AZIENDA OSPEDALIERA DI PARMA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma

PDTA lesioni focali epatiche

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Parma, 6 giugno 2017

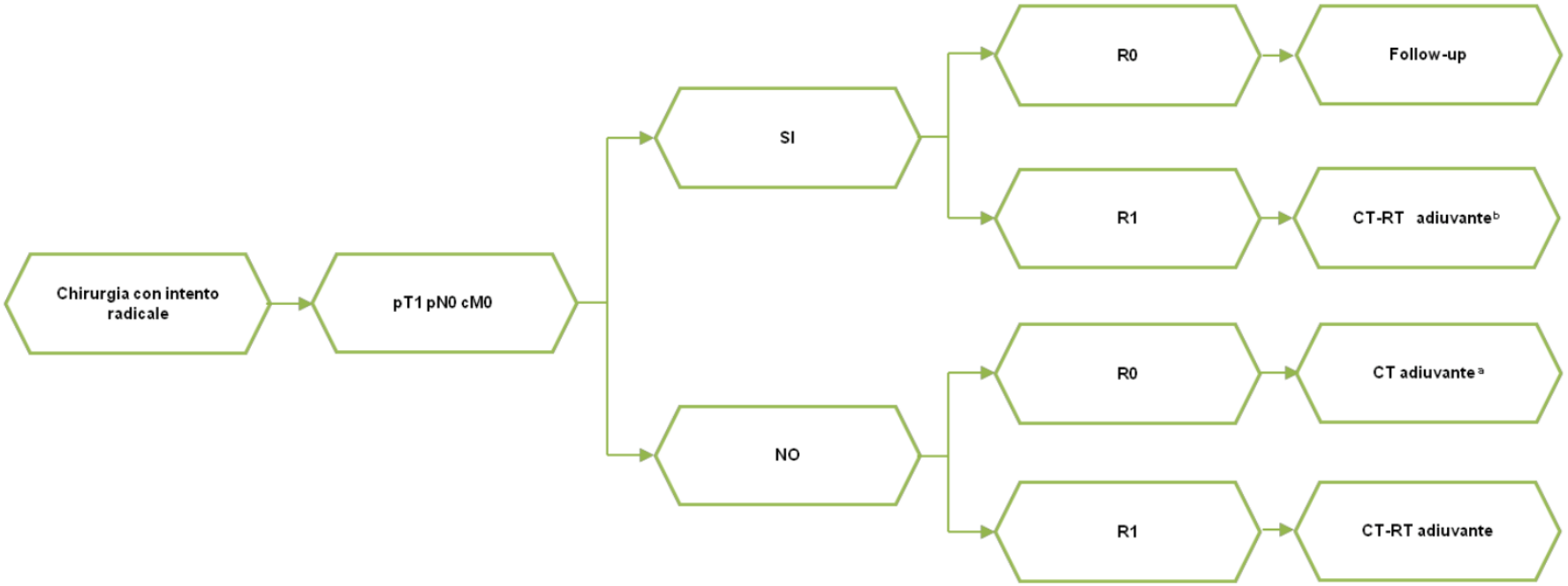
Casi discussi

- **Colangiocarcinomi**
- **Epatocarcinomi**

Linee guida

TUMORI DELLE VIE BILIARI

Edizione 2016

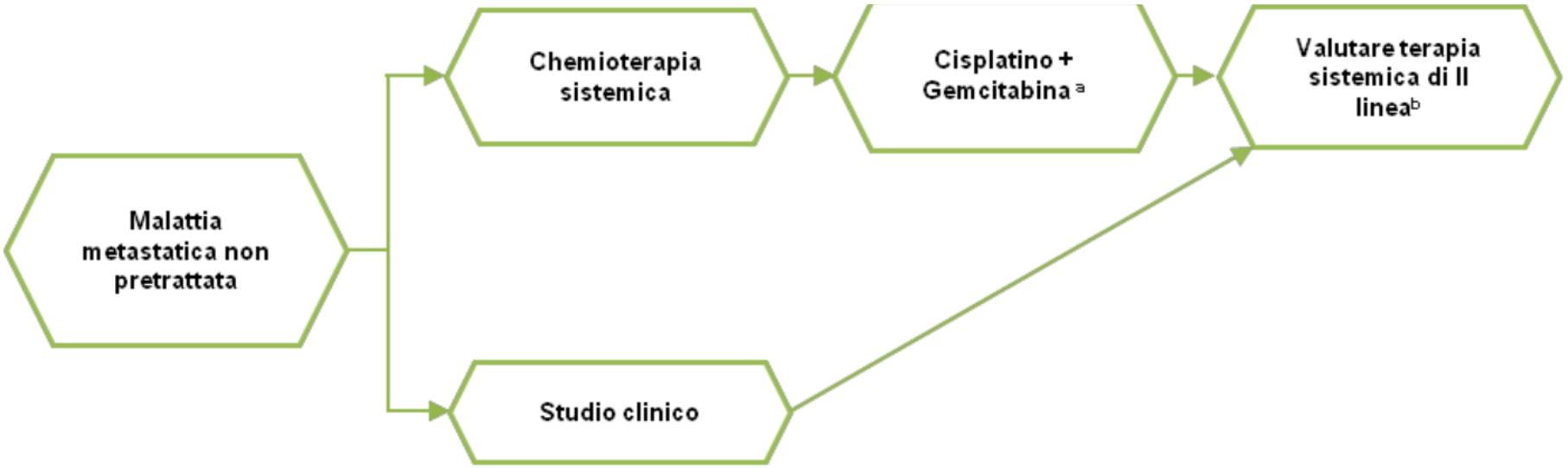


Takada T et al, 2002
Horgan AM et al, 2012

Linee guida

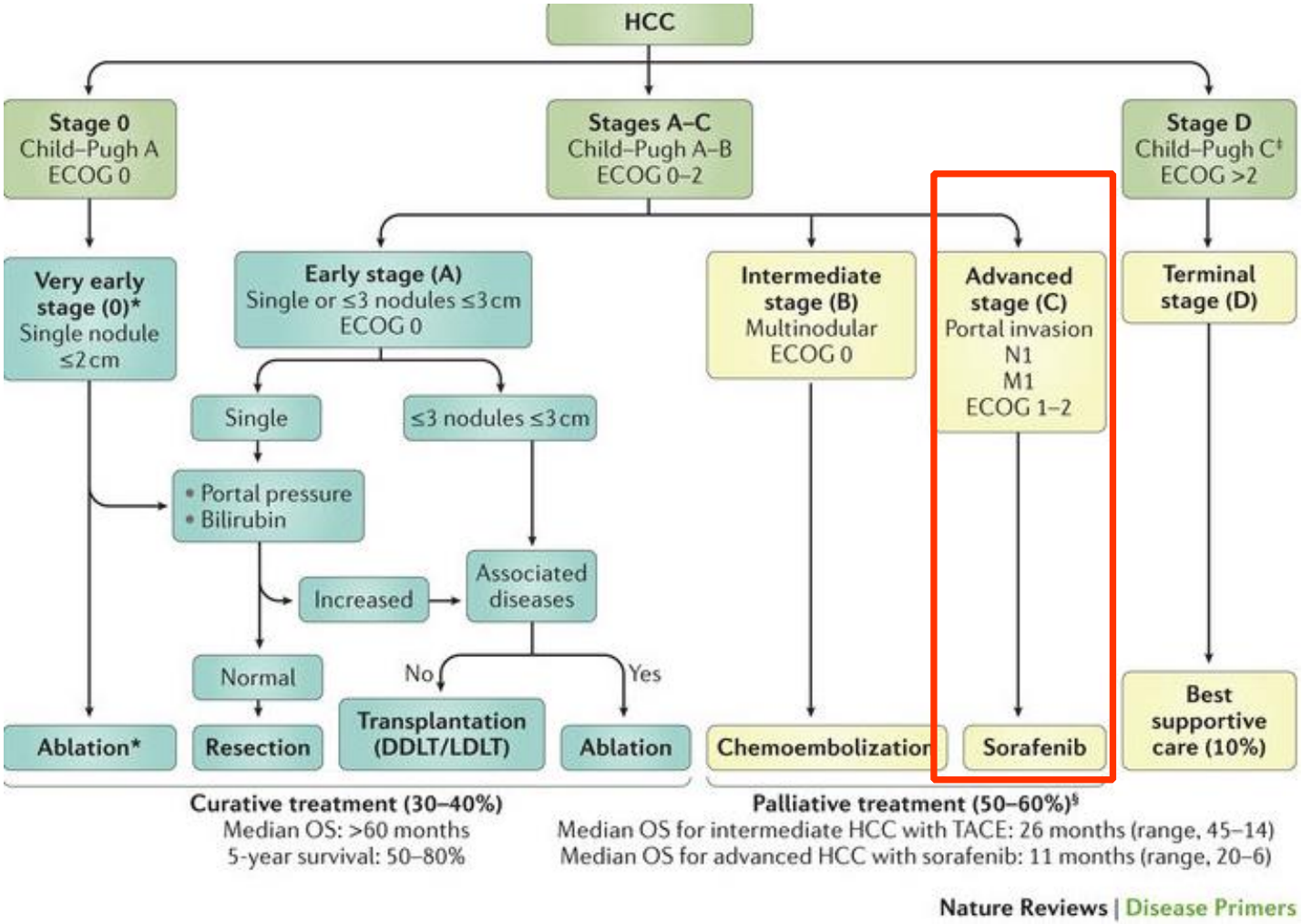
TUMORI DELLE VIE BILIARI

Edizione 2016

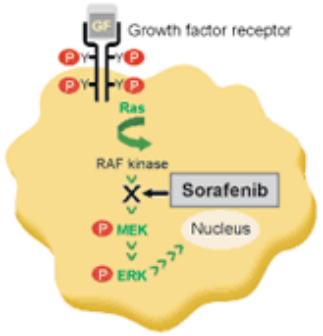


Valle J et al, 2010

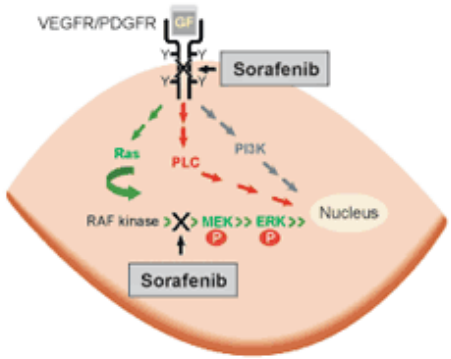
BCLC staging system and therapeutic strategy: EASL–EORTC guidelines



Sorafenib targets both tumor-cell proliferation and angiogenesis in vitro



BAY 43-9006 inhibits tumor cell proliferation by targeting the RAF/MEK/ERK pathway at the level of RAF kinase.



BAY 43-9006 exerts an antiangiogenic effect by targeting the receptor tyrosine kinases VEGFR-2 and PDGFR and their associated signaling cascades.

Strumberg D, 2005

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sorafenib in Advanced Hepatocellular Carcinoma

