ΕΘΝΙΚΟ & ΚΑΠΟΔΙΣΤΡΙΑΚΟ
ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ

Ηπατοκυτταρικό καρκίνωμα: Νεότεροι φαρμακευτικοί θεραπευτικοί ορίζοντες

Ευάγγελος Χολόγκιτας
Αναπληρωτής καθηγητής Παθολογίας ΕΚΠΑ
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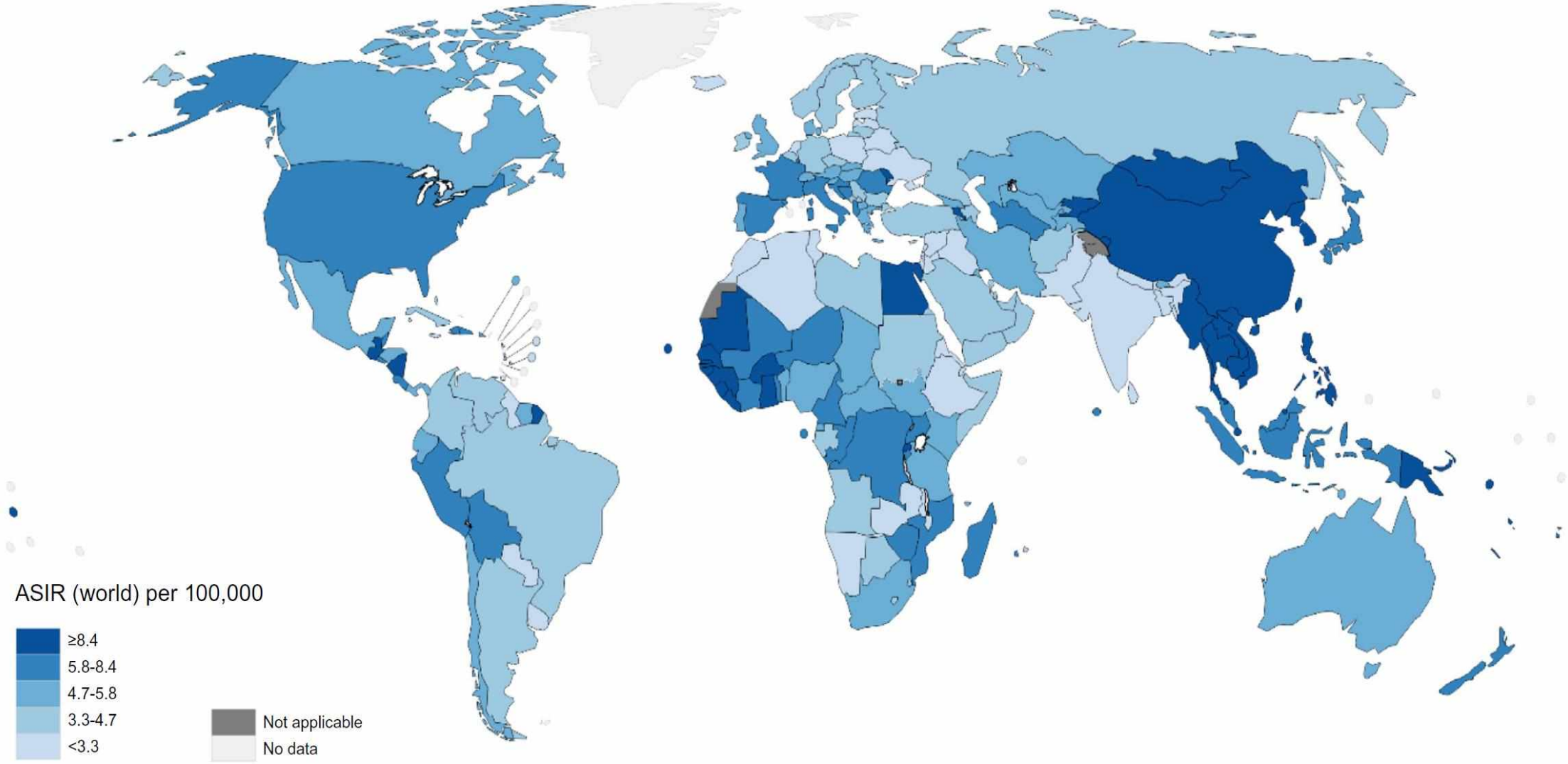
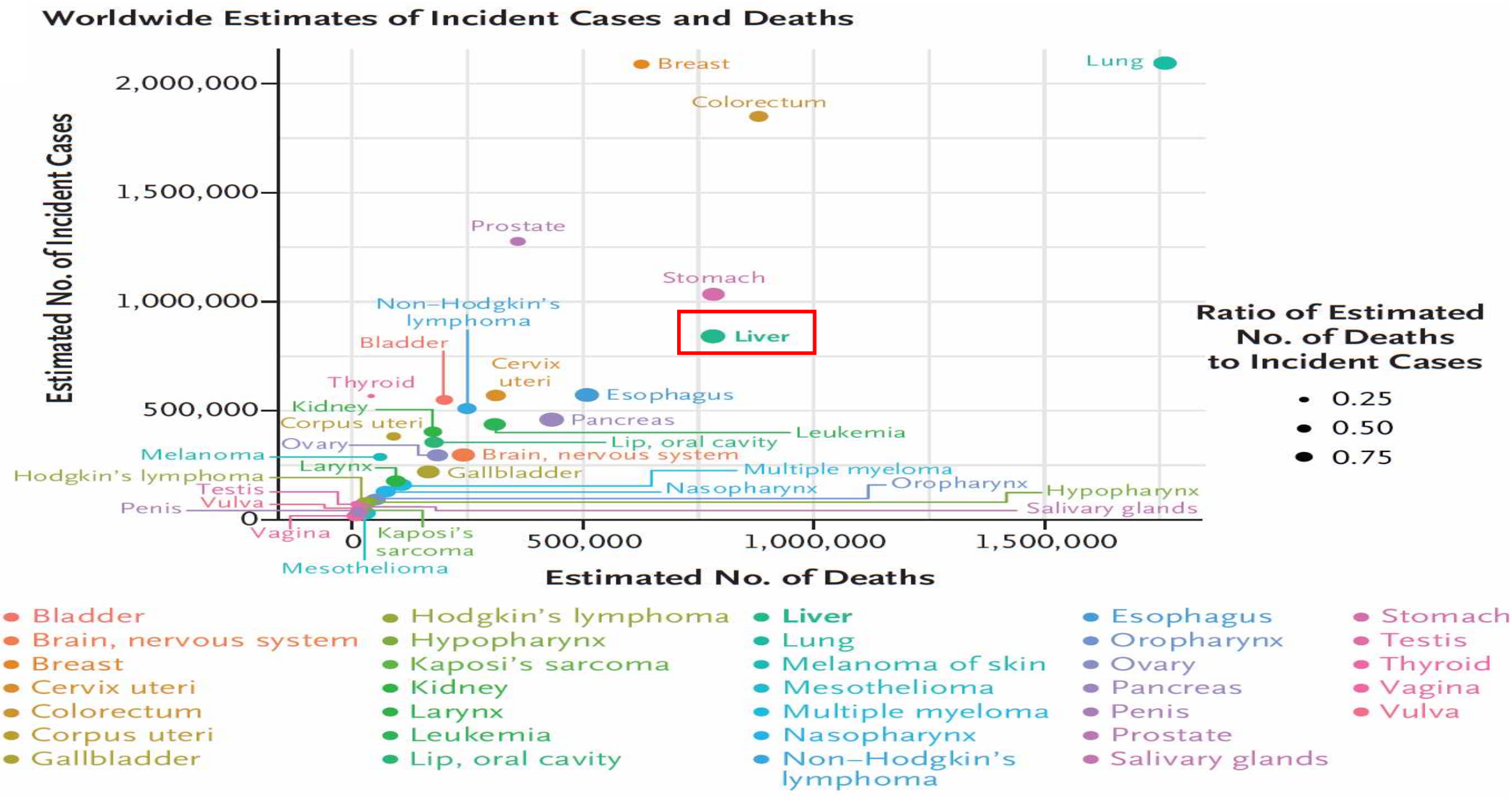
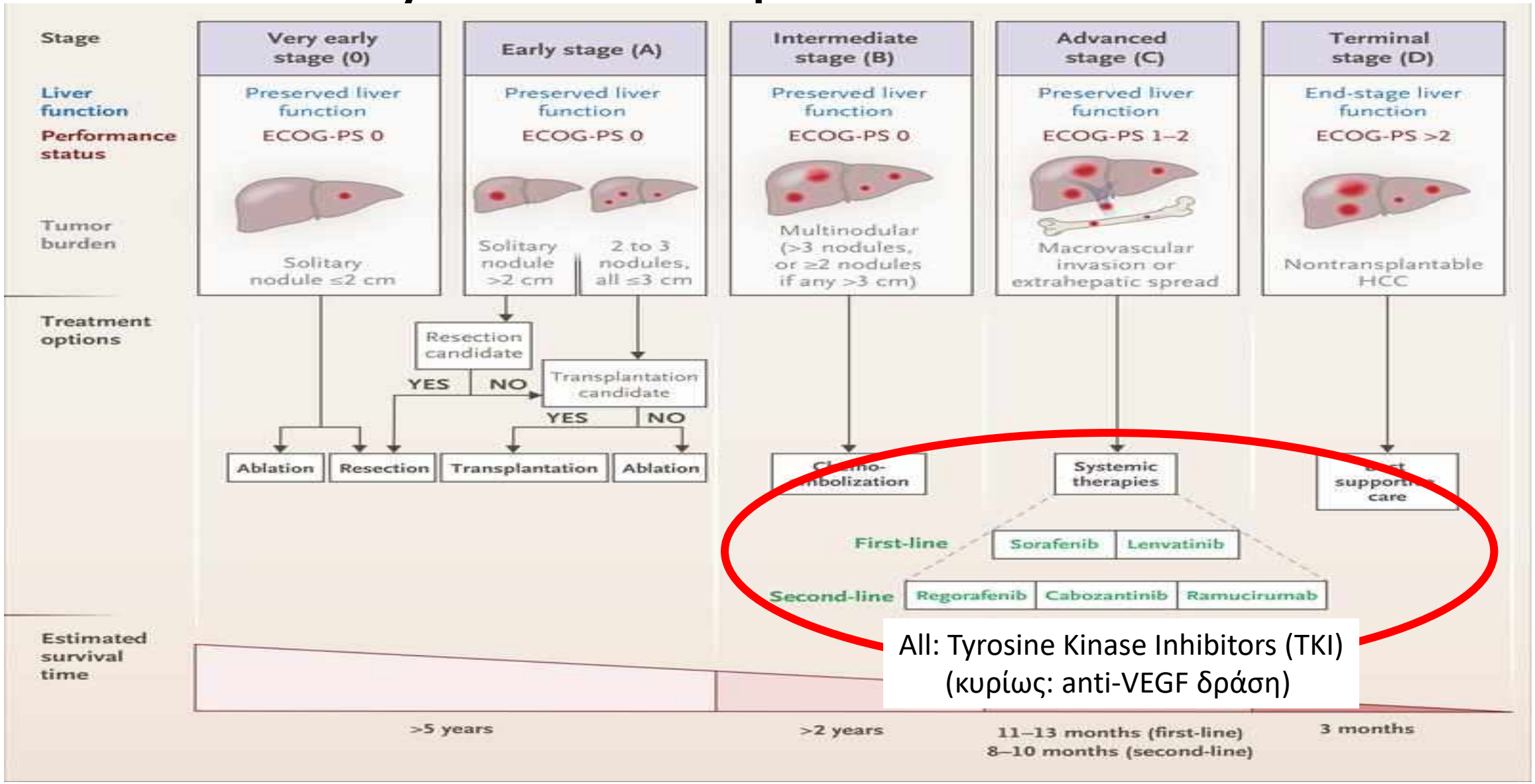
15η Πανελλήνια Εκπαιδευτική Συνάντηση ΕΛΙΓΑΣΤ
Αθήνα 7 Μαρτίου 2020

Επιπολασμός Ηπατοκυτταρικού καρκίνου (ΗΚΚ)




Worldwide Estimates of Incident Cases and Deaths
Estimated No. of Incident Cases
2,000,000
1,500,000
1,000,000
500,000
0
Breast
Lung
Colorectum
Prostate
Stomach
Liver
Non–Hodgkin's lymphoma
Bladder
Cervix uteri
Thyroid
Esophagus
Kidney
Pancreas
Corpus uteri
Leukemia
Lip, oral cavity
Ovary
Melanoma
Brain, nervous system
Larynx
Gallbladder
Multiple myeloma
Hodgkin's lymphoma
Nasopharynx
Oropharynx
Hypopharynx
Testis
Vulva
Penis
Salivary glands
Vagina
Kaposi's sarcoma
Mesothelioma
0
500,000
1,000,000
1,500,000
Estimated No. of Deaths
Ratio of Estimated No. of Deaths to Incident Cases
0.25
0.50
0.75
Bladder
Brain, nervous system
Breast
Cervix uteri
Colorectum
Corpus uteri
Gallbladder
Hodgkin's lymphoma
Hypopharynx
Kaposi's sarcoma
Kidney
Larynx
Leukemia
Lip, oral cavity
Liver
Lung
Melanoma of skin
Mesothelioma
Multiple myeloma
Nasopharynx
Non–Hodgkin's lymphoma
Esophagus
Oropharynx
Ovary
Pancreas
Penis
Prostate
Salivary glands
Stomach
Testis
Thyroid
Vagina
Vulva

