A**l**

Primary Objective	**Corresponding Endpoint**
To evaluate the safety of atezolizumab + bevacizumab in terms of bleeding/haemorrhage	• Incidence of Grade 3-5 NCI CTCAE v.5 bleeding/haemorrhage
Main Secondary Objective	**Corresponding Endpoint**
To evaluate the efficacy of atezolizumab + bevacizumab	Overall survival (OS), defined as the time from initiation of study treatment to death from any cause

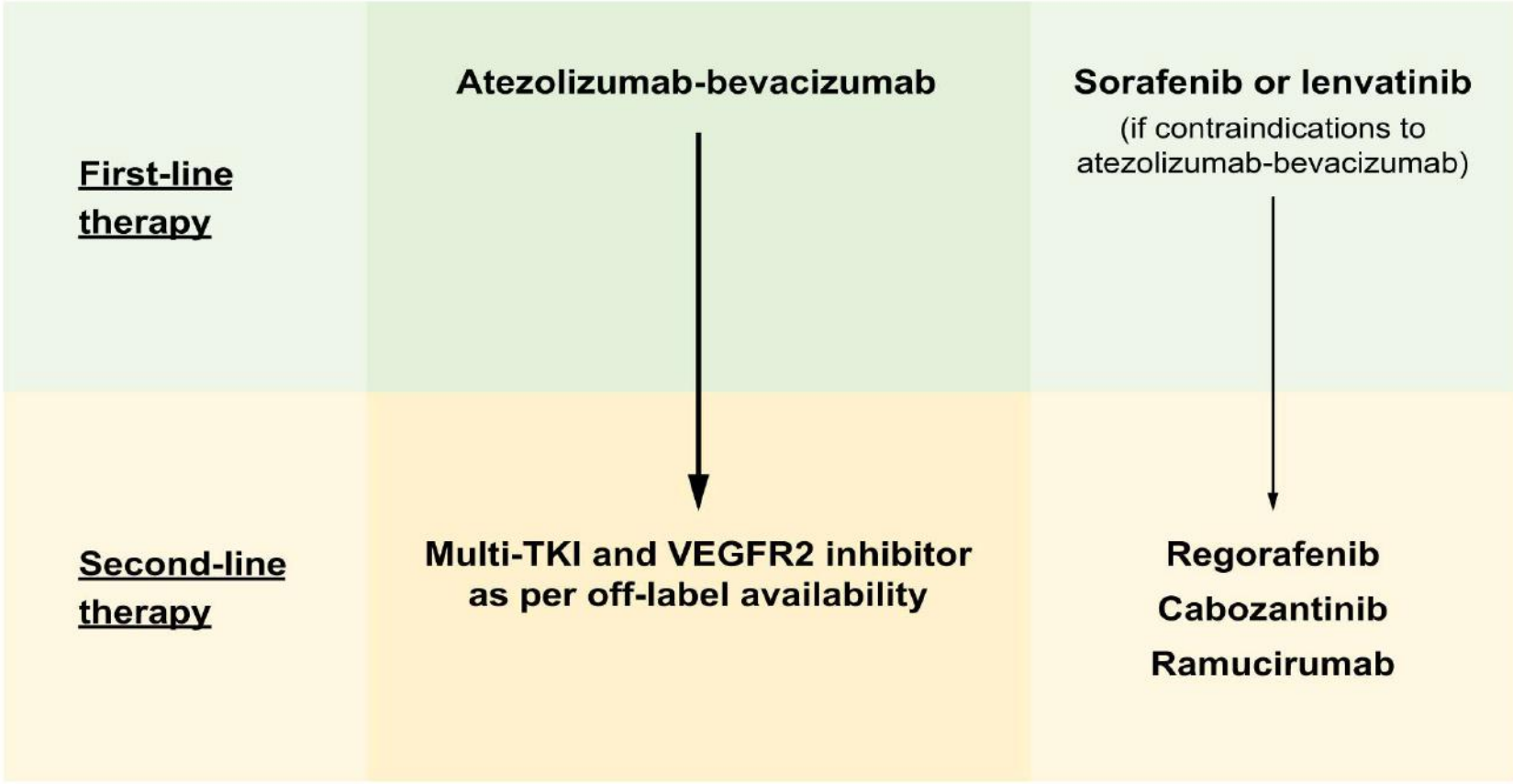
~150 PATIENTS
FROM 21 SITES
ACROSS ITALY