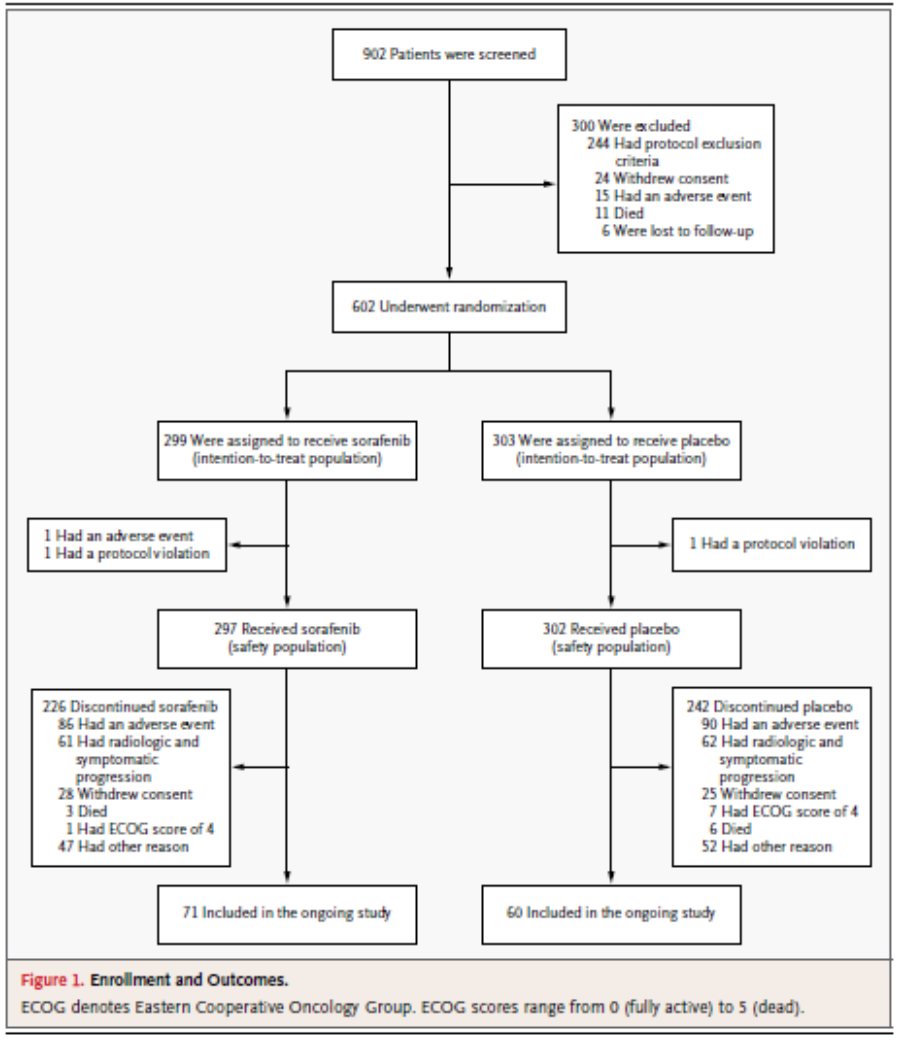


Figure 1. Enrollment and Outcomes.
ECOG denotes Eastern Cooperative Oncology Group. ECOG scores range from 0 (fully active) to 5 (dead).

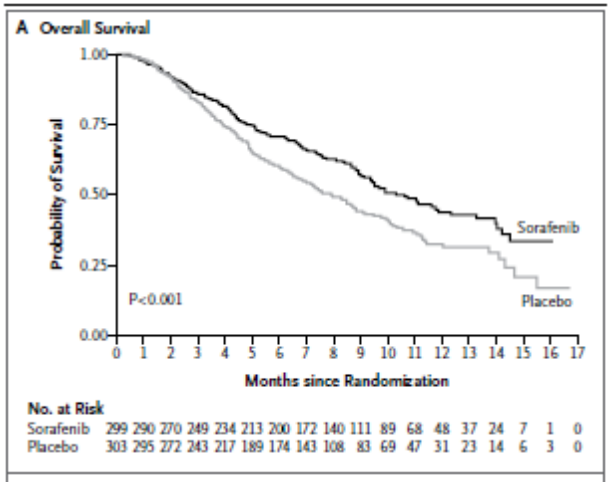


Table 2. Summary of Efficacy Measures.*

Outcome	Sorafenib (N = 299)	Placebo (N = 303)	Hazard Ratio (95% CI)	P Value
Overall survival (mo)			0.69 (0.55–0.87)	<0.001
Median	10.7	7.9		
95% CI	9.4–13.3	6.8–9.1		
1-yr survival rate (%)	44	33		0.009
Time to symptomatic progression (mo)†			1.08 (0.88–1.31)	0.77
Median	4.1	4.9		
95% CI	3.5–4.8	4.2–6.3		
Time to radiologic progression (mo)			0.58 (0.45–0.74)	<0.001
Median	5.5	2.8		
95% CI	4.1–6.9	2.7–3.9		
Level of response (%)‡				
Complete	0	0		NA
Partial	2	1		0.05
Stable disease	71	67		0.17
Disease-control rate (%)§	43	32		0.002

Llovet JM, et al. NEJM 2008

ORIGINAL ARTICLE

Sorafenib in Advanced Hepatocellular Carcinoma

Table 3. Incidence of Drug-Related Adverse Events (Safety Population).*

Adverse Event	Sorafenib (N=297)			Placebo (N=302)			P Value	