BCLC system for Hepatocellular carcinoma



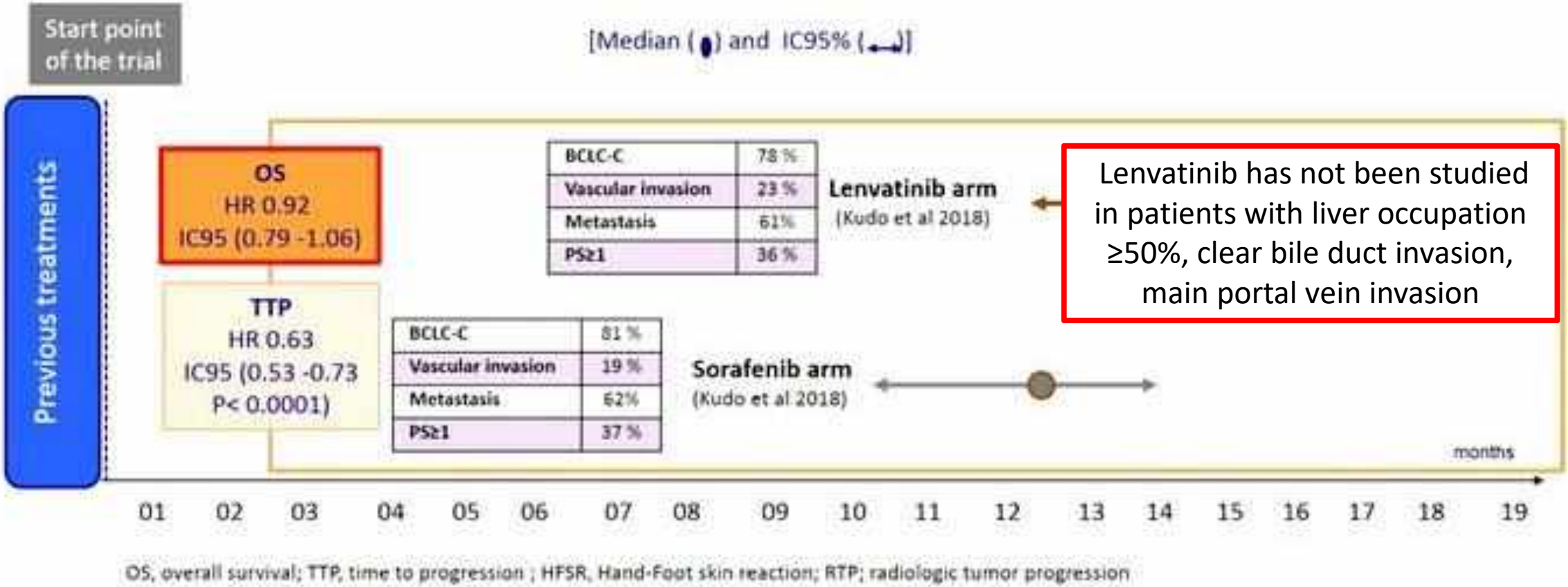
All: Tyrosine Kinase Inhibitors (TKI)
(κυρίως: anti-VEGF δράση)

HCC Treatment Landscape: First-line Systemic Therapy

Agent	FDA Indication	Key Trial
Sorafenib (TKI)	Unresectable HCC	SHARP
Lenvatinib (TKI)	First-line treatment of patients with unresectable HCC	REFLECT

Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial

Reflect trial (Lenvatinib vs Sorafenib)



Lenvatinib has not been studied in patients with liver occupation ≥50%, clear bile duct invasion, main portal vein invasion

OS, overall survival; TTP, time to progression ; HFSR, Hand-Foot skin reaction; RTP; radiologic tumor progression

Adverse events: Lenvatinib vs Sorafenib

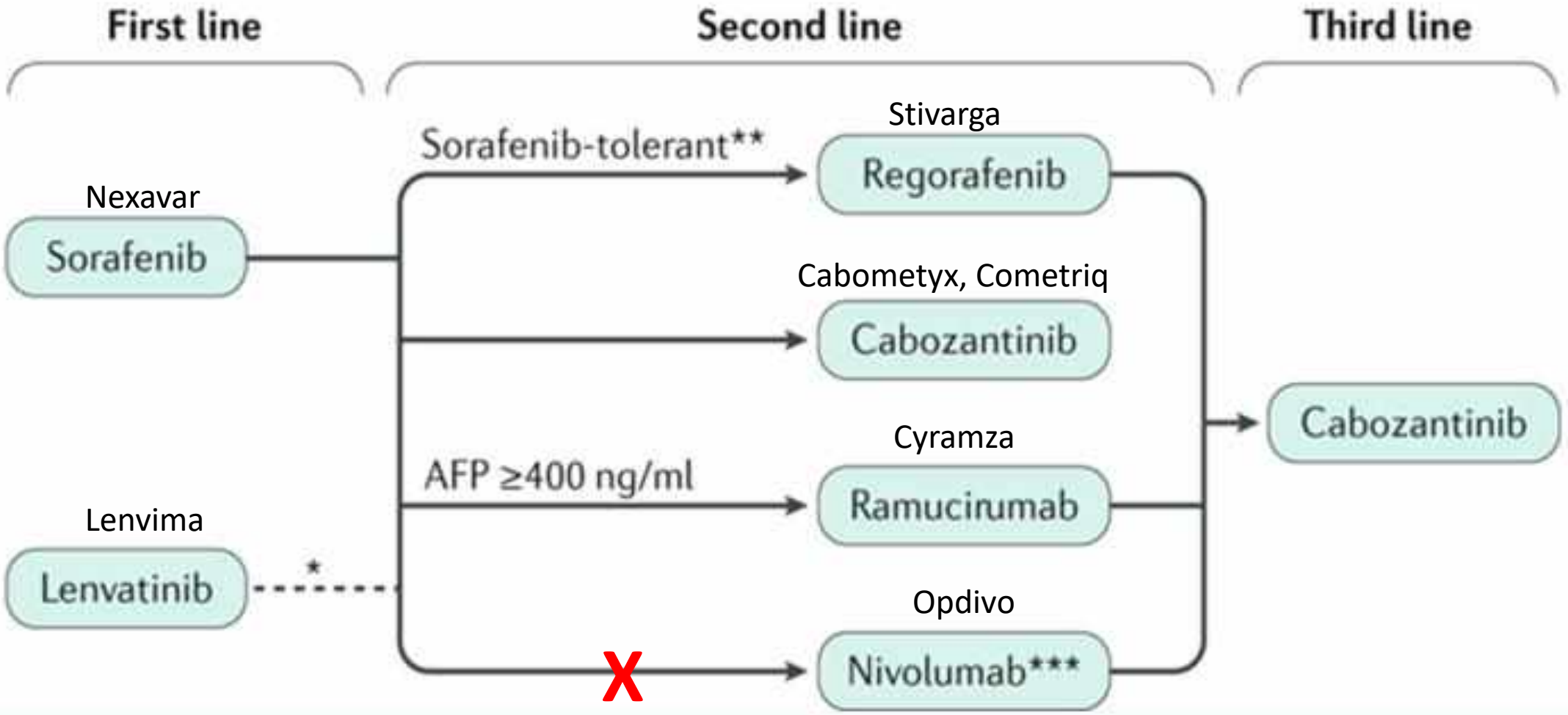
	Lenvatinib (n=476)	Sorafenib (n=475)
Total treatment-emergent adverse events	470 (99%)	472 (99%)
Total treatment-related treatment-emergent adverse events	447 (94%)	452 (95%)
Treatment-emergent adverse events of grade ≥3	357 (75%)	316 (67%)
Treatment-related treatment-emergent adverse events of grade ≥3	270 (57%)	231 (49%)
Serious treatment-emergent adverse events	205 (43%)	144 (30%)
Serious treatment-related treatment-emergent adverse events	84 (18%)	48 (10%)

HCC Treatment Landscape: Second-Line and Beyond

Approved for Patients Previously Treated With Sorafenib		
Agent	**Key Trials**	**Population**
Cabozantinib (TKI)	CELESTIAL	Child-Pugh A
Nivolumab (anti-PD1)*	CheckMate-040	Child-Pugh A/B7
Pembrolizumab (anti-PD1)*	KEYNOTE-224, -240	Child-Pugh A
Ramucirumab (TKI)	REACH-2	Child-Pugh A, AFP ≥ 400 ng/mL
Regorafenib (TKI)	RESORCE	Child-Pugh A, tolerated first-line sorafenib

*anti-PD1 immunotherapy: Approved by the FDA based on phase II data, not approved by the EMA

Abou-Alfa. NEJM. 2018;379:54. El-Khoueiry. Lancet. 2017;389:2492. Zhu. Lancet Oncol.2018;19:940.
Bruix. Lancet. 2017;389:56. Zhu. Lancet Oncol. 2019;20:282. Finn. ASCO 2019. Abstr 4004.



i) all phase III second-line studies to date have been after prior sorafenib, not lenvatinib;

ii) the CELESTIAL (cabozantinib) trial enrolled also third line patients

2nd line therapy for HCC

Drug, Target, Route, Schedule

	Regorafenib	Cabozantinib	Ramucirumab
Drug Class	TKI	TKI	moAb
Targets	VEGFR1-3, RAF, KIT, RET, PDGFR, TIE2, FGFR 1	VEGFR 1-3, MET, AXL	VEGFR 2
Route of administration	Oral	Oral	IV
Schedule	Once daily, 3 weeks on / 1 week off	Once daily, continuously	Every 2 weeks

2nd line therapy for HCC

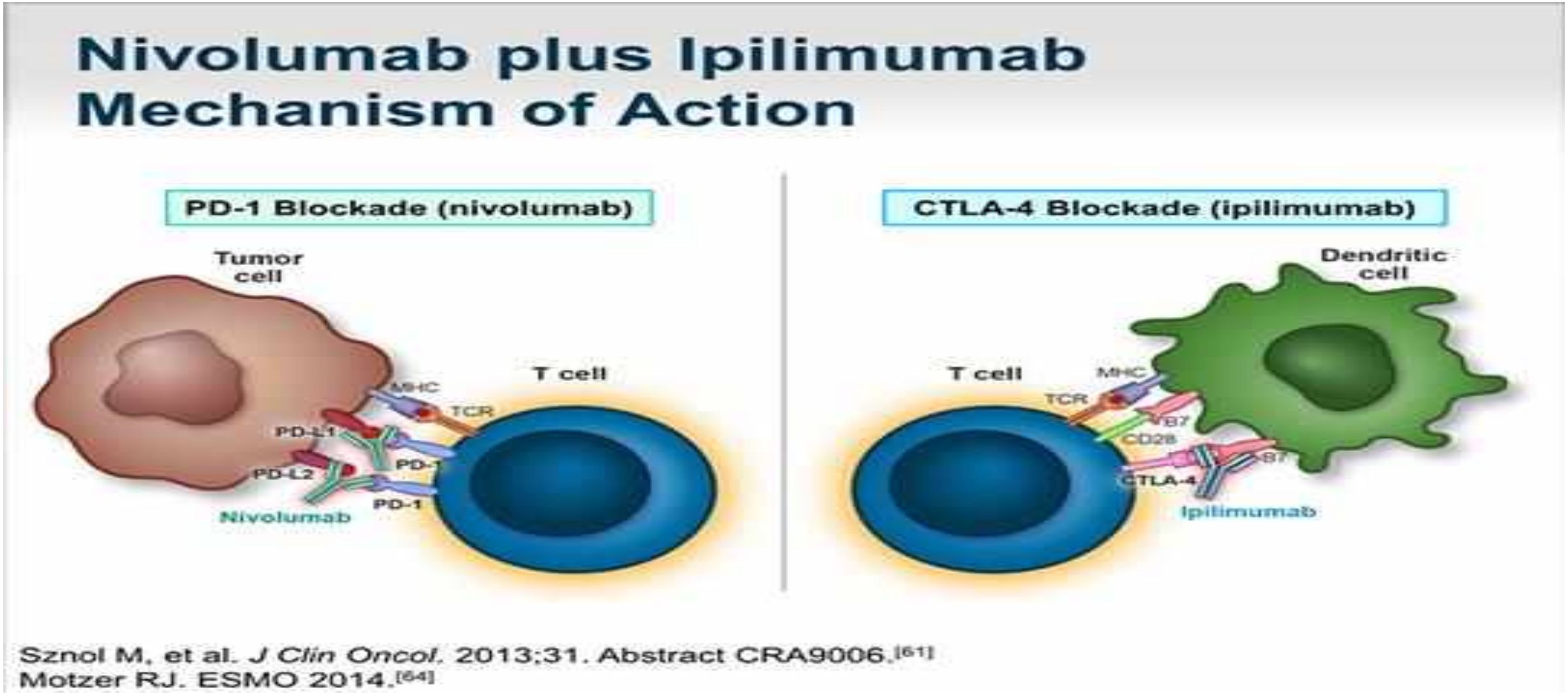
Grade ≥3 AEs in ≥10% of Patients

	Regorafenib	Cabozantinib	Ramucirumab
Skin toxicity	13%	17%	--
Hypertension	15%	16%	13%
AST increase	10%	12%	--
Bilirubin increase	10%	--	--
Fatigue	--	10%	--
Diarrhea	--	10%	--

Το (άμεσο) μέλλον στη συστηματική θεραπεία του ΗΚΚ

- Συνδυασμός ανοσοθεραπειών με διαφορετικό μηχανισμό δράσης
- Συνδυασμός TKI (anti-VEGF) και ανοσοθεραπείας

The future: combination of immunotherapy



Sznol M, et al. *J Clin Oncol.* 2013;31. Abstract CRA9006.[61]
Motzer RJ. ESMO 2014.[64]

CheckMate 040: Nivolumab + Ipilimumab for Advanced HCC as Second-Line

Patients with advanced HCC and prior sorafenib treatment, intolerance, or progression; uninfected or infected with HBV or HCV; CP score A5-A6; ECOG PS 0-1

Randomized 1:1:1

Arm A
Nivolumab 1 mg/kg **+ Ipilimumab** 3 mg/kg Q3W x 4 doses

Arm B
Nivolumab 3 mg/kg + **Ipilimumab** 1 mg/kg Q3W x 4 doses

Arm C
Nivolumab 3 mg/kg Q22W + **Ipilimumab** 1 mg/kg Q6W

Nivolumab 240 mg IV Q2W flat dose

- Primary endpoints: safety, tolerability (NCI CTCAE 4.0), ORR and DOR (investigator assessment)
- Secondary endpoints: DCR, PFS, OS, TTP, TTR

CheckMate 040: nivolumab + ipilimumab in patients with advanced hepatocellular carcinoma (aHCC)

Objective:

To assess the safety and efficacy of nivolumab (NIVO; PD-1 inhibitor) plus ipilimumab (IPI; CTLA-4 inhibitor) in the CheckMate-040 study, the first prospective study of this immunotherapy combination in patients with aHCC treated with sorafenib

