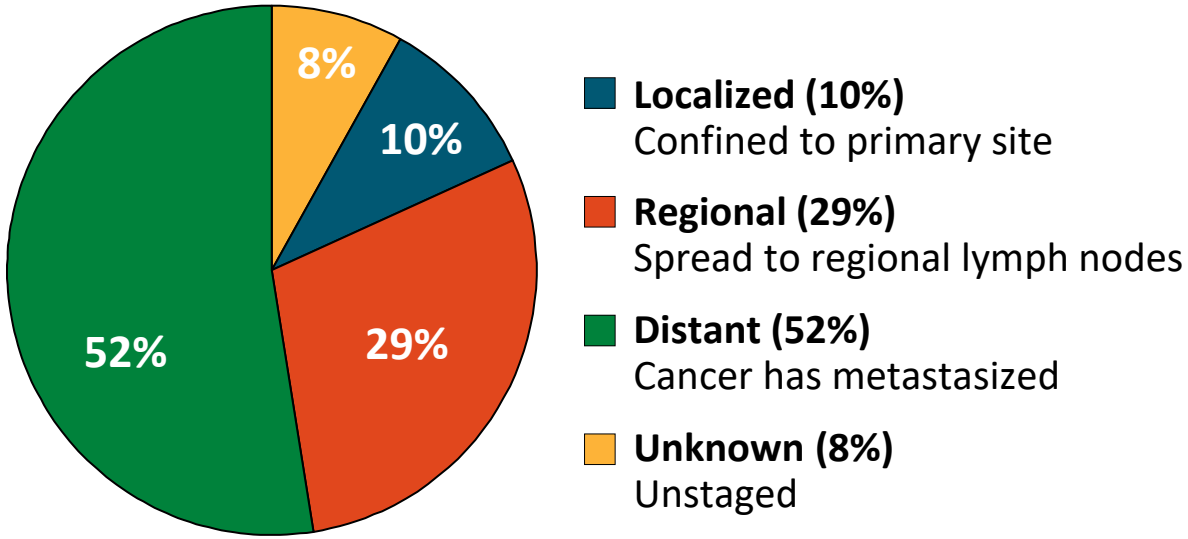
Notübüler GIS Kanserlerinin Bugünü

Dr. Işıl Somalı
DEÜ Onkoloji Enstitüsü
Tıbbi Onkoloji Bilim Dalı

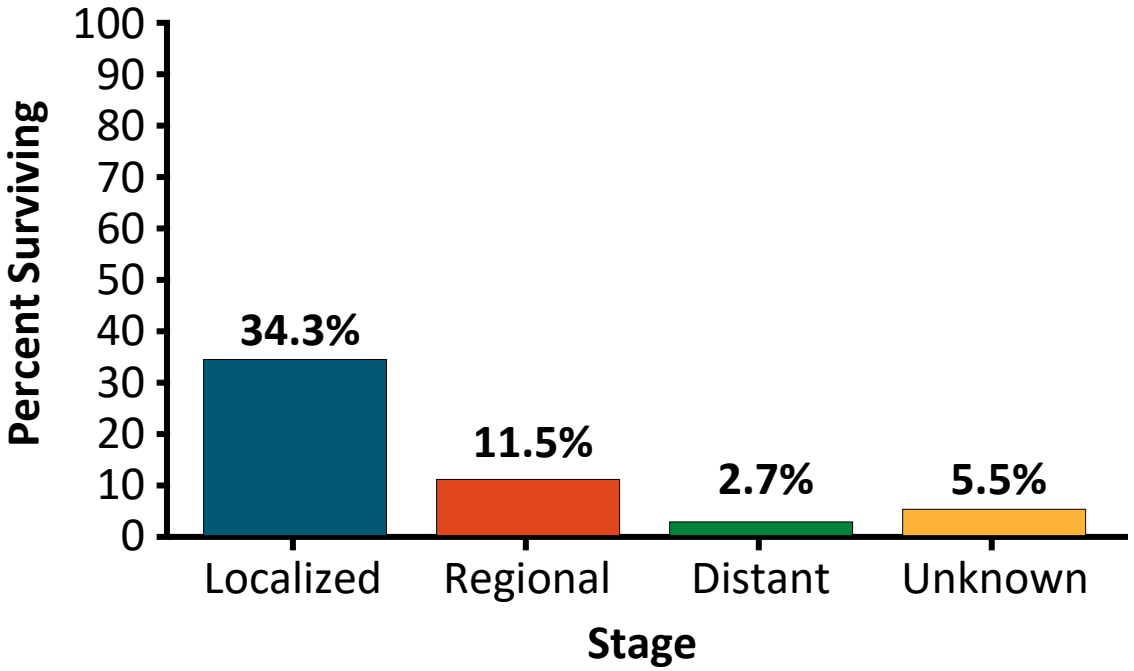
Pankreas Kanseri

Pancreatic Cancer: Prognosis

Percent of Cases by Stage

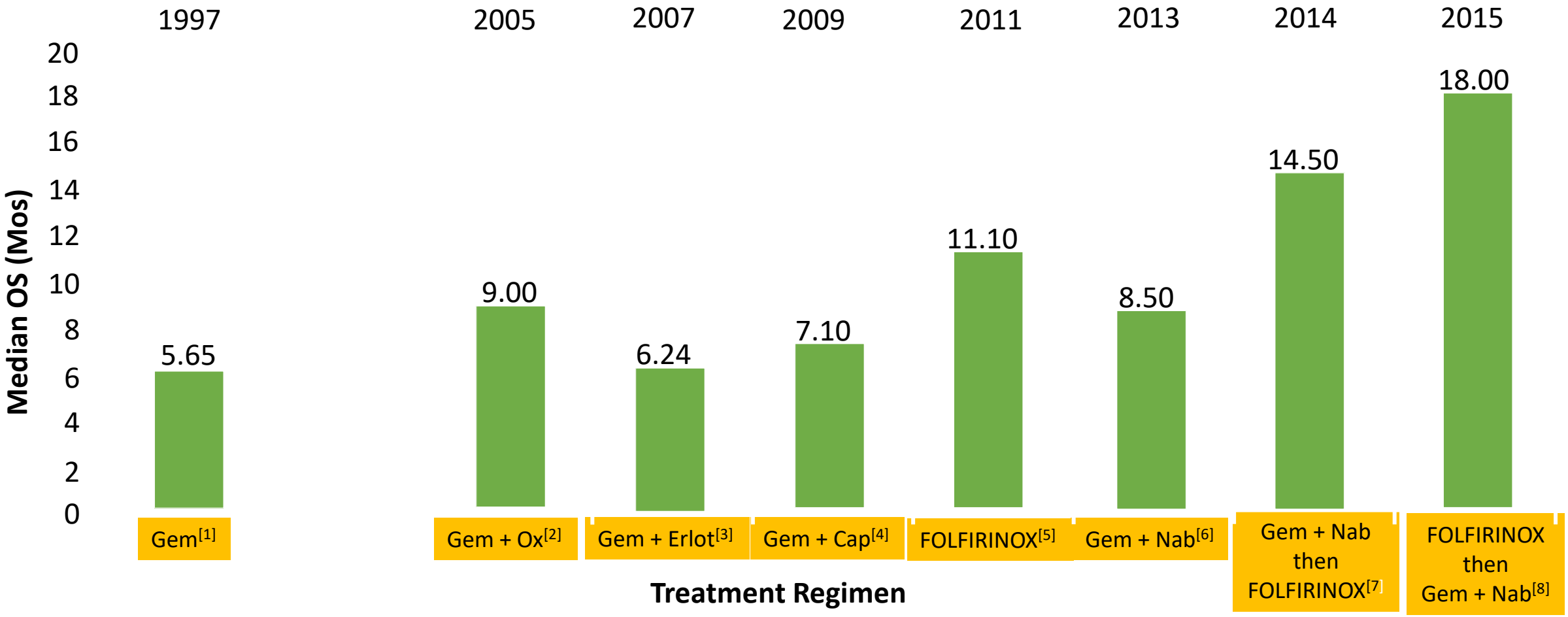


5-Yr Relative Survival



NIH, National Cancer Institute, SEER 18 2008-2014

Extending Survival



1. Burris. JCO. 1997;15:2403. 2. Louvet. JCO. 2005;23:3509. 3. Moore. JCO. 2007;25:1960. 4. Cunningham. JCO. 2009;27:5513. 5. Conroy. NEJM. 2011;364:1817. 6. Von Hoff. NEJM. 2013;369:1691. 7. Ramanathan. ASCO 2013. Abstr 233. 8. Portal. Br J Cancer. 2015;113:989.

Pankreas Kanserinde Adjuvan Tedavi

Earlier Randomized Postoperative Adjuvant Therapy Trials in Pancreatic Cancer

Study	Tx	R1, %	LN+, %	Locoregional Recurrence, %	Median OS, Mos	*P* Value	Median DFS, Mos	*P* Value	Grade 3/4 AE, %
ESPAC-1 (N = 289)	5-FU CRT	19 19	53 50	35 --	20.1 15.9	.009	15.2 10.7	.04	4 6
ESPAC-3 (N = 1149)	5-FU Gem	14 15	62 60	NR NR	23.0 23.6	.39	14.1 14.3	.53	14 7.5
RTOG 9704 (N = 451)	5-FU/CRT Gem/CRT	33 35	65 68	30 31	16.9 18.8	.15	11.1 11.2	NR	62 79
CONKO-001 (N = 354)	Gem Obs	19 15	71 73	34 41	22.8 20.2	.01	13.4 6.7	< .001	5 1
JSAP-02 (N = 378)	Gem Obs	19 8	67 70	23 32	22.3 18.4	< .001	11.4 5.0	.01	26 NR
GITSG (N = 43)	CRT Obs	19 24	29 27	15 15	20.0 11.0	.03	11.0 9.0	.01	7 NR
CONKO-005 (N = 436)	Gem Gem/erlotinib	0 0	66 64	NR NR	26.5 24.6	.406	11.6 11.6	.291	45.4 63.0

Ahn. Cancer Treat Rev. 2016;42:10.

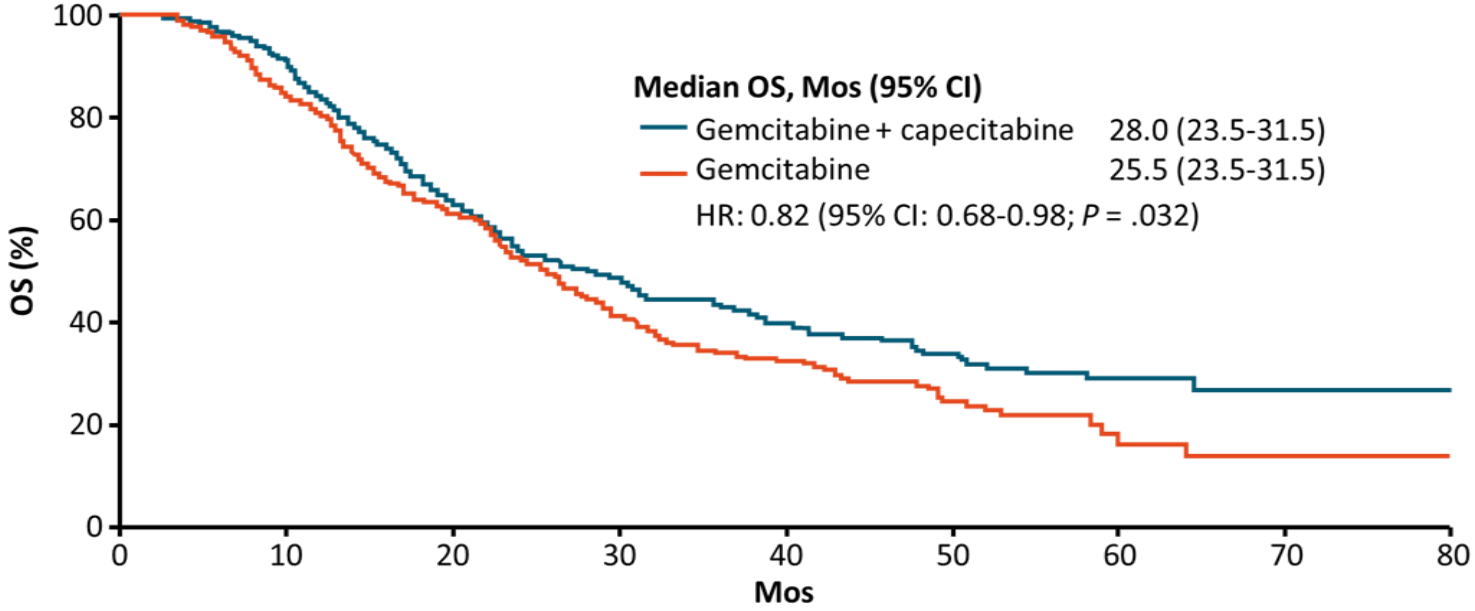
Adjuvan Tedavi

- ESPAC-4
- PRODİGE-24

Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial

ESPAC-4: Adjuvant Gemcitabine ± Capecitabine in Resected Pancreatic Cancer

- Multicenter, randomized, open-label phase III trial (N = 732)



Neoptolemos. Lancet. 2017;389:1011.

Slide credit: clinicaloptions.com

PRODIGE 24/CCTG PA.6: Adjuvant mFOLFIRINOX vs Gemcitabine in Resected Pancreatic Cancer

- Multicenter, randomized phase III trial

Patients 18-79 years of age with histologically confirmed R0 or R1 resected pancreatic ductal adenocarcinoma; CA19-9 level < 180 U/mL ≤ 12 wks post surgery; ECOG PS 0/1; no prior chemotherapy or RT (N = 493)

→ **mFOLFIRINOX***
Q2W x 12 cycles
(n = 247†)

→ **Gemcitabine** 1000 mg/m^2
Day 1, 8, 15 of 28-day cycle x 6 cycles
(n = 246‡)

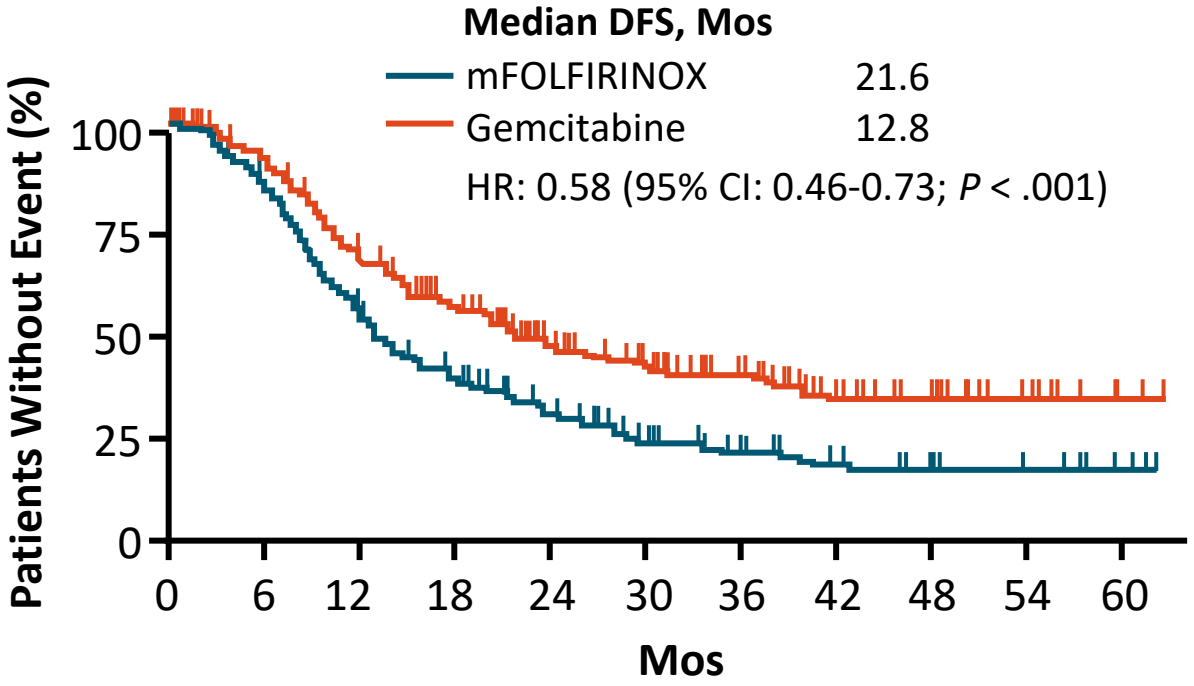
→ ***CT scans every 3 mos***

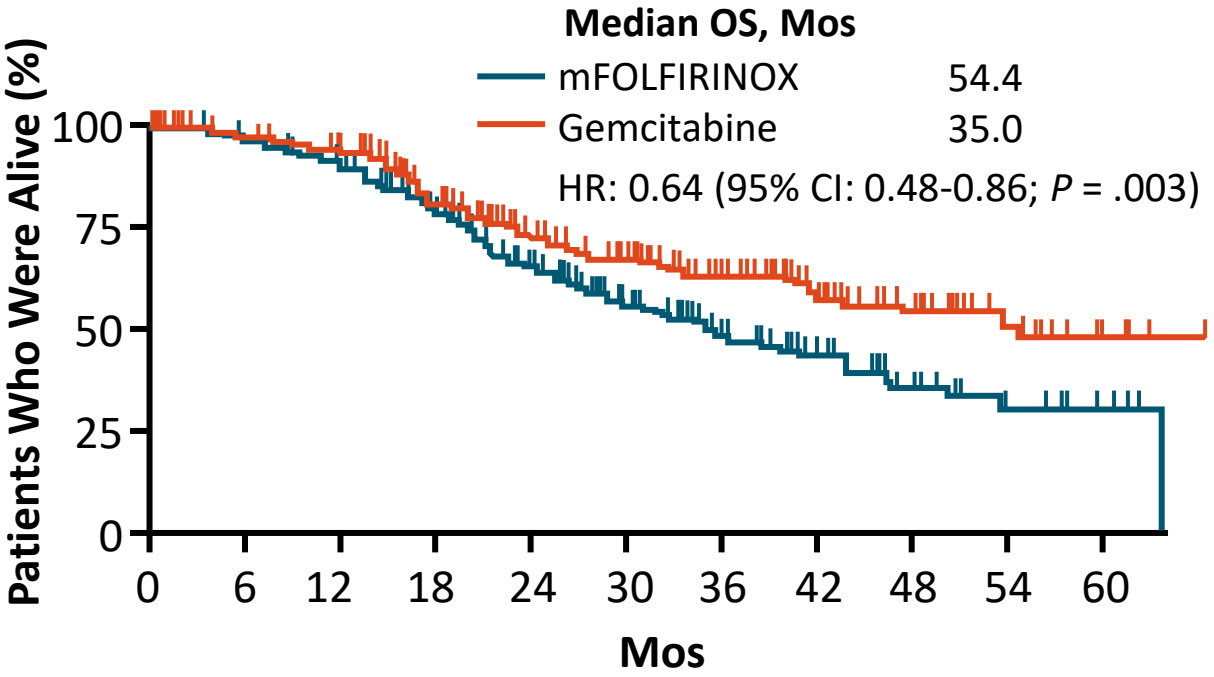
*On Day 1 of each cycle, oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and irinotecan 180 mg/m^2 (reduced to 150 mg/m^2 due to 20% grade 3/4 diarrhea rate in first 30 patients); continuous fluorouracil IV 2.4 g/m^2 over 46 hrs. †n = 238 treated. ‡n = 243 treated.

- Primary endpoint: DFS
- Secondary endpoints: toxicity, OS, cancer-specific survival, metastasis-free survival

Conroy. NEJM. 2018;379:2395.

PRODIGE 24/CCTG PA.6: Survival Outcomes





Survival Outcome	mFOLFIRINOX (n = 247)	Gemcitabine (n = 246)
3-yr DFS, % (95% CI)	39.7 (32.8-46.6)	21.4 (15.8-27.5)

Survival Outcome	mFOLFIRINOX (n = 247)	Gemcitabine (n = 246)
3-yr OS, %	63.4 (55.7-70.1)	48.6 (40.9-55.8)

Conroy. NEJM. 2018;379:2395.

PRODIGE 24/CCTG PA.6: Safety

AE, %	mFOLFIRINOX (n = 238)		Gemcitabine (n = 243)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Diarrhea	84.4	18.6*	49	3.7
Fatigue	84	11	77.6	4.6
PN	61.2	9.3	8.7	--
Vomiting	46	5	29	1.2
Mucositis	33.8	2.5	14.9	0
Alopecia	27	--	19.5	--
Hand–foot syndrome	5	0.4	0.8	--

AE, %	mFOLFIRINOX (n = 238)		Gemcitabine (n = 243)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Headache	8.4	--	19.4	--
Fever	16.5	0.4	32.4	0.4
Flu-like symptoms	1.3	--	5.0	0.4
ALT increase	64	4.2	73.5	5.0
AST increase	67	3.8	69	3.3

Conroy. NEJM. 2018;379:2395.