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3 or 4
	percent							
Overall incidence	80			52				
Constitutional symptoms								
Fatigue	22	3	1	16	3	<1	0.07	1.00
Weight loss	9	2	0	1	0	0	<0.001	0.03
Dermatologic events								
Alopecia	14	0	0	2	0	0	<0.001	NA
Dry skin	8	0	0	4	0	0	0.04	NA
Hand–foot skin reaction	21	8	0	3	<1	0	<0.001	<0.001
Pruritus	8	0	0	7	<1	0	0.65	1.0
Rash or desquamation	16	1	0	11	0	0	0.12	0.12
Other	5	1	0	1	0	0	<0.001	0.12
Gastrointestinal events								
Anorexia	14	<1	0	3	1	0	<0.001	1.00
Diarrhea	39	8	0	11	2	0	<0.001	<0.001
Nausea	11	<1	0	8	1	0	0.16	0.62
Vomiting	5	1	0	3	1	0	0.14	0.68
Voice changes	6	0	0	1	0	0	<0.001	NA
Hypertension	5	2	0	2	1	0	0.05	0.28
Liver dysfunction	<1	<1	0	0	0	0	0.50	0.50
Abdominal pain not otherwise specified	8	2	0	3	1	0	0.007	0.17
Bleeding	7	1	0	4	1	<1	0.07	1.00

* Listed are adverse events, as defined by the National Cancer Institute Common Terminology Criteria (version 3.0), that occurred in at least 5% of patients in either study group. NA denotes not applicable.