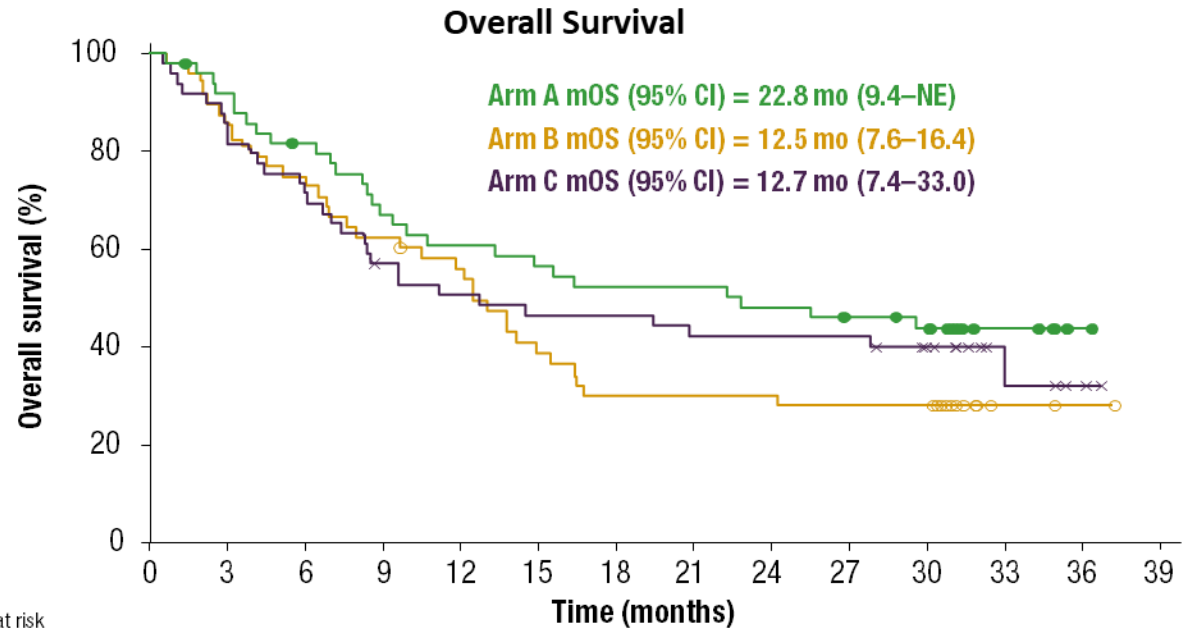
Methods:

Patients treated with SOR were randomized to 3 arms: [A] NIVO 1 mg/kg + IPI 3 mg/kg Q3W (4 doses) or [B] NIVO 3 mg/kg + IPI 1 mg/kg Q3W (4 doses), each followed by NIVO 240 mg Q2W, or [C] NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W, until intolerable toxicity or disease progression. Primary endpoints were safety and tolerability, objective response rate (ORR), and duration of response (DOR; investigator assessment using RECIST v1.1).

Main Findings:

- Investigator-assessed ORR: 32%, 27%, and 29% in arms A, B, and C, respectively, concordant with BICR-assessed responses; median DOR: 17.5, 22.2, and 16.6 months, respectively.
- Any-grade immune-mediated hepatic AEs: 20%, 12%, and 6% of patients in arms A, B, and C, respectively
  - The proportion of hepatic events (median time to resolution) that resolved: 90% (6.6 weeks) in arm A, 83% (7.9 weeks) in arm B, and 67% (6.1 weeks) in arm C.
  - Of the 10, 6, and 3 patients who had an immune-mediated hepatic AE, 7, 3, and 2 patients received high-dose glucocorticoids (≥ 40 mg of prednisone per day or equivalent) for a median (range) of 2 weeks (0.4–147.6), 1 week (0.6 –1.1), and 3 weeks (2.0–3.0) in arms A, B, and C, respectively.
  - No patients who were rechallenged with NIVO or IPI after experiencing an immune-mediated hepatic AE experienced a recurrence of the event.

Sangro B, et al, Abstract 200



AE, adverse event; BICR, blinded independent central review; CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte antigen; mOS, median overall survival; NE, not estimable; PD-1, programmed death-1; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Conclusions:

NIVO + IPI demonstrated durable responses and a manageable safety profile in patients with aHCC treated with SOR.

CheckMate 040: Treatment-Related AEs

TRAEs, n (%)	Arm A: NIVO1/IPI3 Q3W (n = 49)		Arm B: NIVO3/IPI1 Q3W (n = 49)		Arm C: NIVO3 Q2W/IPI1 Q6W (n = 48)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any TRAE	46 (94)	26 (53)	35 (71)	14 (29)	38 (79)	15 (31)
Skin and subcutaneous tissue	30 (61)	4 (8)	24 (49)	2 (4)	23 (48)	1 (2)
Investigations (including liver laboratory abnormalities	24 (49)	16 (33)	21 (43)	11 (22)	15 (31)	7 (15)
General and administration site	19 (39)	2 (4)	15 (31)	0	16 (33)	0
Gastrointestinal	18 (37)	3 (6)	18 (37)		17 (35)	2 (4)
Endocrine	16 (33)				9 (19)	1 (2)
Metabolism and nutrition					6 (13)	1 (2)
Respiratory, thoracic, and me			2 (4)	0	3 (6)	0
Nervous system		0	6 (12)	0	2 (4)	0
Musculoskeletal and connecti	6 (12)	0	3 (6)	0	6 (13)	0
Hepatobiliary	3 (6)	3 (6)	1 (2)	0	1 (2)	0

8.9% patients discontinuing study treatment due to treatment-related adverse events

Although rates of any-grade TRAEs were higher in Arm A, the types of TRAEs observed were similar across arms. No new safety signals were observed, and most TRAEs were manageable and reversible. Serious TRAEs were reported in 11 patients (22%) in Arm A, 9 patients (18%) in Arm B, and 7 patients (15%) in Arm C. One serious hepatobiliary disorder reported in Arm A (drug-induced liver injury); 3 serious hepatic investigations reported (elevated AST in Arm A; elevated AST and elevated ALT in Arm B).

FDA Grants Priority Review for Nivolumab Plus Ipilimumab in Advanced HCC

Nichole Tucker
Published Online:7:42 PM, Mon November 11, 2019

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A supplemental Biologics License Application (sBLA) for the combination of nivolumab (Opdivo) and ipilimumab (Yervoy) for the treatment of patients with advanced hepatocellular carcinoma (HCC) previously treated with sorafenib (Nexavar) has been accepted by the FDA and given Priority Review status. The sBLA was given a Prescription Drug User Fee Act goal date of March 10, 2020, according to a press release from Bristol-Myers Squibb.[1]

CheckMate 9DW: Nivolumab + Ipilimumab for Advanced HCC as First-Line

- Multicenter, randomized, open-label, phase III trial

Patients with advanced HCC;
no previous systemic therapy,
Child-Pugh 5 or 6;
ECOG PS ≤ 1
(Planned N = 1084)

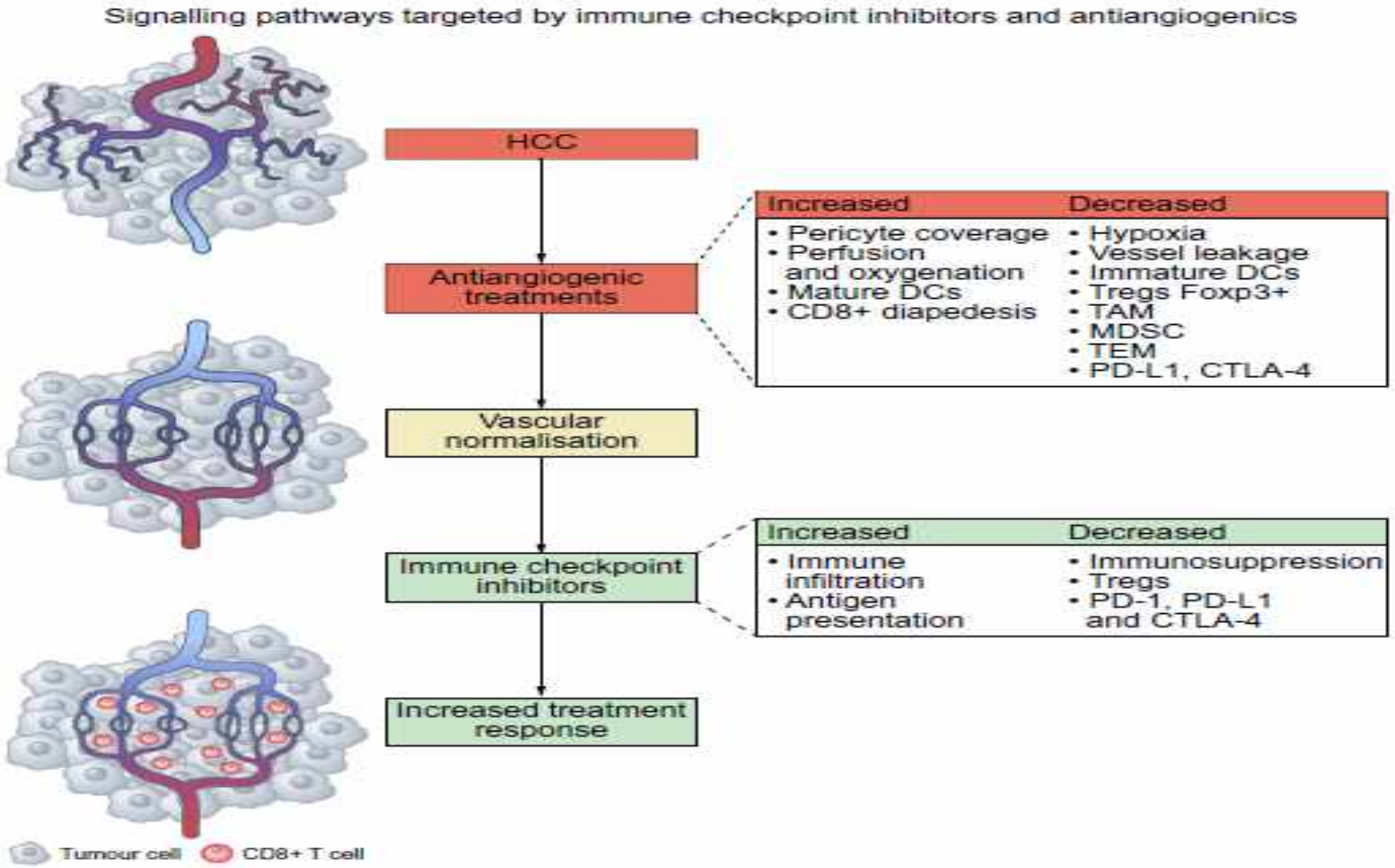
Nivolumab* + Ipilimumab

Sorafenib or Lenvatinib

- Primary endpoints: OS
- Secondary endpoints: ORR, DOR, TTSD

*Nivolumab as monotherapy 1st line: no efficacy

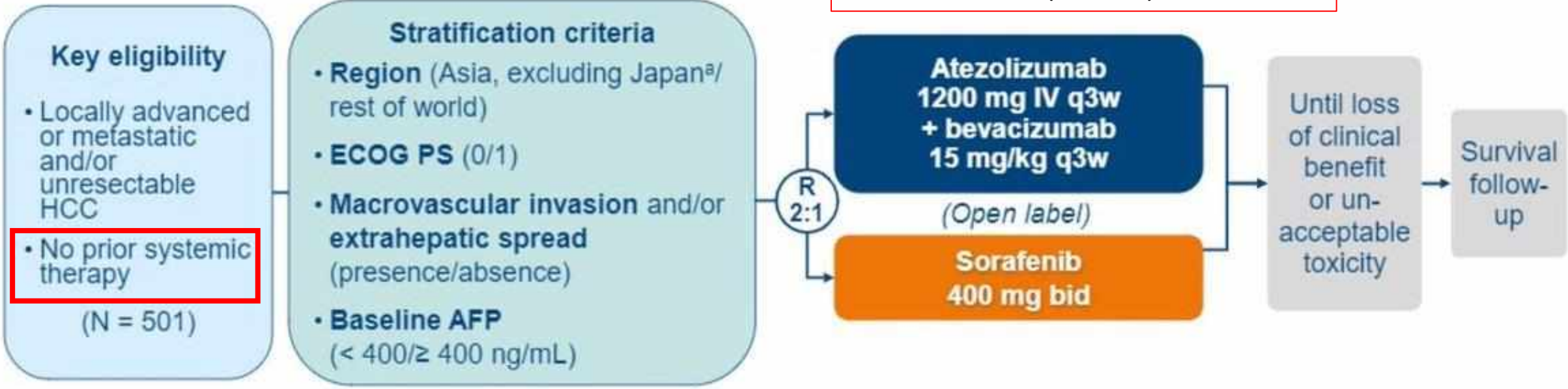
The future: combination anti-VEGF and Immunotherapy*



*** Anti-VEGF agents have also immunomodulatory effects**
Anti-VEGF-induced hypoxia leads to escape from immune surveillance

IMbrave150 Study Design

First line systemic therapy
Atezolimumab (Tecentriq): anti-PD-L1
Bevacizumab (Avastin): anti-VEGF



Co-primary endpoints
- OS
- IRF-assessed PFS per RECIST 1.1

Secondary endpoints include
- IRF-assessed ORR per RECIST 1.1 and HCC mRECIST
- PROs: TTD[b] of QOL, physical and role functioning (EORTC QLQ-C30)

Exploratory PRO endpoints
- TTD[c] of symptoms (EORTC QLQ-HCC18)
- Patients (%) with clinically meaningful deterioration in QOL, physical and role functioning

EORTC, European Organisation for Research and Treatment of Cancer; IRF, independent review facility; mRECIST, modified RECIST; TTD, time to deterioration.
[a] Japan is included in rest of world. [b] Time from randomization to first decrease from baseline of ≥ 10 points maintained for 2 consecutive assessments or 1 assessment followed by death from any cause within 3 weeks. [c] Time from randomization to the first increase from baseline of ≥ 10 points in the symptom scales maintained for 2 consecutive assessments or 1 assessment followed by death from any cause within 3 weeks.

