Hepatosellüler Karsinom (HCC)Tedavi Seçenekleri

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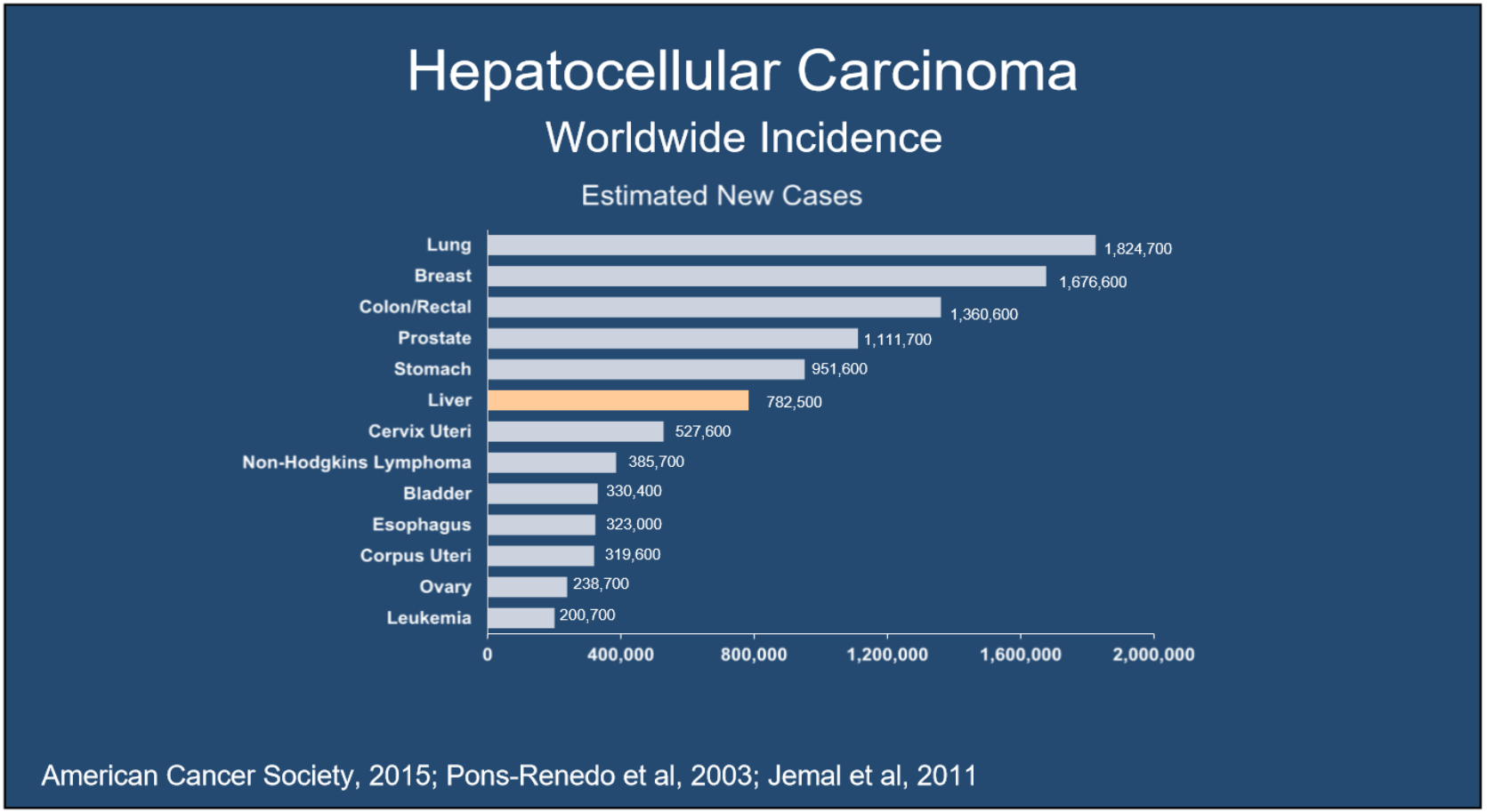
Tıbbi Onkoloji

Hepatosellüler Karsinom İnsidans ve Mortalite



Hepatosellüler Karsinom İnsidans ve Mortalite

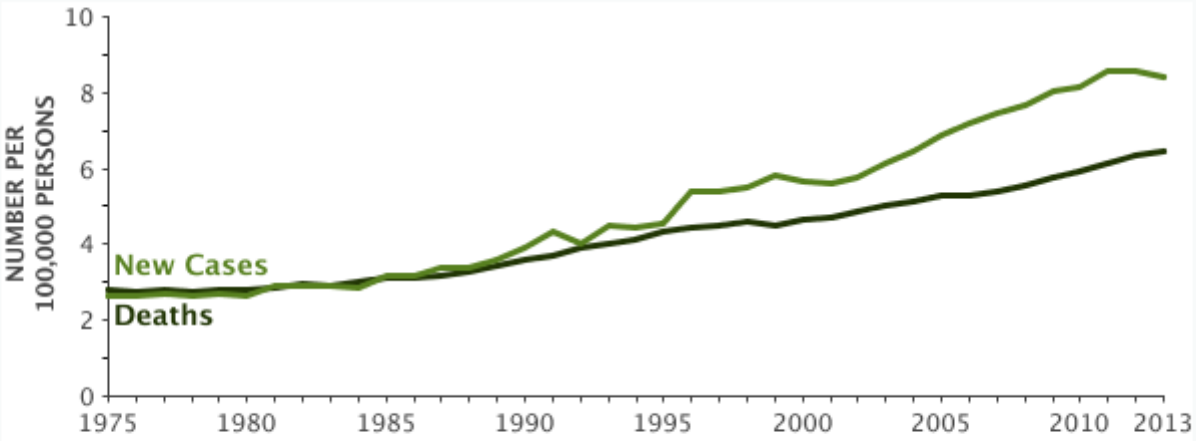
Changes Over Time

Keeping track of the number of new cases, deaths, and survival over time (trends) can help scientists understand whether progress is being made and where additional research is needed to address challenges, such as improving screening or finding better treatments.

Using statistical models for analysis, rates for new liver and intrahepatic bile duct cancer cases have been rising on average 3.0% each year over the last 10 years. Death rates have been rising on average 2.7% each year over 2004–2013. 5-year survival trends are shown below the figure.

New Cases, Deaths and 5-Year Relative Survival

View Data Table

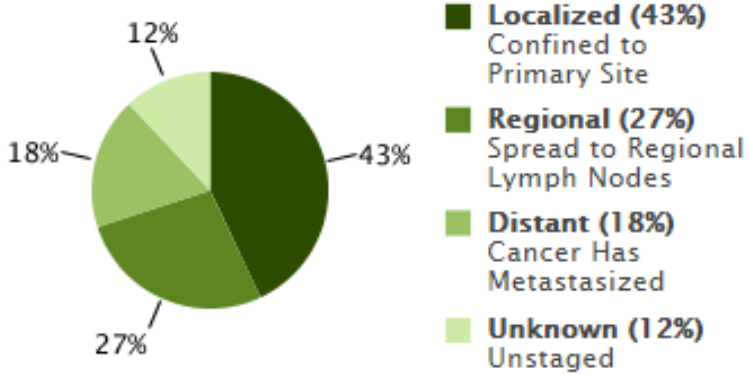


Year	1975	1980	1985	1990	1995	2000	2004	2008
5-Year Relative Survival	3.0%	3.2%	7.0%	5.3%	5.7%	11.7%	14.5%	18.5%

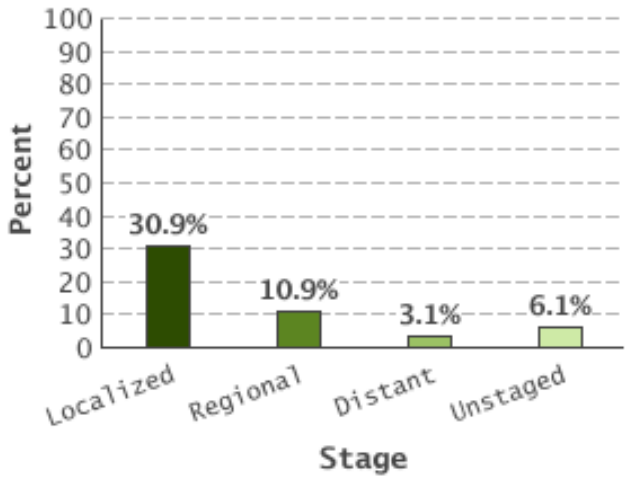
Hepatosellüler Karsinom İnsidans ve Mortalite

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Liver and Intrahepatic Bile Duct Cancer

Percent of Cases by Stage



5-Year Relative Survival

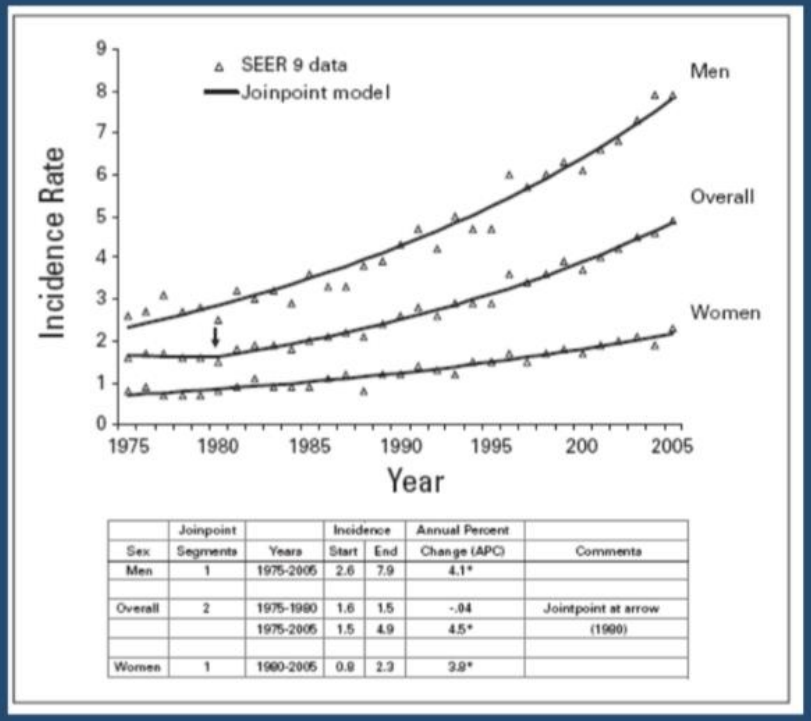


SEER 18 2006-2012, All Races, Both Sexes by SEER Summary Stage 2000

Hepatosellüler Karsinom İnsidans ve Mortalite

Hepatocellular Carcinoma

US Incidence



Sex	Joinpoint Segments	Years	Incidence Start	Incidence End	Annual Percent Change (APC)	Comments
Men	1	1975-2005	2.6	7.9	4.1*	
Overall	2	1975-1990	1.6	1.5	-.04	Jointpoint at arrow
		1975-2005	1.5	4.9	4.5*	(1990)
Women	1	1990-2005	0.9	2.3	3.9*	

Altekruse et al, 2009; Ryerson et al, 2016

Hepatosellüler Karsinom İnsidans ve Mortalite

HCC Risk Factors

- Cirrhosis: >90% of HCC cases in patients with antecedent liver cirrhosis (all causes)
- Viral hepatitis infection
  - Hepatitis B virus (HBV)
    - Can develop in HBV patients without cirrhosis
    - Viral load a factor
  - Hepatitis C virus (HCV): HCV treatment associated with risk reduction
- Obesity, metabolic syndrome: likely through increased incidence of NAFLD, NASH

NAFLD = non-alcoholic fatty liver disease; NASH = non-alcoholic steatohepatitis
Chen et al, 2006; Omland et al, 2012; Van der Meer et al, 2012; Welzel et al, 2011

Hepatosellüler Karsinom İnsidans ve Mortalite

HCC Risk Factors (cont.)