Slide credit: clinicaloptions.com

Pankreas Kanserinde Neoadjuvan Tedavi

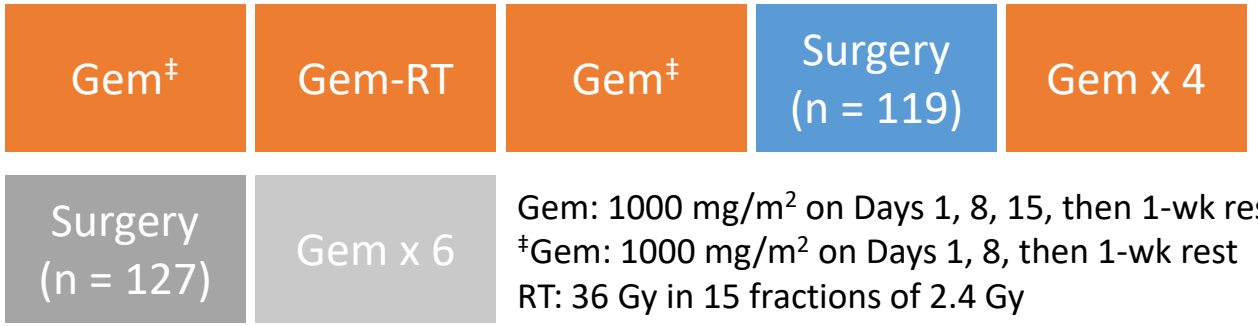
Neoadjuvan Tedavi

- PREOPANC-1
- Prep-02/JSAP-05

PREOPANC-1: Neoadjuvant Chemoradiotherapy vs Immediate Surgery for Resectable Pancreatic Cancer

- International, randomized, controlled phase III trial

Adult patients with WHO PS 0/1 and resectable* or borderline resectable† pancreatic cancer (N = 246)



Gem: 1000 mg/m^2 on Days 1, 8, 15, then 1-wk rest
‡Gem: 1000 mg/m^2 on Days 1, 8, then 1-wk rest
RT: 36 Gy in 15 fractions of 2.4 Gy

All patients followed for 12 mos

*No contact with superior mesenteric, celiac trunk, or common hepatic arteries and ≤ 90° contact with superior mesenteric portal vein.
†≥ 1 of the following required: ≤ 90° contact with superior mesenteric, celiac trunk, or common hepatic arteries or 90° to 270° contact with superior mesenteric portal vein and no occlusion.

- Primary endpoint: OS (ITT)
- Secondary endpoints: R0 resection rate, DFS, distant metastases–free interval, locoregional recurrence-free interval, perioperative complications

van Tienhoven. ASCO 2018. Abstr LBA4002.

Slide credit: clinicaloptions.com

PREOPANC-1: Efficacy

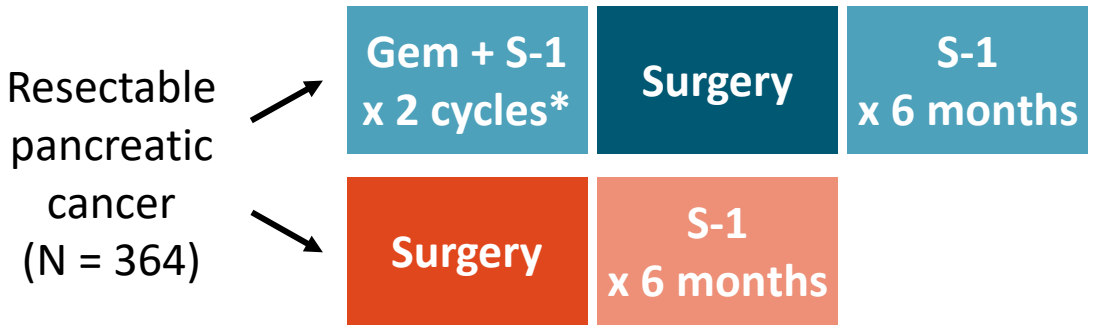
Outcome	Preoperative Radiochemotherapy (n = 119)	Immediate Surgery (n = 127)		HR
Median OS, mos (ITT population)*	**17.1**	**13.7**	**0.74**	**.074**
▪ **Subset with R0/R1 resection†**	**42.1**	**16.8**	**NR**	**< .001**
Resection rate, n (%)	72 (60)	91 (72)	--	.065
R0 resection rate, n/N (%)	45/72 (63)	28/91 (31)	--	< .001
Median DFS, mos	9.9	7.9	0.71	.023
Median distant metastases–free interval, mos	18.4	10.6	0.71	.013
Median locoregional recurrence-free interval, mos	Not reached	11.8	0.55	.002
Serious AEs, n (%)	55 (46)	49 (39)	--	.28

*Preliminary analysis; only 149/176 events. †Preoperative radiochemotherapy, n = 72; immediate surgery, n = 91.

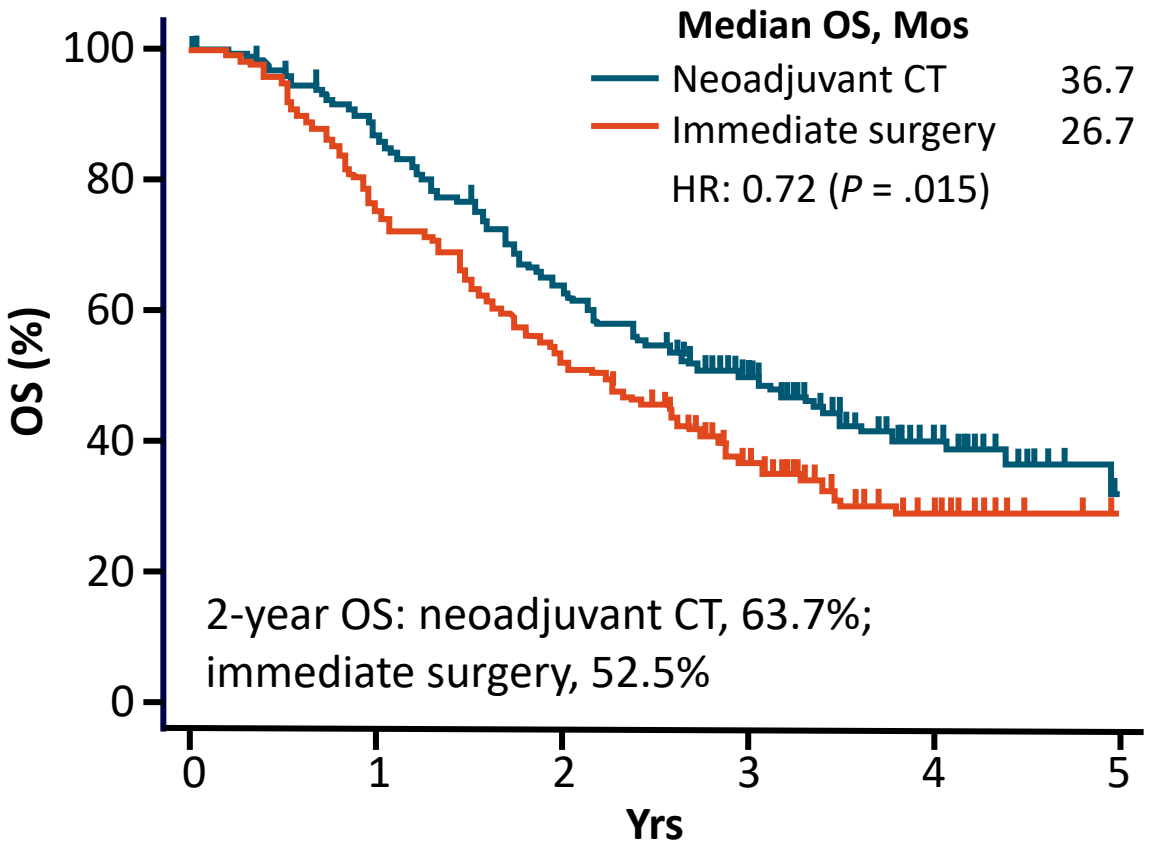
van Tienhoven. ASCO 2018. Abstr LBA4002.

Prep-02/JSAP-05: Neoadjuvant Chemotherapy vs Immediate Surgery

- Randomized phase II/III trial



*Gemcitabine: 1 g/m^2 on Days 1, 8; oral S-1: 40 mg/m^2 BID on Days 1-14.



Unno. ASCO GI 2019. Abstr 189.

Slide credit: clinicaloptions.com

Metastatik Pankreas Kanserinde Güncel Durum

Metastatik Hastalıkta Tedavi

1. basamak tedavi çalışmaları

- MPACT
- ACCORD 11

2. basamak tedavi çalışmaları

- NAPOLI-1

Devam tedavisi

- POLO

MPACT: Gemcitabine ± nab-Paclitaxel for Patients With Metastatic Pancreatic Cancer

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

Patients with metastatic pancreatic cancer, no previous treatment for metastatic disease, KPS ≥ 70, bilirubin ≤ ULN (N = 861)

→ **Gemcitabine** 1000 mg/m²/wk IV + **nab-Paclitaxel** 125 mg/m²/wk IV for 7 wks, and then on Days 1, 8, 15 Q4W (n = 431)

→ **Gemcitabine** 1000 mg/m²/wk IV for 7 wks, and then on Days 1, 8, 15 Q4W (n = 430)

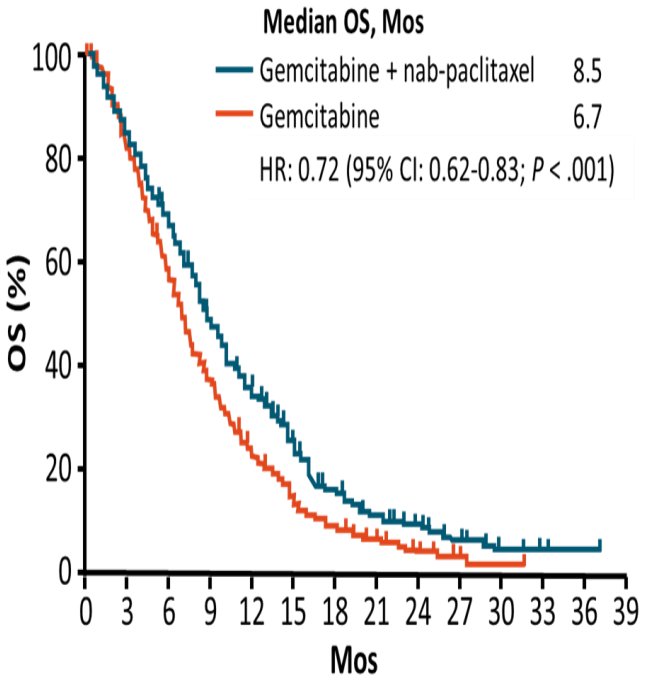
→ *Treat until PD*

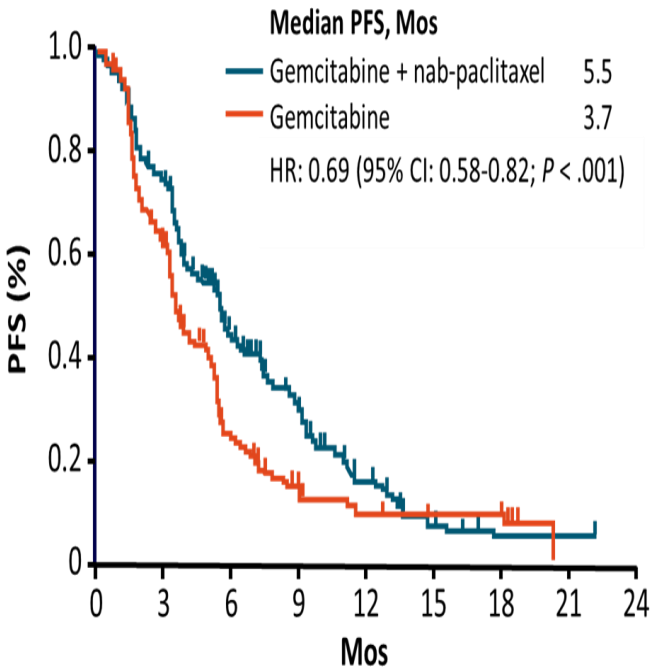
- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, safety

Von Hoff. NEJM. 2013;369:1691.

Slide credit: clinicaloptions.com

MPACT: OS and PFS





Von Hoff. NEJM. 2013;369:1691.

Slide credit: clinicaloptions.com

ACCORD 11 Faz 3 Çalışma;

FOLFIRINOX vs Gemcitabine for Patients With Metastatic Pancreatic Cancer

- Multicenter, randomized, phase II/III trial

Patients with untreated metastatic pancreatic cancer; < 76 years of age; ECOG PS 0/1; adequate BM, platelet count, liver and renal function (N = 342)

FOLFIRINOX
Oxaliplatin 85 mg/m^2 + LV 400 mg/m^2 + Irinotecan 180 mg/m^2 + 5-FU bolus 400 mg/m^2, then 2400 mg/m^2 IV over 46 hrs
(n = 171)

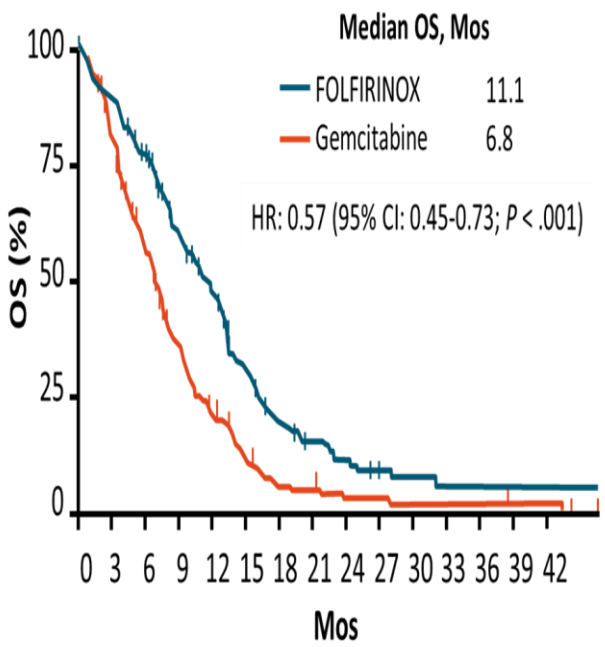
Gemcitabine
1000 mg/m^2 weekly x 7 of 8, then weekly x 3 of 4
(n = 171)

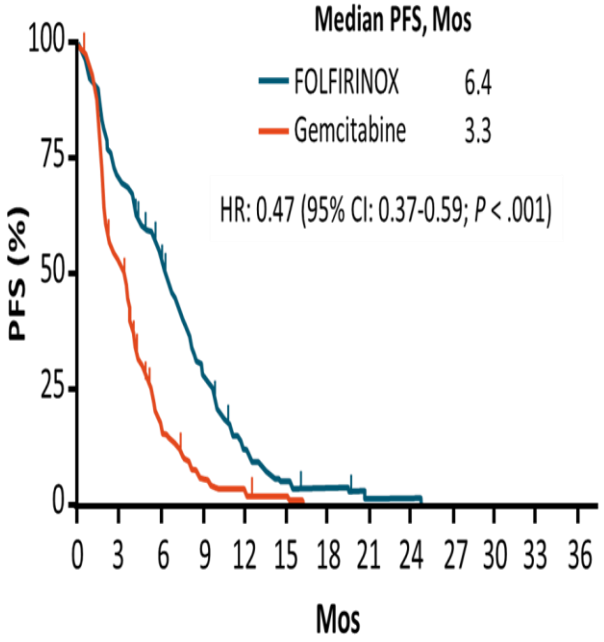
- Primary endpoints: ORR (phase II), OS (phase III)

Conroy. NEJM. 2011;364:1817.

Slide credit: clinicaloptions.com

FOLFIRINOX vs Gemcitabine: OS and PFS



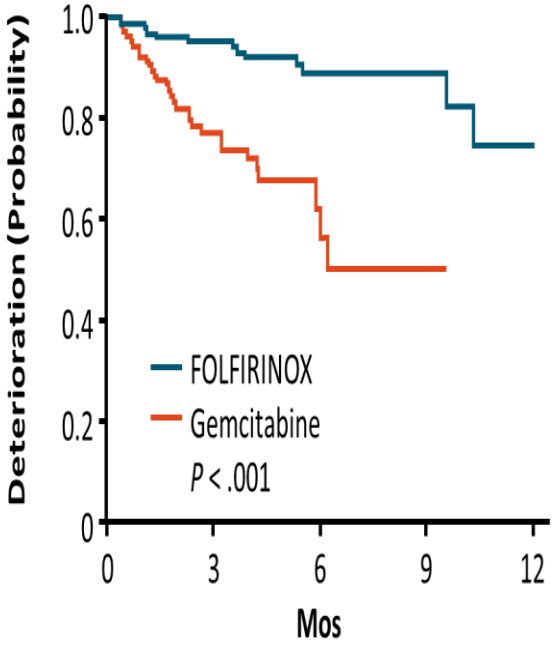


Conroy. NEJM. 2011;364:1817.

Slide credit: clinicaloptions.com

FOLFIRINOX vs Gemcitabine: Quality of Life

Time Until Definitive Deterioration > 20 Points, EORTC-C30 Global Health Status/QoL Questionnaire



- Prolongation of QoL in patients treated with FOLFIRINOX compared with gemcitabine, despite greater toxicity
- Specifically, longer time to deterioration in:
  - Global health status
  - Physical, cognitive, and social functioning
  - Symptoms such as fatigue, nausea/vomiting, pain, and anorexia

Trial Characteristics and Outcomes	FOLFIRINOX vs Gem (N = 342)[1]	nab-Pac + Gem vs Gem (N = 861)[2]
Median age, yrs (range)	61 (25-76)	62 (27-86)
Male, %	62	57
Region (NA/WE/EE/A), %	0/100 (France)/0/0	62/9/15/14
ECOG PS/KPS (0/100, 1/80-90, 2/60-70), %	37/62/1	16/76/8
Tumor location (H/B/T), %	39/31/26	43/31/25
Median involved metastatic sites, n	2	2.5
ORR, %	32 vs 9	23 vs 7
Disease control rate, %	70 vs 51	48 vs 33
Median PFS, mos	6.4 vs 3.3	5.5 vs 3.7
Median OS, mos	11.1 vs 6.8	8.5 vs 6.7

Gourgou-Bourgade. JCO. 2013;31:23.

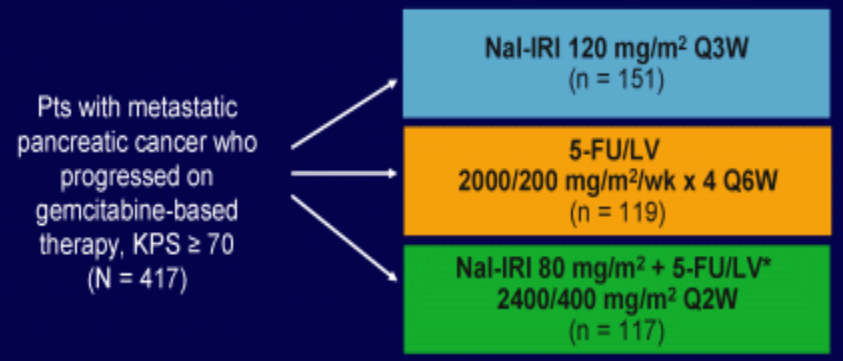
Slide credit: clinicaloptions.com

1. Conroy. NEJM. 2011;364:1817. 2. Von Hoff. NEJM. 2013;369:1691.

Slide credit: clinicaloptions.com

NAPOLI-1: Nanoliposomal Irinotecan ± 5-FU/LV vs 5-FU/LV

- Phase III trial

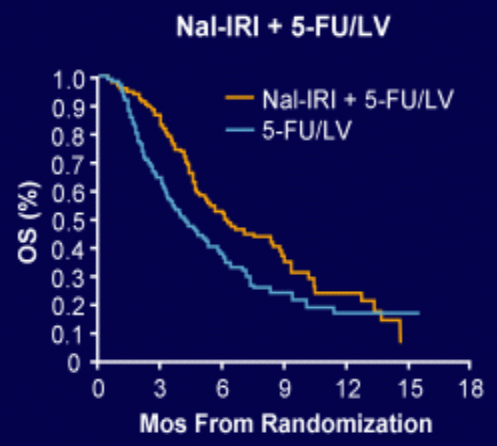


NAPOLI-1: Nanoliposomal Irinotecan ± 5-FU/LV vs 5-FU/LV—Results

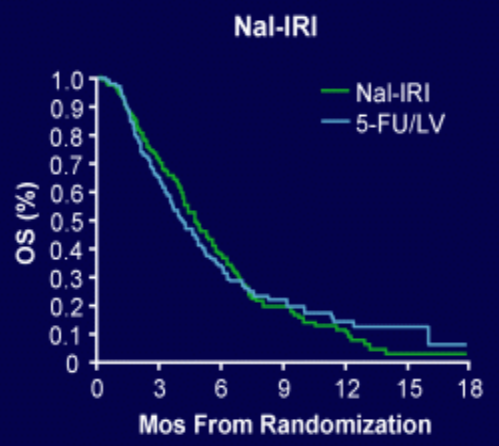
Tumor Response and Control	Nal-IRI + 5-FU/LV (n = 117)	5-FU/LV (n = 119)
Median PFS, mos (95% CI)	3.1 (2.7-4.2)	1.5 (1.4-1.8)
	P = .0001	
ORR, % (95% CI)	16 (9.6-22.9)	1 (0-2.5)
	P < .001	
CA19-9 reduction, %	36	12
	P = .0009	

Wang-Gillam A, et al. Lancet. 2016;387:545-557.