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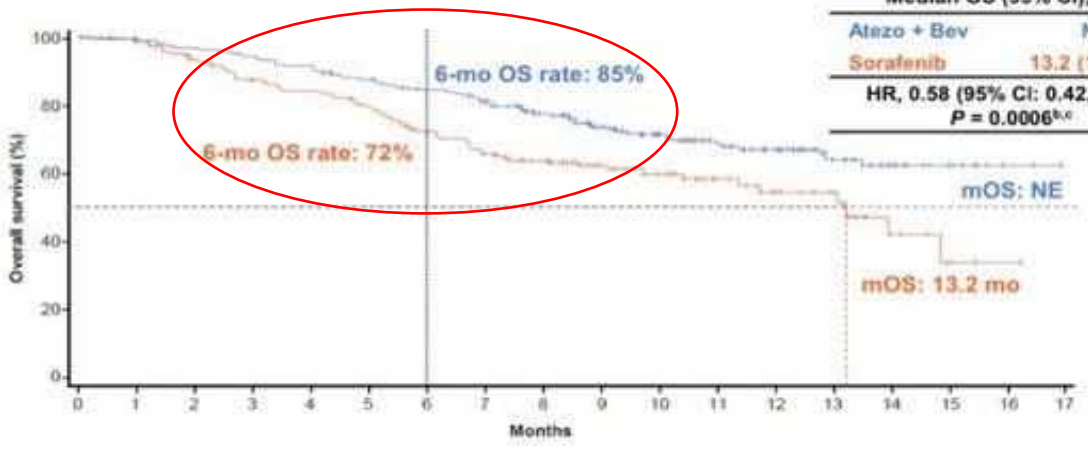
IMbrave 150 Phase 3 Study

Atezolizumab in Combination With Bevacizumab Compared With Sorafenib in Patients With Untreated Locally Advanced or Metastatic Hepatocellular Carcinoma

SINGAPORE 2019 ESMO ASIA

SINGAPORE
22-24 NOVEMBER 2019

OS: co-primary endpoint



Median OS (95% CI), mo[a]	
Atezo + Bev	NE
Sorafenib	13.2 (10.4, NE)
HR, 0.58 (95% CI: 0.42, 0.79)[b] *P* = 0.0006[b,c]	

No. at risk

Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE
Atezo + Bev	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE

NE, not estimable. [a] 96 patients (29%) in the Atezo + Bev arm vs 65 (39%) in the sorafenib arm had an event. [b] HR and *P* value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [c] The 2-sided *P* value boundary based on 161 events is 0.0033. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

Conclusions

IMbrave150 demonstrated statistically significant and clinically meaningful improvement with atezolizumab + bevacizumab over sorafenib for OS and IRF-assessed PFS per RECIST 1.1

- OS HR, 0.58 (95% CI: 0.42, 0.79); *P* = 0.0006
- IRF-PFS HR, 0.59 (95% CI: 0.47, 0.76); *P* < 0.0001

} Co-primary endpoints in ITT population

PFS and OS benefits were generally consistent across subgroups

Statistically significant and clinically meaningful improvements were seen in ORR and responses were durable with atezolizumab + bevacizumab

The safety and tolerability profile of atezolizumab + bevacizumab was in line with the known safety profiles of each individual component and the underlying disease

Treatment with atezolizumab + bevacizumab resulted in a clinically meaningful delay in deterioration of patient-reported quality of life vs sorafenib

Atezolizumab + bevacizumab should be considered a practice-changing treatment for patients with unresectable HCC who have not received prior systemic therapy

Results were presented at ESMO Asia 2019 and study investigators concluded that the combination of atezolizumab plus bevacizumab is a promising first-line treatment of unresectable Hepatocellular Carcinoma.

Atezolizumab/Bevacizumab Developers Submit Application to FDA for Unresectable HCC

Nichole Tucker
Published Online:4:00 PM, Mon January 27, 2020

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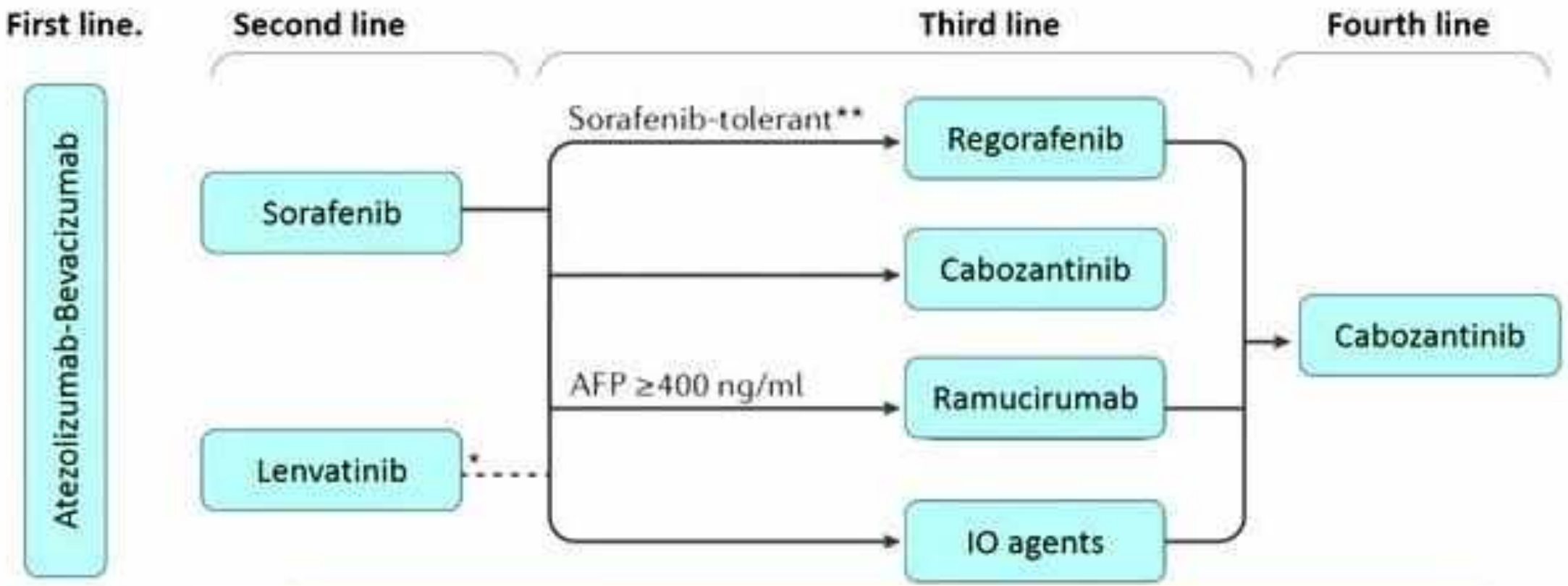
A supplemental Biologics License Application (sBLA) has been submitted to the FDA for the combination of atezolizumab (Tecentriq) and bevacizumab (Avastin) for the treatment of patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy, according to a press release from Roche.[1]

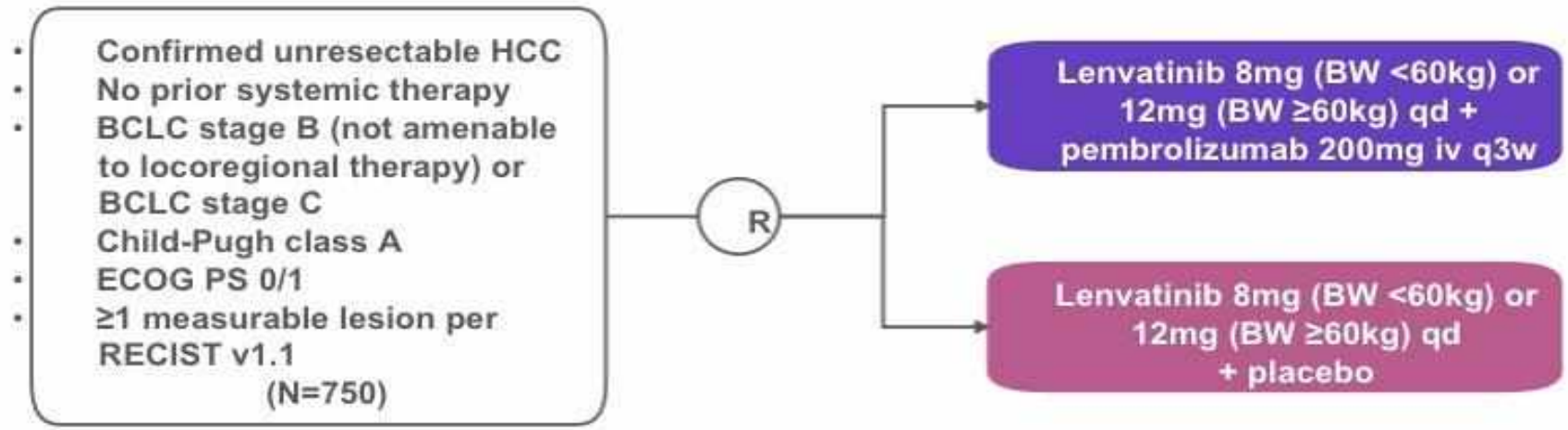
The near future for systemic therapy?



anti-VEGF

anti-PD-1

Phase III LEAP-002 trial of lenvatinib + pembrolizumab in 1L advanced HCC is currently recruiting1



- **Co-primary endpoints:** PFS BICR-assessed by RECIST v1.1, OS
- **Key secondary endpoints:** ORR,* DoR,* DCR,* TTP,* PFS,‡ safety and pharmacokinetics

*Per RECIST v1.1 and HCC mRECIST; ‡Per HCC mRECIST
BICR, blinded independent central review
BW, body weight; qd, once daily; TTP, time to progression

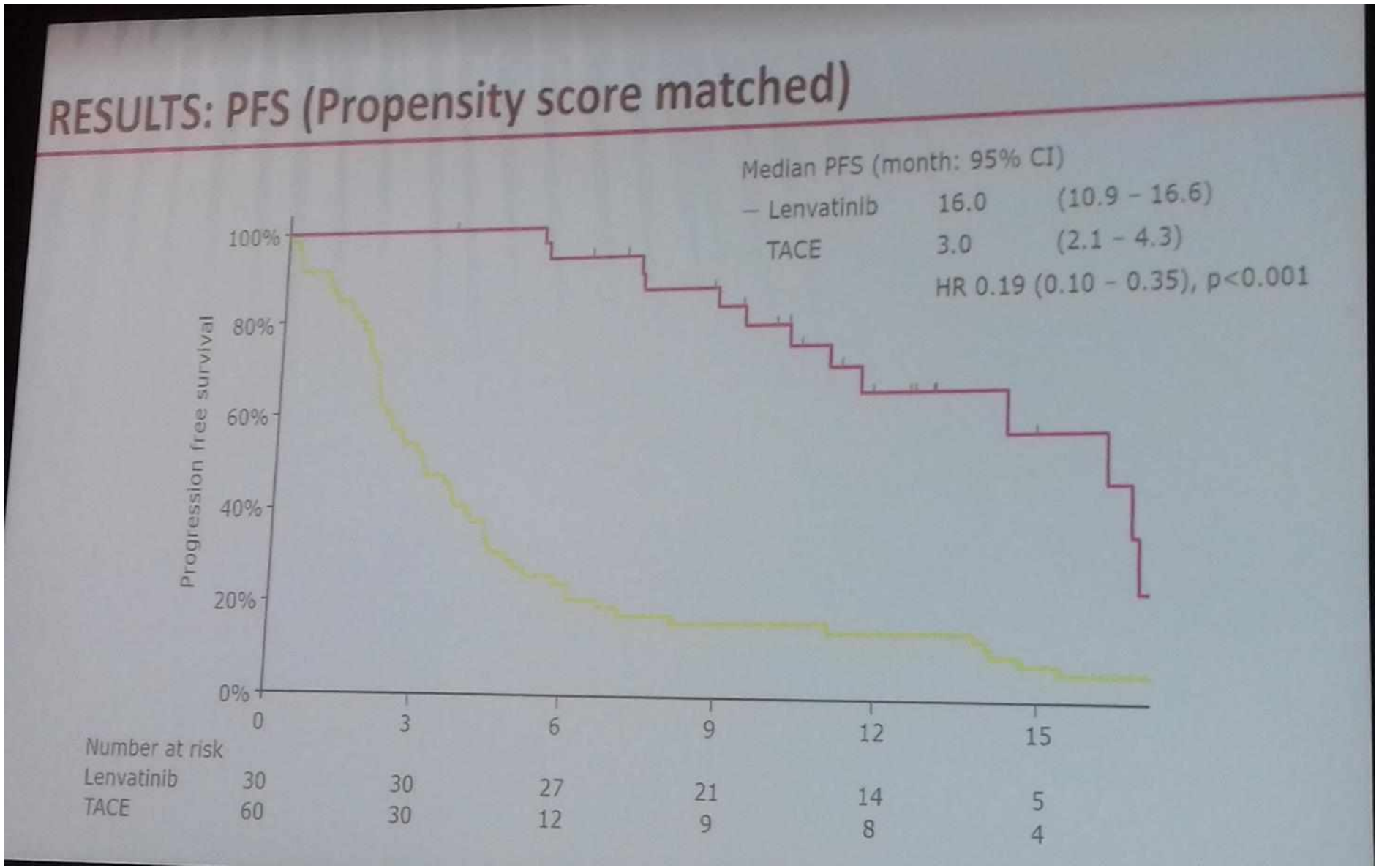
1. NCT03713593

Table 2. Ongoing trials of novel combinations of molecular therapies for HCC.