- Male sex: 4x incidence
- Alcoholic cirrhosis
- Rare causes
  - Aflatoxin exposure
  - Hemochromotosis
  - Porphyria
  - Alpha-1 antitrypsin deficiency
  - History of Fontan cardiac surgery

Chen et al, 2006; Omland et al, 2012; Van der Meer et al, 2012; Welzel et al, 2011

Hepatosellüler Karsinom Yüksek Risk Grubu İçin Tarama

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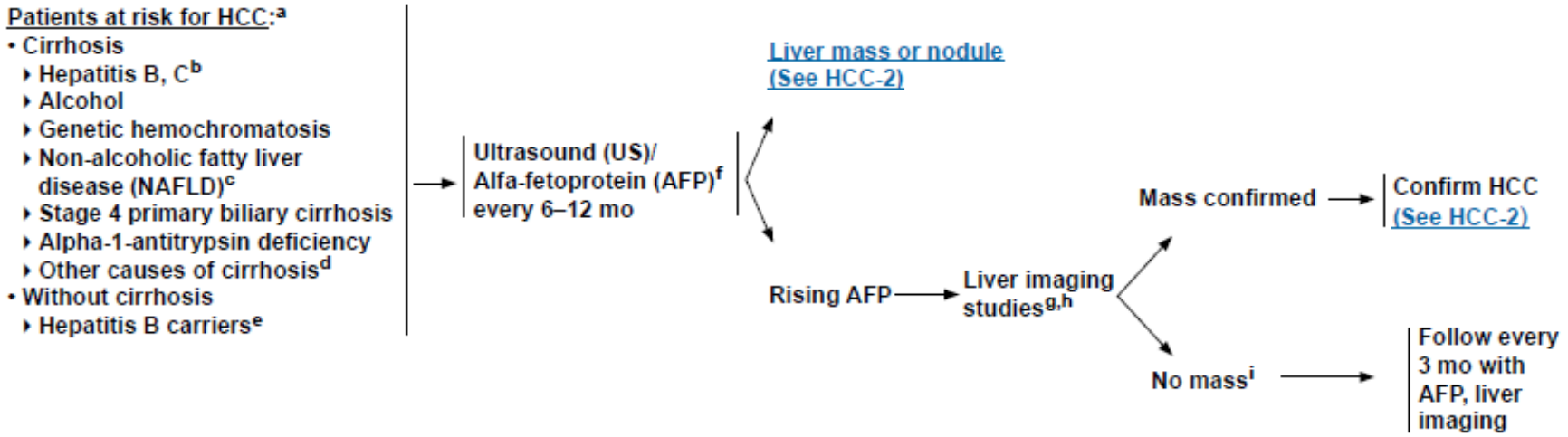
HEPATOCELLULAR CARCINOMA (HCC)
SCREENING



Hepatosellüler Karsinom Yüksek Risk Grubu İçin Tarama

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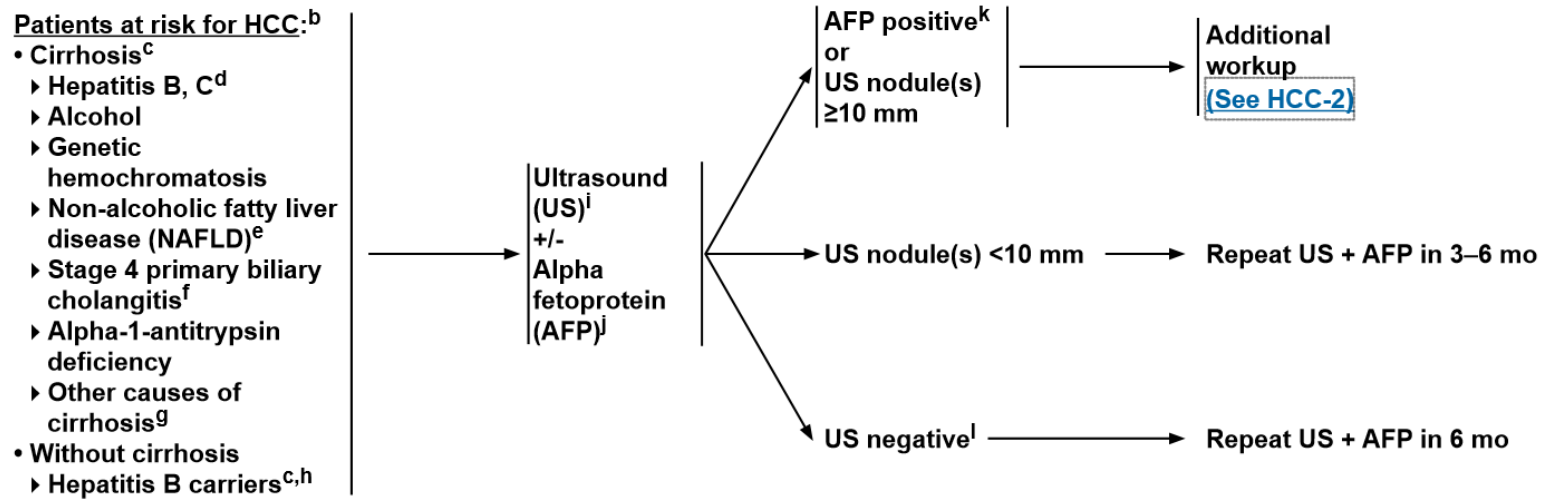
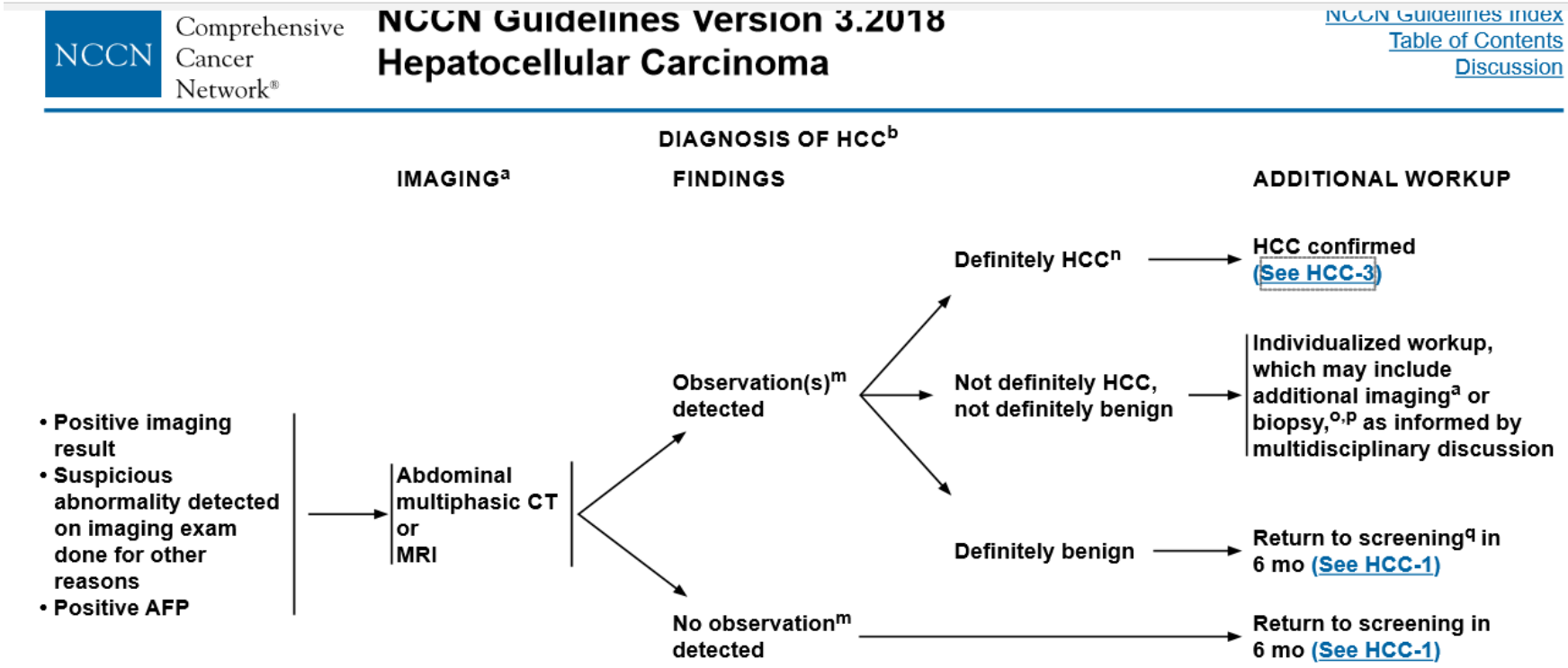
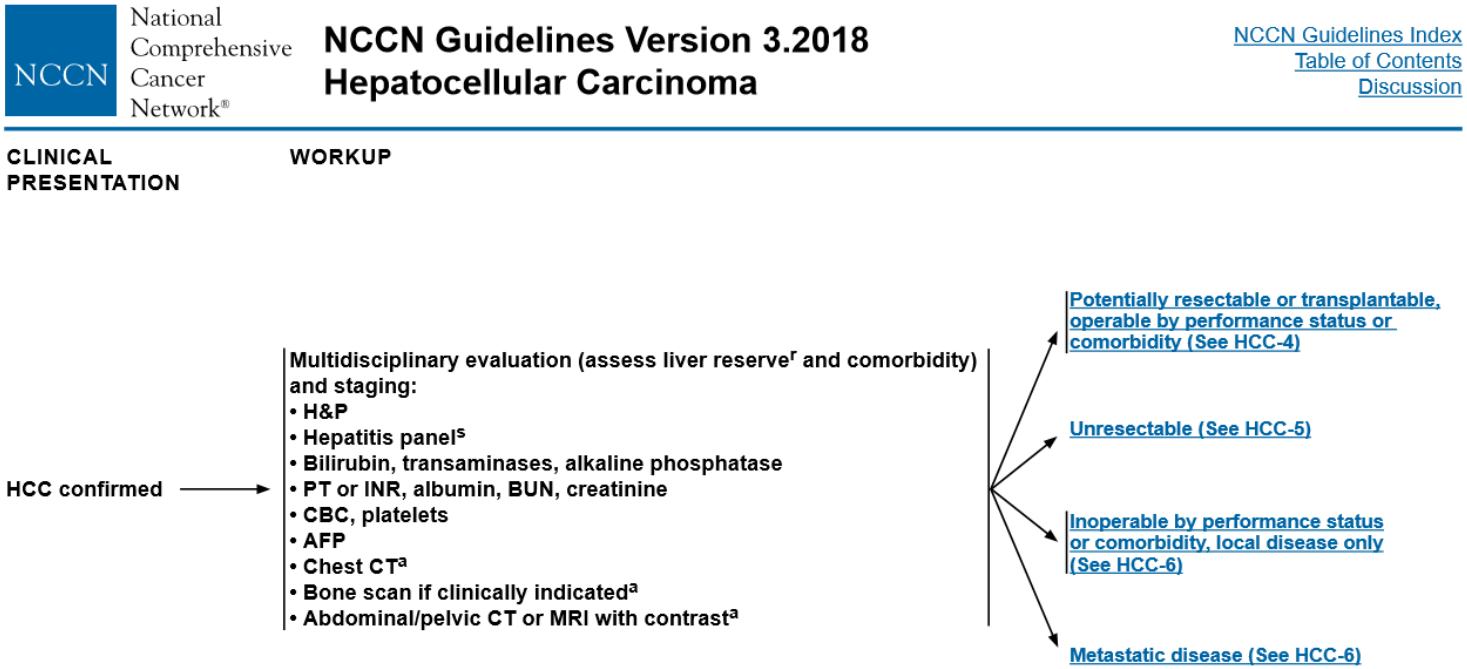
HEPATOCELLULAR CARCINOMA (HCC) SCREENING[a]