Linee guida

EPATOCARCINOMA

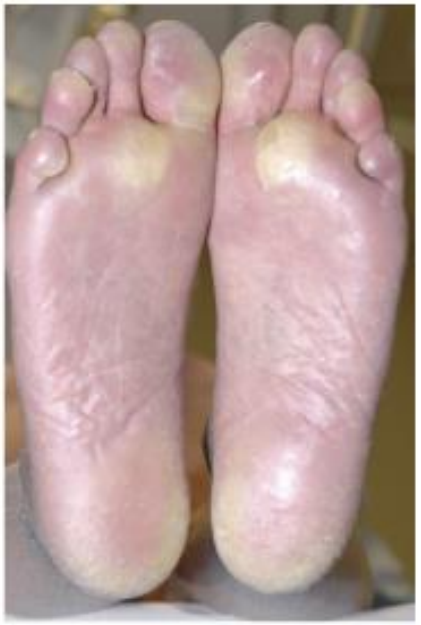
Dose piena	400 mg bis in die
Primo livello di riduzione	200 mg bis in die
Secondo livello di riduzione	200 mg bis in die ogni 2 giorni

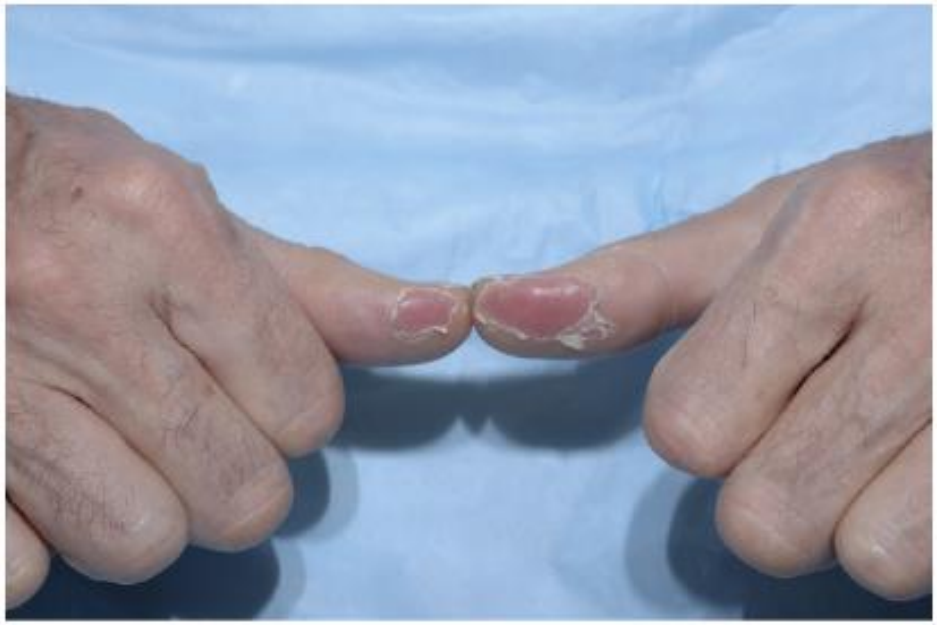
Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
B	Nei pz con HCC avanzato e funzionalità epatica piuttosto compromessa (classe Child-Pugh B), il sorafenib non dovrebbe essere utilizzato. (115)	**Negativa debole**