Trial name/ identifier	Setting	Treatment	Primary endpoints	Study type	Planned enrollment, n
Phase I/II trials					
GO30140/ NCT02715531*	Advanced HCC/first-line	Bevacizumab + atezolizumab	Safety, ORR, PFS	Phase Ib	430 (across all cohorts)
NCT03006926	Advanced HCC/first-line	Lenvatinib + pembrolizumab	Dose escalation: Safety, DLTs Dose expansion: ORR, DOR	Phase Ib (dose-escalation and dose-expansion)	97
NCT03418922	Advanced HCC/first-line	Lenvatinib + nivolumab	Part 1: DLTs, safety Part 2: Safety	Phase Ib (part 1 and part 2)	26
NCT03895970	Advanced hepatobiliary tumors/second-line	Lenvatinib + pembrolizumab	ORR, DCR, PFS	Phase IIb	50
CheckMate 040/ NCT01658878*	Advanced HCC/first- or second-line	Cabozantinib + nivolumab +/– ipilimumab	Safety, ORR	Phase I/II (dose-escalation, dose-expansion)	620 (across all cohorts)
COSMIC-021/ NCT03170960	Advanced solid tumors, HCC/first-line	Cabozantinib + atezolizumab	Dose escalation: MTD, Recommended dose Dose expansion: ORR	Phase Ib (dose-escalation and dose-expansion)	1000 (across all cohorts)
CaboNivo/ NCT03299946	Locally advanced HCC/neoadjuvant	Cabozantinib + nivolumab	Safety, number of patients who complete preoperative treatment and proceed to surgery	Phase Ib	15
CAMILLA/ NCT03539822	Advanced GI tumors, HCC/second-line	Cabozantinib + durvalumab	MTD	Phase Ib	30
NCT03347292	Advanced HCC/first-line	Regorafenib + pembrolizumab	Safety, DLTs	Phase Ib (dose-escalation and dose-expansion	40
REGOMUNE/ NCT03475953	Advanced GI tumors, HCC/second-line	Regorafenib + avelumab	Part 1: Recommended phase II dose of regorafenib art 2: ORR	Phase I/II (part 1 and part 2)	212
NCT02572687	Advanced solid tumors, HCC/second-line and AFP ≥1.5x upper limit of normal	Ramucirumab + durvalumab	DLTs	Phase I	114
NCT02082210	Advanced solid tumors, HCC/second-line	Ramucirumab + emibetuzumab	Part A: DLTs Part B: ORR	Phase I/II	97
NCT02423343	Advanced solid tumors, HCC/second-line and AFP ≥200 ng/mL	Galunisertib + nivolumab	Phase Ib: MTD	Phase Ib/II (dose escalation and cohort expansion)	75
Phase III trials					
IMbrave150/ NCT03434379	Advanced HCC/first-line	Atezolizumab + bevacizumab *vs.* sorafenib	OS, PFS	Phase III, randomised, open-label	480
LEAP-002/ NCT03713593	Advanced HCC/first-line	Lenvatinib + pembrolizumab *vs.* lenvatinib + placebo	PFS, OS	Phase III, randomised, double-blinded	750
COSMIC-312/ NCT03755791	Advanced HCC/first-line	Cabozantinib + atezolizumab *vs.* sorafenib *vs.* cabozantinib	PFS, OS	Phase III randomised, open-label	740

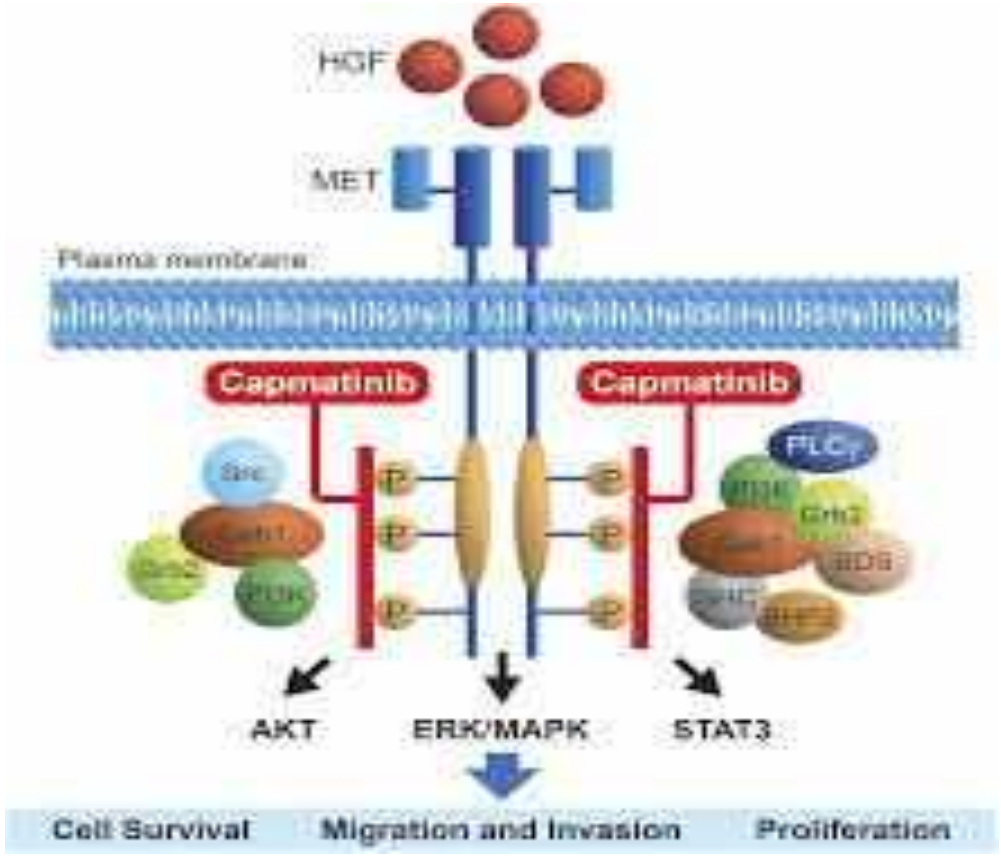
TACE vs Systemic Therapy

RESULTS: PFS (Propensity score matched)



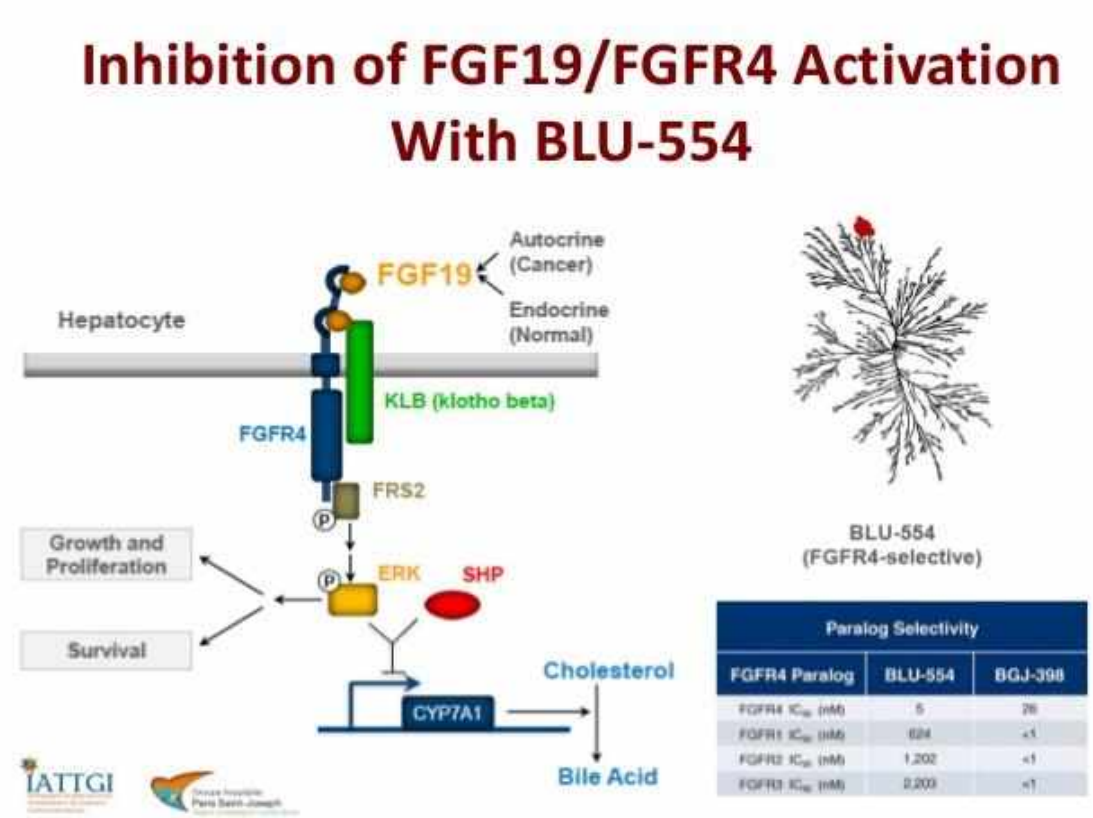
Το (απώτερο) μέλλον στη συστηματική θεραπεία του ΗΚΚ

MET inhibitors (Tepotinib / Capmatinib)



FGFR4 inhibitors

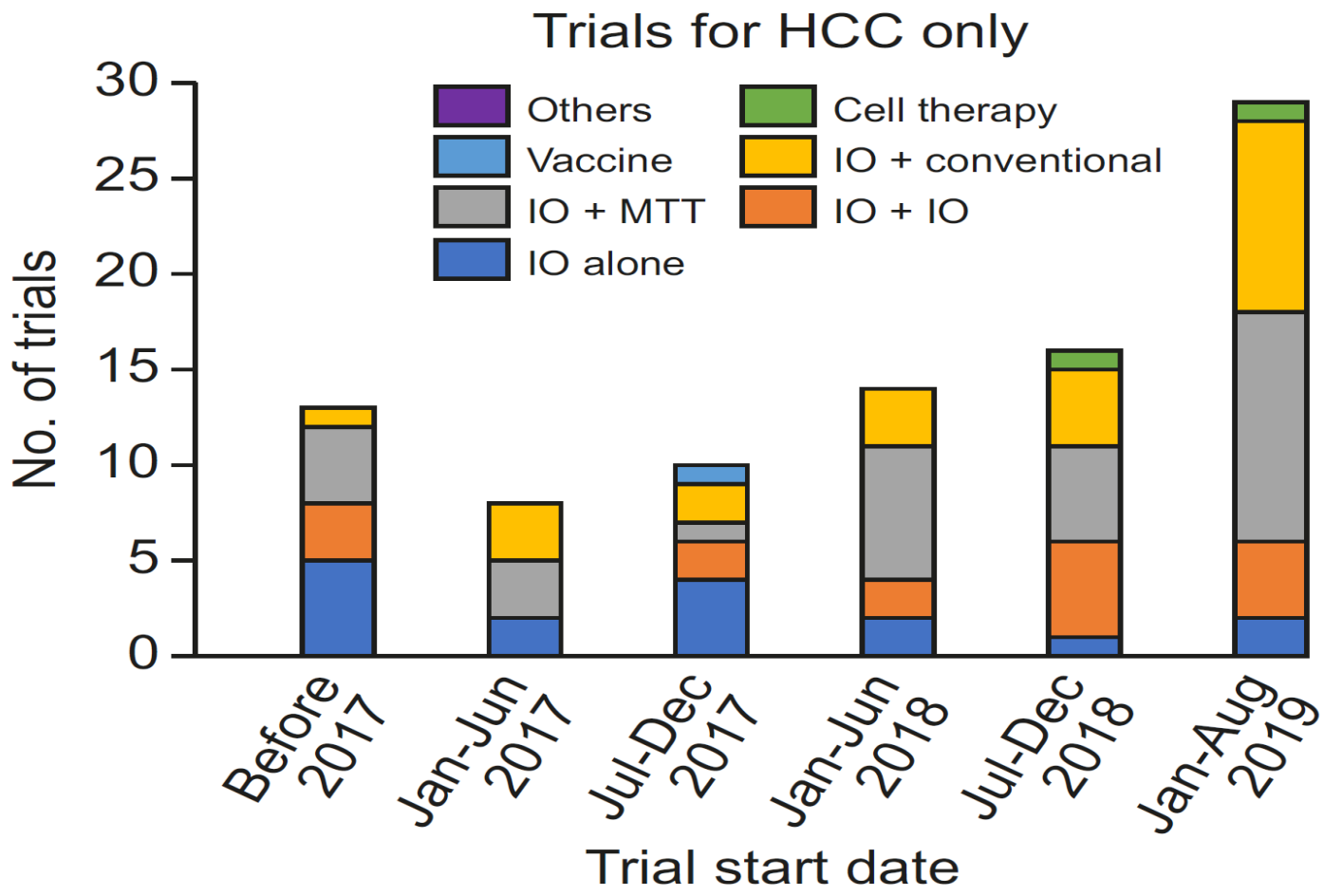
FGF19 has been correlated with early recurrence and resistance to sorafenib



Τι επιπλέον έχουμε ανάγκη?

- CheckMate-40 trial: OS for those with PD-L1 ≥1% vs <1% were 28mo vs. 16mo (p = 0.032)
    - Only aFp in ramucirumab
- (Neo)-Adjuvant therapy with nivolumab or nivolumab/ipilimumab
- Trials: very strict criteria regarding viral replication, severity of liver disease etc

Number of trials for HCC based on PD1/PDL1



VOLUME 72 No. 2 FEBRUARY 2020

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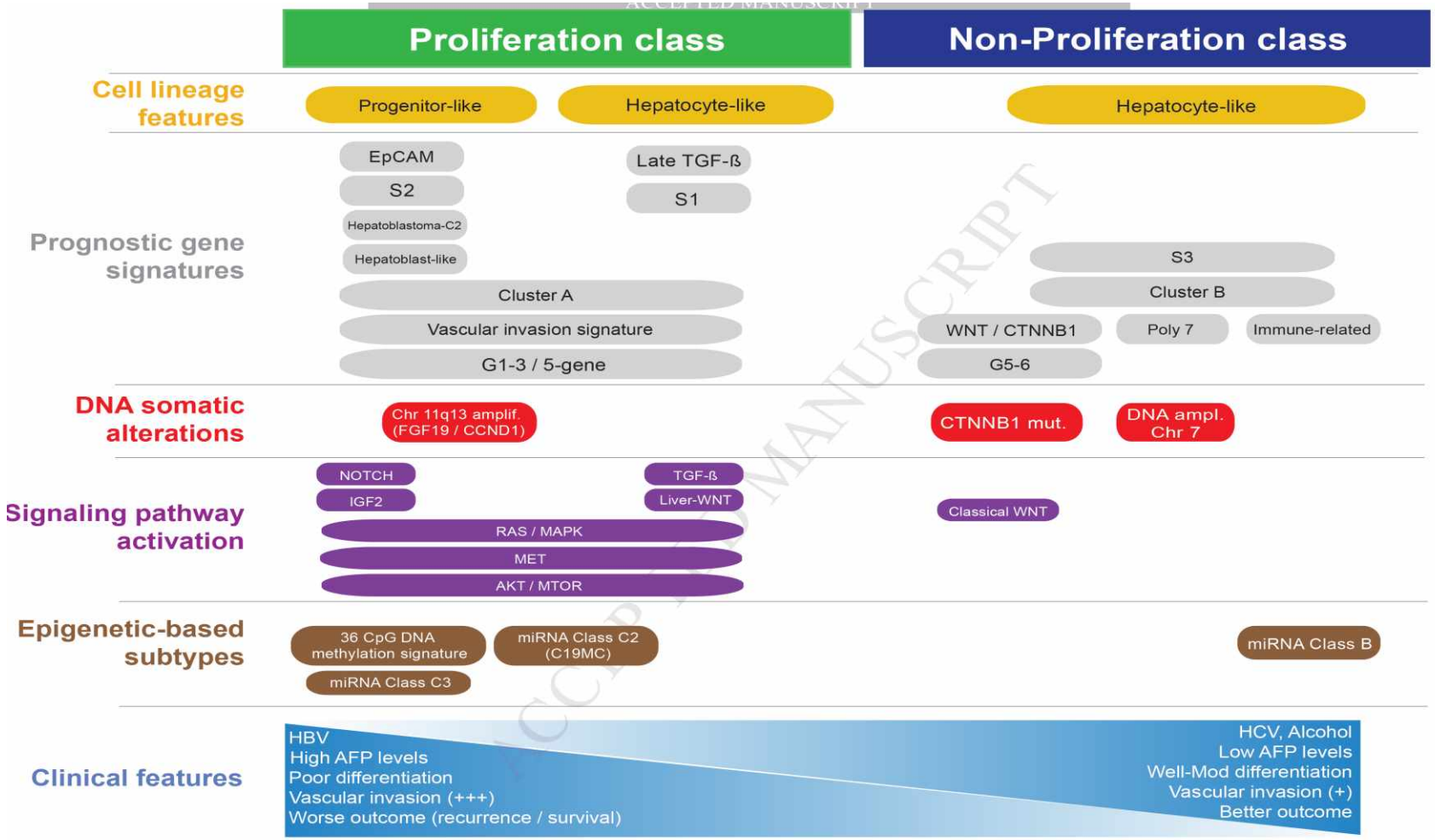
The Home of Liver Research