Hepatosellüler Karsinom Yüksek Risk Grubu İçin Tarama



Hepatosellüler Karsinom Yüksek Risk Grubu İçin Tarama



[a] See Principles of Imaging (HCC-A).
[r] See Child-Pugh Score (HCC-C) and assessment of portal hypertension (eg, varices, splenomegaly, thrombocytopenia).
[s] An appropriate hepatitis panel should preferably include:
- Hepatitis B surface antigen (HBsAg). If the HBsAg is positive, check HBeAg, HBeAb, and quantitative HBV DNA and refer to hepatologist.
- Hepatitis B surface antibody (for vaccine evaluation only).
- Hepatitis B core antibody (HBcAb) IgG. The HBcAb IgM should only be checked in cases of acute viral hepatitis. An isolated HBcAb IgG may still be chronic HBV and should prompt testing for a quantitative HBV DNA.
- Hepatitis C antibody. If positive, check quantitative HCV RNA and HCV genotype and refer to hepatologist.

Hepatosellüler Karsinom Evreleme

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CHILD-PUGH SCORE

Chemical and Biochemical Parameters	Scores (Points) for Increasing Abnormality		
	1	2	3
Encephalopathy (grade)[1]	None	1–2	3–4
Ascites	Absent	Slight	Moderate
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time[2] Seconds over control INR	 <4 <1.7	 4–6 1.7–2.3	 >6 >2.3
Bilirubin (mg/dL) • For primary biliary cirrhosis	<2 <4	2–3 4–10	>3 >10

Class A = 5–6 points; Class B = 7–9 points; Class C = 10–15 points.

Class A: Good operative risk
Class B: Moderate operative risk
Class C: Poor operative risk

Hepatosellüler Karsinom Evreleme

HCC Staging Systems

Parameter	Okuda	CLIP	CUPI	TNM7	JIS	HKLC	BCLC
Cirrhosis-Related Parameters							
Albumin	X	X			X	X	X
Bilirubin	X	X	X		X	X	X
Ascites	X	X	X		X	X	X
PT/INR		X			X	X	X
Encephalopathy		X			X	X	X
Alkaline phosphatase			X				
Tumor-Related Parameters							
Tumor extent/stage	X	X	X	X	X	X	X
Venous invasion		X			X	X	X
AFP		X	X				
Asymptomatic			X				
Performance status						X	X

PT/INR = prothrombin time/international normalized ratio; AFP = alpha-fetoprotein;
TNM-7 = tumor, node, metastasis classification, 7th ed.; Subramaniam et al, 2013

Hepatosellüler Karsinom Evreleme

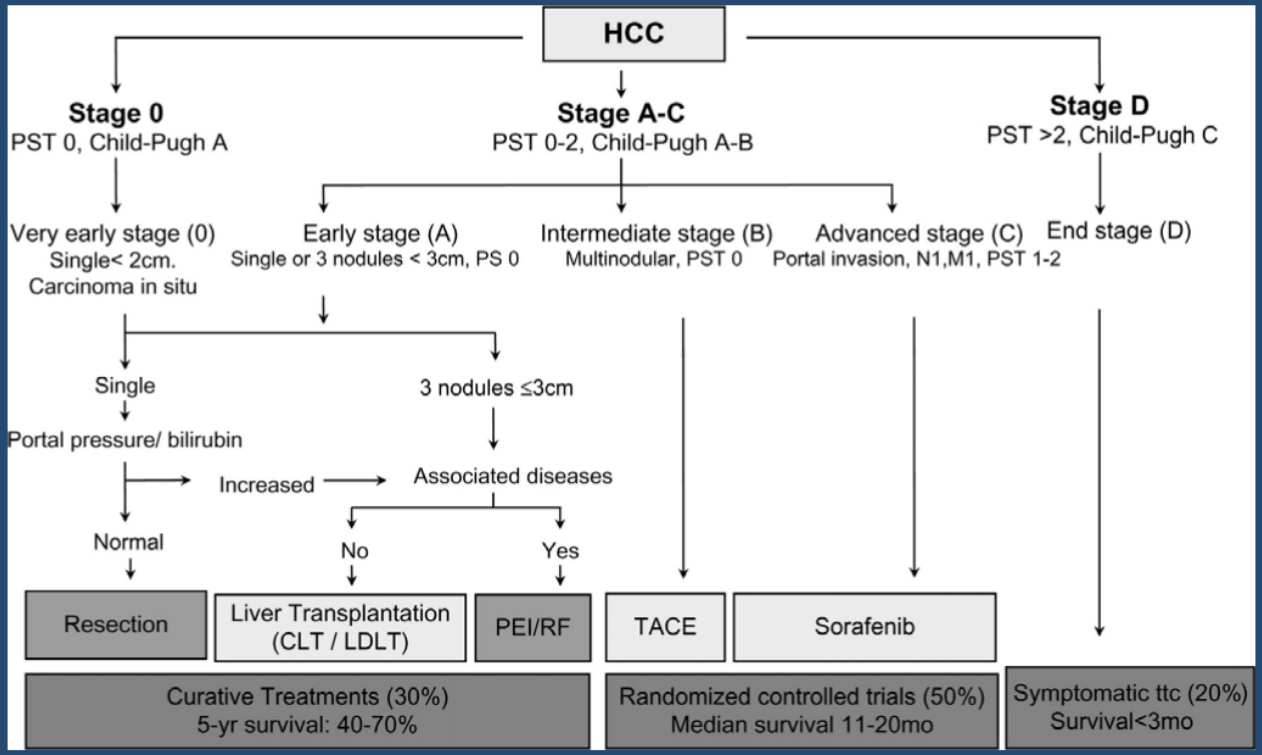
BCLC Staging

BCLC Stage		ECOG PS	Tumor Size/Number, Vascular Involvement, Etc	Child-Pugh Score
0	Very early	0	Solitary <2 cm nodule	A
A	Early	0	Solitary <5 cm nodule or up to 3 nodules each ≤3 cm	A - B
B	Intermediate	0	Large/multinodular	A - B
C	Advanced	1-2	Portal venous invasion and/or extrahepatic spread (N+ or M+)	A - B
D	Terminal	>2	Any of the above	C

BCLC = Barcelona Clinic Liver Cancer; ECOG PS = Eastern Cooperative Oncology Group performance status.
Llovet et al, 1999

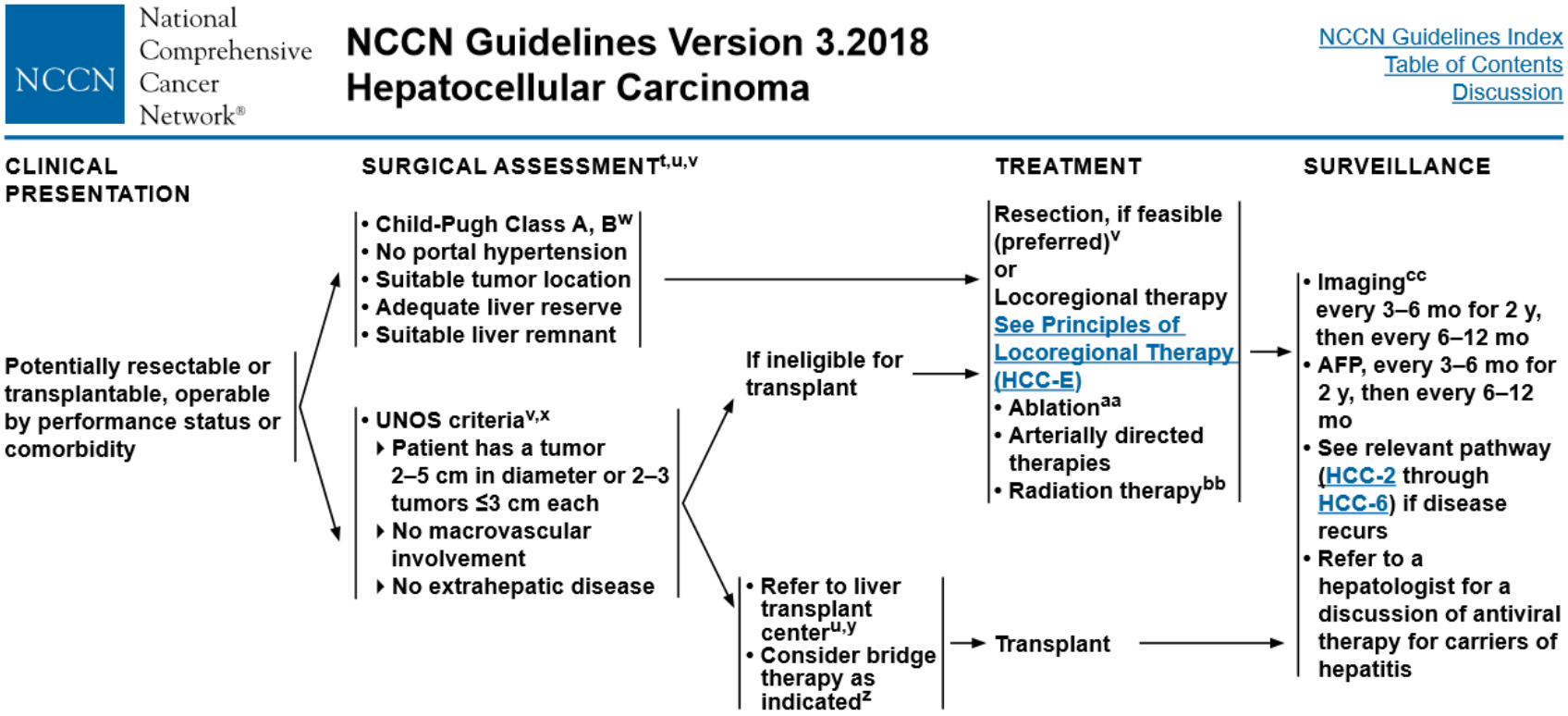
Hepatosellüler Karsinom Evreleme

BCLC Staging and Treatment Algorithm



Llovet et al, J Natl Cancer Inst 2008

Hepatosellüler Karsinom Evreleme



Hepatosellüler Karsinom Evreleme

HEPATOCELLULAR CARCINOMA

- Transplant
  - Milan criteria:
    - Established 1996
    - solitary HCC < 5 cm or with up to three nodules less than 3 cm
    - 75% survival at 5 years
  - Expanded criteria [UCSF]:Yao et al.
    - 30- 90% survival at 5 years
- Liver transplant:
  - 1st line therapy for advanced cirrhosis