NAPOLI-1: Nanoliposomal Irinotecan ± 5-FU/LV vs 5-FU/LV—OS



Median OS: 6.1 vs 4.2 mos
HR: 0.57 (95% CI: 0.41-0.80; *P* = .0009)



Median OS: 4.9 vs 4.2 mos
HR: 0.93 (95% CI: 0.71-1.21; *P* = .5545)

Wang-Gillam A, et al. Lancet. 2016;387:545-557.

NAPOLI-1: Nanoliposomal Irinotecan ± 5-FU/LV vs 5-FU/LV in Metastatic Pancreatic Cancer: AEs

AEs, %	Safety Population			
	Nal-IRI + 5-FU/LV (n = 117)		5-FU/LV Control (n = 134)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Diarrhea	59	13	26	4
Vomiting	52	11	26	3
Nausea	51	8	34	3
Decreased appetite	44	4	32	2
Fatigue	40	14	28	4
Neutropenia	39	27	5	1
Anemia	38	9	23	7
Hypokalemia	12	3	9	2

Wang-Gillam A, et al. Lancet. 2016;387:545-557.

ASCO Now Recommends Genetic Testing For All Patients With Pancreatic Cancer

ASCO Updates Published
November 20, 2018

"All patients diagnosed with pancreatic adenocarcinoma should undergo assessment of risk for hereditary syndromes known to be associated with an increased risk for pancreatic adenocarcinoma….Germline genetic testing may be discussed with individuals diagnosed with pancreatic cancer, even if family history is unremarkable."

"Germline genetic testing should be performed using a multigene panel[a]."

[a]Genes included in multigene panel: *APC, ATM, BRCA1/2, CDKN2A*, Lynch syndrome genes (*MLH1/2, MSH6, PMS2, EPCAM*), *PALB2, STK11, TP53.*

Stoffel. JCO. 2019;37:153.

Slide credit: clinicaloptions.com

PRIME therapies for patients with advanced-stage pancreatic ductal adenocarcinoma

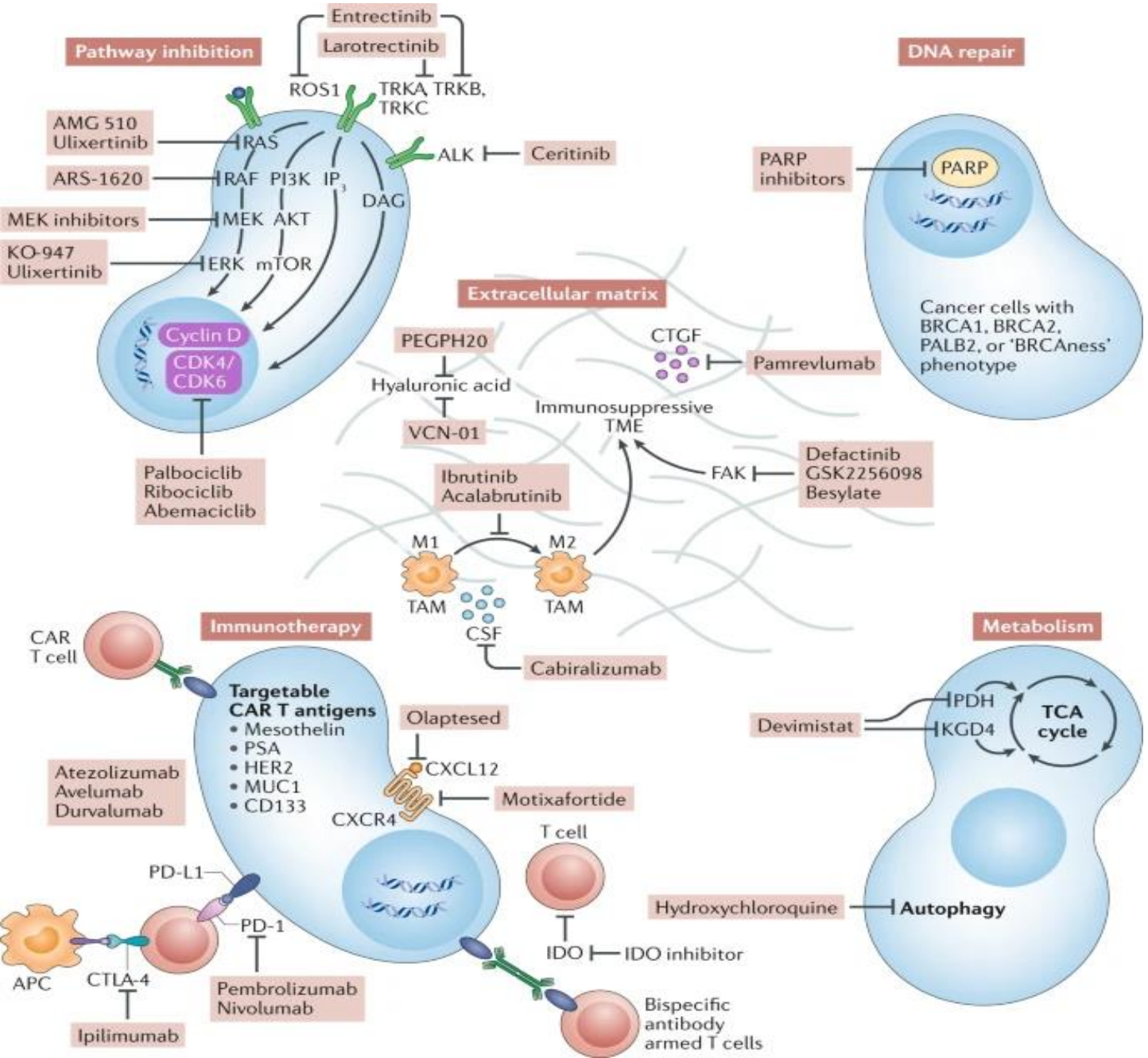
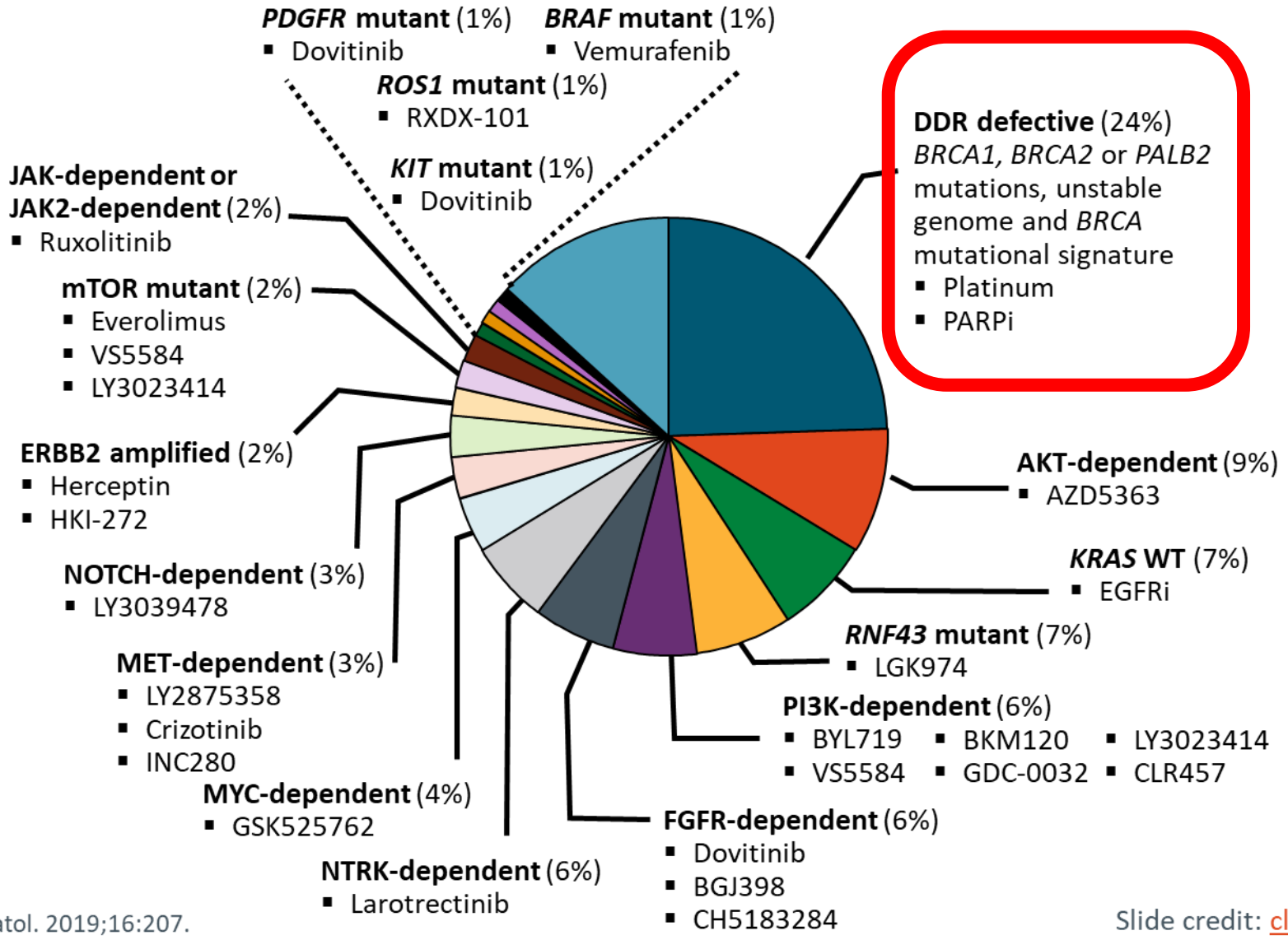


Table 1 | PRIME categories of treatments for PDAC

Category	Examples of therapeutic strategies
Pathway inhibitors	ERK1/2, TRKA/B/C, ROS1, ALK and CDK4/6 inhibitors
Repair	Poly (ADP-ribose) polymerase inhibitors
Immunotherapy	Immune checkpoint inhibitors, CAR T cell therapy and cancer vaccines
Metabolism	Devimistat and hydroxychloroquine
Extracellular matrix	Recombinant hyaluronidase; FAK, BTK and CTGF inhibitors

Nature Reviews Clinical Oncology volume 17, (2020

The Putative Actionable Genome of Pancreatic Cancer



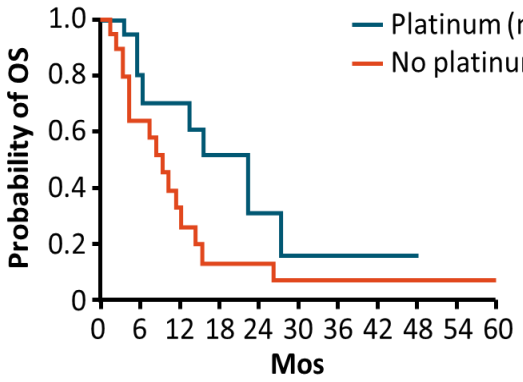
Collisson. Nature Rev Gastroenterol Hepatol. 2019;16:207.

Slide credit: clinicaloptions.com

Genetik testler neden önemli?

- Yeni tanı alan Pankreas kanserli tüm hastalarda genetik testlerin yapılması önerilmektedir.
- Pankreas kanserlerinde DDR gen mutasyon oranı %17-25 oranında saptanmaktadır.
- *Pankreas kanserinde, BRCA1/2* mutasyonu 5% to 7% oranında saptanmaktadır.
- Saptanan genetik değişikliklere göre uygun tedaviler ile yaşam süresi uzayabiliyor.

- Superior OS (22 vs 9 mos; *P* = .039) for patients with *BRCA1/2* mutations and stage 3/4 disease treated with platinum vs non-platinum chemotherapy regimens[1]

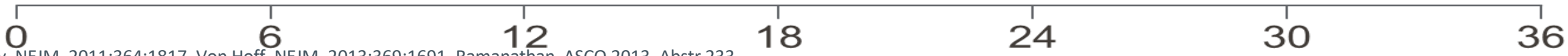


- PARP inhibitors impair BER, inhibit SSBR/DSBR
- Phase II study of olaparib for patients with germline *BRCA 1/2* mutation and prior gemcitabine: ORR in 5 of 23 (21.7%) patients[2]

1. Golan. Br J Cancer. 2014;111:1132. 2. Kaufman. JCO. 2015;33:244.

Slide credit: clinicaloptions.com

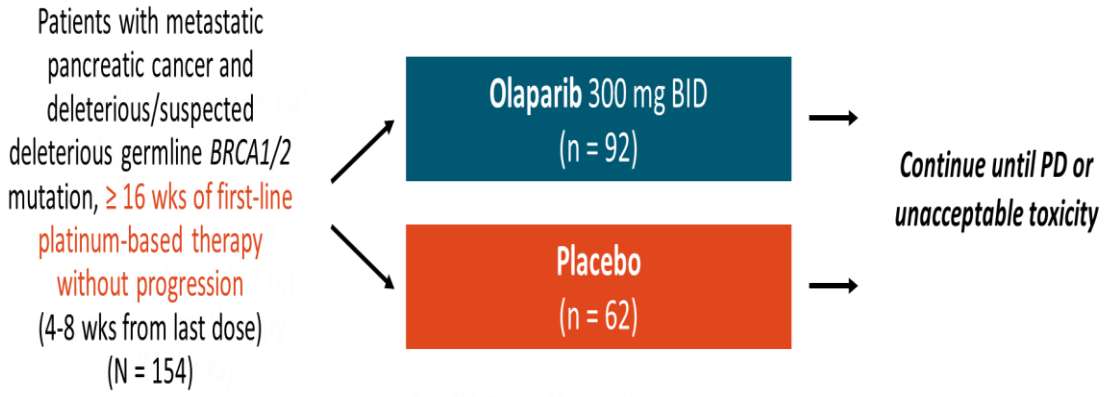
Months



Conroy. NEJM. 2011;364:1817. Von Hoff. NEJM. 2013;369:1691. Ramanathan. ASCO 2013. Abstr 233.
Portal. Br J Cancer. 2015;113:989. Pishvaian. Lancet Oncol. 2020;21:508.

POLO: Maintenance Olaparib vs Placebo After First-line Platinum-based Therapy in Metastatic Pancreatic Cancer

- International, randomized, double-blind phase III trial

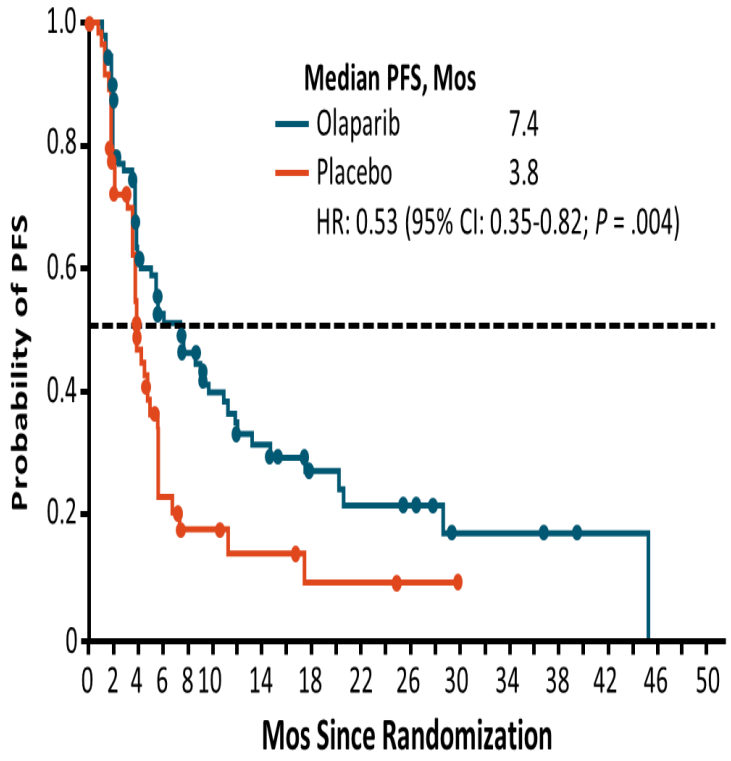


- 3315 patients screened; 247 had germline *BRCA* mutation (7.5%)
- Primary endpoint: PFS by blinded independent central review
- Key secondary endpoints: safety/tolerability, PFS2, ORR, OS, HRQoL

Kindler. ASCO 2019. Abstr LBA4. Golan. NEJM. 2019;381:317.

Slide credit: clinicaloptions.com

POLO: PFS and Response



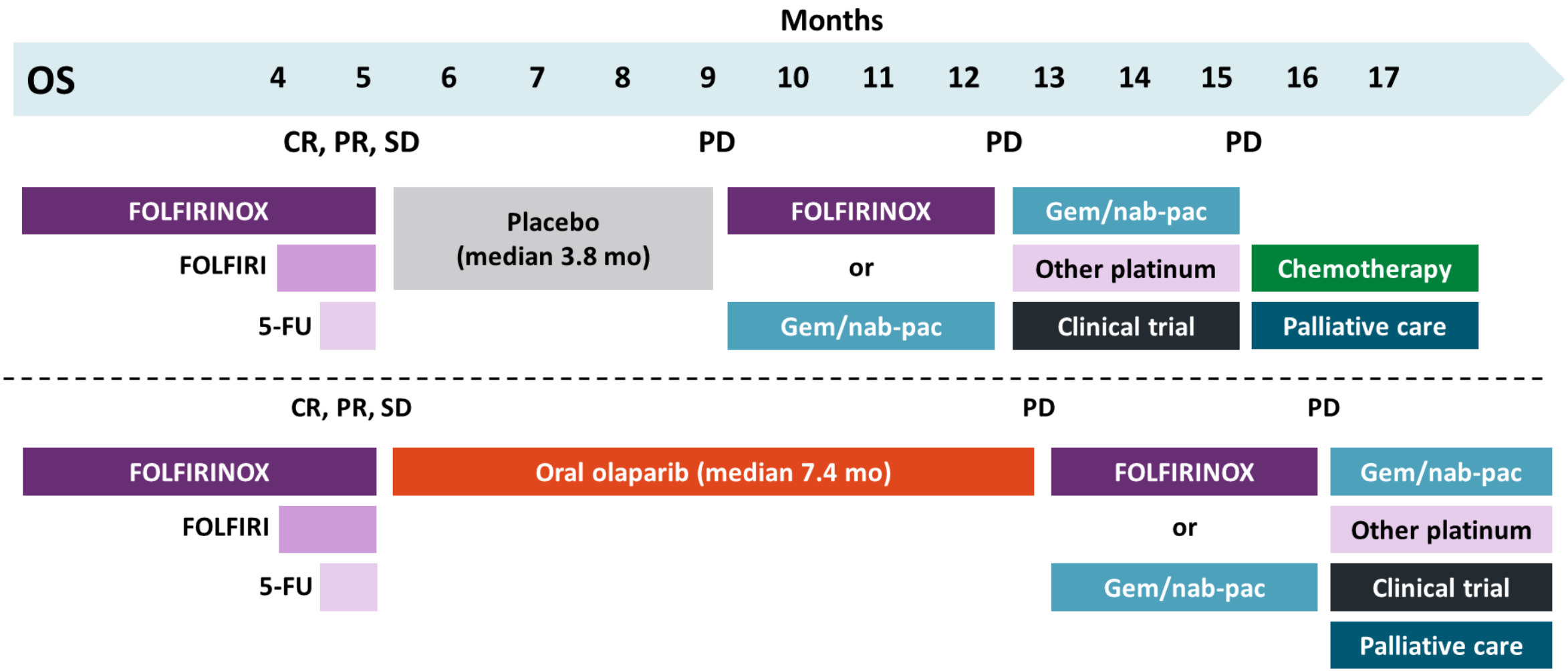
Patients With Measurable Disease at Baseline	Olaparib (n = 78)	Placebo (n = 52)
Objective response,* n (%)	18 (23.1)	6 (11.5)
Median time to response, mos	5.4	3.6
Median duration of response, mos	24.9	3.7

*Modified RECIST v1.1; 2 patients in olaparib arm with ongoing CR at data cutoff (January 15, 2019).