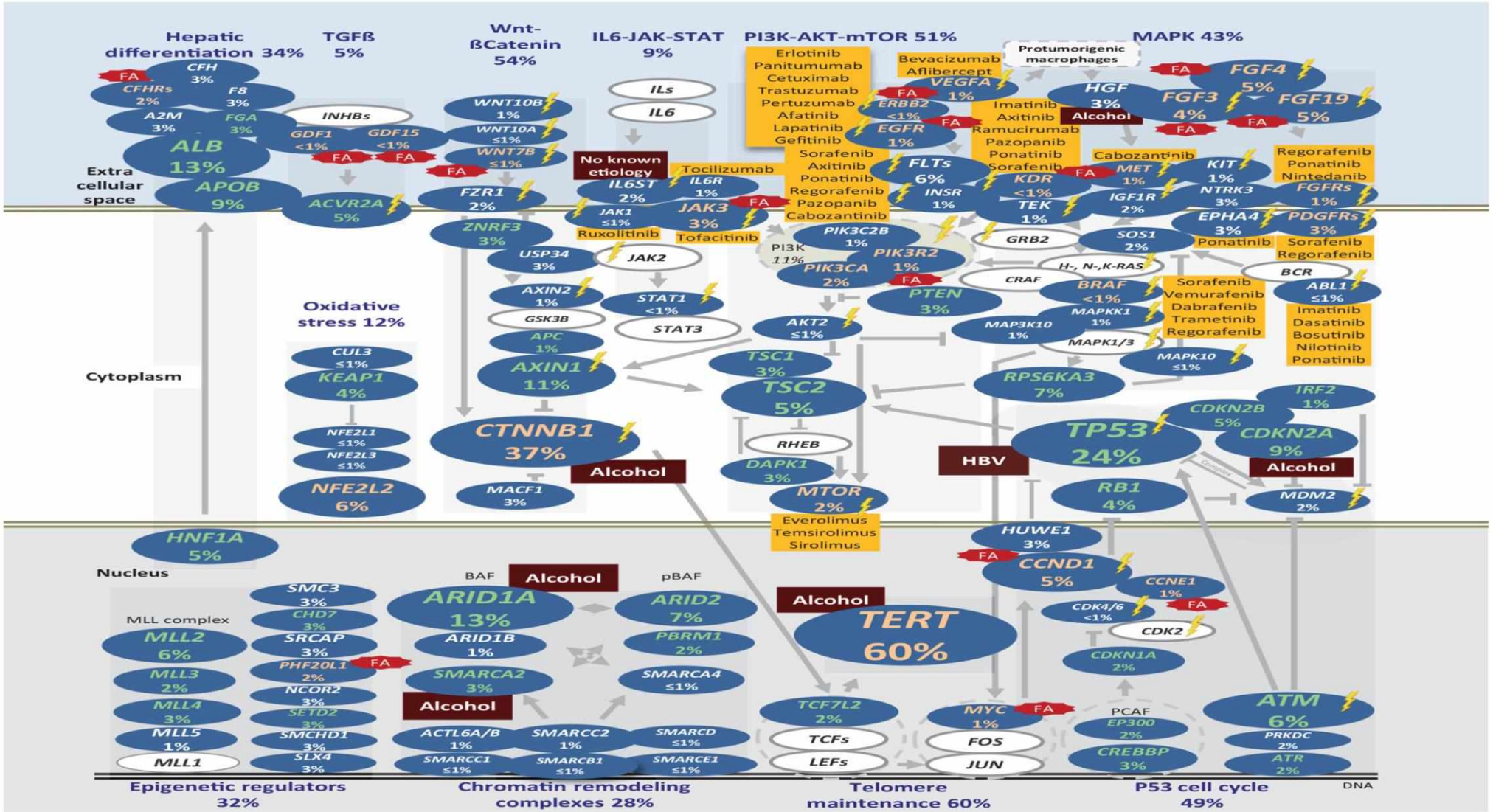
LIVER CANCER

EASL

Μοριακή ταξινόμηση ΗΚΚ



Στοχευμένες θεραπείες στον ΗΚΚ



Molecular pathways and treatment

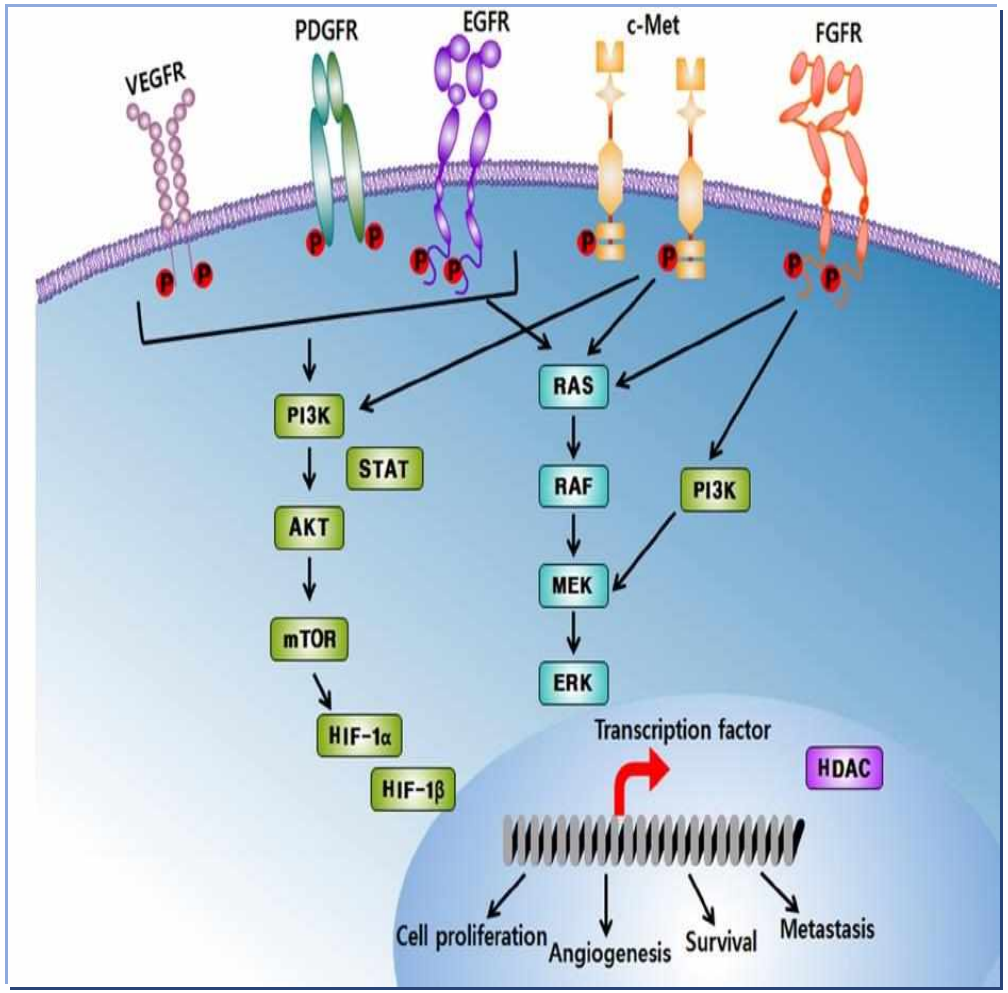
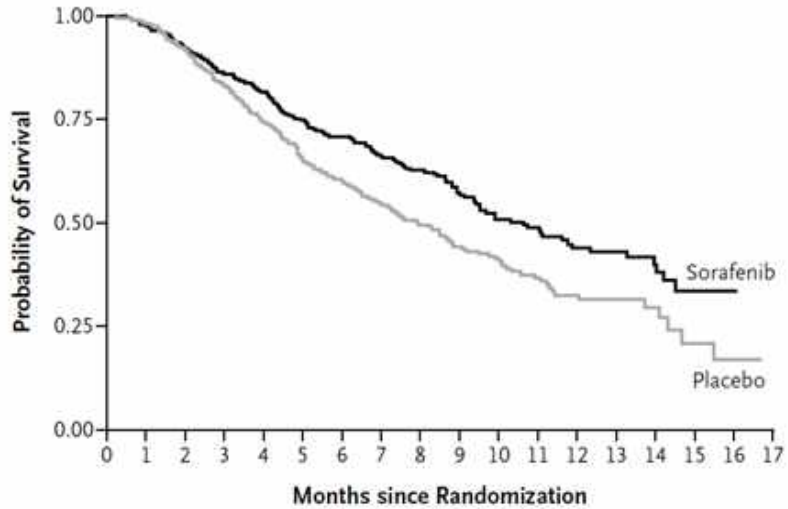


Table 1. List of Molecular Targeted Agents Used for Clinical Trials against HCC

Agents	Main target
Sorafenib	VEGFR, PDGFR, Raf
Brivanib	VEGFR2, FGFR1
Linifanib	VEGFR, PDGFR
Sunitinib	VEGFR, PDGFR, c-KIT, RET
Erlotinib	EGFR
Everolimus	mTOR
Ramucirumab	VEGFR
Lenvatinib	VEGFR, PDGFR, FGFR, RET, SCFR
Regorafenib	VEGFR, PDGFR, BRAFFGFR, KIT, RET
Cabozantinib	c-MET, VEGFR, RET
Gefitinib	EGFR
Bevacizumab	VEGF
Cediranib	VEGFR, PDGFR, c-KIT
BIBF-1120	VEGFR, PDGFR, FGFR
E-7080	VEGFR, FGFR, PDGFR, c-KIT
TSU-68	VEGFR2, FGFR, PDGFR
XL-184	VEGFR2, MET, RET
Vandetanib	VEGFR, EGFR
Cetuximab	EGFR
Tivantinib	c-MET
MEDI-575	PDGFR
BAY73-4506	VEGFR, PDGFR, FGFR-1Raf, RET, c-KIT

Sorafenib for advanced disease

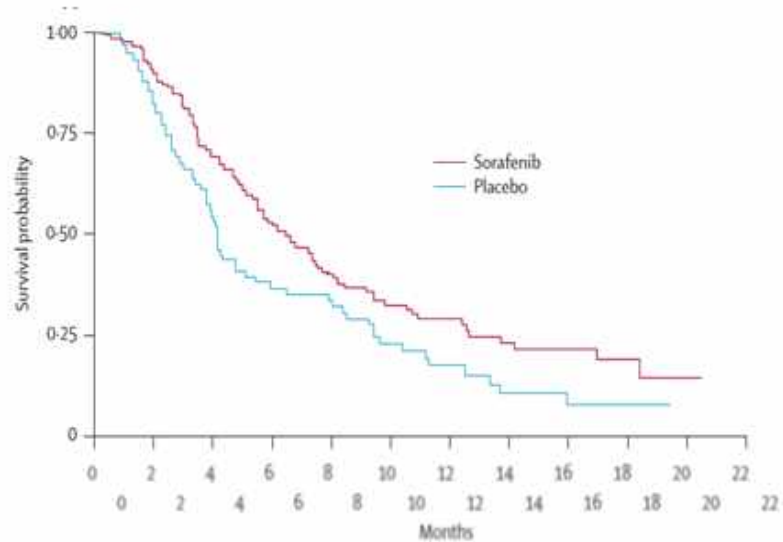
SHARP Trial



Median Overall Survival
S = 10.7 months
P = 7.9 months
HR 0.69 (95% CI 0.55 to 0.87 ; p<0.001

Llovet et al NEJM 2008

Asia-Pacific Trial



Median Overall Survival
S = 6.5 months
P = 4.2 months
HR 0.68 (95% CI 0.5-0.93; p=0.014)

Cheng et al Lancet Oncology 2009

Drugs

Approved Drugs

Hematology/Oncology (Cancer) Approvals & Safety Notifications

Drug Information Soundcast in Clinical Oncology (D.I.S.C.O.)