Hepatosellüler Karsinom Tedavi Cerrahi-Transpalantasyon

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PRINCIPLES OF SURGERY

- Patients must be medically fit for a major operation.
- Hepatic resection is indicated as a potentially curative option in the following circumstances:
  - Adequate liver function (generally Child-Pugh Class A without portal hypertension, but small series show feasibility of limited resections in patients with mild portal hypertension)[1]
  - Solitary mass without major vascular invasion
  - Adequate future liver remnant (FLR) (at least 20% without cirrhosis and at least 30%–40% with Child-Pugh Class A cirrhosis, adequate vascular and biliary inflow/outflow)
- Hepatic resection is controversial in the following circumstances, but can be considered:
  - Limited and resectable multifocal disease
  - Major vascular invasion
- For patients with chronic liver disease being considered for major resection, preoperative portal vein embolization should be considered.[2]
- Patients meeting the UNOS criteria ([single lesion ≤5 cm, or 2 or 3 lesions ≤3 cm] http://www.unos.org) should be considered for transplantation (cadaveric or living donation). More controversial are those patients whose tumor characteristics are marginally outside of the UNOS guidelines and may be considered at some institutions for transplantation.[3] Furthermore, patients with tumor characteristics beyond Milan criteria that are downstaged to within criteria can also be considered for transplantation.[4]
- The Model for End-stage Liver Disease (MELD) score is used by UNOS to assess the severity of liver disease and prioritize the allocation of the liver transplants.[3] MELD score can be determined using the MELD calculator (http://optn.transplant.hrsa.gov/resources/MeldPeldCalculator.asp?index=98). Additional MELD "exception points" may be granted to patients with HCC eligible for liver transplant.[5]
- Patients with Child-Pugh Class A liver function, who fit UNOS criteria and are resectable could be considered for resection or transplant. There is controversy over which initial strategy is preferable to treat such patients. These patients should be evaluated by a multidisciplinary team.

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HCC Treatment Landscape

Line	FDA Approved	Not Yet FDA Approved	
		Completed trials	Ongoing trials
1L	Sorafenib [SHARP]	Lenvatinib [REFLECT]	Nivolumab [CM-459]
			Durvalumab + Tremelimumab [HIMALAYA]
			Pexa-Vec [PHOCUS]
			Galunisertib +/- Sorafenib
			Atezolizumab + Bevacizumab/Vanucizumab
			PDR001 + Sorafenib
2L	Regorafenib [RESORCE]	Cabozantinib [CELESTIAL]	Pembrolizumab [KN-240, KN-394]
	Nivolumab [CM-40]	Pembrolizumab [KN-224]	Ramucirumab [REACH-2]
			Durvalumab + Tremelimumab

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CLINICAL PRESENTATION

TREATMENT

Inoperable by performance status or comorbidity, local disease or local disease with minimal extrahepatic disease only →

Options:[dd]
- **Locoregional therapy preferred[ee]**
  - **Ablation**
  - **Arterially directed therapies**
  - **Radiation therapy[bb]**
- **Systemic therapy**
  - **Sorafenib (Child-Pugh Class A [category 1] or B)[r,gg,hh]** →
    - **If progression on or after sorafenib:**
      - **Regorafenib (Child-Pugh Class A only) (category 1)[jj]**
      - **Nivolumab (Child-Pugh Class A or B7 only)**
      - **Cabozantinib (Child-Pugh Class A only) (category 1)**
  - **Lenvatinib (Child-Pugh Class A only)**
  - **Chemotherapy[ii]**
    - ◊ **Systemic (category 2B)**
    - ◊ **Intra-arterial**
- **Clinical trial**
- **Best supportive care**

Metastatic disease or Extensive liver tumor burden → **Consider biopsy to confirm metastatic disease[p]** →

Options:[dd]
- **Systemic therapy**
  - **Sorafenib (Child-Pugh Class A [category 1] or B)[r,gg,hh]** →
    - **If progression on or after sorafenib:**
      - **Regorafenib (Child-Pugh Class A only) (category 1)[jj]**
      - **Nivolumab (Child-Pugh Class A or B7 only)**
      - **Cabozantinib (Child-Pugh Class A only) (category 1)**
  - **Lenvatinib (Child-Pugh Class A only)**
  - **Chemotherapy[ii]**
    - ◊ **Systemic (category 2B)**
    - ◊ **Intra-arterial**
- **Clinical trial**
- **Best supportive care**

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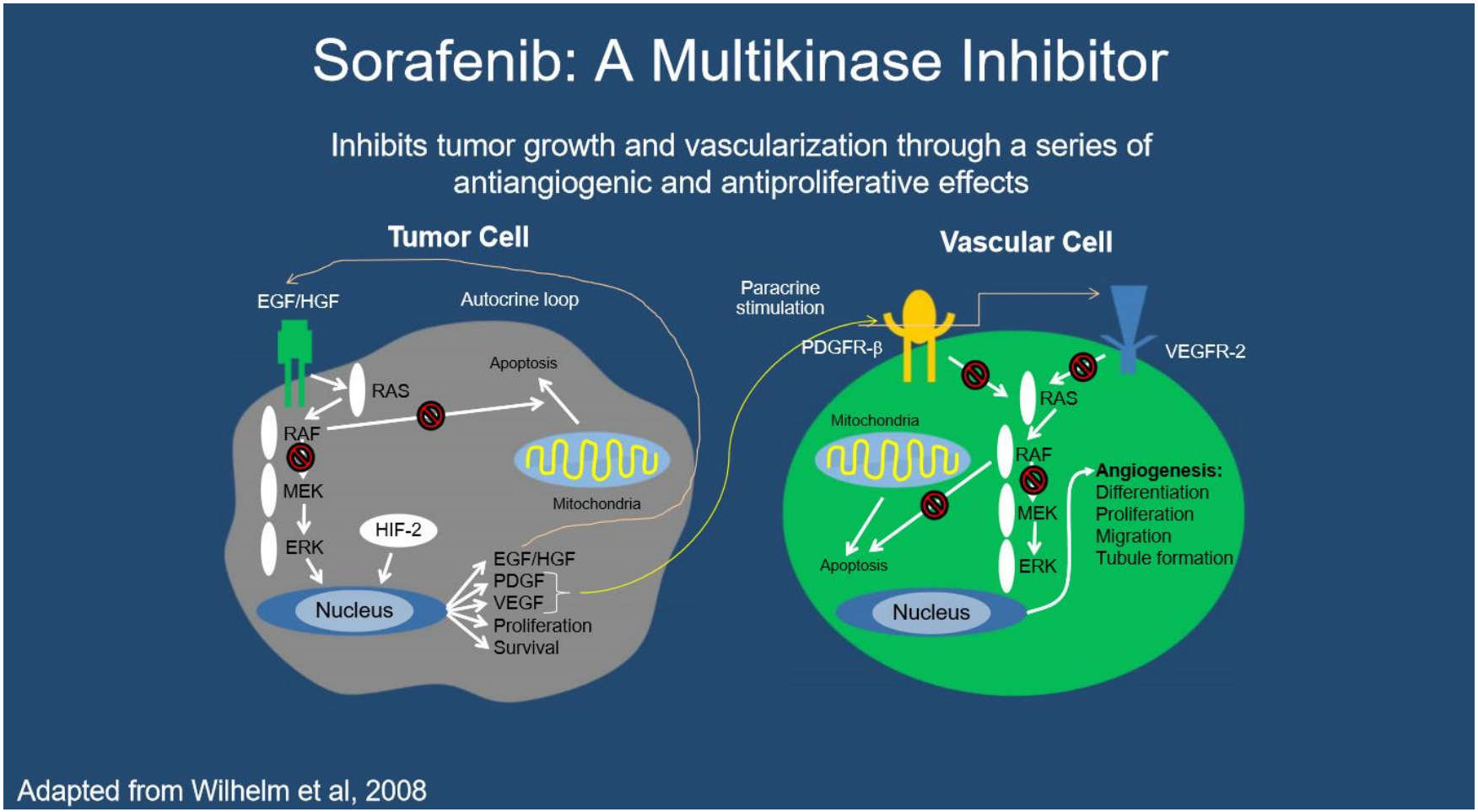

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SHARP: Phase III Trial of Sorafenib in Advanced HCC

Eligibility

- Advanced stage HCC
- ECOG PS ≤2
- Child-Pugh A
- No prior treatment
- Age ≥18 years

Study Design

- Double blind, placebo-controlled
- 121 sites primarily in North America and Europe
- Primary end point: OS