Golan. NEJM. 2019;381:317.

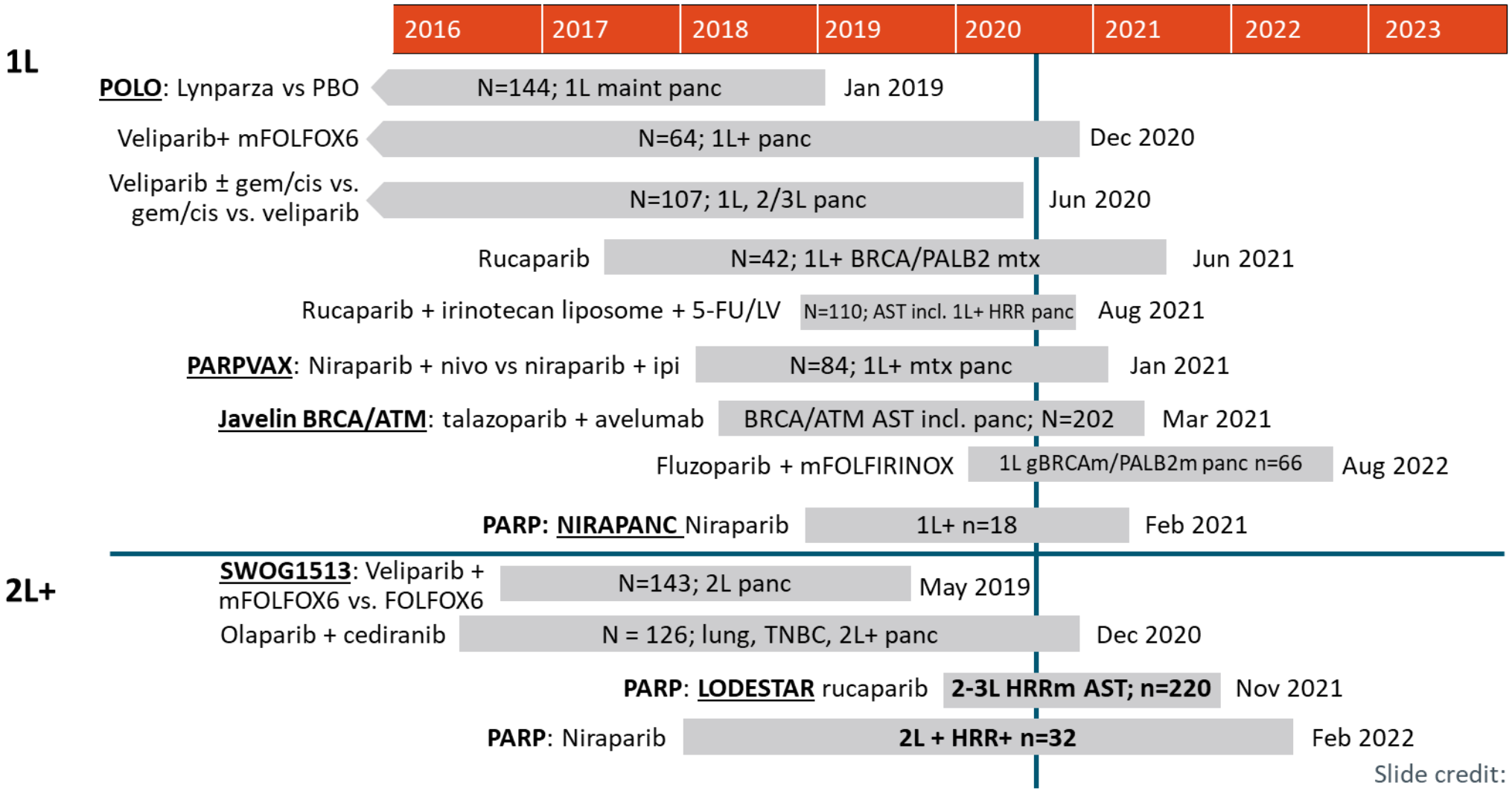
Slide credit: clinicaloptions.com

Maintenance: Contributing to the Therapeutic Sequence



Slide credit: clinicaloptions.com

PARP Inhibitor Studies in Pancreatic Cancer



Slide credit: clinicaloptions.com

Pankreas Kanseri 2020……

- Erken evre hastalıkta;
  - Adjuvan tedavide FOLFIRINOX etkinliği ve Faz III çalışma verileri ile gösterilmiş ve klavuzlarda önerilmektedir. ECOG PS iyi olan hastalarda ilk planda düşünülmelidir.
  - Neoadjuvan tedavilerin kullanımı giderek artmaktadır. R0 rezeksiyon yapılmasını sağlayarak yaşam süresi üzerine anlamlı katkı sağladığı belirtilmektedir.
- Metastatik hastalıkta;
  - FOLFIRINOX ve gemcitabine/nab-paclitaxel ile tek ajan Gemsitabine göre yaşam süresinde anlamlı bir uzama gösterilmiştir,
  - 2. sıra tedavide nanoliposomal irinotecan ve 5-FU/LV etkinliği gösterilmiştir.
  - Genetik testlerin özellikle BRCA1ve 2 başta olmak üzere bakılmalıdır.

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PRINCIPLES OF SYSTEMIC THERAPY

Metastatic Disease (First-Line Therapy)

- Patients who progress with metastatic disease are not candidates for radiation unless required for palliative purposes.

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Good PS	• FOLFIRINOX (category 1) or modified FOLFIRINOX[e,f,6] • Gemcitabine + albumin-bound paclitaxel[f,7] (category 1) Only for known BRCA1/2 or PALB2 mutations: • FOLFIRINOX (category 1) or modified FOLFIRINOX[e,f,6] • Gemcitabine + cisplatin[10]	• Gemcitabine + erlotinib[g,8] (category 1) • Gemcitabine (category 1) • Gemcitabine + capecitabine[9] • Fixed-dose-rate gemcitabine, docetaxel, capecitabine (GTX regimen)[11] (category 2B) • Fluoropyrimidine + oxaliplatin (eg, 5-FU + leucovorin + oxaliplatin [OFF][12] or CapeOx[13]) (category 2B)	• None
Poor PS	• Gemcitabine ‣ 1000 mg/m2 over 30 minutes, weekly for 3 weeks every 28 days (category 1) ‣ Fixed-dose-rate gemcitabine (10 mg/m²/min) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B) • Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B)	• None	• Pembrolizumab[j,14] (only for MSI-H or dMMR tumors) • Larotrectinib (if NTRK gene fusion positive) • Entrectinib (if NTRK gene fusion positive) (category 2B)

See Maintenance Therapy for Metastatic Disease on PANC-F (5 of 8)

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PRINCIPLES OF SYSTEMIC THERAPY

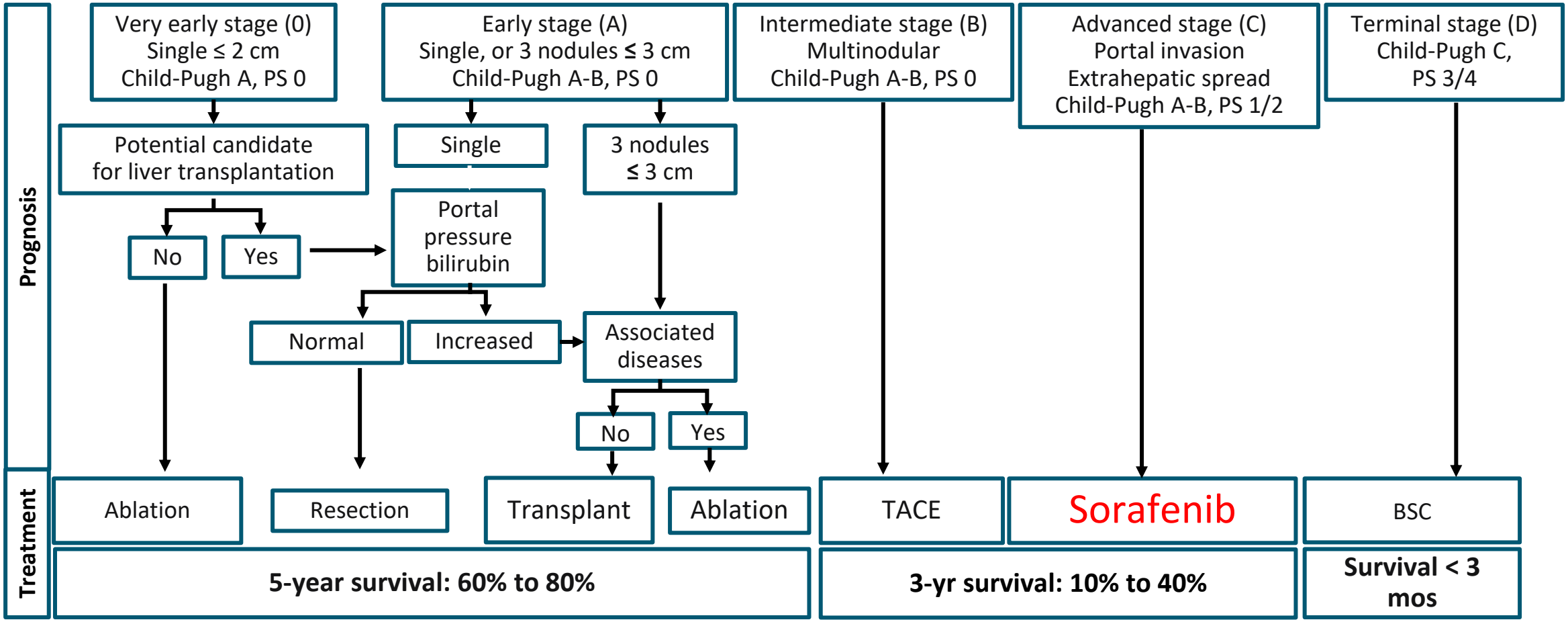
Metastatic Disease (Maintenance Therapy)

- Patients who have response or stable disease after 4–6 months of chemotherapy may undergo maintenance therapy.

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• If previous platinum-based chemotherapy: ‣ Olaparib (only for germline *BRCA1/2* mutations)	• Clinical trial or • If previous first-line FOLFIRINOX: ‣ Capecitabine or • If previous first-line gemcitabine + nab-paclitaxel: ‣ Gemcitabine + nab-paclitaxel modified schedule (category 2B) ‣ Gemcitabine single agent (category 2B)	• If previous first-line FOLFIRINOX: ‣ 5-FU ± irinotecan[k] ‣ FOLFOX[l] (category 2B)

Hepatosellüler Kanserler

Early 2017: BCLC Staging and Treatment Strategy for HCC



Bruix. Gastroenterology. 2016;150:835. Llovet. NEJM. 2008;359:378.

Slide credit: clinicaloptions.com

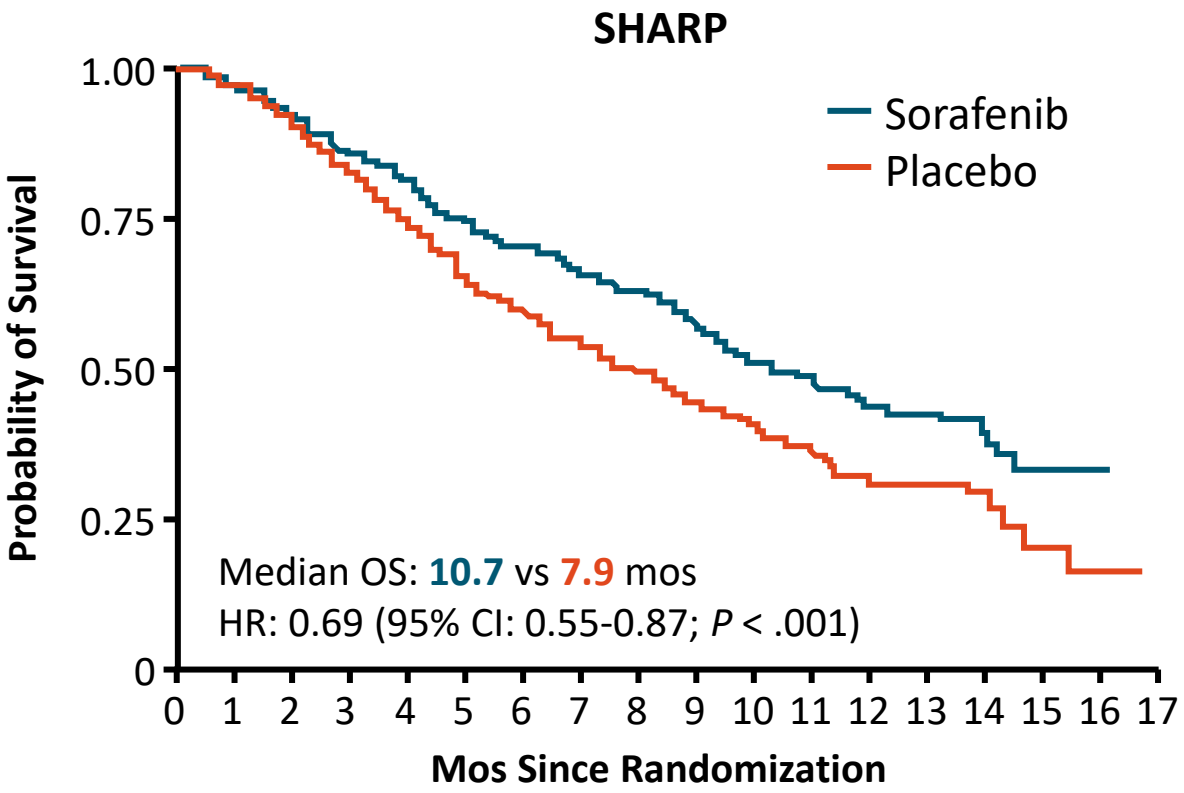
HCC ve Hedef Tedaviler

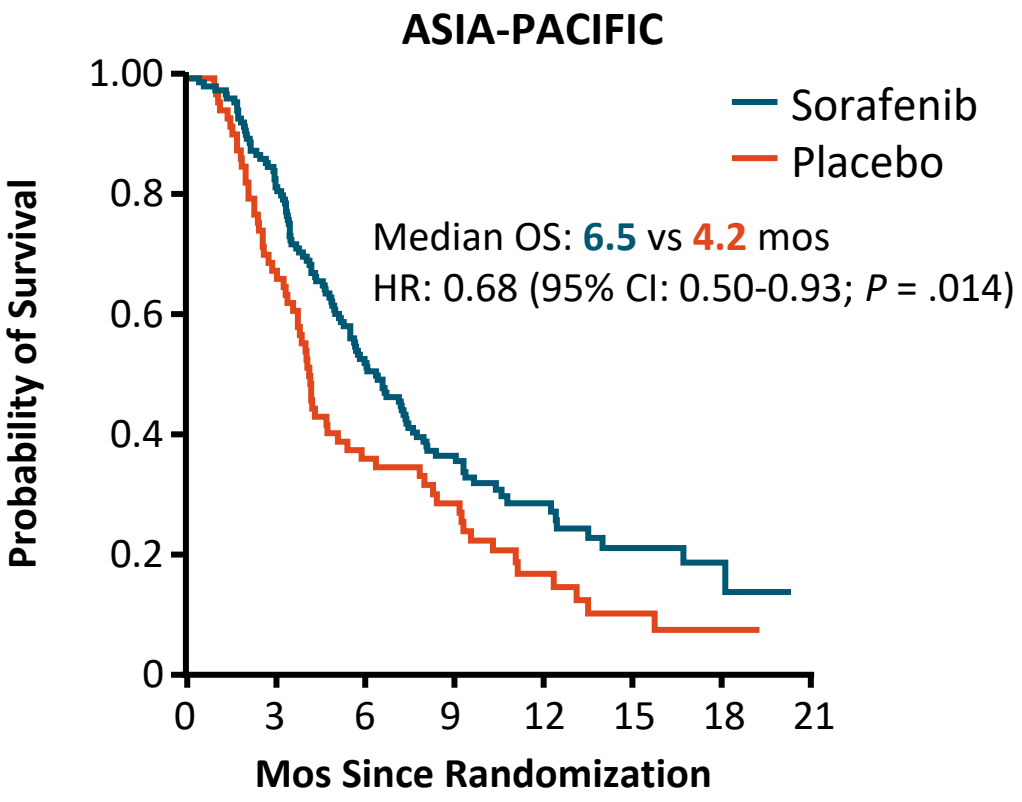
Birinci Basamak Tedavi Çalışmaları;

- Sharp
- Asia- Pacific
- Reflect Çalışmaları

Sorafenib;

- Sorafenib consistently increased OS in different patient populations across geographic regions, etiologies

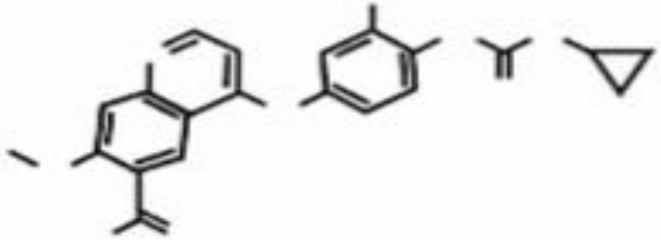


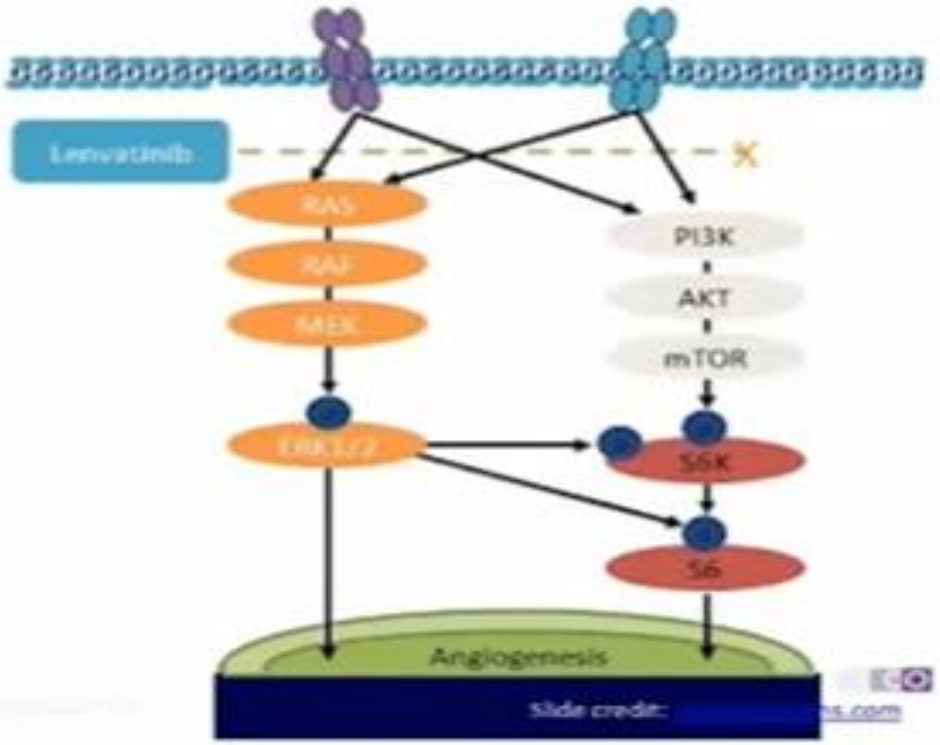


Llovet. NEJM. 2008;359:378. Cheng. Lancet Oncol. 2009;10:25.