Top recruiter

Systemic treatment of hepatocellular carcinoma: An EASL position paper

Jordi Bruix, Stephen L. Chan, Peter R. Galle, Lorenza Rimassa, Bruno Sangro



J Hep 2021

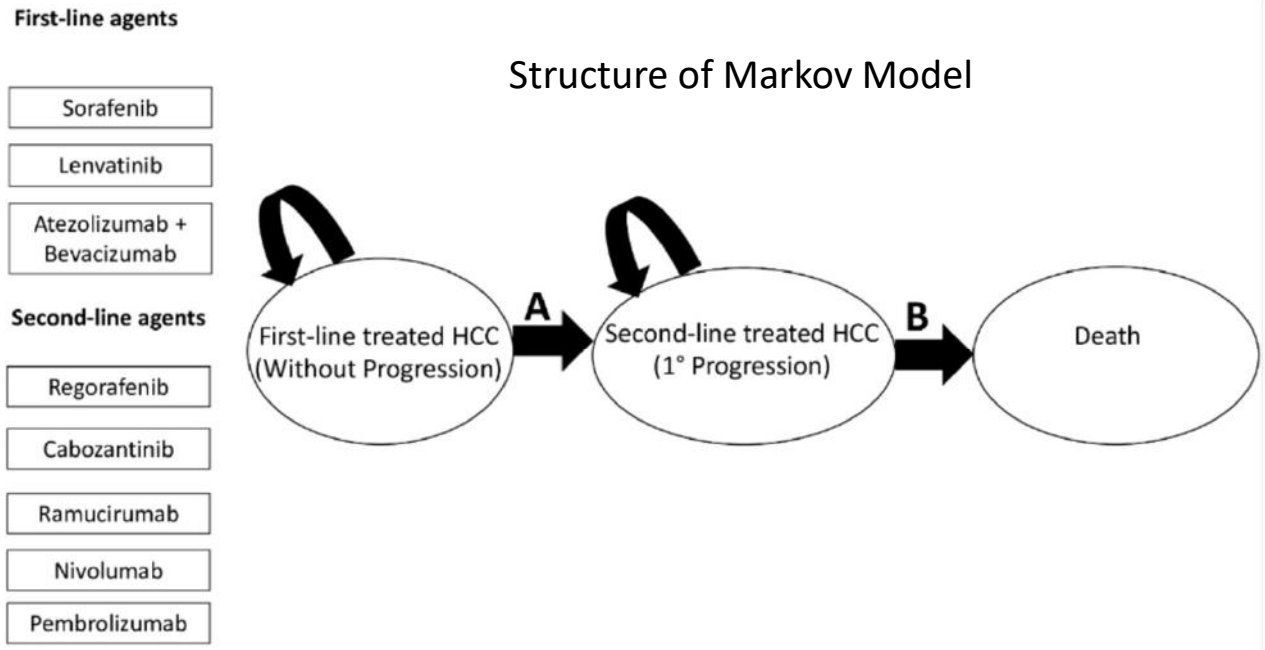
cancers

Article

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,*]