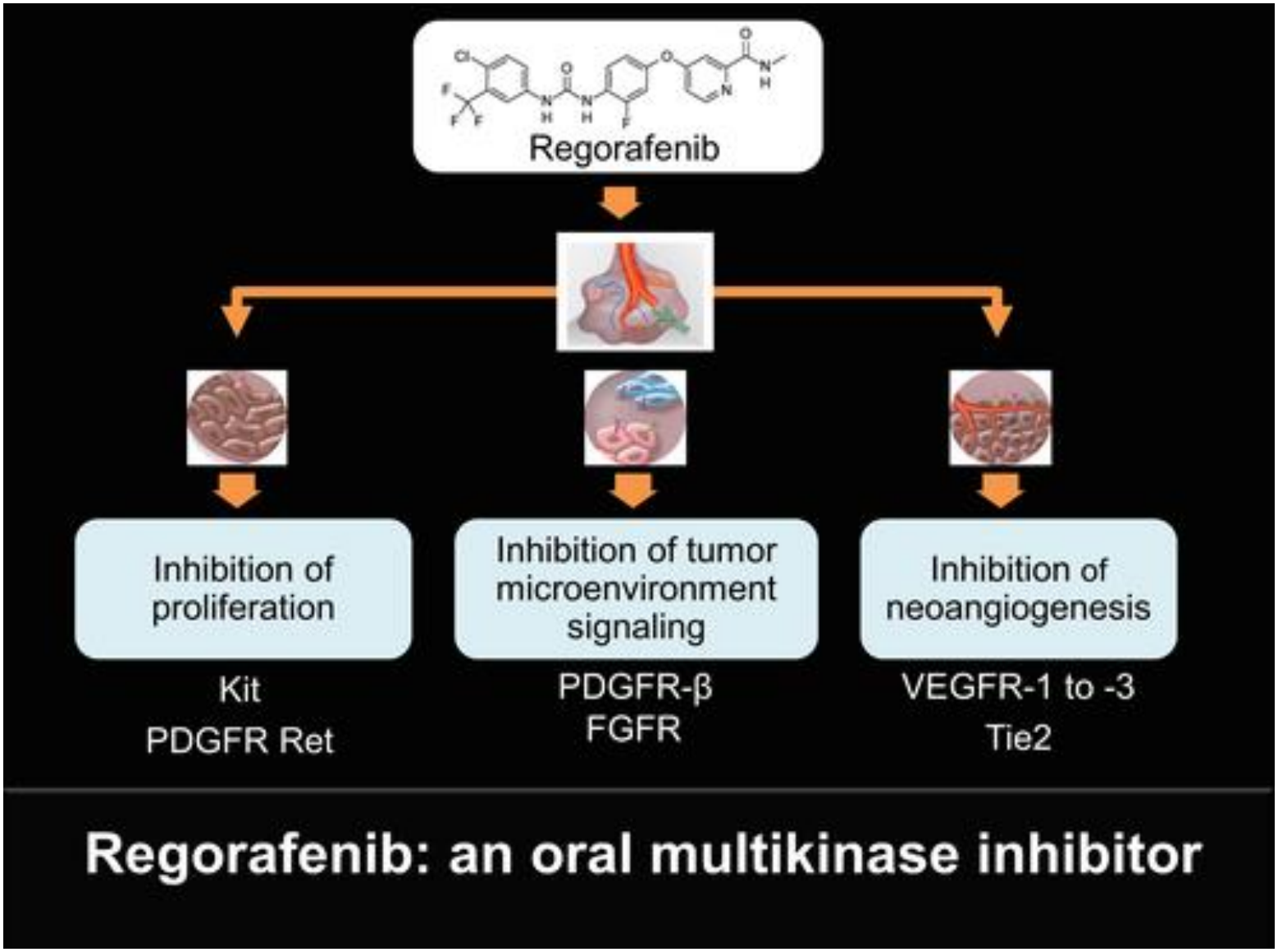
Abou-Alfa GK et al, 2006

Implication for clinical management

- Dose reductions due to adverse events 26% of the patients
- Dose interruptions due to adverse events 44% of the patients (11% permanent treatment discontinuation)