RANDOMIZE

602 pts randomly assigned 1:1 for 90% power to detect a 40% increase in OS

Arm 1 (sorafenib) N=299

Arm 2 (placebo) N=303

OS = overall survival

Llovet et al, N Engl J Med 2008

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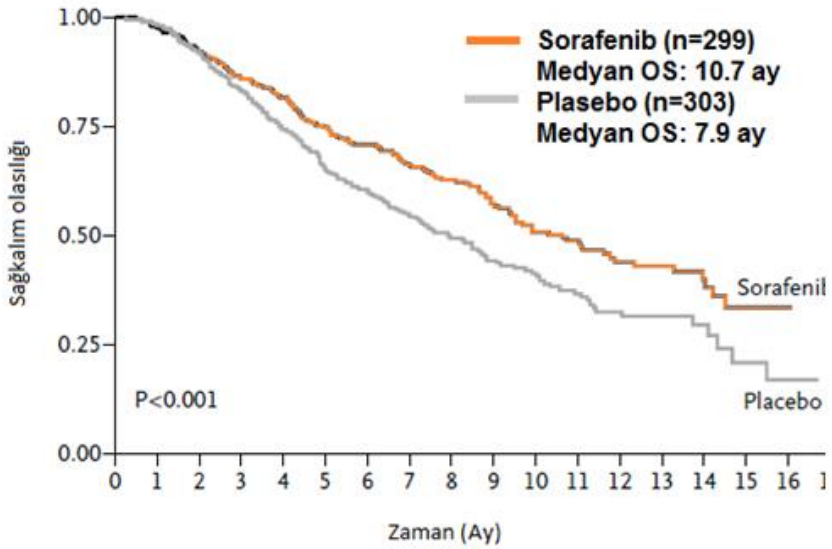
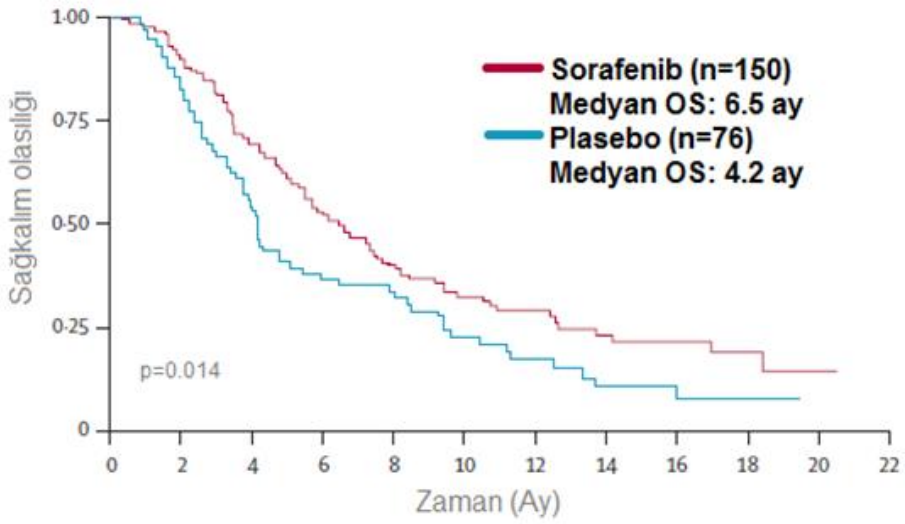
SHARP[1]



HR=0.69

Asya–Pasifik[2]



HR=0.68

Hepatosellüler Karsinom Tedavi

SHARP: Treatment-Emergent AEs

AEs, %	Sorafenib (n=297)			Placebo (n=302)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Constitutional sx's						
Fatigue	46	9	1	45	12	2
Weight loss	30	2	0	10	1	0
Dermatology/skin						
Rash/desquamation	19	1	0	14	0	0
HFSR	21	8	0	3	<1	0
Alopecia	14	0	0	2	0	0
Gastrointestinal						
Diarrhea	55	10	<1	25	2	0
Anorexia	29	3	0	18	3	<1
Nausea/Vomiting	39	3	0	22	4	0
Hepatic dysfunction	11	2	1	8	2	1

AEs = adverse events, HFSR = hand-foot skin reaction
Kane et al, 2009

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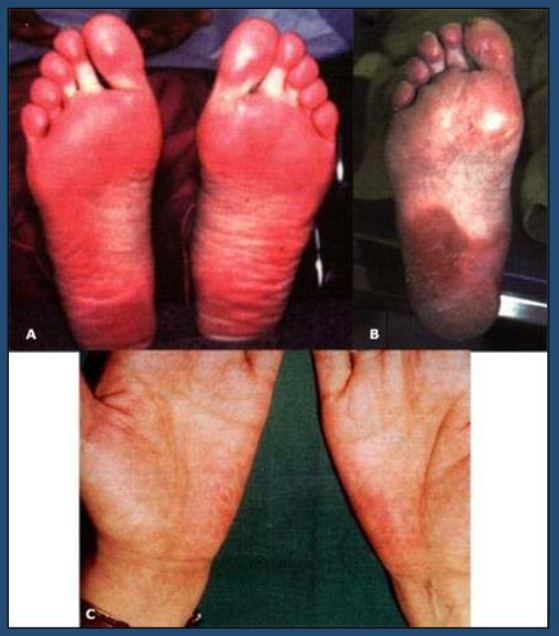
Hand-Foot Skin Reaction

- General principle is to treat the hyperkeratosis and skin inflammation
  - Creams or ointments containing urea, ammonium lactate, or salicylic acid
- Topical corticosteroids may help reduce grade 2 or higher inflammation
- When grade 3 or intolerable, treatment should be withheld for 7 days or until symptoms resolve
  - May be restarted at a lower dose



Lacouture et al, 2008

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ORIGINAL PAPER

First interim analysis of the GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib) non-interventional study

R. Lencioni,[1] M. Kudo,[2] S.-L. Ye,[3] J.-P. Bronowicki,[4] X.-P. Chen,[5] L. Dagher,[6] J. Furuse,[7] J. F. Geschwind,[8] L. L. de Guevara,[9] C. Papandreou,[10] A. J. Sanyal,[11] T. Takayama,[12] S. K. Yoon,[13] K. Nakajima,[14] F. Cihon,[15] S. Heldner,[16] J. A. Marrero[17]

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

ORIGINAL PAPER

GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with : second interim analysis

udo,[2] S.-L. Ye,[3] J.-P. Bronowicki,[4] X.-P. Chen,[5] L. Dagher,[6] J. Furuse,[7] L. Ladrón de Guevara,[9] C. Papandreou,[10] T. Takayama,[11] S. K. Yoon,[12] K. hr,[14] S. Heldner,[15] A. J. Sanyal[16]

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

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RESEARCH ARTICLE

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Impact of sorafenib dosing on outcome from the European patient subset of the GIDEON study

Bruno Daniele[*,1], Adina Croitoru[2], Christos Papandreou[3], Jean-Pierre Bronowicki[4], Philippe Mathurin[5], Fatima Serejo[6], Per Stål[7], Juan Turnes[8], Vlad Ratziu[9] & György Bodoky[10]

- **G**lobal **I**nvestigation of therapeutic **DE**cisions in hepatocellular carcinoma **[HCC] and O**f its treatment with sorafe**N**ib
- Sorafenib kullanan HSK hastalarında büyük ölçekli, global, prospektif, gözlemsel, çalışma
- Hasta sayısı 3371, 39 ülke, 5 kıta
- Primer amaç: klinik pratikte sorafenib kullanımının güvenliliğini değerlendirmek
- Sekonder amaçlar: sorafenib için etkililik, dozlama ve pratikte uygulama paternlerini

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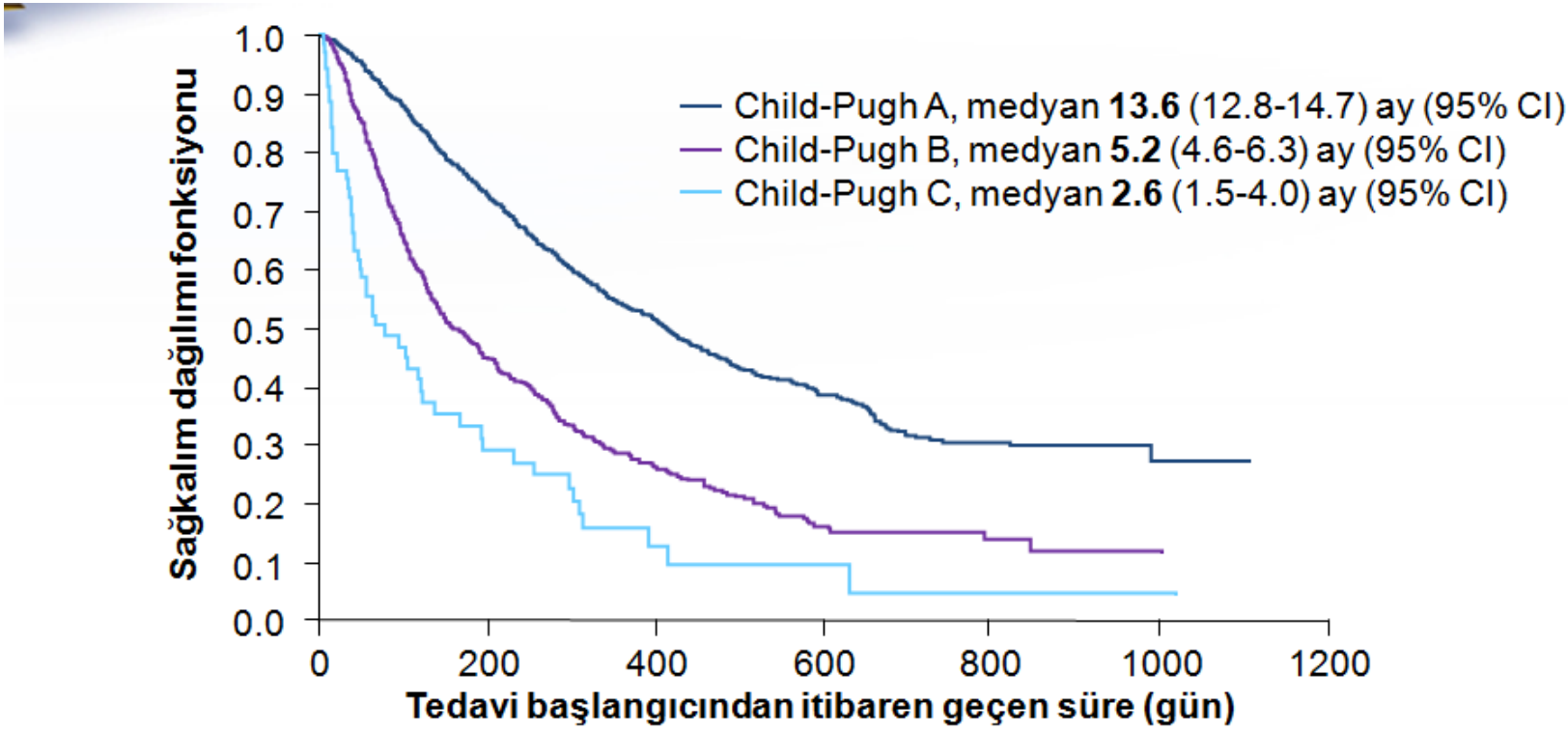

3213 hastanın analizi

Hepatosellüler Karsinom Tedavi

Regorafenib in HCC: Rationale

- Multikinase inhibitor that differs from sorafenib by the addition of a lone fluorine atom
- Broader and more potent target profile than sorafenib: VEGFR1, RET, FGFR-1, and c-KIT
- Regorafenib metabolites (M-2 and M-5) have continued anti-neoplastic effect during 1-week washout period

Trojan & Waidmann, 2016

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RESORCE: Phase III Trial of Regorafenib in Post-Sorafenib HCC

Eligibility

- Advanced HCC with POD on sorafenib treatment
- ECOG PS 0 or 1
- BCLC stage B or C
- Child-Pugh A
- Age ≥18 years

Study Design

- Double blind, placebo-controlled
- 152 sites in North and South America, Europe, Australia, and Asia
- Primary end point: OS

RANDOMIZE

573 pts randomly assigned 2:1 for 90% power to detect a 43% increase in OS

Regorafenib 160 mg daily, 3 weeks on/1 week off (n=379)

Placebo (n=194)