Structure of Markov Model



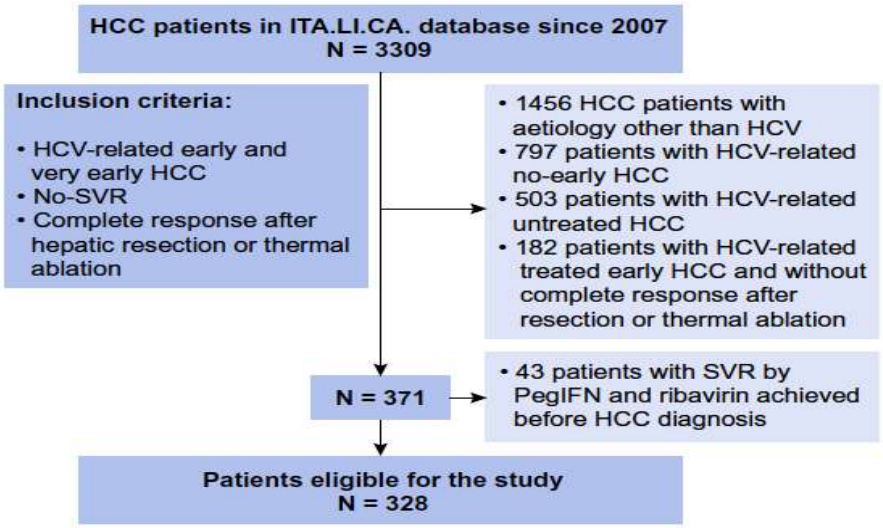
A: Progression Free Survival of first-line. B: Overall survival of second-line.

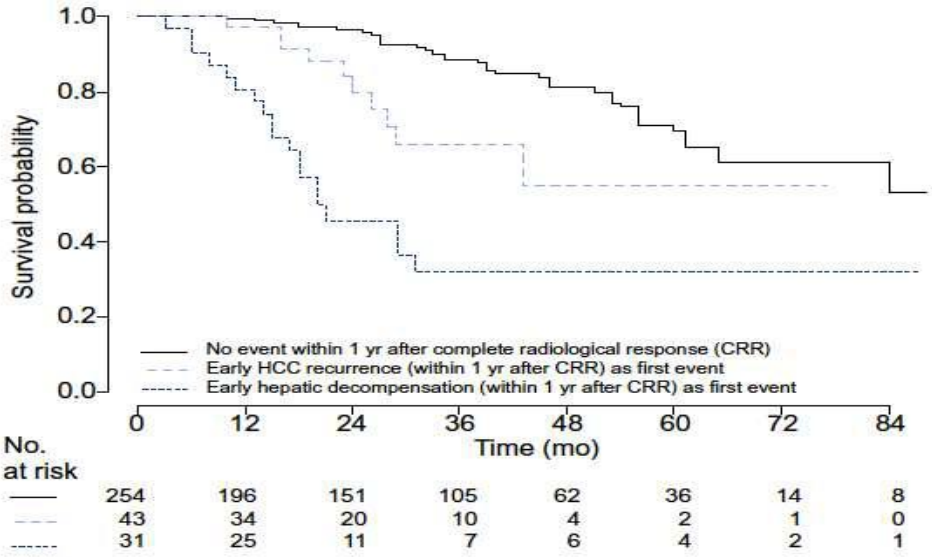
Treatment Sequence	Median OS (mo)
Lenvatinib-Nivolumab	27
Lenvatinib-Pembrolizumab	25
Atezolizumab plus Bevacizumab-Nivolumab	24
Sorafenib-Nivolumab	23
Atezolizumab plus Bevacizumab-Pembrolizumab	23
Lenvatinib-Ramucirumab	22
Lenvatinib-Regorafenib	22
Lenvatinib-Cabozantinib	22
Sorafenib-Pembrolizumab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