Lenvatinib: Etki Mekanizması

- Multitargeted, PO small molecular TKI
  - Potent against VEGFR2 and VEGFR3
  - Also targets VEGFR1, FGFR1-3, PDGFRα, RET, and KIT





REFLECT: Frontline Lenvatinib vs Sorafenib in Unresectable HCC

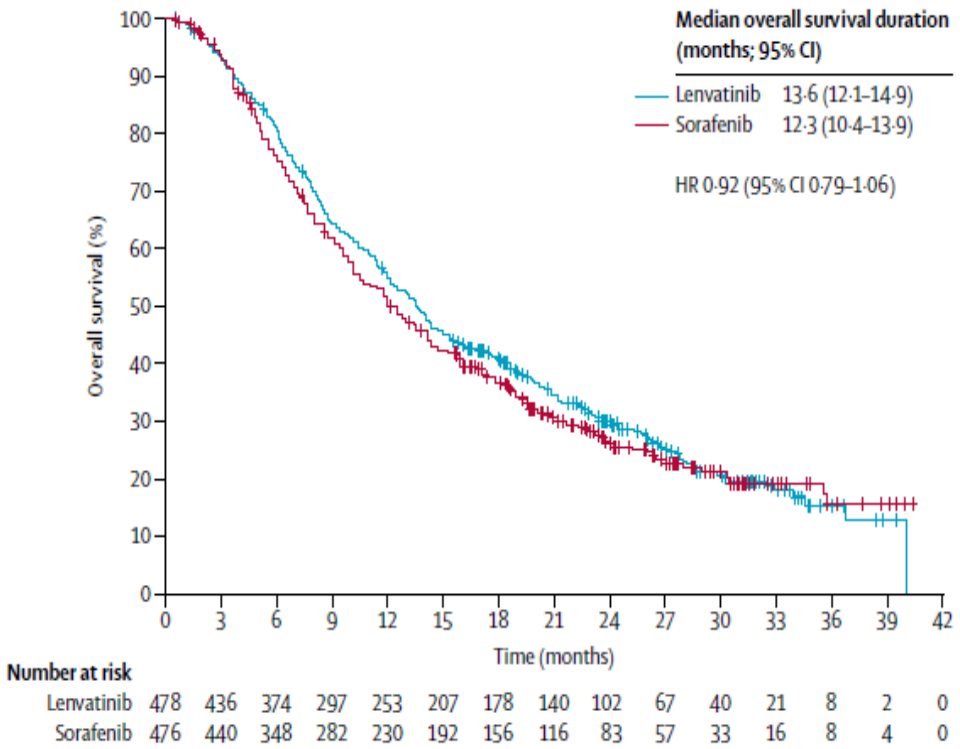
- Randomized, open-label, noninferiority phase III trial

Adult patients with unresectable HCC, no prior systemic therapy, Child-Pugh A, BCLC stage B or C, ECOG PS 0/1[†] (N = 954)

→ **Lenvatinib QD*** (n = 478)

→ **Sorafenib 400 mg BID** (n = 476)

- Primary endpoint: OS
- Secondary endpoints: PFS, TTP, ORR, PK, QoL

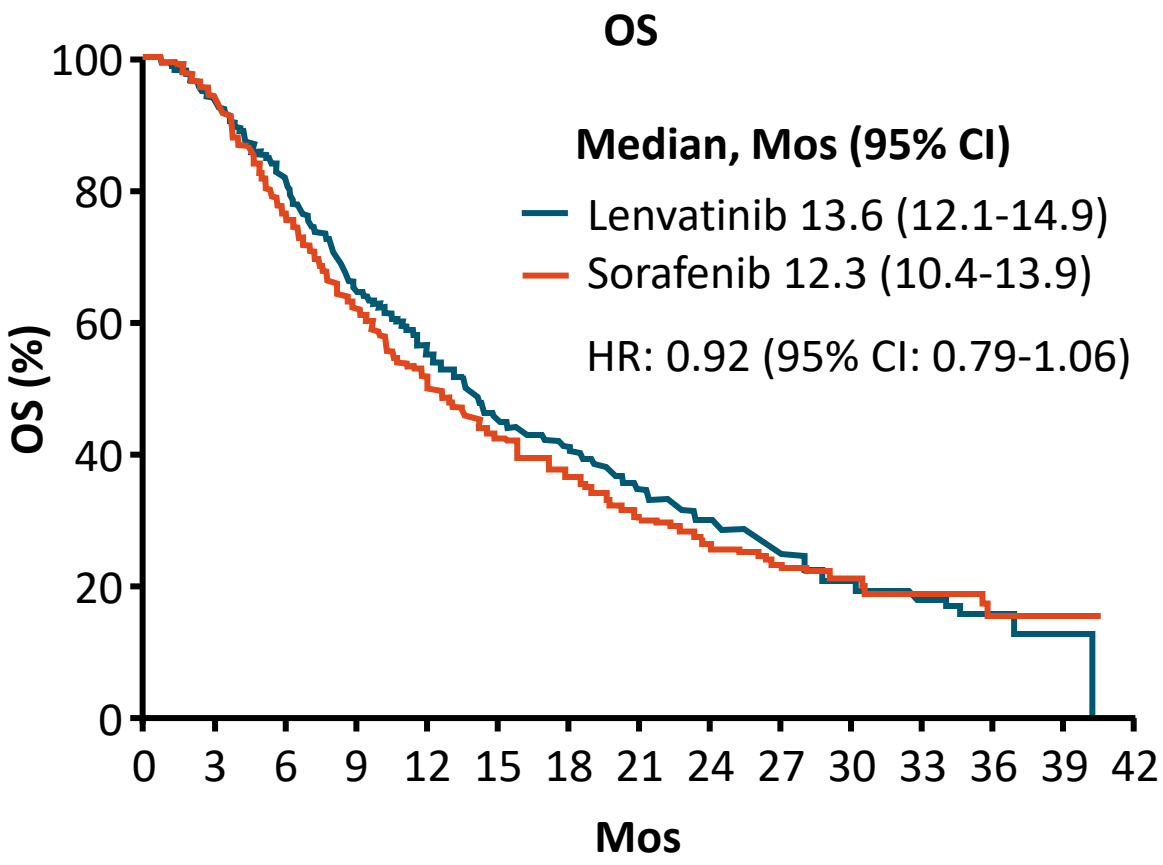


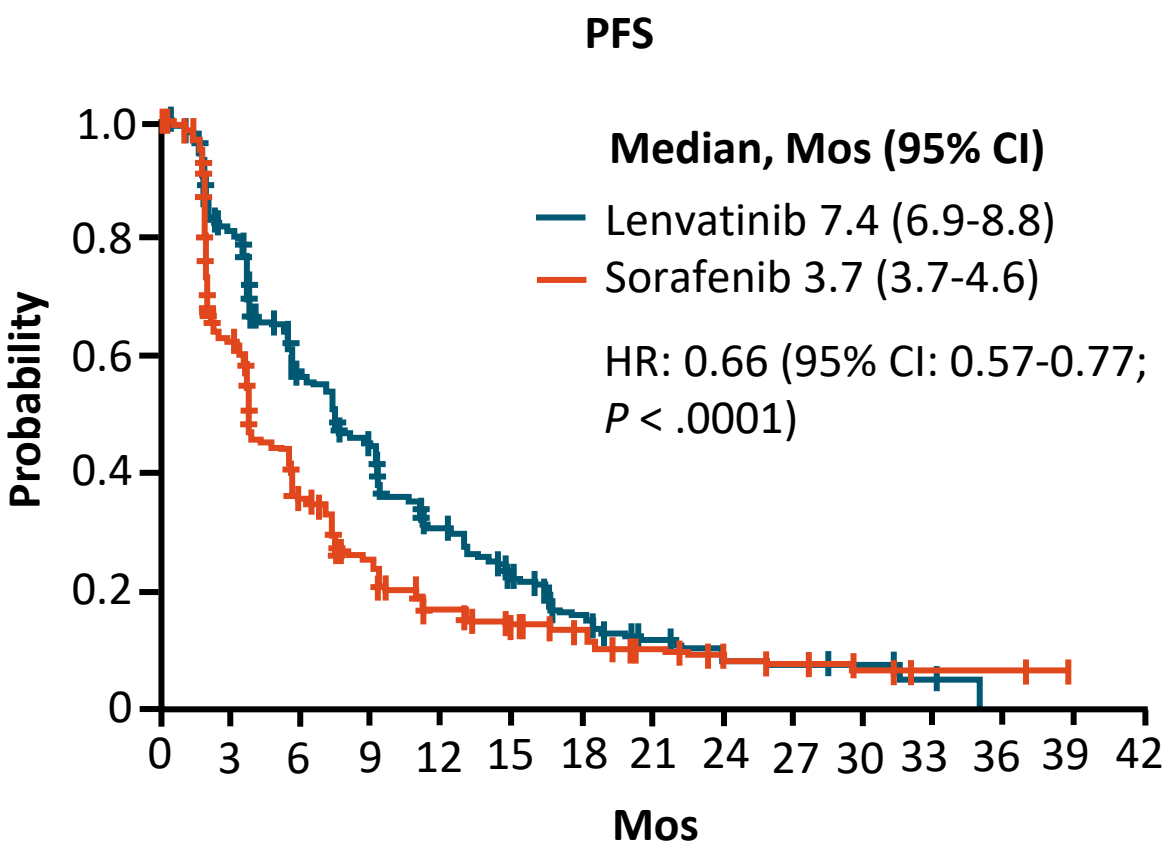
*Lenvatinib; Body weight < 60 kg, 8 mg; body weight ≥ 60 kg, 12 mg.

[†]Exclusion criteria included 50% or higher liver occupation, obvious invasion of bile duct, or invasion at main portal vein.

Kudo. Lancet. 2018;391:1163. Lenvatinib PI.

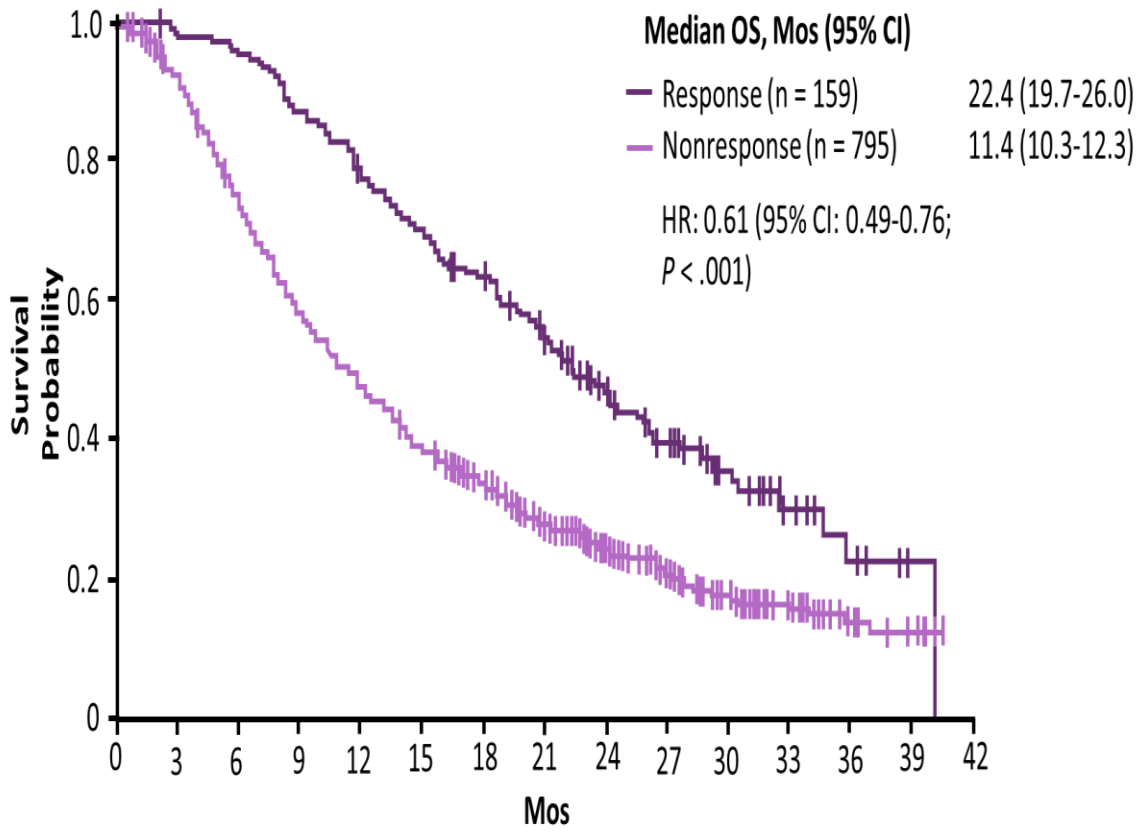
REFLECT: Survival





Kudo. Lancet. 2018;391:1163.

REFLECT: OS by OR (Overall Population)



Kudo. ASCO GI 2019. Abstr 186.

Slide credit: clinicaloptions.com

REFLECT: Select Treatment-Emergent AEs

AE, %	Lenvatinib (n = 476)		Sorafenib (n = 475)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Total	99	75	99	67
HFSR	**27**	**3**	**52**	**11**
Hypertension	**42**	**23**	**30**	**14**
Diarrhea	39	4	46	4
Decreased appetite	34	5	27	1
Decreased weight	31	8	22	3
Fatigue	30	4	25	4
Alopecia	**3**	**0**	**25**	**0**
Proteinuria	**25**	**6**	**11**	**2**
Dysphonia	**24**	**< 1**	**12**	**2**
Nausea	20	1	14	1

Kudo. Lancet. 2018;391:1163.

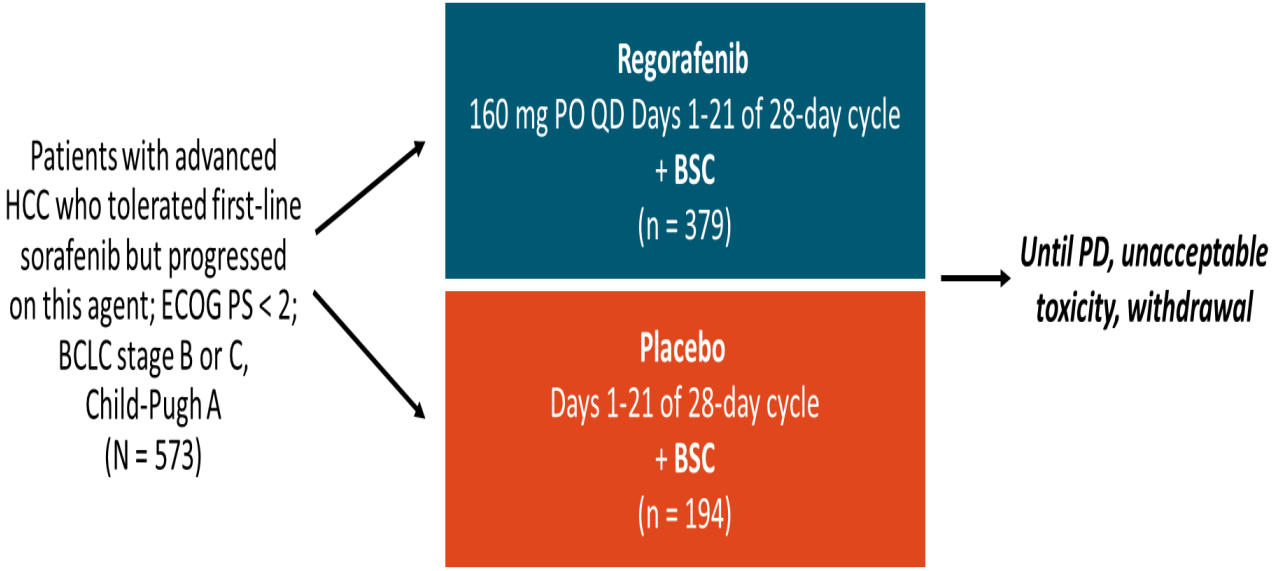
Slide credit: clinicaloptions.com

HCC’de 2. Basamak Hedef Tedavi Çalışmaları

- RESORCE Trial
- CELESTIAL Trial
- REACH -2 Trial

RESORCE: Second-Line Regorafenib vs Placebo in HCC With Progression

- Multicenter, randomized, double-blind phase III trial

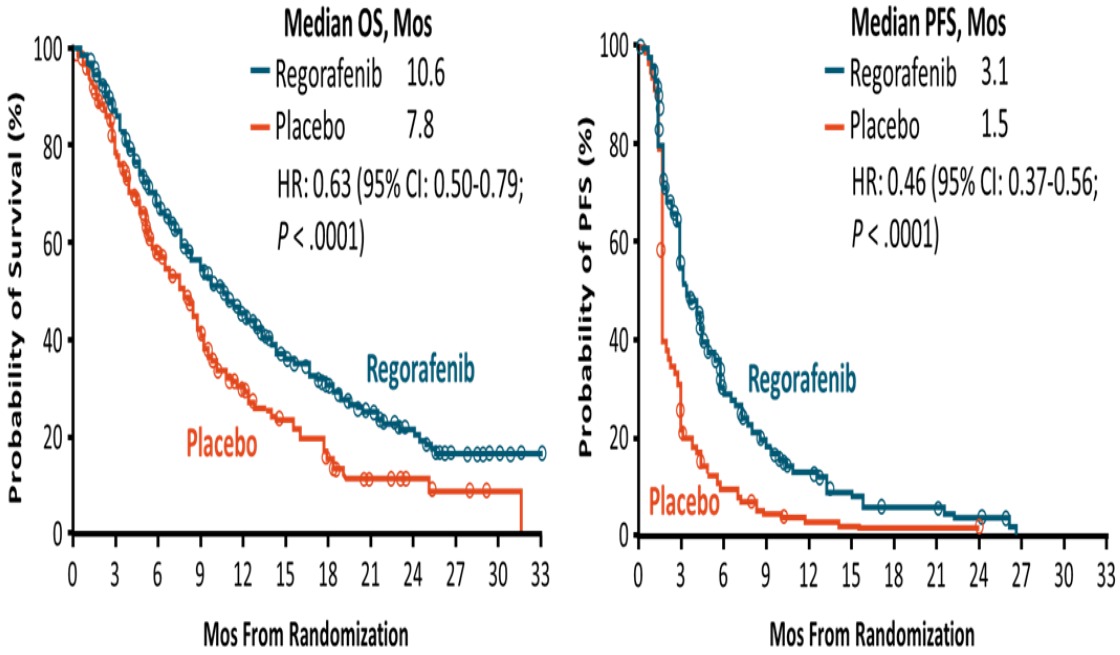


- Primary endpoint: OS
- Secondary endpoints: PFS, TTP, ORR, disease control rate

Bruix. Lancet. 2017;389:56.

Slide credit: clinicaloptions.com

RESORCE: OS and PFS



Bruix. Lancet. 2017;389:56.

Slide credit: clinicaloptions.com

RESORCE: Select Treatment-Emergent AEs

AEs, %	Regorafenib (n = 379)			Placebo (n = 194)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Hand–foot syndrome	**53**	**13**	**N/A**	**8**	**1**	**N/A**
Diarrhea	**41**	**3**	**0**	**15**	**0**	**0**
Fatigue	**40**	**9**	**N/A**	**32**	**5**	**N/A**
Hypertension	**31**	**15**	**< 1**	**6**	**5**	**0**
Anorexia	31	3	0	15	2	0
Bilirubin increased	29	10	1	18	8	3
Abdominal pain	28	3	0	22	4	0
AST increased	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**

Bruix. Lancet. 2017;389:56.

Slide credit: clinicaloptions.com

CELESTIAL: Cabozantinib for Previously Treated HCC

- Randomized, double-blind phase III trial
  - **Cabozantinib**: **multitargeted TKI**; inhibits **MET, VEGFR-1, -2, -3, AXL**, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, and TIE-2

Adult patients with advanced HCC who experienced PD after sorafenib; may have **received up to 2 previous systemic regimens**; Child-Pugh class A; ECOG PS 0/1 (N = 707)

→ **Cabozantinib** 60 mg* PO QD (n = 470)

→ **Placebo** PO QD (n = 237)

→ ***Until loss of clinical benefit, unacceptable toxicity***

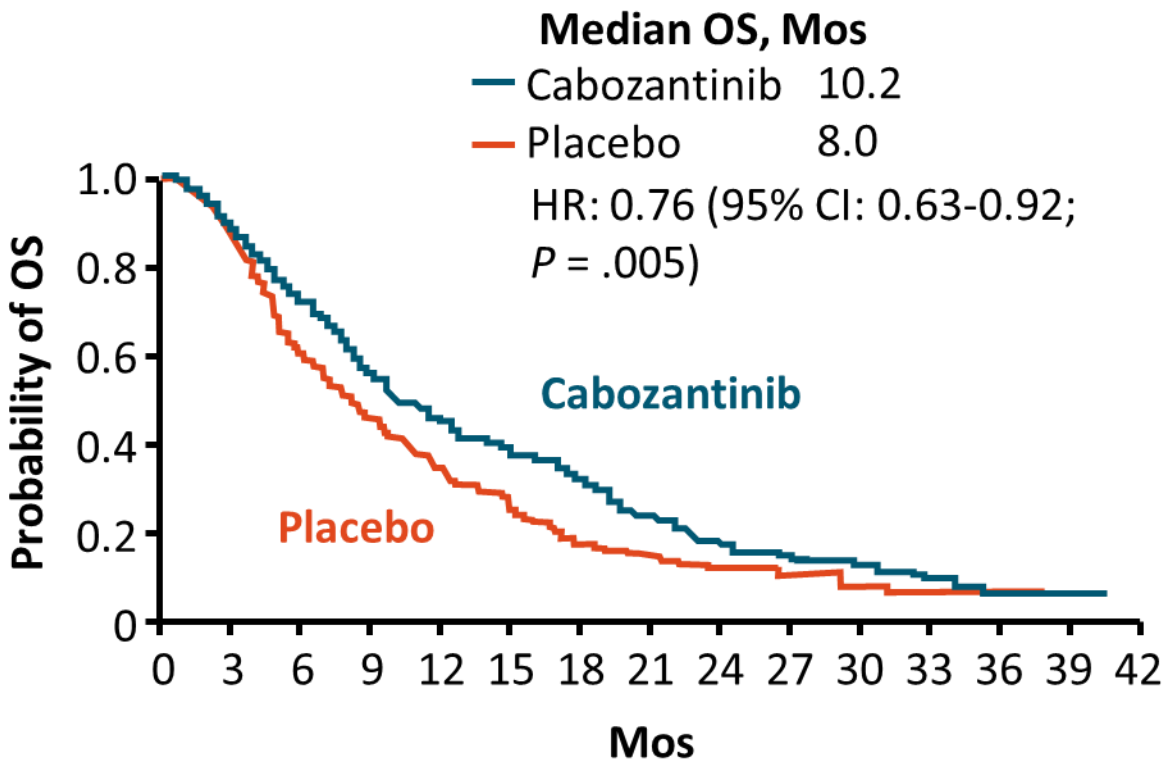
*Treatment interruptions, dose reductions (to 40 mg, then 20 mg) used to manage AEs.