POD = progression of disease;
Bruix et al, 2017

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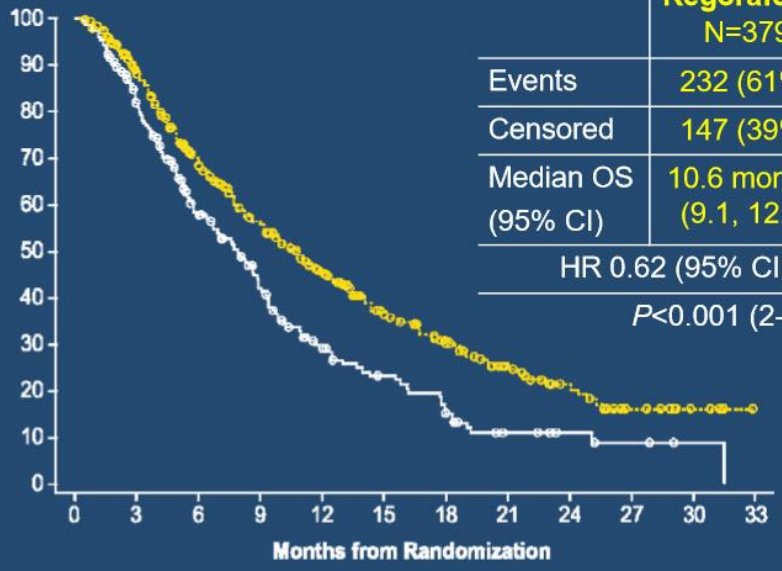
RESORCE: OS



	Regorafenib N=379	Placebo N=194
Events	232 (61%)	140 (72%)
Censored	147 (39%)	54 (28%)
Median OS (95% CI)	10.6 months (9.1, 12.1)	7.8 months (6.3, 8.8)
HR 0.62 (95% CI: 0.50, 0.78)		
P<0.001 (2-sided)		

Number at risk

Regorafenib	379	316	224	170	122	78	54	34	21	10	4	0
Placebo	194	149	95	62	37	26	16	8	5	3	1	0

Bruix et al, 2017

RESORCE: Efficacy

	Regorafenib (n = 379)	Placebo (n = 194)	HR	*p*-value
Median PFS[1]	3.1 mo	1.5 mo	0.46	<0.0001
Median OS (updated analysis)[2]	10.7 mo	7.9 mo	0.61	<0.0001
ORR (mRECIST)[1]	11%	4%	—	0.0047
Disease control rate[1]	65%	36%	—	<0.0001

Bruix J et al. *Lancet* 2017;389(10064):56-66; [2] Bruix J et al. *Proc ESMO World Congress GI* 2017;Abstract O-009.

Hepatosellüler Karsinom Tedavi

RESORCE: AE's

Treatment-Emergent AE's	Any Grade	Gr 3	Gr 4	Any Grade	Gr 3	Gr 4
HFSR	53%	13%	NA	8%	1%	NA
Fatigue	41%	9%	NA	32%	5%	NA
Hypertension	31%	15%	<1%	6%	5%	0
Bilirubin elevation	29%	10%	1%	18%	8%	3%
AST elevation	25%	10%	1%	20%	10%	2%
Ascites	16%	4%	0	16%	6%	0
Anemia	16%	4%	1%	11%	5%	1%
Hypophosphatemia	10%	8%	1%	2%	2%	0
Lipase elevation	7%	5%	2%	3%	2%	0

AE = Adverse event, HFSR = hand-foot skin reaction
Bruix et al, 2017

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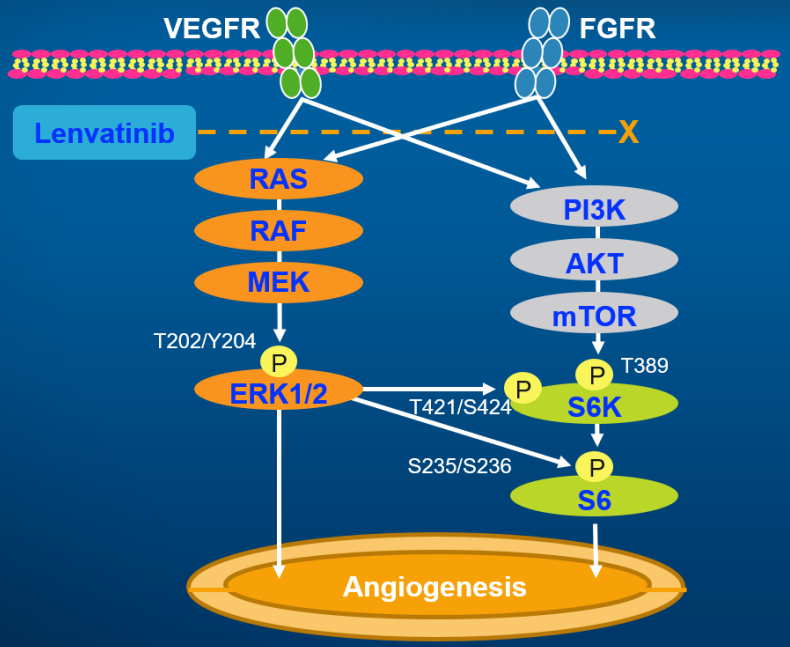
Mechanism of Action of Lenvatinib



- Orally available inhibitor of multiple tyrosine kinases including VEGF receptors, FGFR, RET, PDGFR and KIT
- Demonstrated promising radiographic response rates and survival results in Phase II and III trials in HCC

Finn RS et al. *Proc ASCO* 2014;Abstract TPS4153; Stjepanovic N et al. *Biologics* 2014;8:129-39; Cheng AL et al. *Proc ASCO* 2017;Abstract 4001; Ikeda K et al. *J Gastroenterol* 2017;52(4):512-9.

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

Masatoshi Kudo, Richard S Finn, Shukui Qin, Kwang-Hyub Han, Kenji Ikeda, Fabio Piscaglia, Ari Baron, Joong-Won Park, Guohong Han, Jacek Jassem, Jean Frederic Blanc, Arndt Vogel, Dmitry Komov, T R Jeffry Evans, Carlos Lopez, Corina Dutcus, Matthew Guo, Kenichi Saito, Silvija Kraljevic, Toshiyuki Tamai, Min Ren, Ann-Lii Cheng

Kudo M et al. *Lancet* 2018;391(10126):1163-73.

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REFLECT: Primary and Secondary Endpoints

	Lenvatinib (n = 478)	Sorafenib (n = 476)	HR/odds ratio	*p*-value
Median OS	13.6 mo	12.3 mo	0.92	NR
Median PFS	7.4 mo	3.7 mo	0.66	<0.00001
Median TTP	8.9 mo	3.7 mo	0.63	<0.00001
ORR	24.1%	9.2%	3.13*	<0.00001

NR = not reported; TTP = time to progression

* Odds ratio

- Lenvatinib is noninferior to sorafenib with regard to OS

Kudo M et al. *Lancet* 2018;391(10126):1163-73; Cheng AL et al. *Proc ASCO* 2017;Abstract 4001.

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REFLECT: Treatment-Emergent AEs

- Grade 3 and higher events were more common in the lenvatinib arm (57% vs 49%)
- Most common AEs in the lenvatinib arm:
  - Hypertension (42% overall with 23% grade ≥3)
  - Diarrhea (39%)
  - Decreased appetite (34%)
  - Weight loss (31% with 8% grade ≥3)
  - Fatigue (30%)
- Grade 3 HFSR was more common in the sorafenib arm (11% vs 3%)

Cheng et al, 2017

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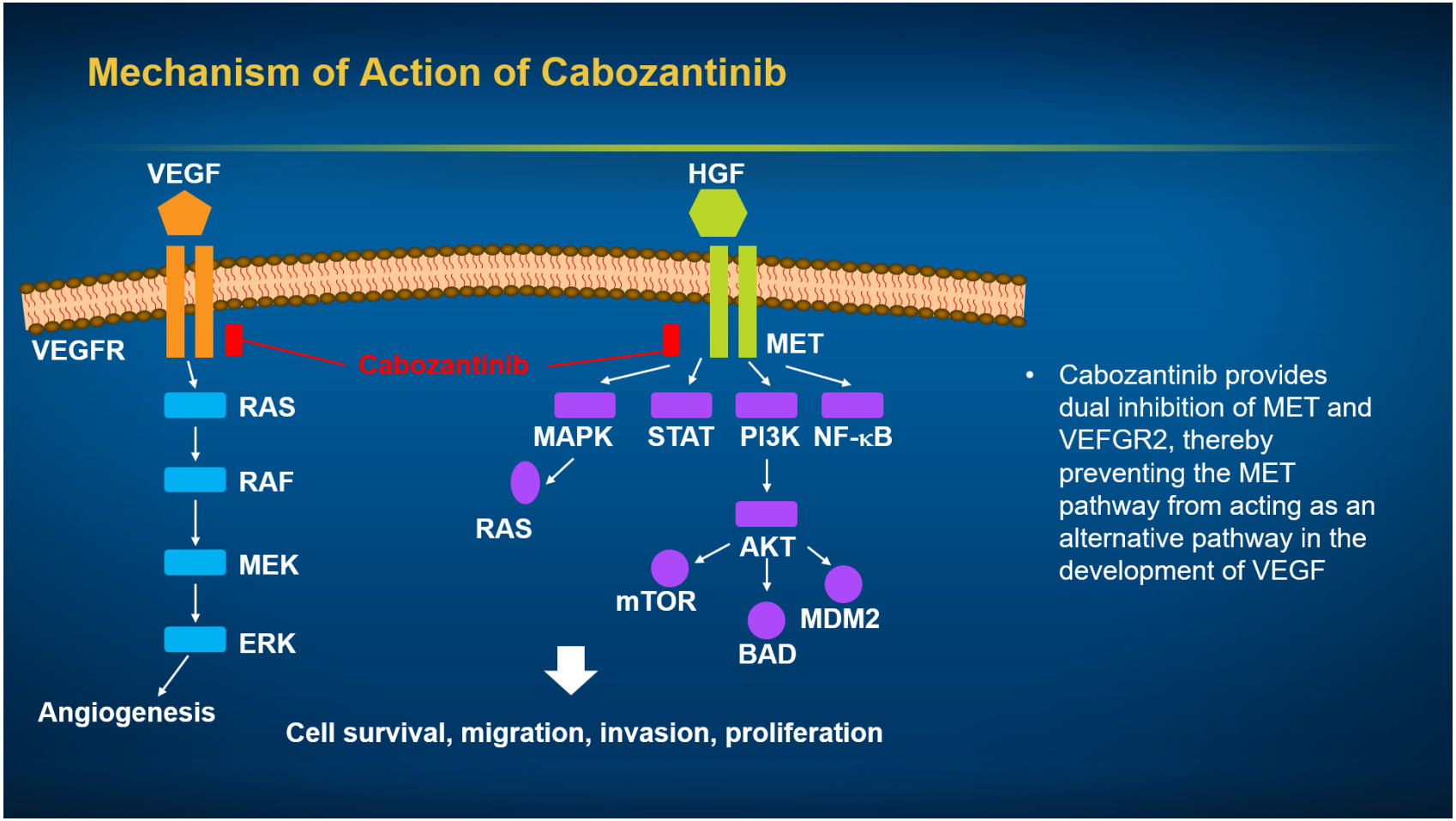