Cabibbo, Celsa et al. Cancers 2020

EASL | JOURNAL OF HEPATOLOGY

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





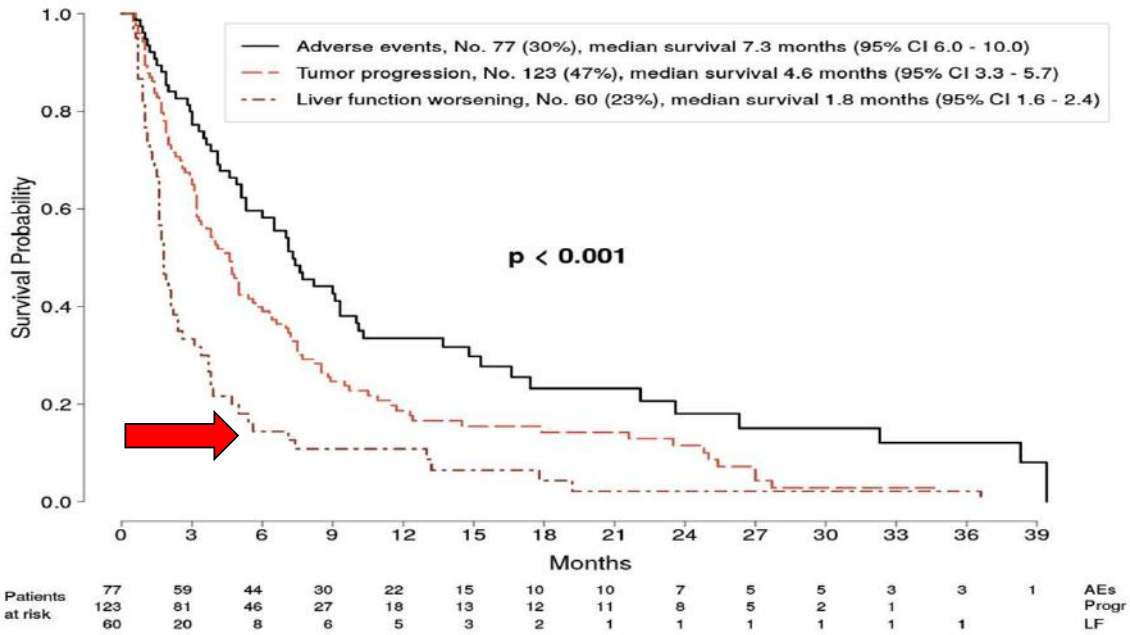
Time dependent Cox model (MV analysis)

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

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Predictors of Survival of Patients with Advanced HCC Who Permanently Discontinued Sorafenib



Conclusions:

1) The survival following sorafenib discontinuation is significantly influenced by reason for drug withdrawal, i.e. adverse effects, liver impairment and tumour progression pattern.