Approved Drug Products

Regorafenib

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

On April 27, 2017 the U.S. Food and Drug Administration expanded the indications of regorafenib (STIVARGA, Bayer HealthCare Pharmaceuticals Inc.) to include the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

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

*Jordi Bruix, Shukui Qin, Philippe Merle, Alessandro Granito, Yi-Hsiang Huang, György Bodoky, Marc Pracht, Osamu Yokosuka, Olivier Rosmorduc, Valeriy Breder, René Gerolami, Gianluca Masi, Paul J Ross, Tianqiang Song, Jean-Pierre Bronowicki, Isabelle Ollivier-Hourmand, Masatoshi Kudo, Ann-Lii Cheng, Josep M Llovet, Richard S Finn, Marie-Aude LeBerre, Annette Baumhauer, Gerold Meinhardt, Guohong Han, on behalf of the RESORCE Investigators**

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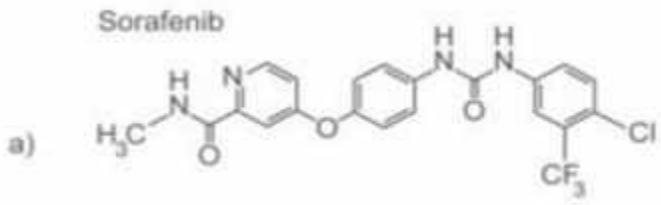
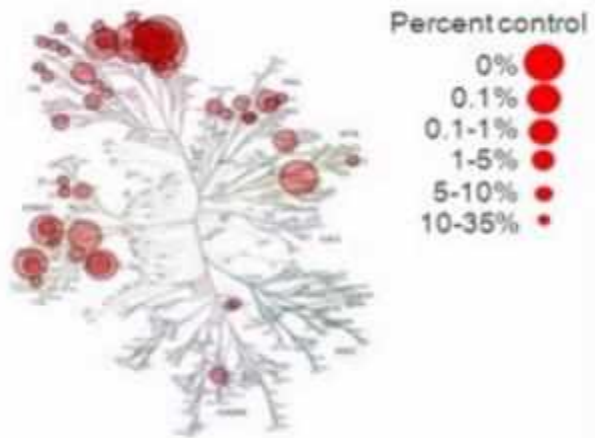
Regorafenib a Mutikinase Inhibitor





phase III RESORCE trial

Stratify by:

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

RANDOMIZE
2 : 1
(Target N=530)

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

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

ECOG PS, Eastern Cooperative Oncology Group performance status

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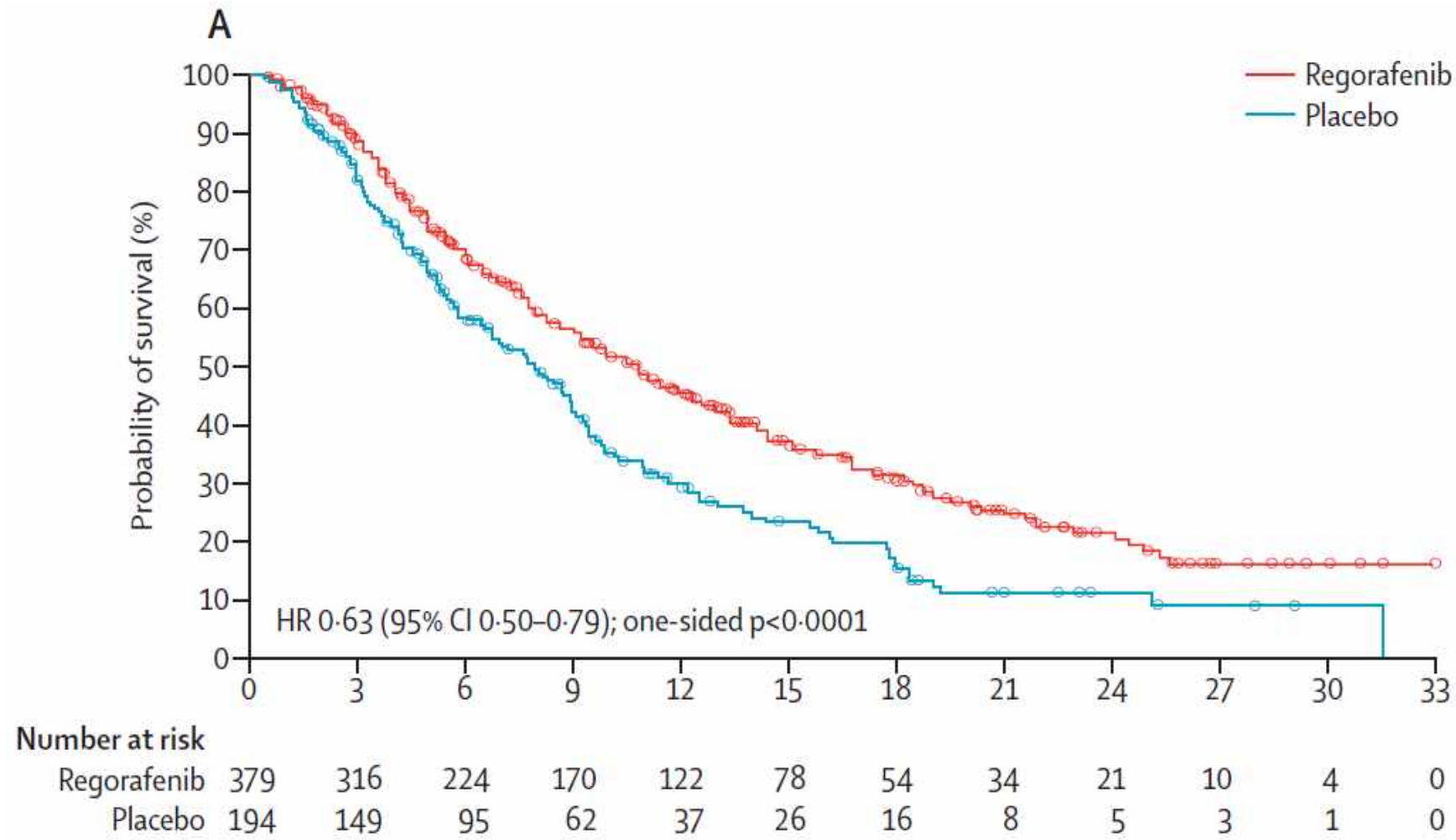
Κυριότερα χαρακτηριστικά των ασθενών

	Regorafenib (n=379)	Placebo (n=194)
Age	64 (54-71)	62 (55-68)
Hepatitis B	143 (38%)	73 (38%)
Number of lesions n=2	175 (46%)	88 (45%)
Child-Pugh A	373 (98%)	188 (97%)
BCLC stage C	325 (86%)	172 (89%)

Phase III Regorafenib 2nd line (RESORCE)

	Regorafenib (n=379)	Placebo (n=194)	HR (95%CI)	P-value
Median OS, month (Primary endpoint)	**10.6**	**7.8**	**0.62 (0.50-0.78)**	**< 0.001**
Median PFS, month	**3.1**	**1.5**	0.46 (0.37-0.56)	< 0.001
Median TTP, month	**3.2**	**1.5**	0.44 (0.36-0.55)	< 0.001
RR, %	**10.6**	**4.1**	-	0.005
DCR, %	**65.2**	**36.1**	-	< 0.001
Any AE; ≥ grade 3, %	**79.7**	**58.5**	-	-
Deaths within 30 days of the last dose, %	**13.4**	**19.7**	-	-
Median treatment duration (range), month	**3.6 (0.03-29.4)**	**1.9 (0.2-27.4)**	-	-
Dose modification due to AE, %	**68.2**	**31.1**	-	-

Καμπύλη επιβίωσης των ασθενών

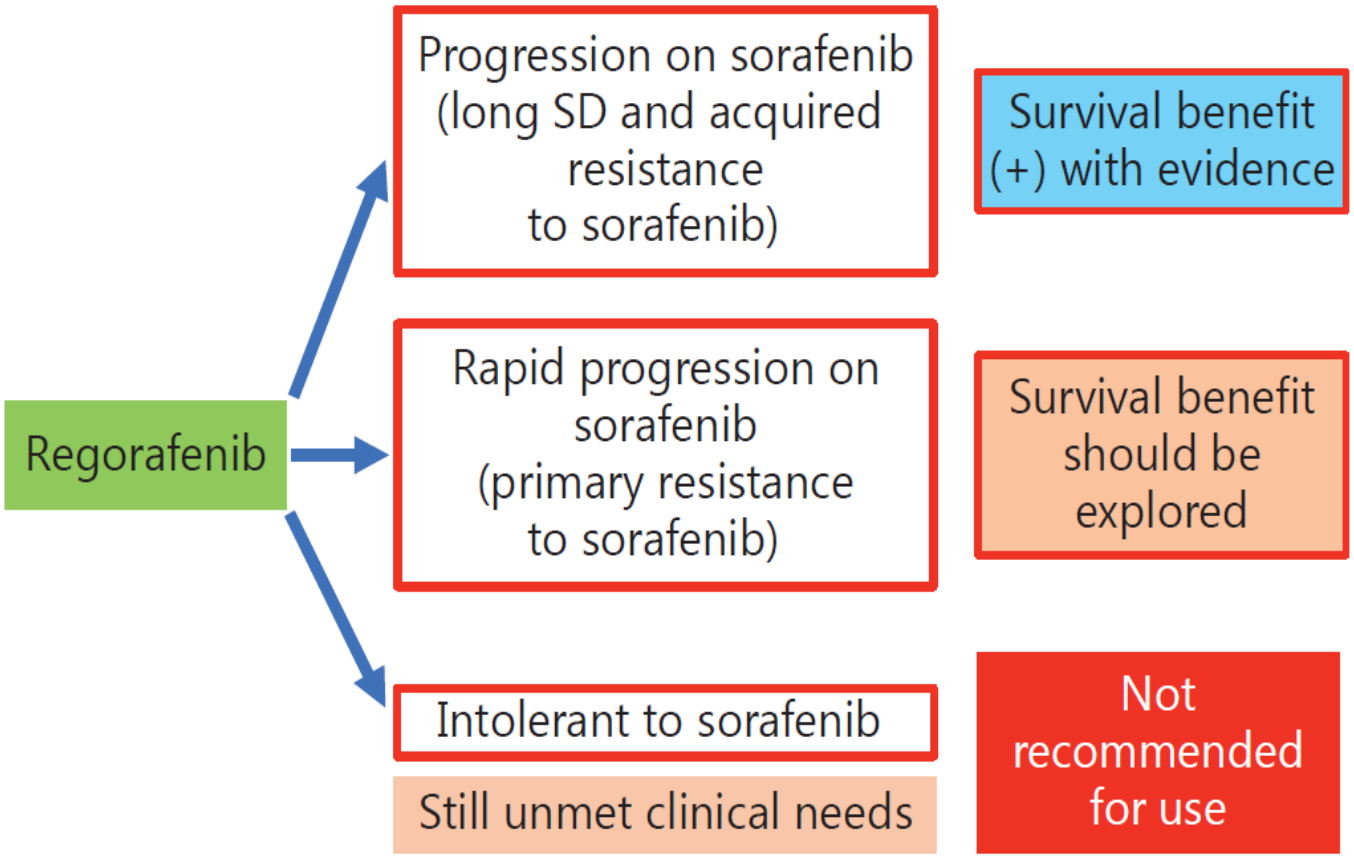


Regorafenib: Hand-Foot Syndrome & other reactions

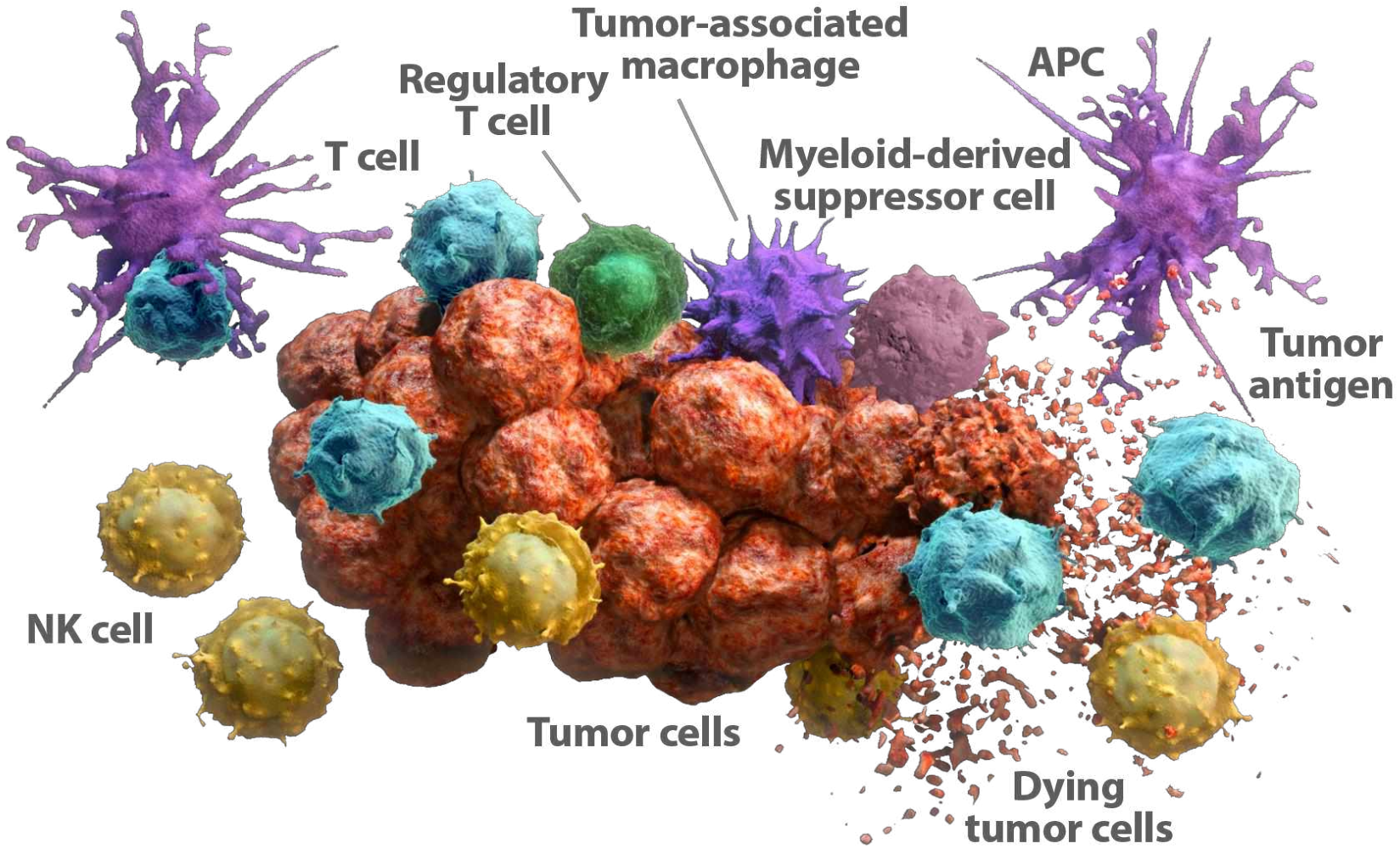
HFSR: erythema and desquamation on fingers.

Facial rash: desquamation at the hairline.

Θέση του regorafenib στην αντιμετώπιση του ΗΚΚ



Ανοσιακό σύστημα και κακοήθεια



FDA Approves Nivolumab for Hepatocellular Carcinoma

Published Online: Friday, Sep 22, 2017

The FDA has granted an accelerated approval to nivolumab (Opdivo) for the treatment of patients with hepatocellular carcinoma (HCC) following prior sorafenib (Nexavar), regardless of PD-L1 status.