- Cabozantinib provides dual inhibition of MET and VEFGR2, thereby preventing the MET pathway from acting as an alternative pathway in the development of VEGF

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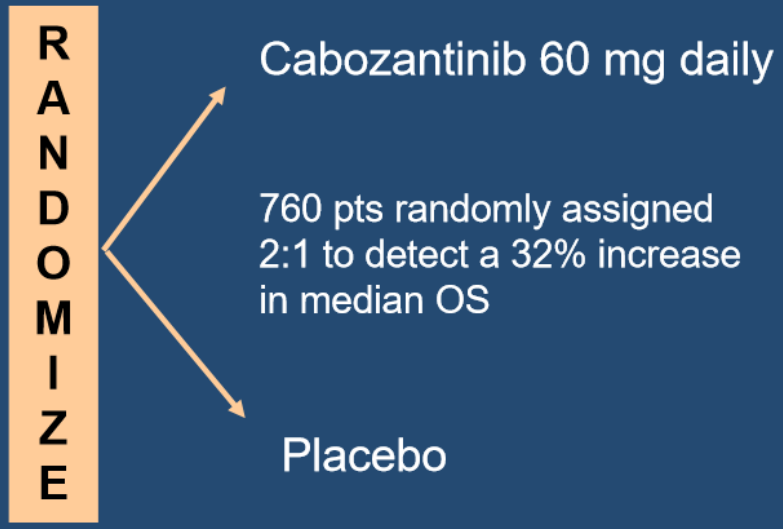
CELESTIAL: Cabozantinib vs Placebo in Post-Sorafenib HCC

Eligibility

- Advanced stage HCC with up to two previous HCC treatments including sorafenib
- ECOG PS 0 or 1
- Child-Pugh A
- Age ≥18 years
- No uncontrolled hypertension

Study Design

- Phase III, double blind, placebo-controlled
- 104 sites in North and South America, Europe, Australia, and Asia



Adapted from Abou-Alfa 2018 Gastrointestinal Cancers Symposium

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CELESTIAL: Clinical Outcomes

All patients	Cabozantinib (n = 470)	Placebo (n = 237)	HR	*p*-value
Median OS	10.2 mo	8.0 mo	0.76	0.0049
Median PFS	5.2 mo	1.9 mo	0.44	<0.0001
Prior sorafenib only	**n = 331**	**n = 164**	**HR**	***p*-value**
Median OS	11.3 mo	7.2 mo	0.70	NR
Median PFS	5.5 mo	1.9 mo	0.40	NR

NR = not reported

Abou-Alfa GK et al. Gastrointestinal Cancers Symposium 2018;Abstract 207.

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CELESTIAL: All-Causality Grade 3/4 Adverse Events

	Cabozantinib (n = 467)	Placebo (n = 237)
Any Grade 3 or 4 adverse event	68%	36%
Palmar-plantar erythrodysesthesia	17%	0%
Hypertension	16%	2%
Increased AST	12%	7%
Fatigue	10%	4%
Diarrhea	7%	2%
Asthenia	7%	2%
Anemia	4%	5%

- Treatment-related Grade 5 AEs:
  - — Cabozantinib (6 patients): Hepatic failure, esophagobronchial fistula, portal vein thrombosis, upper GI hemorrhage, pulmonary embolism, hepatorenal syndrome
  - — Placebo (1 patient): Hepatic failure

Abou-Alfa GK et al. Gastrointestinal Cancers Symposium 2018;Abstract 207.

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REACH-2: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Ramucirumab versus Placebo as Second-Line Treatment in Patients with Advanced Hepatocellular Carcinoma (HCC) and Elevated Baseline Alpha-Fetoprotein (AFP) Following First-Line Sorafenib

Zhu AX et al

ASCO 2018; Abstract 4003

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REACH-2: Clinical Outcomes

All patients	Ramucirumab (n = 197)	Placebo (n = 95)	HR	*p*-value
Median OS	8.5 mo	7.3 mo	0.710	0.0199
Median PFS	2.8 mo	1.6 mo	0.452	<0.0001
Overall response rate	4.6%	1.1%	—	0.1156
Disease control rate	59.9%	38.9%	—	0.0006

First positive Phase III study conducted in a biomarker-selected patient population with HCC

Zhu AX et al. ASCO 2018;Abstract 4003.

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Immune System Checkpoints

- Surface glycoproteins expressed on a variety of immune cells[1]
- Deliver inhibitory signals to T- or NK-cell activation
- Induce and maintain tumor immune tolerance
  - PD-1
    - Expressed on activated T cells, B cells, NK cells, Tregs and others[2]
    - When PD-1 binds its ligand (PD-L1/PD-L2), CD8+ T cell activation is blocked and Tregs are upregulated[3]
  - CTLA-4
    - Expressed on activated T cells and Tregs[4]
    - Promotes immunosuppression in tumor microenvironment[4,5]
    - Interferes with dendritic cell function
  - Other checkpoints

- PD-1 inhibitors (nivolumab, pembrolizumab)
- CTLA-1 inhibitors (tremelimumab)
  - Both classes have been shown to have activity in HCC

[1]Prieto Nat Rev Gastro Hepatol 2015; [2]Makarova-Rusher J Hepatol 2015; [3]Hui Science 2017; [4]Wing Science 2008; [5]Pardoll Nat Rev Cancer 2012

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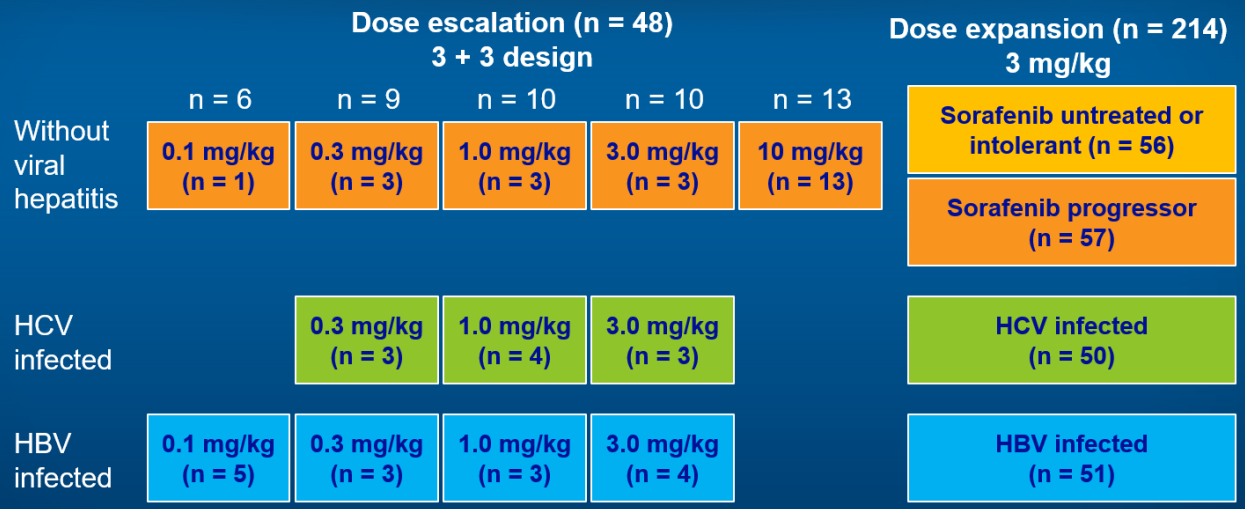
CheckMate 040 Study Design



HCV = hepatitis C virus; HBV = hepatitis B virus

El-Khoueiry AB et al. *Lancet* 2017;389(10088):2492-502.

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CM 040 Baseline Characteristics (cont)

Patients	Sorafenib-Naïve ESC + EXP (n=80)	Sorafenib Experienced ESC (n=37)	Sorafenib Experienced EXP (n=145)
HCC etiology, n (%)			
HCV	25 (31)	5 (14)	30 (21)
HBV	8 (10)	15 (41)	43 (30)
Uninfected	47 (59)	17 (46)	72 (50)
Child-Pugh score, n (%)			
5	58 (73)	34 (92)	97 (67)
6	20 (25)	3 (8)	46 (32)
>6	2 (3)	0	2 (1)
≥1% PD-L1 expression, n (%)	11 (14)	9 (24)	25 (17)
Prior treatments, n (%)			
Surgical resection	42 (53)	27 (73)	95 (66)
Radiotherapy	6 (8)	9 (24)	36 (25)
Local therapy	37 (46)	19 (51)	85 (59)

Crocenzi et al. DOI: 10.1200/JCO.2017.35.15_suppl.4013 Journal of Clinical Oncology 35, no. 15_suppl (May 2017) 4013-4013

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CM 040 Expansion Cohort Results

Investigator-Assessed Best Overall Response	Uninfected: Sorafenib Naïve/Intolerant (n=54)	Uninfected: Sorafenib Progressors (n=58)	HCV (n=51)	HBV (n=51)	Total (n=214)
Objective response, n (%)	11 (20)	11 (19)	7 (14)	6 (12)	35 (16)
CR	0	2 (3)	0	0	2 (1)
PR	11 (20)	9 (16)	7 (14)	6 (12)	33 (15)
SD	32 (59)	27 (47)	29 (57)	23 (45)	111 (52)
PD	11 (20)	18 (31)	12 (24)	22 (43)	63 (29)
Not evaluable	0	2 (3)	3 (6)	0	5 (2)

Crocenzi et al. DOI: 10.1200/JCO.2017.35.15_suppl.4013 Journal of Clinical Oncology 35, no. 15_suppl (May 2017) 4013-4013