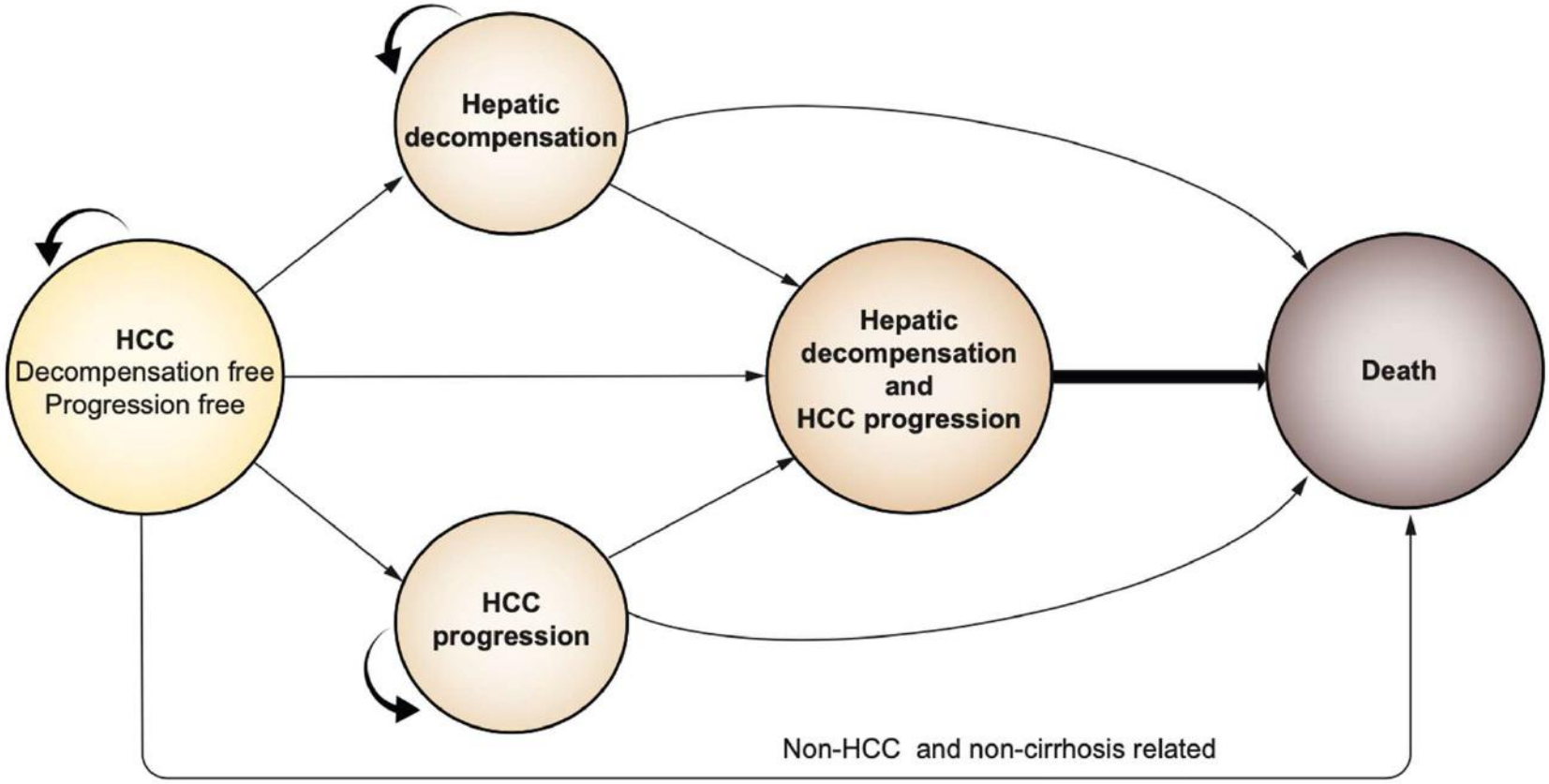
2) In patients eligible to 2nd line trials, survival is determined by reason of sorafenib discontinuation, performance status and extrahepatic tumor burden.

3) In real life practice, these results are keys in prognostic prediction and design/analysis of second line trials.

Iavarone, Cabibbo et al. Hepatology 2015

EASL | JOURNAL OF HEPATOLOGY

Competing risk for survival in HCC patients



Reig M & Cabibbo G, J Hep 2021

Key message: Ruolo del Team Multidisciplinare

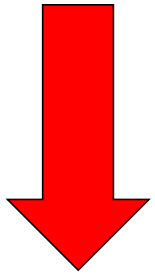
I pazienti con HCC dovrebbero essere riferiti ad un Team Multidisciplinare che dovrebbe includere:

- ✓ **epatologo**
- ✓ **oncologo**
- ✓ **radiologo (diagnostico e interventista)**
- ✓ **chirurgo specializzato in patologia del fegato**
- ✓ **anatomo-patologo**
- ✓ **…**

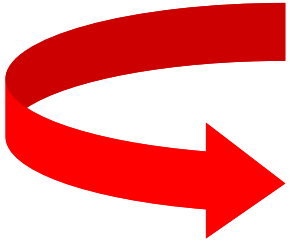
che dovrebbero avere un ruolo attivo nella cura di questi pazienti.