Regorafenib: an oral multikinase inhibitor

Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial

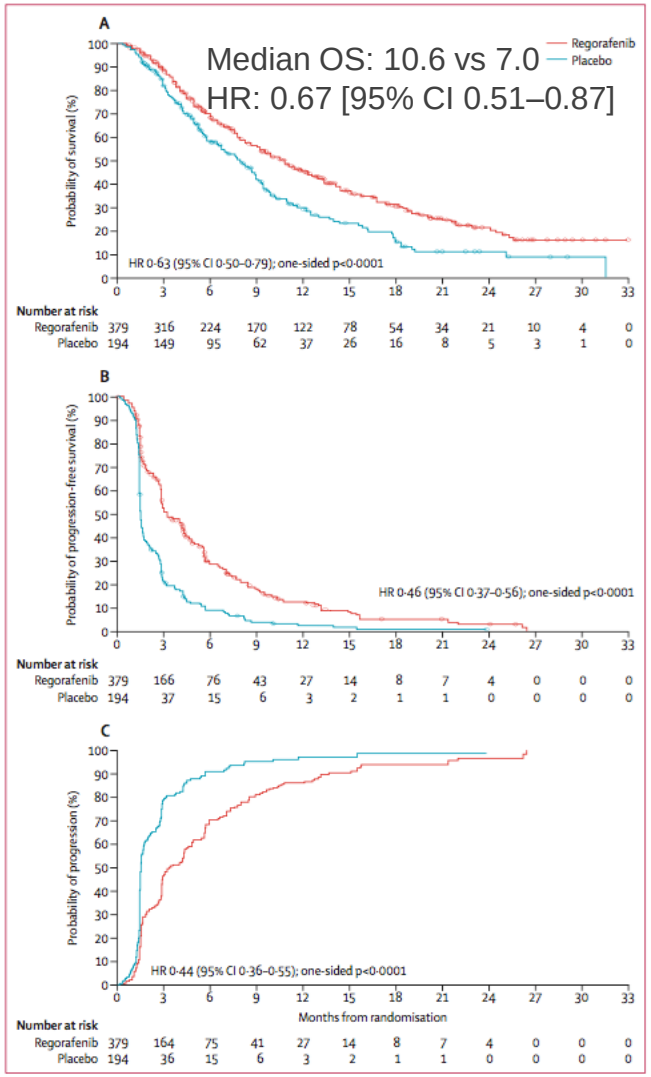


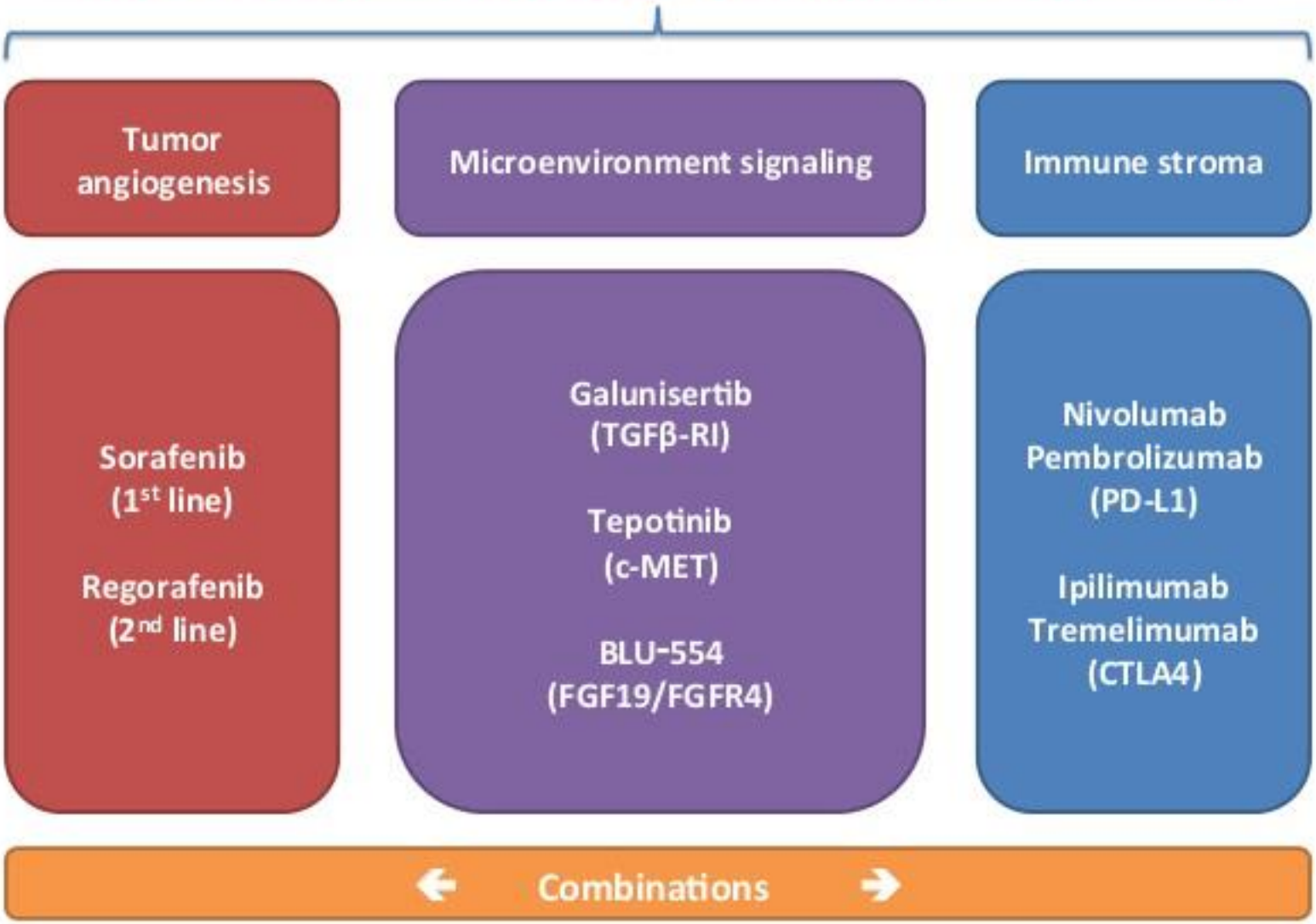
Figure 2: Kaplan-Meier analysis of overall survival (A), progression-free survival (mRECIST; B), and time to progression (mRECIST; C)
mRECIST=modified RECIST for hepatocellular carcinoma.