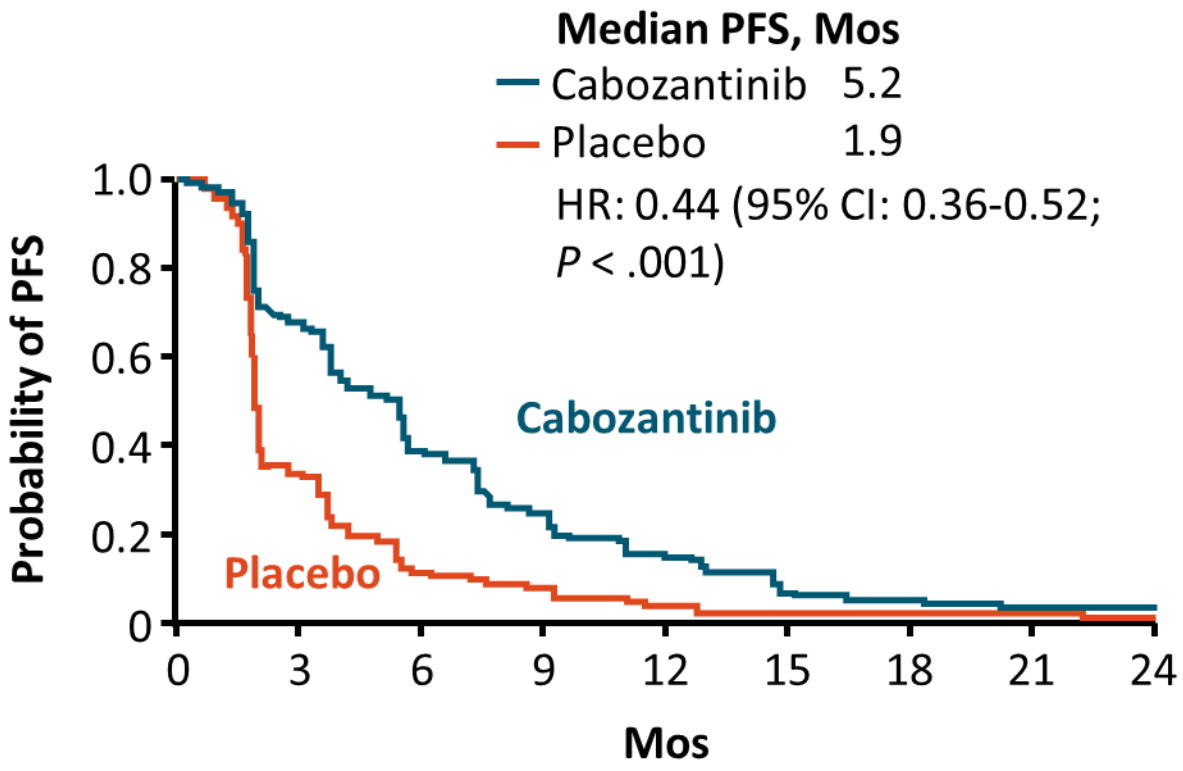
- Primary endpoint: OS
- Secondary endpoints: PFS, ORR

Abou-Alfa. NEJM. 2018;379:54. Cabozantinib PI.

Slide credit: clinicaloptions.com

CELESTIAL: OS and PFS





Abou-Alfa. NEJM. 2018;379:54.

Slide credit: clinicaloptions.com

CELESTIAL: Response

Outcome, %	Cabozantinib (n = 470)	Placebo (n = 237)
ORR	4	< 1
▪ 95% CI	2-6	0-2
▪ *P* value	.009	
Best overall response		
▪ CR	0	0
▪ PR	4	< 1
▪ SD	60	33
▪ PD	21	55
▪ Not evaluable	15	11

Abou-Alfa. NEJM. 2018;379:54.

Slide credit: clinicaloptions.com

CELESTIAL: Select Treatment-Related AEs

AEs, %*	Cabozantinib (n = 467)			Placebo (n = 237)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Diarrhea	**54**	**10**	**< 1**	**19**	**2**	**0**
Decreased appetite	**48**	**6**	**0**	**18**	**< 1**	**0**
Hand–foot syndrome	**46**	**17**	**0**	**5**	**0**	**0**
Fatigue	**45**	**10**	**0**	**30**	**4**	**0**
Nausea	**31**	**2**	**0**	**18**	**2**	**0**
Hypertension	**29**	**16**	**< 1**	**6**	**2**	**0**
Vomiting	26	< 1	0	12	3	0
Increase in aspartate aminotransferase level	22	11	1	11	6	< 1
Asthenia	22	7	<1	8	2	0

*Occurring in ≥ 20% of patients in one treatment group.

Abou-Alfa. NEJM. 2018;379:54.

Slide credit: clinicaloptions.com

REACH-2: Ramucirumab for Patients With Previously Treated HCC and AFP ≥ 400 ng/mL

- Randomized, double-blind, multicenter phase III trial[1]
  - **Ramucirumab**: **anti-VEGFR2 monoclonal antibody**
  - REACH trial: patients with PD on sorafenib were randomly assigned to ramucirumab vs placebo; although the primary endpoint of OS was not met, a prespecified population of patients with **baseline AFP ≥ 400 ng/mL and Child-Pugh class A** demonstrated a significant OS advantage[2]

Patients with advanced HCC, **AFP ≥ 400 ng/mL**, BCLC stage B/C, **Child-Pugh class A**, ECOG PS 0/1, **prior sorafenib** (N = 292)

→ **Ramucirumab + BSC**
8 mg/kg IV Q2W
(n = 197)

→ **Placebo + BSC**
Q2W
(n = 95)

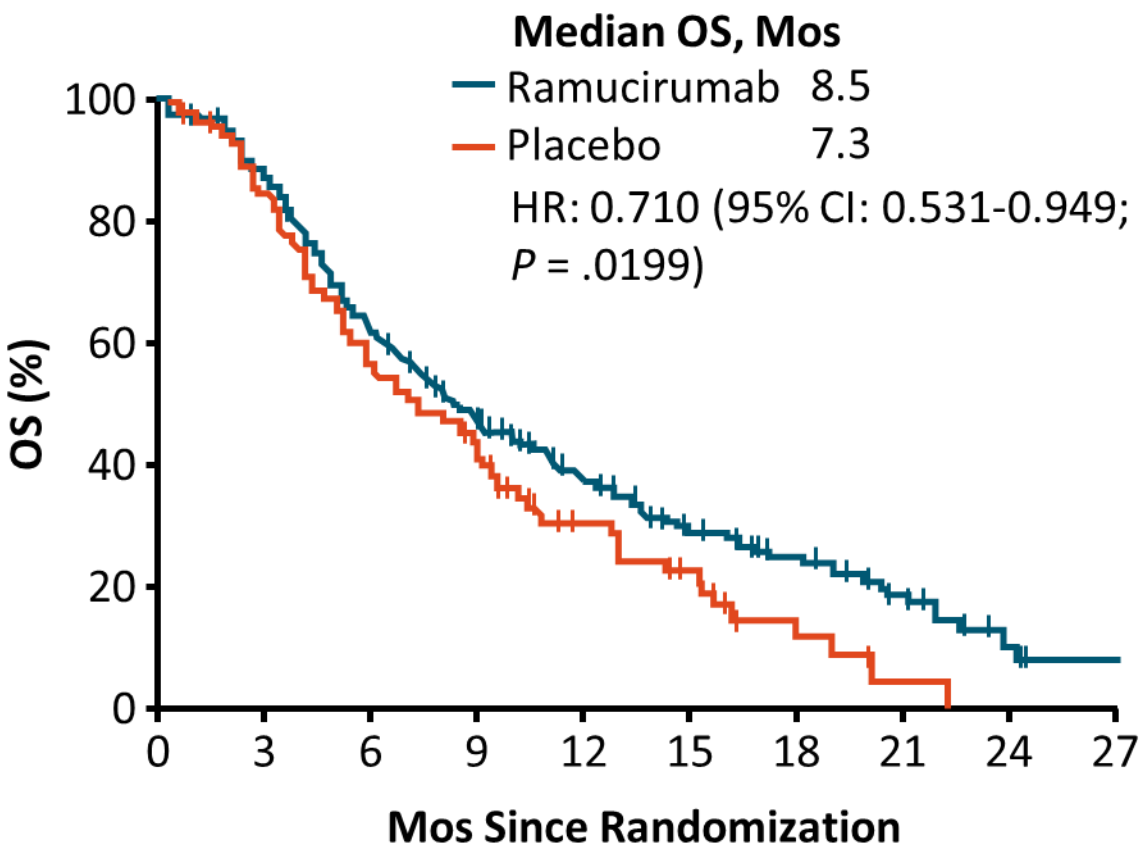
Treatment continued until unacceptable toxicity, withdrawal

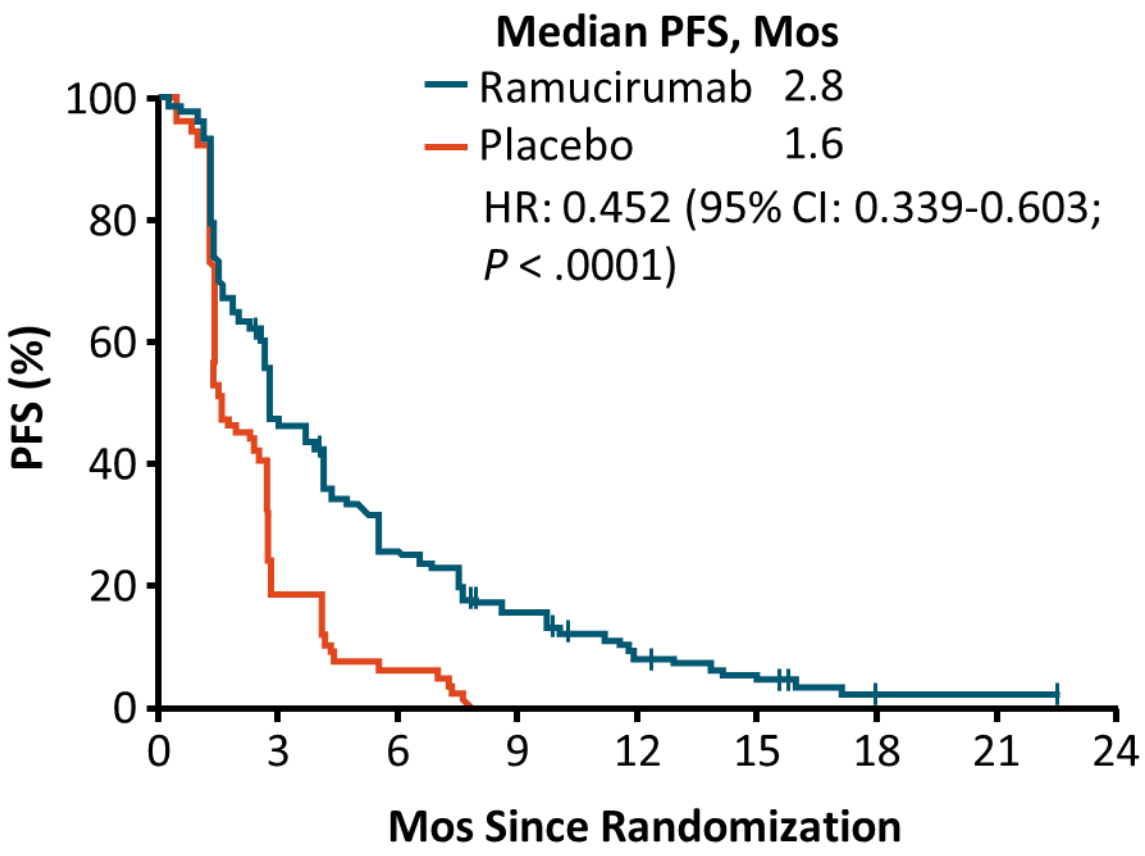
- Primary endpoint: OS; secondary endpoints: PFS, ORR, time to radiographic progression, time to FHSI-8 score decline, time to ECOG PS decline

1. Zhu. Lancet Oncol. 2019;20:282. 2. Zhu. Lancet Oncol. 2015;16:859.

Slide credit: clinicaloptions.com

REACH-2: OS and PFS





Zhu. Lancet Oncol. 2019;20:282.

Slide credit: clinicaloptions.com

REACH-2: Select Treatment-Related AEs

AE, %*	Ramucirumab (n = 197)		Placebo (n = 95)	
	Grades 1/2	Grades 3-5	Grades 1/2	Grades 3-5
Fatigue	24	4	14	3
Peripheral edema	24	2	14	0
Decreased appetite	22	2	19	1
Abdominal pain	18	2	11	2
Nausea	19	0	12	0
Diarrhea	16	0	14	1
Headache	14	0	4	1
Constipation	13	1	19	1
Insomnia	11	0	5	1
Pyrexia	10	0	3	0
Vomiting	10	0	7	0

AE, %*	Ramucirumab (n = 197)		Placebo (n = 95)	
	Grades 1/2	Grades 3-5	Grades 1/2	Grades 3-5
Bleeding/ hemorrhage	19	6	9	3
Epistaxis	13	1	3	0
Hypertension	**12**	**13**	**7**	**5**
Proteinuria	18	2	4	0
Liver injury/ failure	21	18	14	16
Ascites	14	5	5	2

*Occurring in ≥ 10% of patients in one treatment group.

Zhu. Lancet Oncol. 2019;20:282.

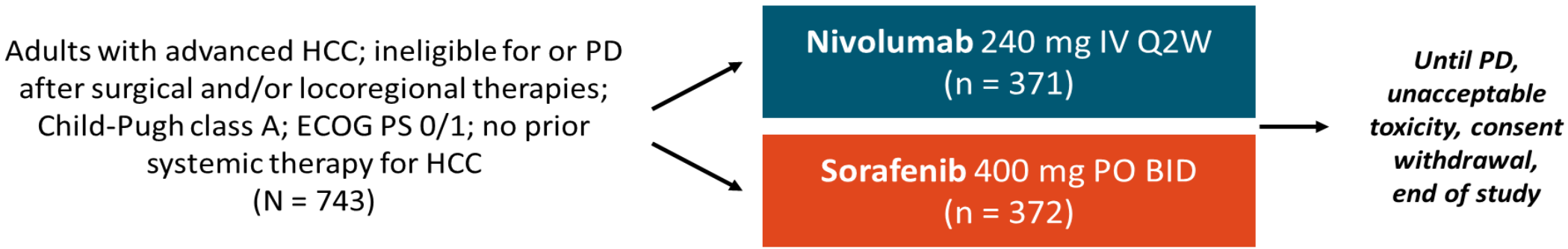
Slide credit: clinicaloptions.com

HCC’de İmmunoterapi

- CHECKMATE 459 Trial
- Imbrave 150 Trial
- KEYNOTE 524 Trial
- CHECKMATE 040 Trial

CheckMate 459: Nivolumab vs Sorafenib as First-line Therapy for Advanced HCC

- International, open-label, randomized phase III trial (minimum follow-up: 22.8 mos)



- Primary endpoint: OS
  - Predefined threshold for statistical significance: HR of 0.84 (P = .0419)
- Secondary endpoints: PFS, ORR, association between PD-L1 expression and efficacy

Yau. ESMO 2019. Abstr LBA38_PR. NCT02576509.

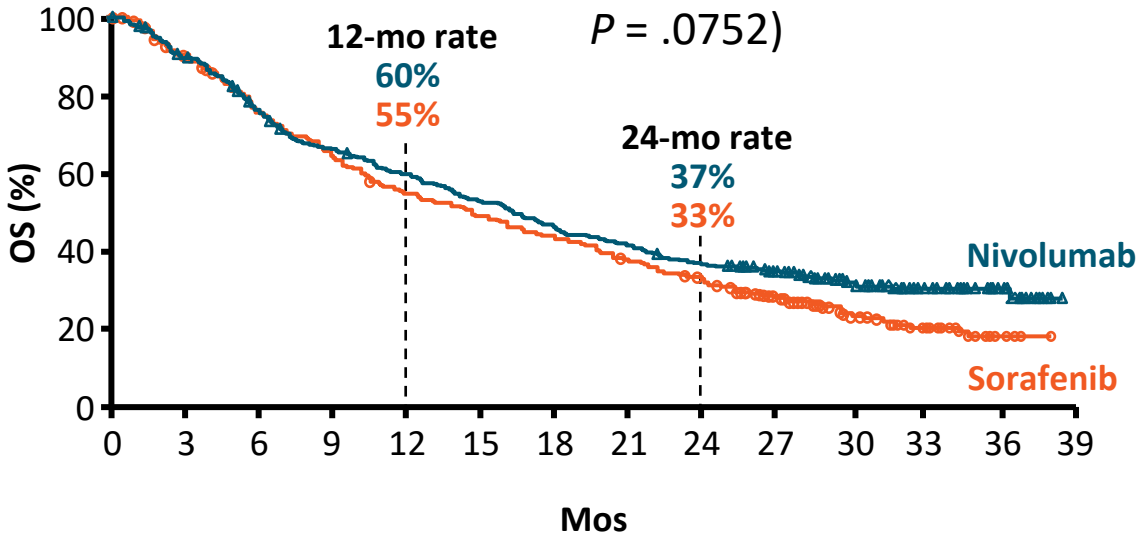
Slide credit: clinicaloptions.com

CheckMate 459: OS and PFS

Median OS, Mos (95% CI)

Nivolumab	16.4 (13.9-18.4)
Sorafenib	14.7 (11.9-17.2)

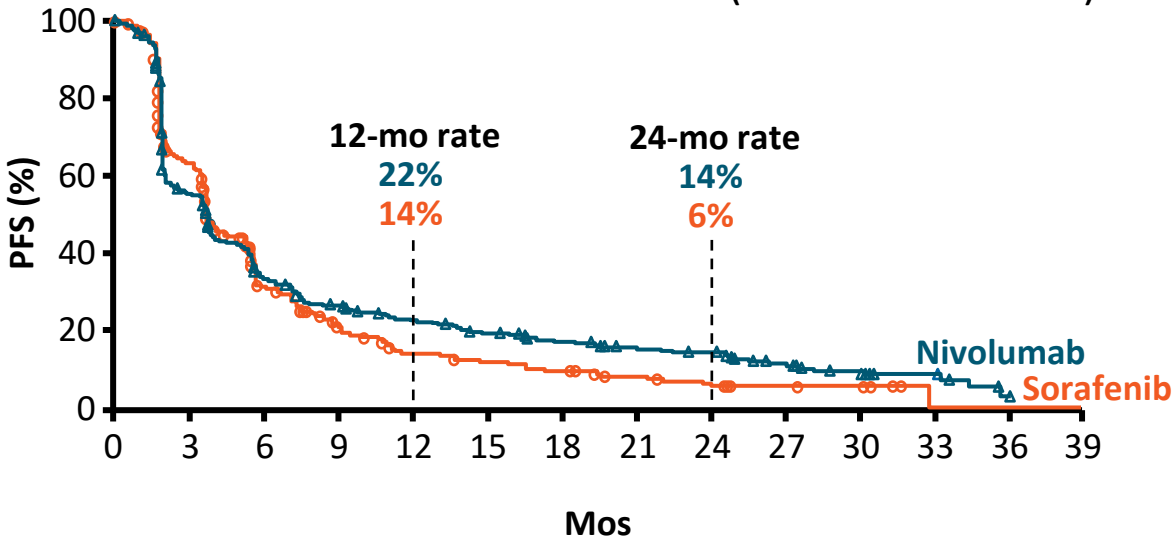
HR: 0.85 (95% CI: 0.72-1.02; *P* = .0752)



Median PFS, Mos (95% CI)

Nivolumab	3.7 (3.1-3.9)
Sorafenib	3.8 (3.7-4.5)

HR: 0.93 (95% CI: 0.79-1.10)



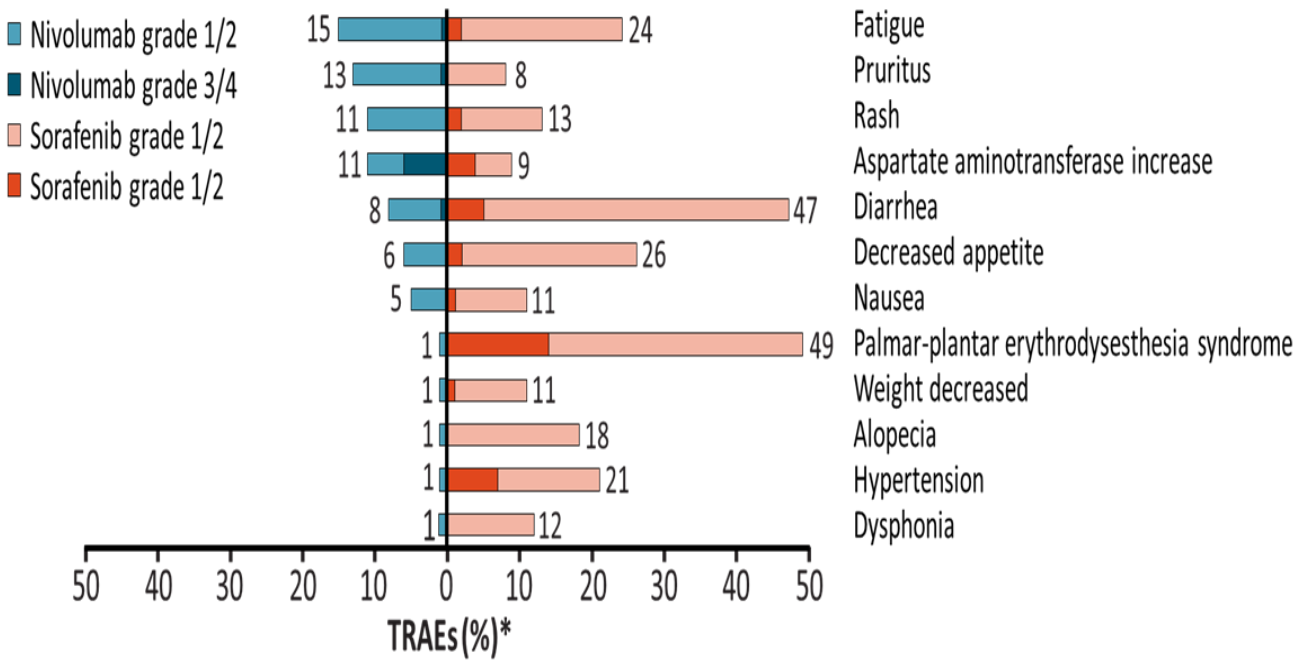
- Predefined threshold of statistical significance for OS with nivolumab not met, although nivolumab demonstrated clinical benefit
- ORR: nivolumab, 15%; sorafenib, 7%

Yau. ESMO 2019. Abstr LBA38_PR.