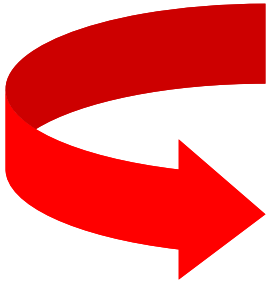
Hepatocellular Carcinoma

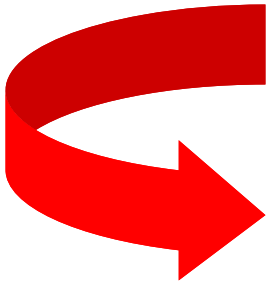
Complexity
(Cirrhosis & HCC)



Heterogeneity







1) Biological

2) Epidemiological

3) Diagnostic

4) Prognostic

5) Therapeutic

6) Metodological

Why a prospective observational study on HCC?

- To assess:

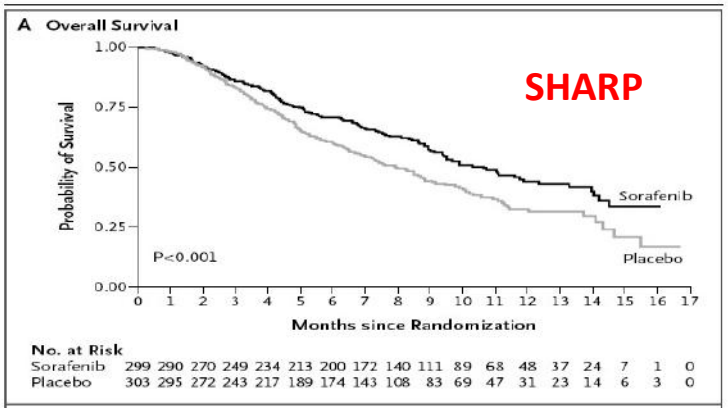
- etiological heterogeneity;
- heterogeneity of treatments;
- heterogeneity in interactions between specialists;

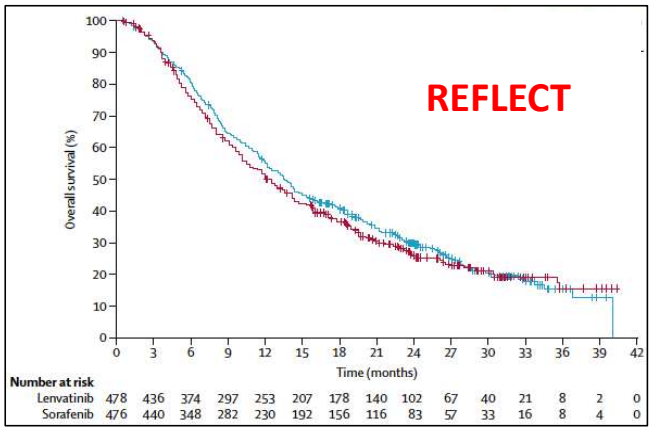
- To better understand:

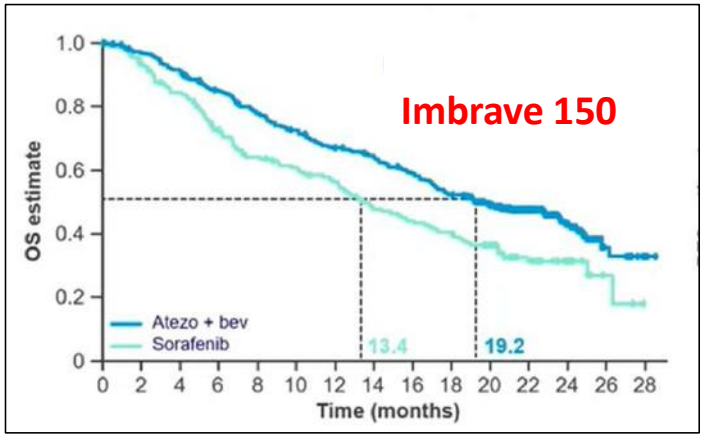
- how the different decisional issues are resolved in clinical practice (i.e. shift to systemic therapy; first-line approach; …)
- …;
- ….