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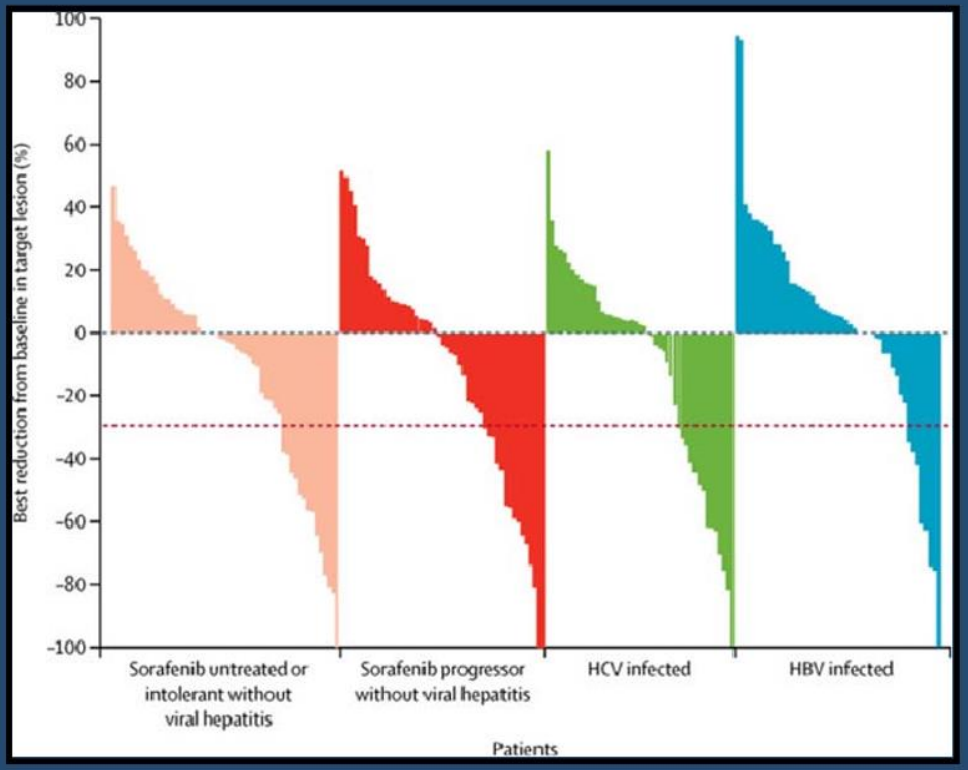
CM 040 Results: Best Target Lesion Change



El-Khoueiry Lancet 2017

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040 Response by PD-L1 expression

	Escalation phase (n=44)*	Expansion phase (n=174)*
PD-L1 ≥1%†	11 (25%)	34 (20%)
Objective response	3/11 (27%; 6-61)	9/34 (26%; 13-44)
Complete response	1 (9%)	1 (3%)
Partial response	2 (18%)	8 (24%)
Stable disease	0	16 (47%)
Progressive disease	7 (64%)	9 (26%)
Not determined	1 (9%)	0
PD-L1 <1%†	33 (75%)	140 (80%)
Objective response	4/33 (12%; 3-28)	26/140 (19%; 13-26)
Complete response	2 (6%)	2 (1%)
Partial response	2 (6%)	24 (17%)
Stable disease	19 (58%)	62 (44%)
Progressive disease	8 (24%)	46 (33%)
Not determined	2 (6%)	6 (4%)

Data are n (%); n/N (%; 95% CI). PD-L1=programmed death-ligand 1.
*Four patients in the dose-escalation phase and 40 patients in the dose-expansion phase did not have tumour PD-L1 expression data available.
†PD-L1 membrane expression on tumour cells.

Table 5: PD-L1 expression on tumour cells and response

El-Khoueiry Lancet 2017

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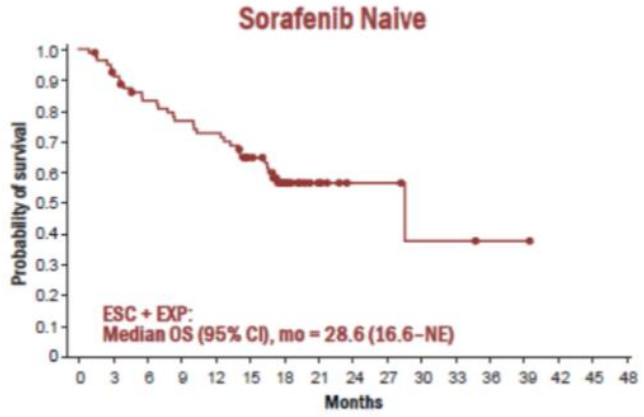
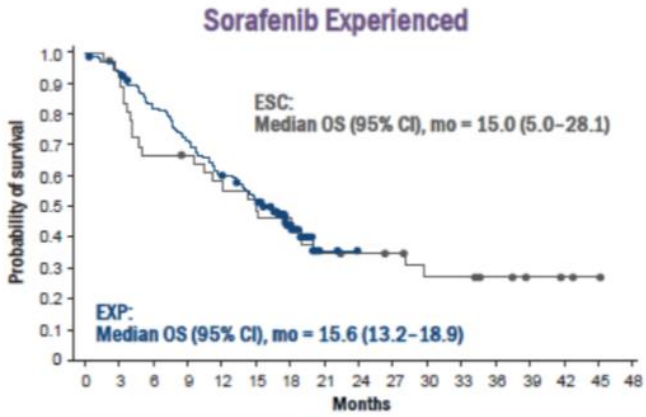
040 Overall Survival

Figure 4. Overall Survival With Nivolumab



OS Rate (95% CI), %	ESC + EXP
12 months	73 (61.3–81.3)
18 months	57 (44.3–67.1)



OS Rate (95% CI), %	ESC	EXP
12 months	58 (40.2–72.2)	60 (51.4–67.5)
18 months	46 (29.5–61.7)	44 (35.3–51.9)

Kaplan-Meier method; closed circles denote censored patients.

Crocenzi et al. DOI: 10.1200/JCO.2017.35.15_suppl.4013 Journal of Clinical Oncology 35, no. 15_suppl (May 2017) 4013-4013

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040 Treatment-Related AEs

N (%)	Sorafenib-Naïve ESC + EXP (n=80)		Sorafenib-Experienced ESC + EXP (n=182)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Patients with any treatment-related AE	62 (78)	23 (29)	141 (77)	32 (18)
Treatment related AEs (≥5%)				
Fatigue	16 (20)	0	40 (22)	4 (2)
Pruritus	19 (24)	0	37 (20)	1 (1)
Rash	13 (16)	1 (1)	33 (18)	1 (1)
Diarrhea	10 (13)	1 (1)	26 (14)	2 (1)
Nausea	7 (9)	0	14 (8)	0
Decreased appetite	4 (5)	0	12 (7)	1 (1)
Anemia	4 (5)	0	9 (5)	1 (1)
Dry mouth	6 (8)	0	10 (5)	0

Crocenzi et al. DOI: 10.1200/JCO.2017.35.15_suppl.4013 Journal of Clinical Oncology 35, no. 15_suppl (May 2017) 4013-4013

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KEYNOTE-224: Pembrolizumab in Patients with Advanced Hepatocellular Carcinoma Previously Treated with Sorafenib

Pembrolizumab (pembro) in Patients with Advanced Hepatocellular Carcinoma (HCC): KEYNOTE-224 Update

Zhu AX et al.
Gastrointestinal Cancers Symposium 2018;Abstract 209.

Zhu AX et al.
ASCO 2018;Abstract 4020.

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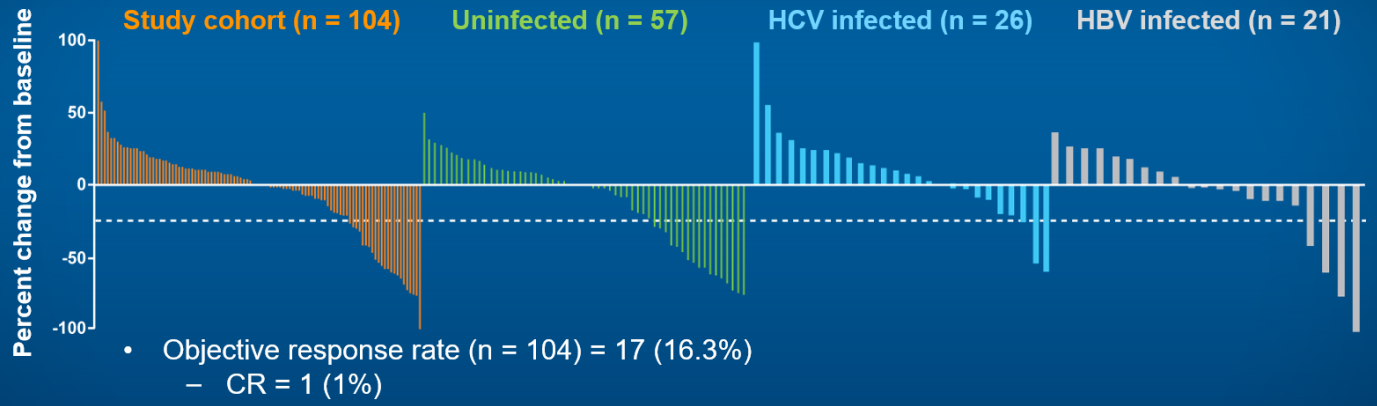
KEYNOTE-224: Response and Survival

Maximum Percentage Changes from Baseline in Target Lesions[1]



- Objective response rate (n = 104) = 17 (16.3%)
  - CR = 1 (1%)

- Disease control rate (n = 104) = 64 (61.5%)[1, 2]
- Median duration of response not reached[2]
- Median OS = 12.9 mo[2]
- Median PFS = 4.9 mo[2]

[1] Zhu AX et al. Gastrointestinal Cancers Symposium 2018;Abstract 209; [2] Zhu AX et al. ASCO 2018;Abstract 4020.

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Anti-tumor Activity

Response†	Total N=104 n (%)	95% CI‡
ORR (CR+PR)	17 (16.3)	9.8 - 24.9
Disease control (CR+PR+SD)	64 (61.5)	51.5 - 70.9
Best overall response		
CR	1 (1.0)	0.0 - 5.2
PR	16 (15.4)	9.1- 23.8
SD	47 (45.2)	35.4 - 55.3
PD	34 (32.7)	23.8 - 42.6
No Assessment§	6 (5.8)	2.1-12.1

†Confirmed best response by independent central review per RECIST v1.1. ‡Based on binomial exact confidence interval method. §Subjects who had a baseline assessment by investigator review or central radiology but no post-baseline assessment on the data cutoff date including discontinuing or death before the first post-baseline scan. Data cutoff date: Aug 24, 2017.

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Zhu AX, et al 2018 Gastrointestinal Cancers Symposium

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KEYNOTE-224

Treatment-related Adverse Events

Adverse events†	Total N=104 n (%)
≥ 1 event	76 (73.1)
≥ Grade 3	26 (25.0)
Led to discontinuation	7 (6.7)
Led to death‡	1 (1.0)
Occurred in ≥10% of patients (all grades)	22 (21.2)
Fatigue	13 (12.5)
Aspartate aminotransferase increased	10 (9.6)
Diarrhea	10 (9.6)
Pruritus	22 (21.2)
Hepatic-related§	
Immune-mediated	3 (2.9)
Viral flare	0 (0)

†Attributed to treatment by investigator. ‡Ulcerative esophagitis. §Sponsor assessed.

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Zhu AX, et al 2018 Gastrointestinal Cancers Symposium

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Ongoing Phase III Studies of Anti-PD-1/PD-L1 Checkpoint Inhibitors for HCC

Protocol ID (Agent)	n	Setting	Treatment arms
CheckMate 9DX	530	Adjuvant; high recurrence risk after resection/ablation	• Nivolumab • Placebo
CheckMate 459	726	First-line, advanced	• Nivolumab • Sorafenib
HIMALAYA	1,200	First-line, unresectable	• Durvalumab monotherapy • Durvalumab + tremelimumab • Sorafenib
KEYNOTE-240	408	Second-line, advanced	• Pembrolizumab + BSC • Placebo + BSC

www.clinicaltrials.gov. Accessed May 2018.