	Regorafenib (n=379)	Placebo (n=194)
Best overall response*		
Complete response	2 (1%; <1–2)	0
Partial response	38 (10%; 7–14)	8 (4%; 2–8)
Stable disease	206 (54%; 49–59)	62 (32%; 26–39)
Non-complete response/ non-progressive disease	1 (<1%; 0–2)	0
Progressive disease	86 (23%; 19–27)	108 (56%; 48–63)
Not evaluable	19 (5%; 3–8)	8 (4%; 2–8)]
Not assessed	27 (7%; 5–10)	8 (4%; 2–8)
Clinical progression†	86 (23%; 19–27)	40 (21%; 15–27)
Objective response (complete response + partial response)*	40 (11%)‡	8 (4%)‡
Disease control*	247 (65%)§	70 (36%)§

Data are n (%; 95% CI). *Based on radiological review using modified Response Evaluation Criteria in Solid Tumors for HCC (mRECIST).[22] †Defined as worsening of ECOG performance status or symptomatic deterioration including increase in liver function tests. ‡One-sided p=0·0047. §One-sided p<0·0001.

Table 2: **Tumour response (efficacy population)**

Bruix J, et al. Lancet 2017


New Targets and New Agents in Hepatocellular Carcinoma
Tumor angiogenesis
Microenvironment signaling
Immune stroma
Sorafenib (1st line)
Regorafenib (2nd line)
Galunisertib (TGFβ-RI)
Tepotinib (c-MET)
BLU-554 (FGF19/FGFR4)
Nivolumab Pembrolizumab (PD-L1)
Ipilimumab Tremelimumab (CTLA4)
Combinations

Nivolumab (nivo) in sorafenib (sor)-naive and -experienced pts with advanced hepatocellular carcinoma (HCC): CheckMate 040 study.

	Sor Naive		Sor Experienced			
	ESC + EXP (n=80)		ESC (n=37)		EXP (n=145)	
	INV	BICR	INV	BICR	INV	BICR
ORR, n (%)[a]	18 (23)	16 (20)	6 (16)	7 (19)	28 (19)	21 (14)
CR	1 (1)	1 (1)	3 (8)	1 (3)	3 (2)	2 (1)
PR	17 (21)	15 (19)	3 (8)	6 (16)	25 (17)	19 (13)
SD	32 (40)	25 (31)	16 (43)	12 (32)	64 (44)	60 (41)
PD	26 (33)	32 (40)	12 (32)	13 (35)	47 (32)	56 (39)
Not evaluable	4 (5)	5 (6)	3 (8)	4 (11)	6 (4)	8 (6)
DOR, median (95% CI), mo[a]	NR (6–NE)	17 (NE–NE)	17 (7–NE)	19 (3–NE)	12 (7–NE)	NR (11–NE)
12-mo OS rate (95% CI), %	73 (61–81)		58 (40–72)		60 (51–67)	

NR, not reached; NE, not estimable. [a]RECIST v1.1; mRECIST ORRs (BICR): sor naive, 24%; sor experienced, 22% (ESC), 19% (EXP)

Crocenzi TS et al, ASCO 2017