CheckMate 459: Response, Disease Control, Durability

Outcome	Nivolumab (n = 371)	Sorafenib (n = 372)
ORR, n (%)	57 (15)	26 (7)
▪ CR	14 (4)	5 (1)
▪ PR	43 (12)	21 (6)
▪ SD	130 (35)	180 (48)
▪ Non-CR/non-PD	16 (4)	9 (2)
▪ PD	136 (37)	105 (28)
▪ Not evaluable	32 (9)	52 (14)
DCR, n (%)	203 (55)	215 (58)
Median duration of disease control, mos (95% CI)	7.5 (6.5-10.7)	5.7 (5.6-7.4)
Median time to response, mos (range)	3.3 (1.6-19.4)	3.7 (1.5-11.1)
Median DoR, mos (range)	23.3 (3.1 to 34.5+)	23.4 (1.9+ to 28.7+)

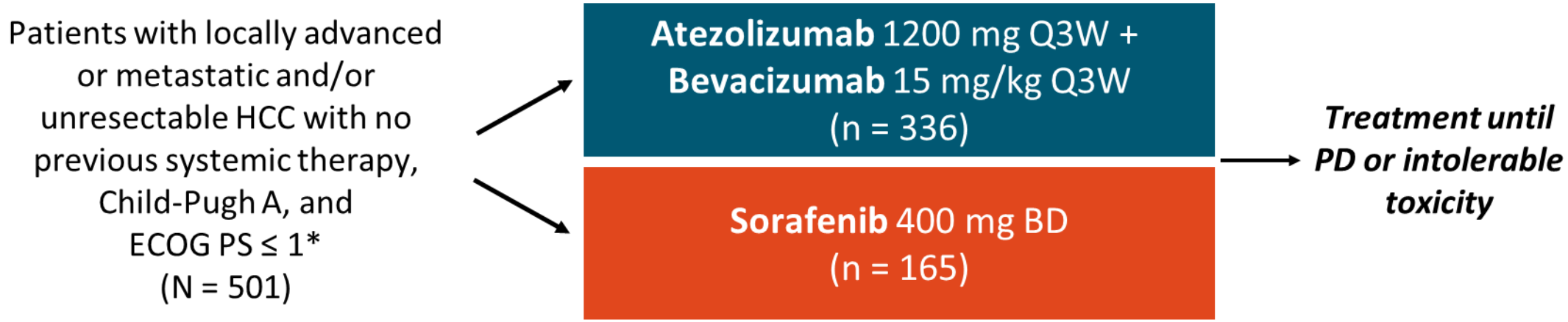
CheckMate 459: Summary of Treatment-Related Adverse Events



- Nivolumab demonstrated improved safety profile compared with sorafenib, with fewer grade 3/4 TRAEs and TRAEs leading to discontinuation vs sorafenib
  - Grade 3/4 TRAEs: nivolumab, 22%; sorafenib, 49%

IMbrave150: Atezolizumab + Bevacizumab vs Sorafenib for First-Line Treatment of Advanced HCC

- Multicenter, randomized, open-label phase III trial[1]
  - GO30140: randomized phase Ib study showed potential benefit of atezolizumab + bevacizumab for patients with advanced HCC (ORR 36%)[2]



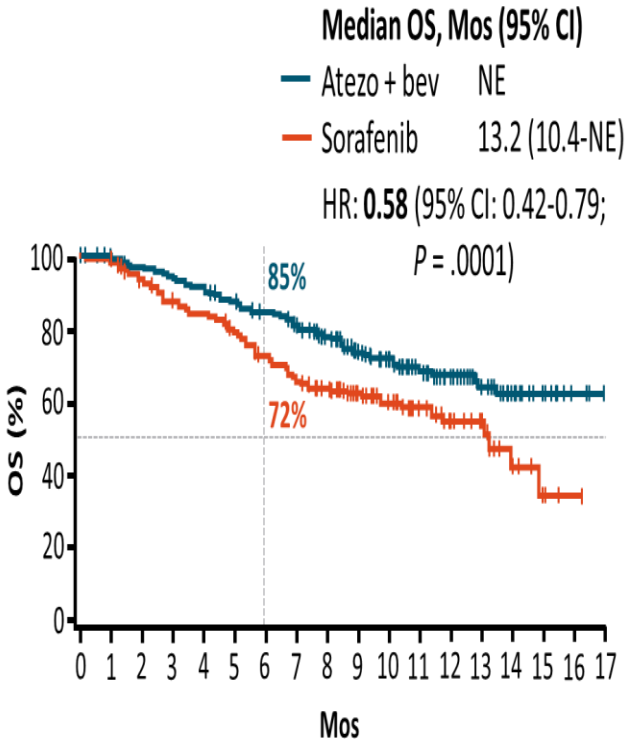
- Coprimary endpoints: OS and PFS

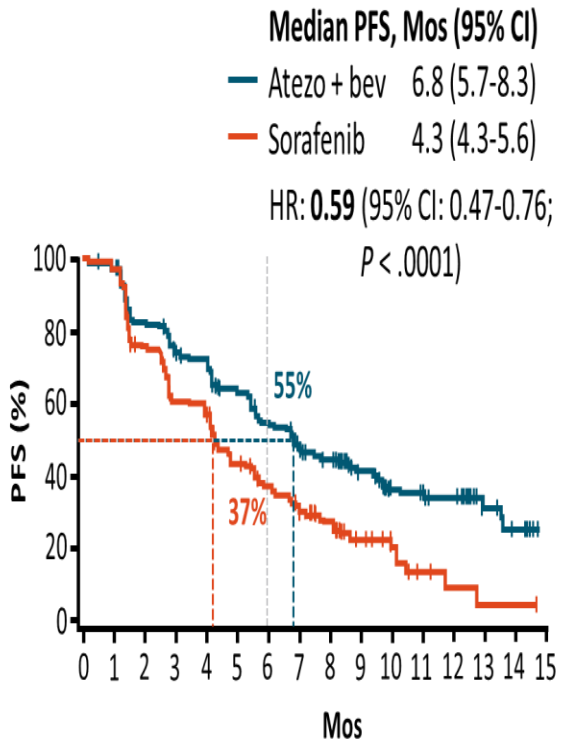
*Trial included subgroups of high-risk patients excluded from other contemporary phase III trials: ≈ 40% had macrovascular invasion; specifically included patients with 50% hepatic involvement or main portal vein invasion or invasion of the portal vein branch contralateral to the primarily involved lobe.

1. Finn. NEJM. 2020;382:1894. 2. Lee. Lancet Oncol. 2020;21:808.

Slide credit: clinicaloptions.com

IMbrave150: OS and PFS





Median follow-up: 8.6 mos.

Finn. NEJM. 2020;382:1894.

Slide credit: clinicaloptions.com

IMbrave150: Response

Variable, n (%)	IRF RECIST 1.1			IRF HCC-Specific mRECIST		
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Difference (*P* Value)	Atezo + Bev (n = 325)	Sorafenib (n = 158)	Difference (*P* Value)
Confirmed objective response	89 (27.3)	19 (11.9)	15.4 (< .001)	108 (33.2)	21 (13.3)	19.9 (< .001)
CR	18 (5.5)	0		33 (10.2)	3 (1.9)	
PR	71 (21.8)	19 (11.9)		75 (23.1)	18 (11.4)	
Stable disease	151 (46.3)	69 (43.4)		127 (39.1)	66 (41.8)	
Disease control rate	240 (73.6)	88 (55.3)		235 (72.3)	87 (55.1)	
Progressive disease	64 (19.6)	39 (24.5)		66 (20.3)	40 (25.3)	
Unevaluable	8 (2.5)	14 (8.8)		10 (3.1)	14 (8.9)	
Data missing	14 (4.3)	18 (11.3)		14 (4.3)	17 (10.8)	
Ongoing objective response, n/N (%)	77/89 (86.5)	13/19 (68.4)		84/108 (77.8)	13/21 (61.9)	

Finn. NEJM. 2020;382:1894.

Slide credit: clinicaloptions.com

IMbrave150: Safety

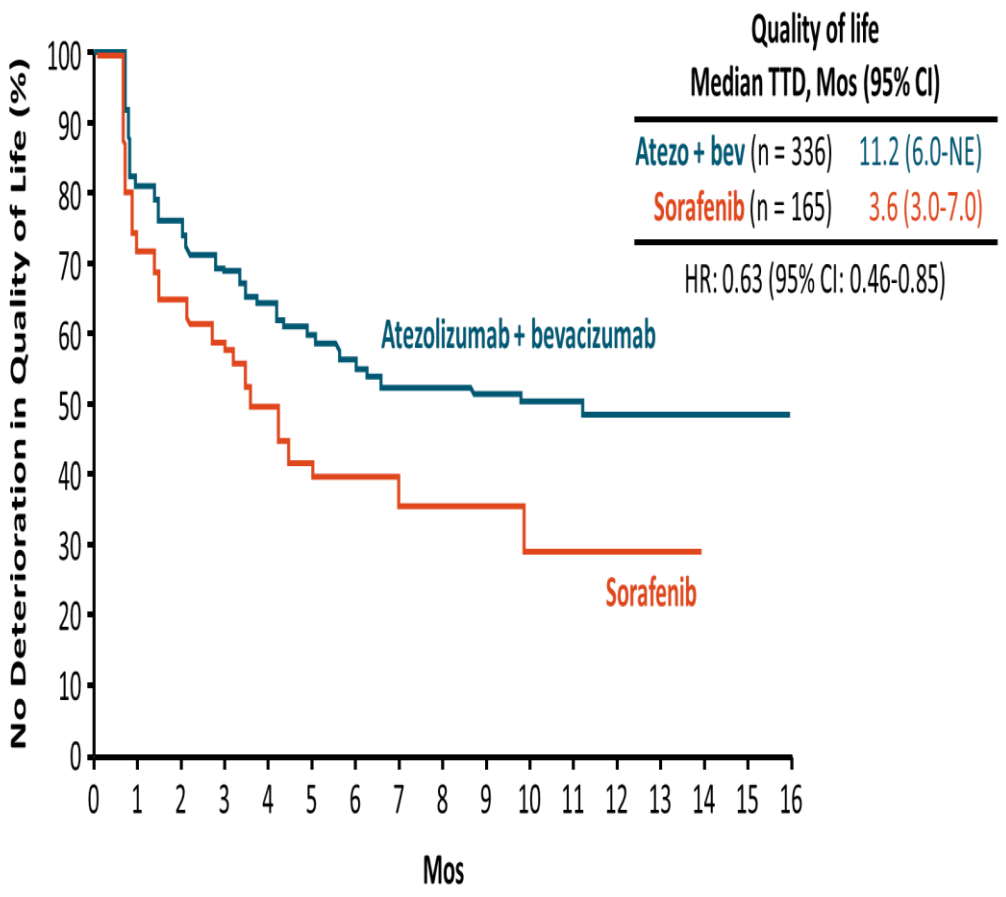
- Median duration of treatment: atezolizumab, 7.4 mos; bevacizumab, 6.9 mos; sorafenib, 2.8 mos
- Mean (± SD) and median (range) dose intensities:
  - Atezolizumab: 95% ± 7% and 98% (54%-104%)
  - Bevacizumab: 93% ± 10% and 97% (44%-104%)
  - Sorafenib: 84% ± 20% and 96% (27%-100%)
- No specific events were responsible for the increased SAE rate in the atezolizumab + bevacizumab group
- No SAEs with a ≥ 2% difference between treatment groups

Outcome, n (%)	Atezo + Bev (n = 329)	Sorafenib (n = 156)
Any-cause AE	323 (98.2)	154 (98.7)
Grade 3 or 4 AE	186 (56.5)	86 (55.1)
Grade 5 AE	15 (4.6)	9 (5.8)
SAE	125 (38.0)	48 (30.8)
AE leading to d/c	51 (15.5)	16 (10.3)
Withdrawal from atezo + bev	23 (7.0)	–
AEs leading to dose mod/interruption	163 (49.5)	95 (60.9)
▪ Dose interruption, any study tx	163 (49.5)	64 (41.0)
▪ Dose modification of sorafenib	–	58 (37.2)

Finn. NEJM. 2020;382:1894.

Slide credit: clinicaloptions.com

IMbrave150: Quality of Life (Patient Reported)



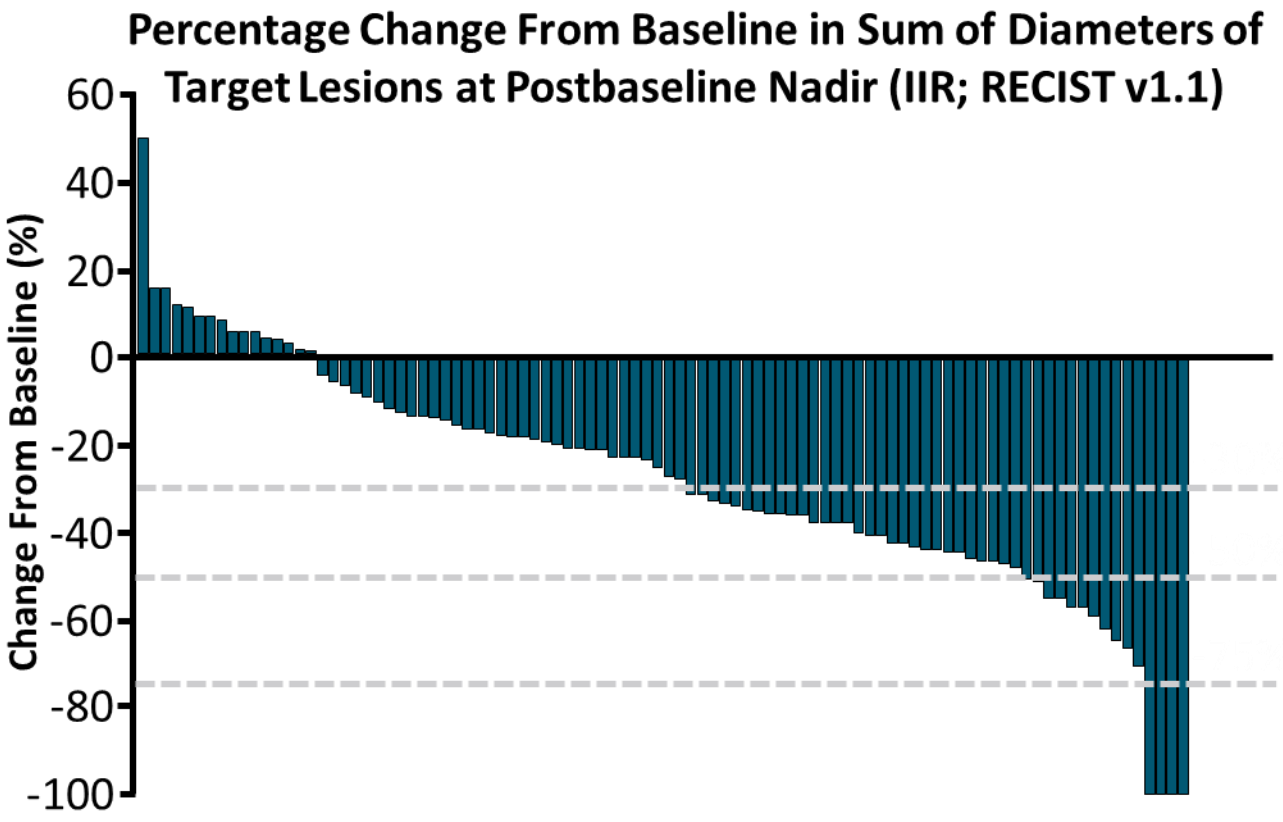
Finn. NEJM. 2020;382:1894.

Slide credit: clinicaloptions.com

KEYNOTE-524: Lenvatinib + Pembrolizumab for Advanced HCC

- Open-label phase Ib study of **lenvatinib** 8 or 12 mg/d + **pembrolizumab** 200 mg Q3W for patients with unresectable HCC with no prior systemic therapy (primary analysis set, N = 100)

Parameter (IIR; RECIST v1.1)	Lenv + Pembro (N = 100)
ORR, % (95% CI)	36 (26.6-46.2)
Best overall response, %	
▪ CR	1
▪ PR	35
▪ Stable disease	52
▪ Progressive disease	7
▪ Unknown/not evaluable	5
Median DoR for confirmed responders, mos (95% CI)	12.6 (6.9-NE)
Median TTR for confirmed responders, mos (range)	2.8 (1.2-7.7)
DCR, % (95% CI)	88 (80.0-93.6)

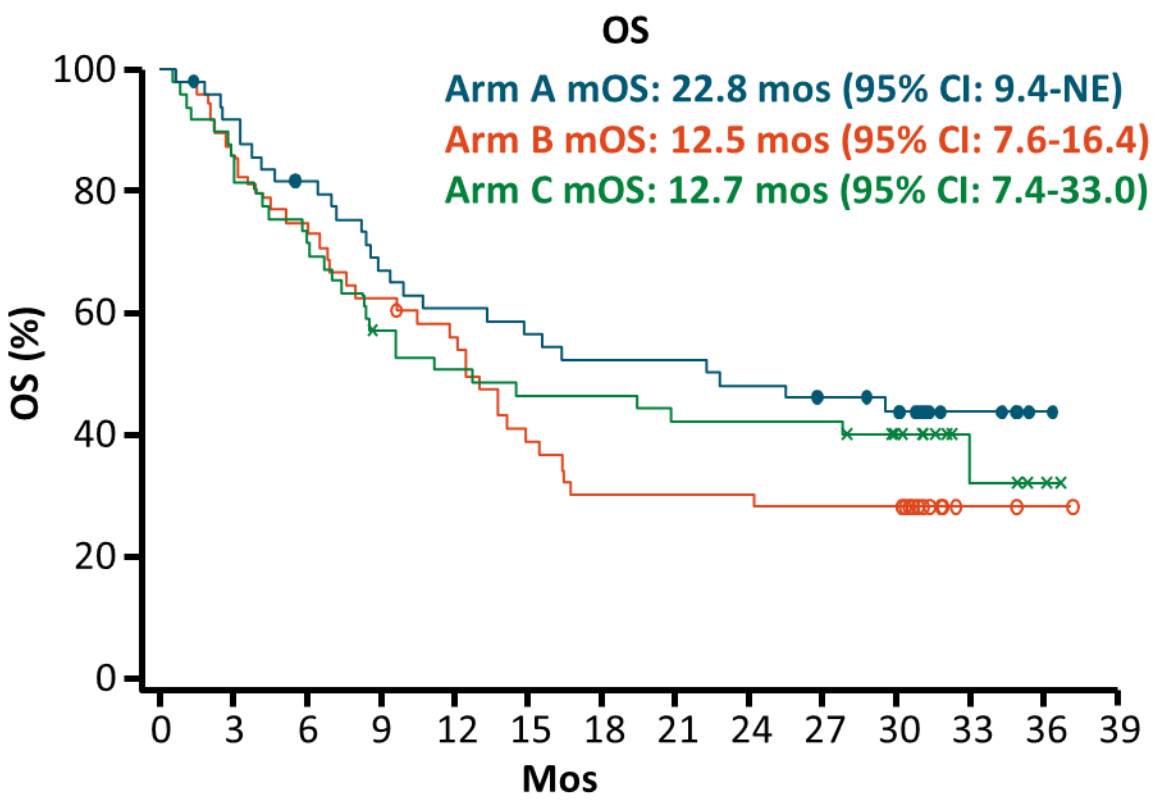


Finn. JCO. 2020;38:2960. Finn. EASL 2019. Abstr LBO09.