First-line Systemic Therapies for HCC

Study (Journal, year)	Arms	Median Overall Survival (months)	Median PFS (months)
SHARP (NEJM, 2008)	**Sorafenib**	**10.7**	2.8 (TTP)
	placebo	7.9	5.5 (TTP)
REFLECT (Lancet 2018)	**Lenvatinib**	**13.6**	7.3
	Sorafenib	12.3	3.7
IMbrave150 (NEJM 2020)	**Atezo+beva**	**19.2**	6.8
	Sorafenib	13.4	4.3

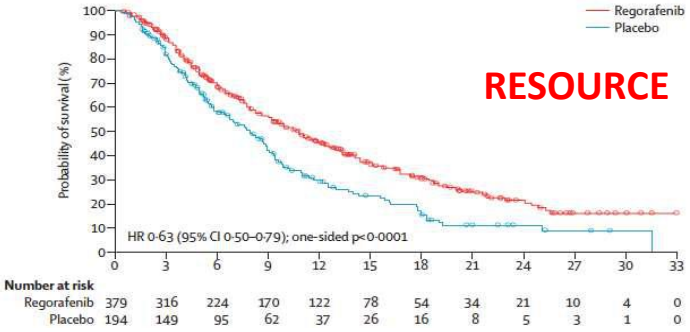




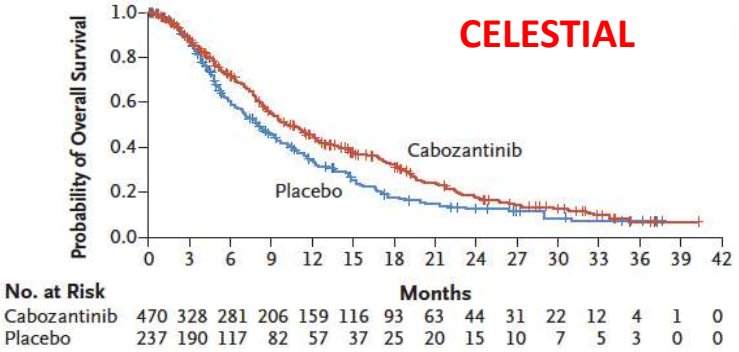


Second-line Systemic Therapies for HCC

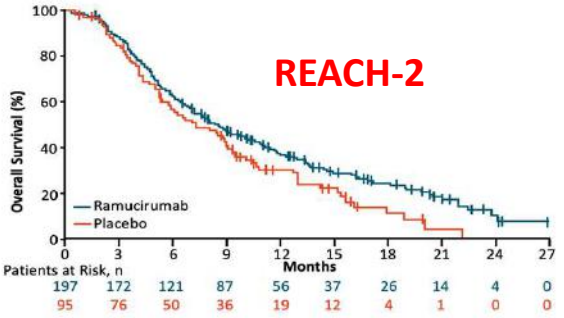
Study drug[reference]	Trial name	n	OS months	PFS months
RESORCE Bruix et al.[8]	Regorafenib	379	10·6	3.4
	Placebo	194	7.8	1.5
CELESTIAL Abou-Alfa et al.[9]	Cabozantinib	470	11.3	5.5
	Placebo	237	7.2	1.9
REACH 2 Zhu et al.[10]	Ramucirumab	197	8.5	2.8
	Placebo	95	7.3	1.6