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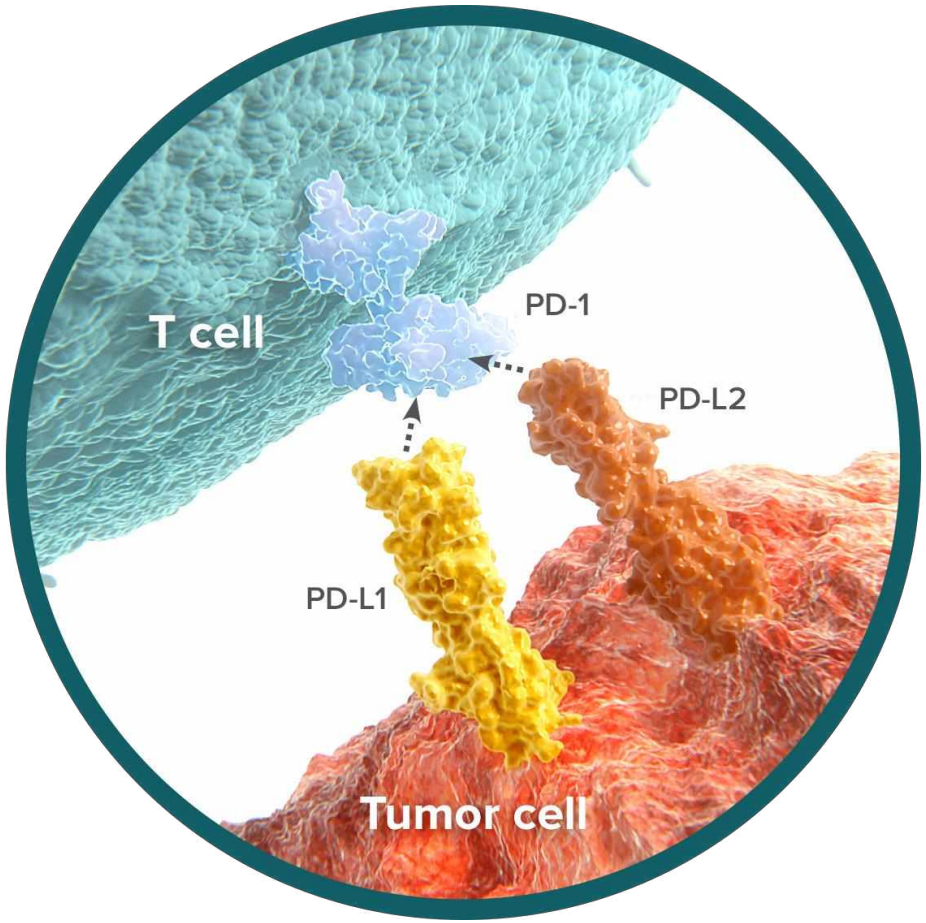
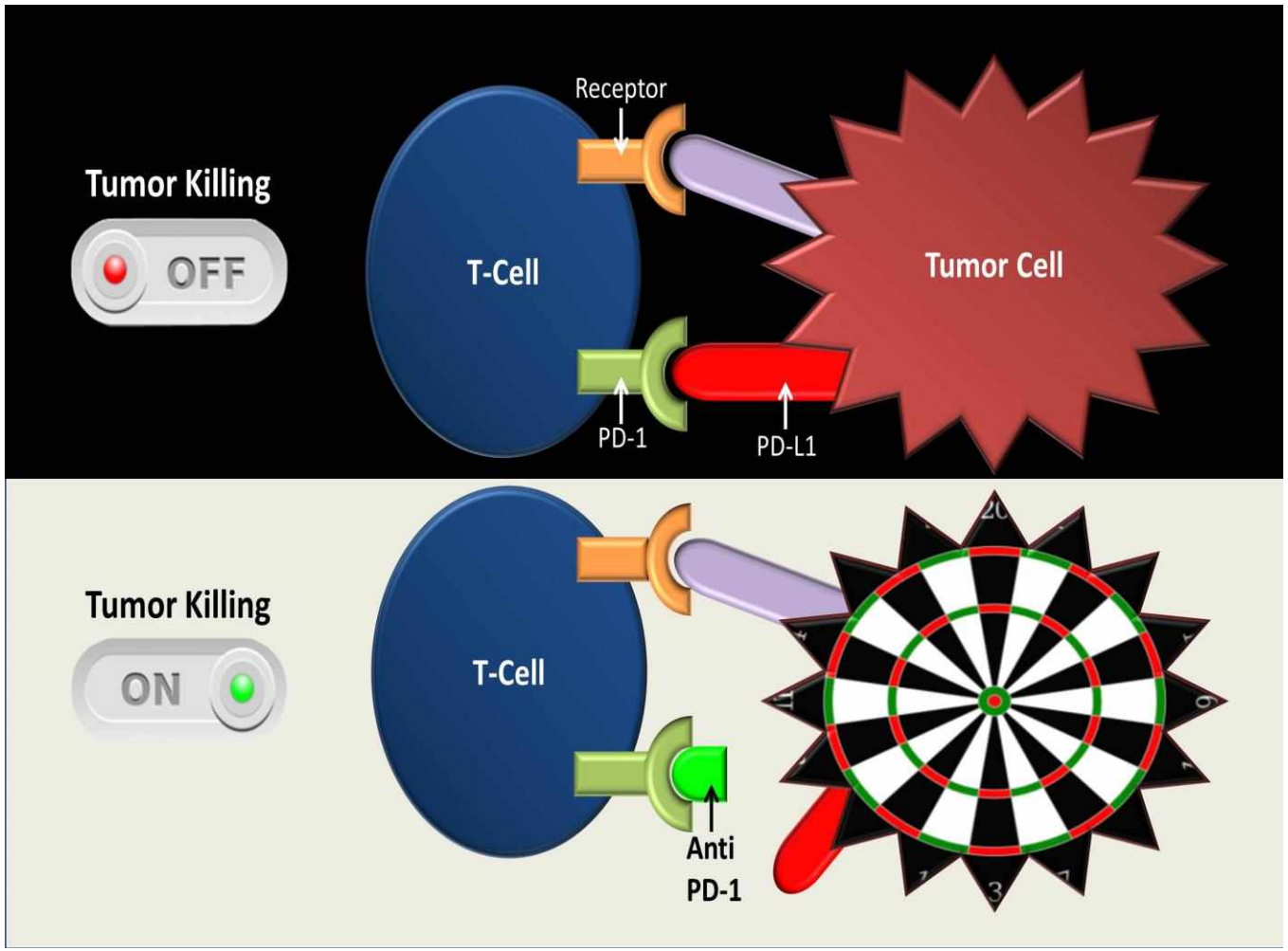
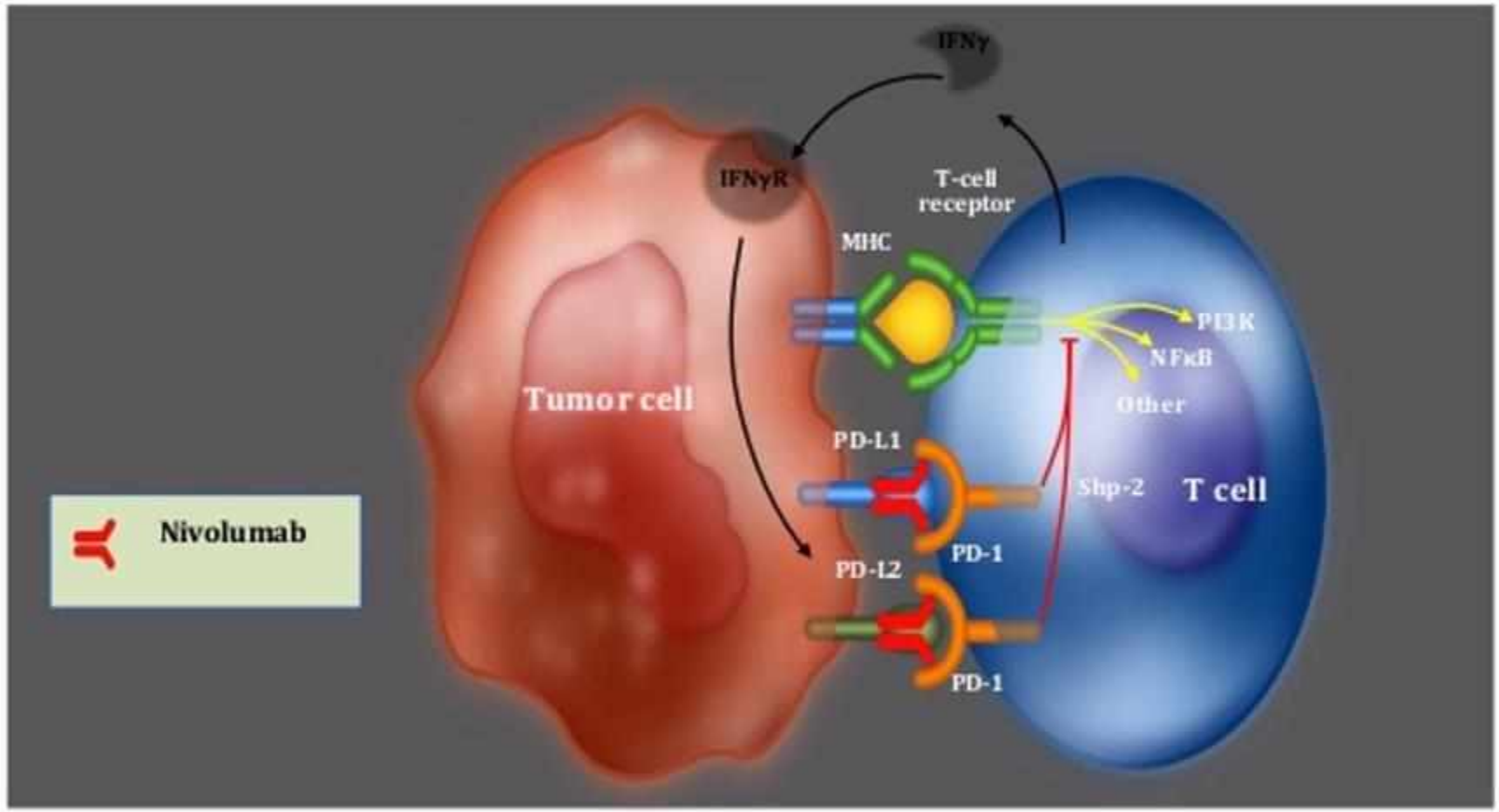
El-Khoueiry A et al. Lancet 2017; 389:2492-502


T cell
PD-1
PD-L2
PD-L1
Tumor cell


Tumor Killing
OFF
Receptor
T-Cell
Tumor Cell
PD-1
PD-L1
Tumor Killing
ON
T-Cell
Anti
PD-1



Topalian SL, et al. NEJM 2012; 366: 2443-2454

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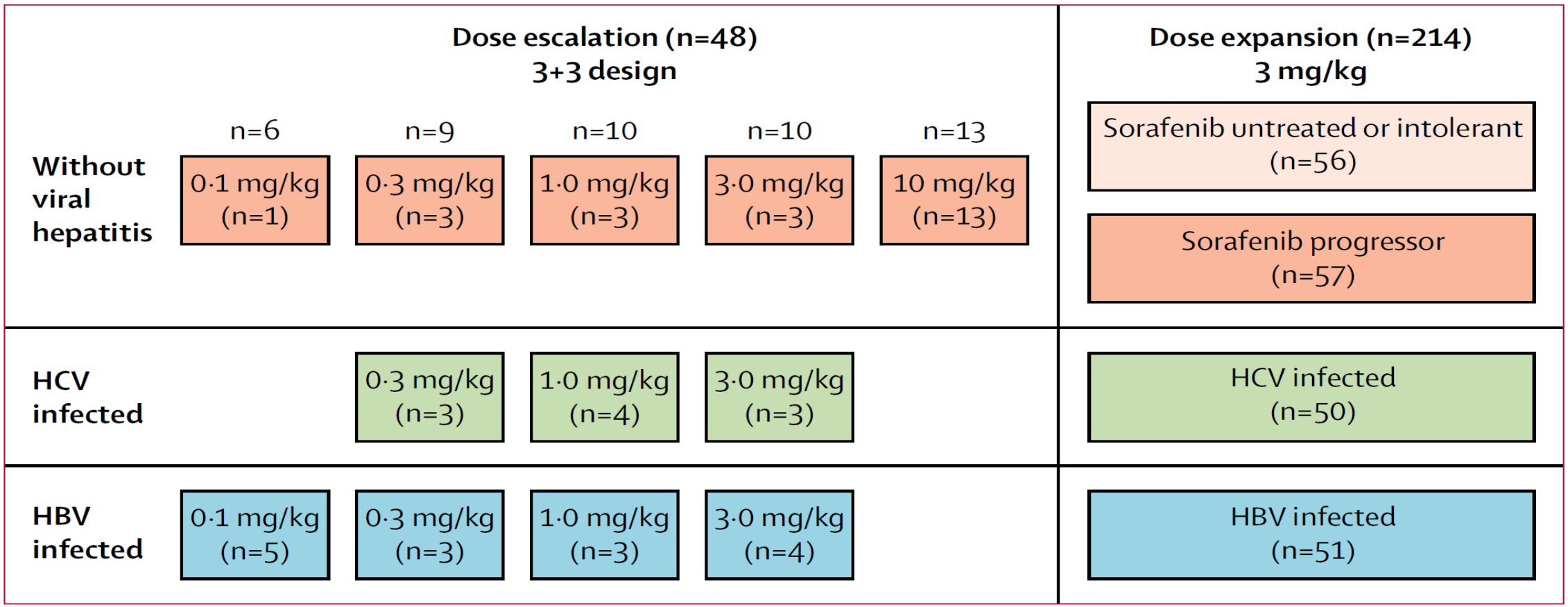
Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial

*Anthony B El-Khoueiry, *Bruno Sangro, *Thomas Yau, Todd S Crocenzi, Masatoshi Kudo, Chiun Hsu, Tae-You Kim, Su-Pin Choo, Jörg Trojan, Theodore H Welling 3rd, Tim Meyer, Yoon-Koo Kang, Winnie Yeo, Akhil Chopra, Jeffrey Anderson, Christine dela Cruz, Lixin Lang, Jaclyn Neely, Hao Tang, Homa B Dastani, Ignacio Melero*



Κυριότερα χαρακτηριστικά των ασθενών

	Nivolumab (n=214)
Age	64 (56-70)
Child-Pugh A	210 (98%)
Extra-hepatic metastases	144 (67%)
Previous therapy with sorafenib	145 (68%)