Lancet 2017



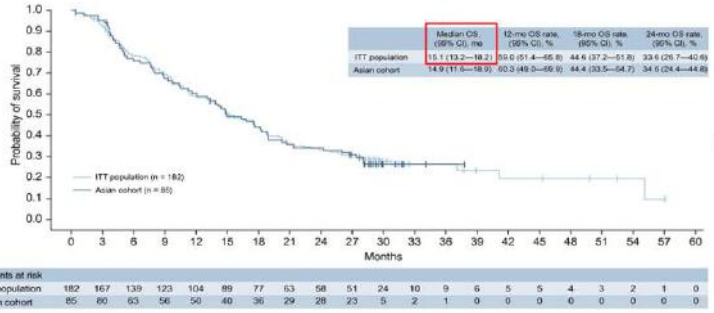
NEJM 2018



Lancet Oncol 2019

Second-line Systemic Therapies for HCC only approved by FDA

Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial

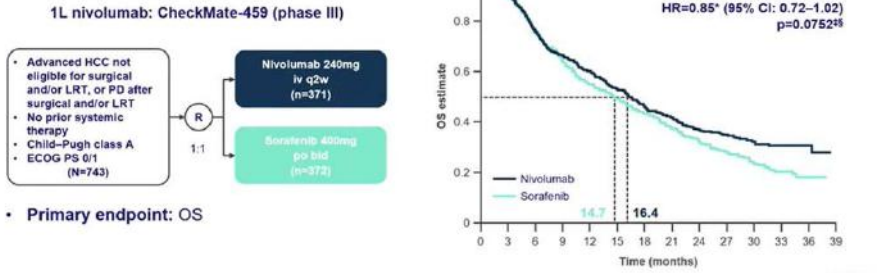


Target: PD-1

El-Khoueiry AB, et al. Lancet 2017

Yau T et al. J Hep 2019

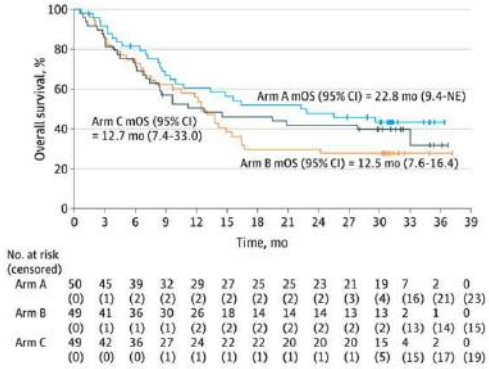
CheckMate-459: nivolumab did not significantly improve outcomes in 1L advanced HCC



*Stratified Cox proportional hazards model; HR is nivolumab over sorafenib
†p value from log-rank test
‡Final OS boundary: 0.0419 for a 2-sided nominal p value
1L, first-line; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; bid, twice a day; HCC, hepatocellular carcinoma; HR, hazard ratio; iv, intravenous; LRT, locoregional therapy; OS, overall survival; PD, progressive disease; po, orally; q2w, every 2 weeks

Adapted from 1. Yau et al. ESMO 2019
Permission for use kindly provided by Thomas Yau

Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients With Advanced Hepatocellular Carcinoma Previously Treated With Sorafenib



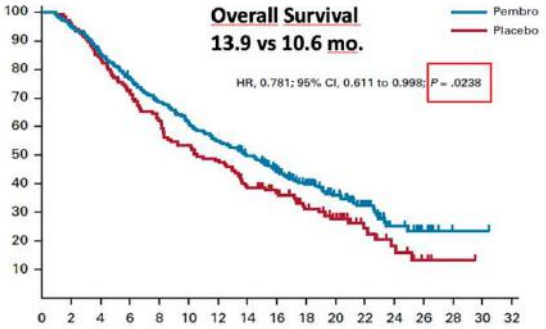
Nivolumab plus ipilimumab phase 1/2 study. **The arm A regimen** (4 doses nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks then nivolumab 240 mg every 2 weeks) **received accelerated approval in the US based on the results of this study.**

Target: PD-1 (Nivo); CTLA-4 (IPI)

Yao et al. JAMA Oncology 2020

Pembrolizumab As Second-Line Therapy in Patients With Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomized, Double-Blind, Phase III Trial

Journal of Clinical Oncology



Target: PD-1

- Designed to meet a dual primary endpoint: OS and PFS
- Prespecified boundaries of P = .0174 for OS (final analysis) and P = .002 for PFS (at the first interim analysis).
- Better than expected survival in placebo group (post-study therapies)