CheckMate 040: Nivolumab + Ipilimumab for Advanced HCC

- Open-label phase I/II trial of 3 different dosing schemes of **nivolumab + ipilimumab** for patients with advanced HCC and prior sorafenib treatment; uninfected or infected with HBV or HCV; CP score A5-A6; ECOG PS 0/1

Response	Arm A NIVO1/IPI3 Q3W (n = 50)	Arm B NIVO3/IPI1 Q3W (n = 49)	Arm C NIVO3 Q2W/ IPI1 Q6W (n = 49)
ORR, n (%)	16 (32)	15 (31)	15 (31)
BOR, n (%)			
▪ CR	4 (8)	3 (6)	0
▪ PR	12 (24)	12 (24)	15 (31)
▪ SD	9 (18)	5 (10)	9 (18)
▪ PD	20 (40)	24 (49)	21 (43)
▪ Undetermined	3 (6)	4 (8)	4 (8)
DCR, n (%)	27 (54)	21 (43)	24 (49)
Median TTR, mos (range)	2.0 (1.1-12.8)	2.6 (1.2-5.5)	2.7 (1.2-8.7)
Median DoR, mos (range)	17.5 (4.6 to 30.5+)	22.2 (4.2 to 29.9+)	16.6 (4.1+ to 32.0+)



Yau. ASCO 2019. Abstr 4012.

Slide credit: clinicaloptions.com

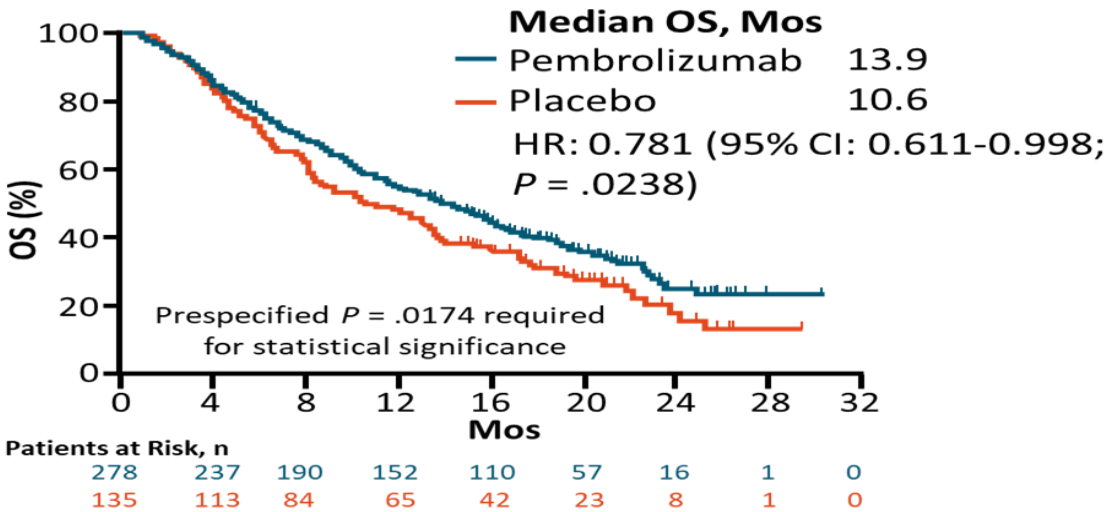
rapid communications

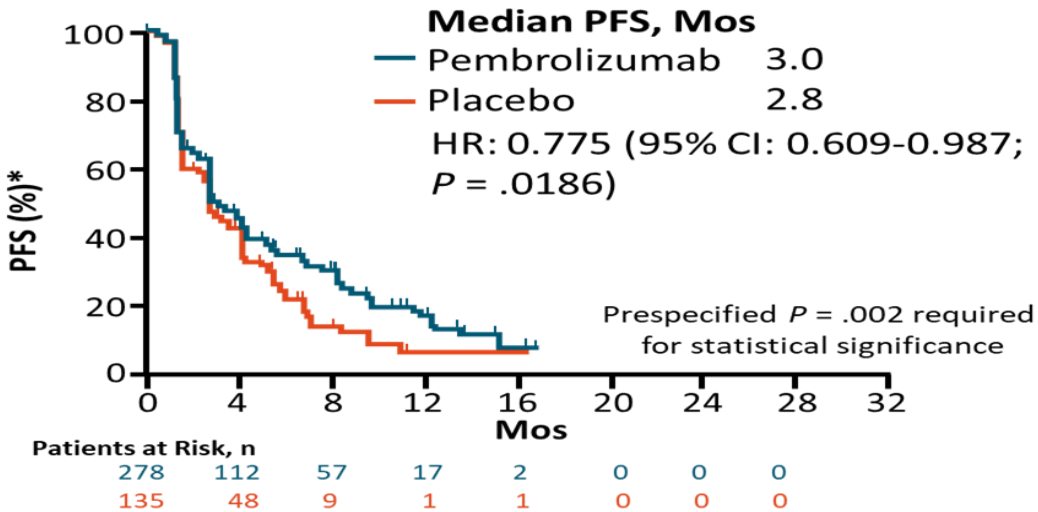
Pembrolizumab As Second-Line Therapy in Patients With Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomized, Double-Blind, Phase III Trial

Richard S. Finn, MD[1]; Baek-Yeol Ryoo, MD, PhD[2]; Philippe Merle, MD, PhD[3]; Masatoshi Kudo, MD, PhD[4]; Mohamed Bouattour, MD[5]; Ho Yeong Lim, MD[6]; Valeriy Breder, MD, PhD[7]; Julien Edeline, MD, PhD[8]; Yee Chao, MD, PhD[9]; Sadahisa Ogasawara, MD[10]; Thomas Yau, MD[11]; Marcelo Garrido, MD[12]; Stephen L. Chan, MD[13]; Jennifer Knox, MD[14]; Bruno Daniele, MD[15]; Scot W. Ebbinghaus, MD[16]; Erluo Chen, MPH[16]; Abby B. Siegel, MD[16]; Andrew X. Zhu, MD, PhD[17]; and Ann-Lii Cheng, MD, PhD[18]; on behalf of the KEYNOTE-240 investigators

KEYNOTE-240: OS and PFS

- Failed to reach prespecified level of statistical significance for OS, PFS



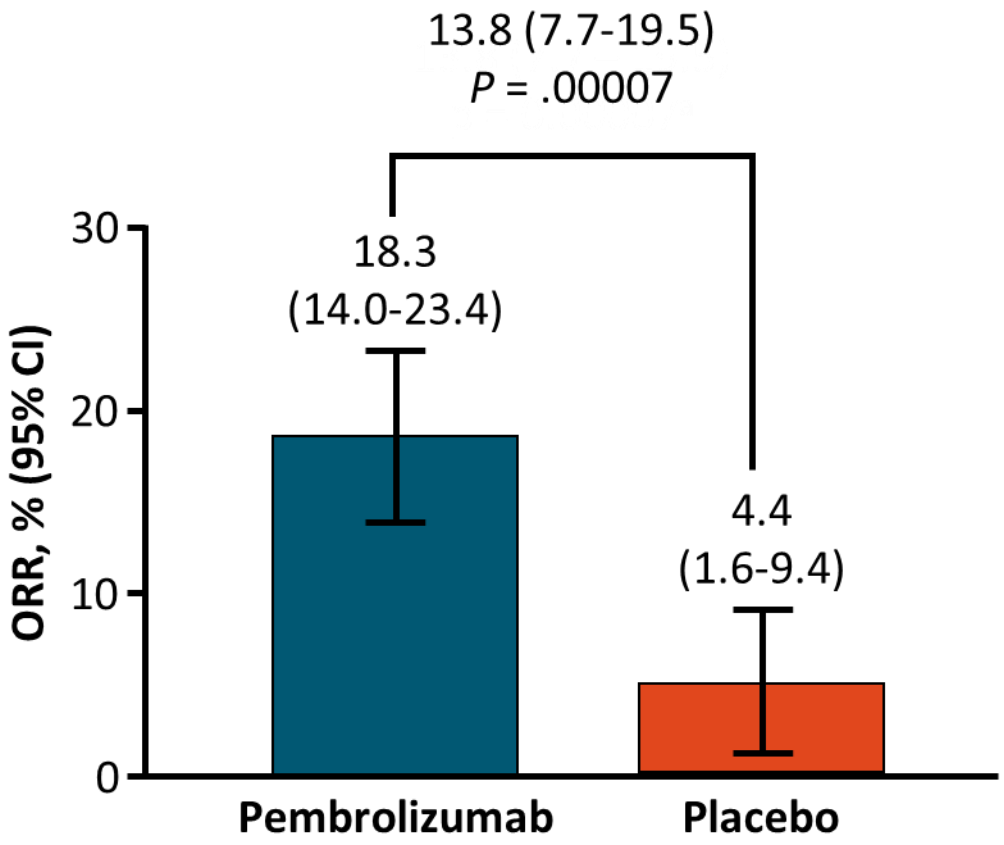


*Primary analysis.

Finn. JCO. 2020;38:193.

Slide credit: clinicaloptions.com

KEYNOTE 240: Response

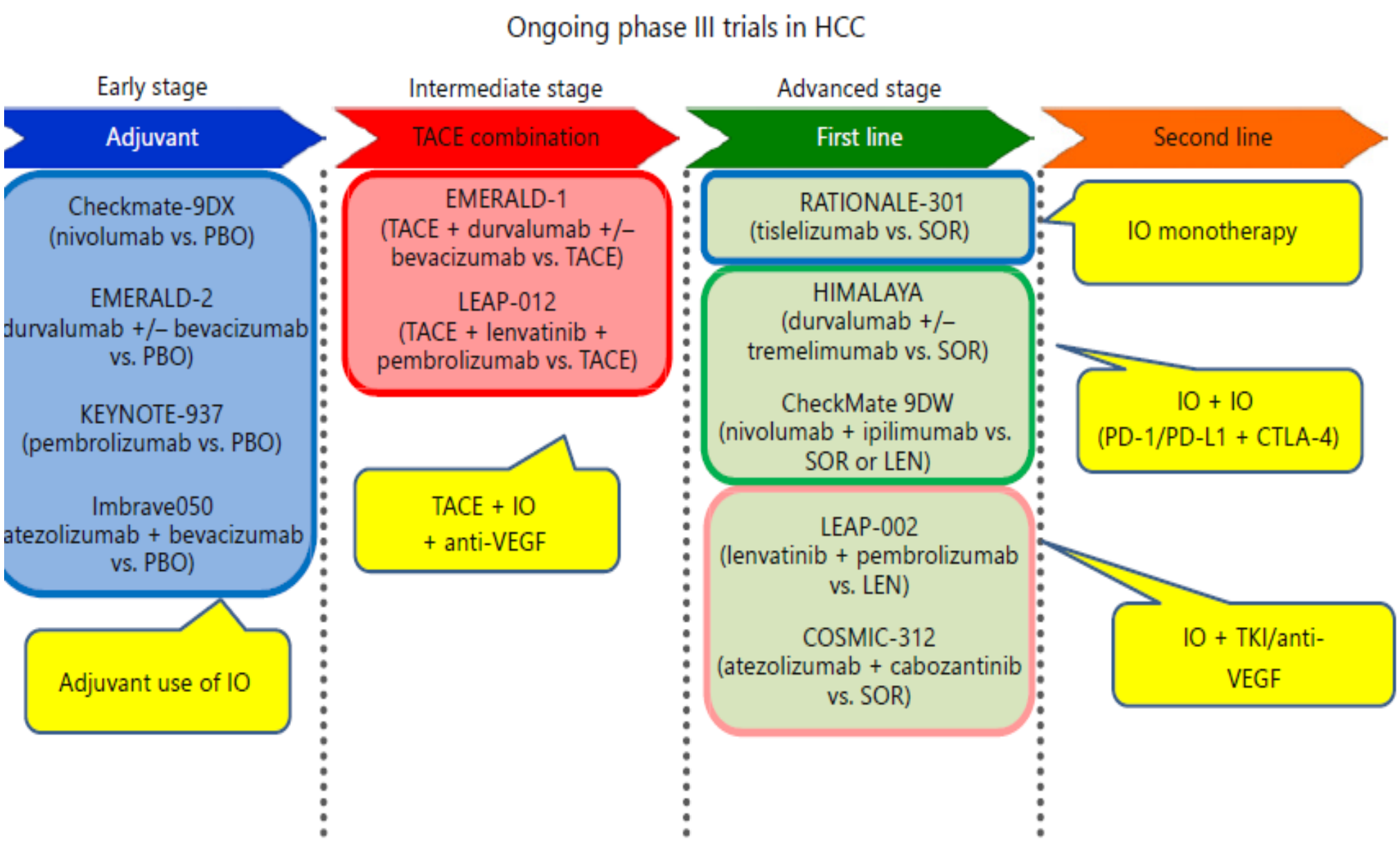


Response n(%)	Pembrolizumab (n = 278)	Placebo (n = 135)
Best overall response		
▪ CR	6 (2.2)	0
▪ PR	45 (16.2)	6 (4.4)
▪ SD	122 (43.9)	66 (48.9)
▪ SD ≥ 23 wks	37 (13.3)	20 (14.8)
Progressive disease	90 (32.4)	57 (42.2)
Disease control rate (CR + PR + SD)	173 (62.2)	72 (53.3)

- Duration of response, median (range):
  - Pembrolizumab: 13.8 mos (1.5+ to 23.6+ mos)
  - Placebo: not reached (2.8 to 20.4+ mos)

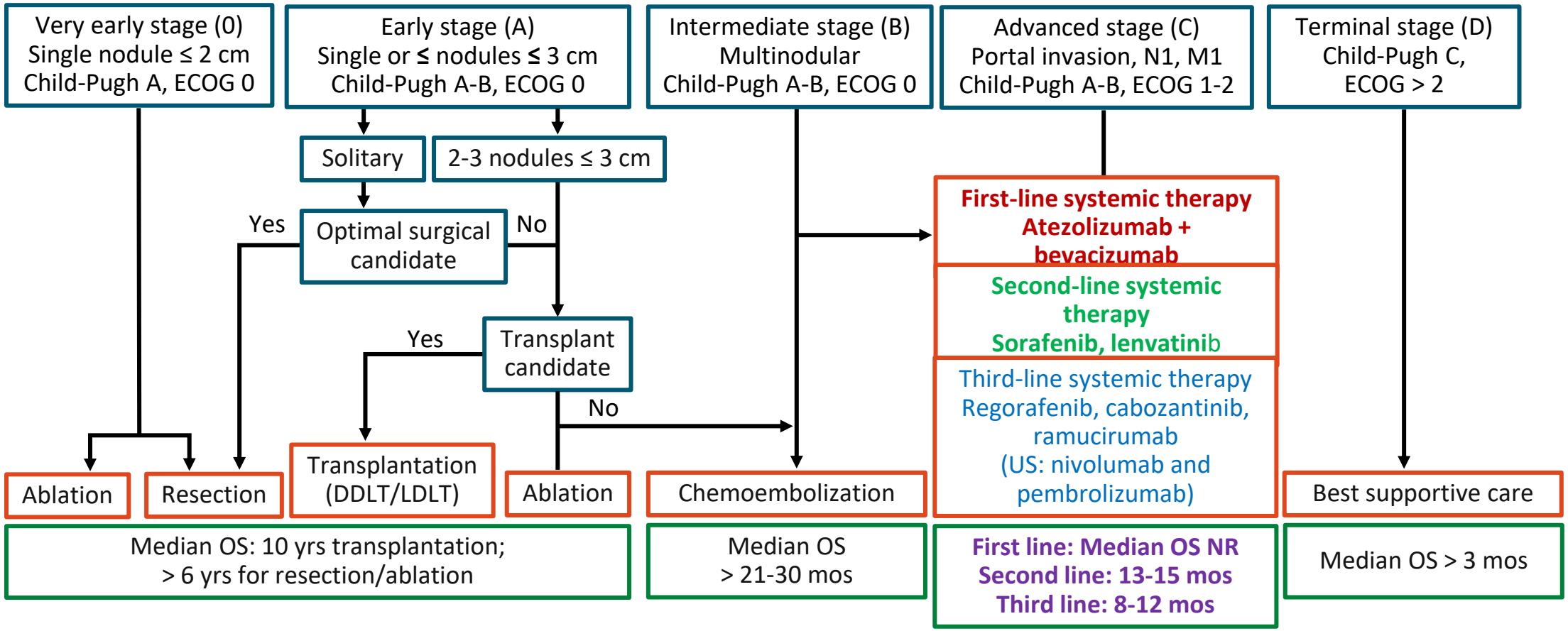
Finn. JCO. 2020;38:193.

Slide credit: clinicaloptions.com



Llovet. Hepatology. 2020;[Epub].

Treatment Strategy in the Management of HCC 2020



Llovet. Hepatology. 2020;[Epub].

Slide credit: clinicaloptions.com

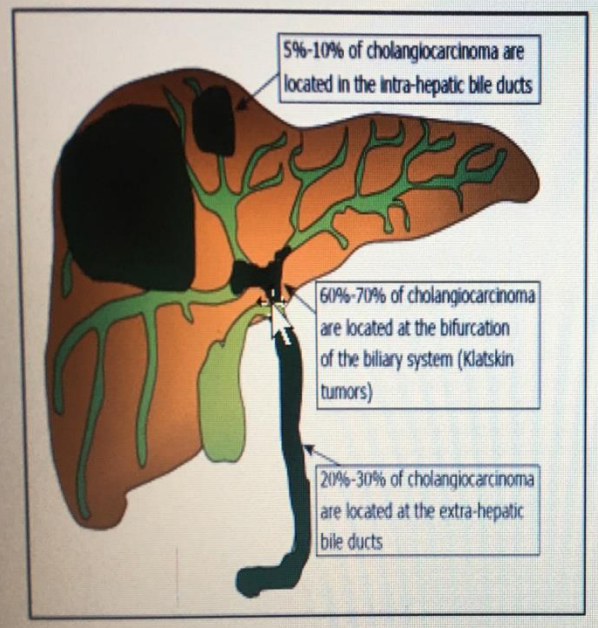
HCC 2020.....

Son 10 yılda beş pozitif çalışma ile HCC tedavisinde yeni gelişmeler olmuştur;

- Atezolizumab+ Bevacizumab ilk sıra tedavide sorafenibe göre üstün (HR:0.58)
- Lenvatinib; ilk sıra tedavide sorafenib ile karşılaştırmasında noninferior (HR; 0,92)
- Regorafenib; sorafenib sonrası 2. sırada plesobaya göre üstün (HR; 0,63)
- Cabozantinib; sorafenib sonrası 2. sırada plesobaya göre üstün (HR; 0,70)
- Ramucirumab; sorafenib sonrası 2. sırada AFP yüksek hastalarda plesobaya göre üstün (HR; 0,71)
- Tek ajan immun checkpoint inhibitörleri ile yapılan çalışmalarda yüksek kanıt düzeylerine ulaşılmamakla birlikte, kombinasyon tedavileri devam etmektedir.

Safra Yolları Kanserleri

SAFRA YOLLARI KANSERLERİ - ANATOMİ

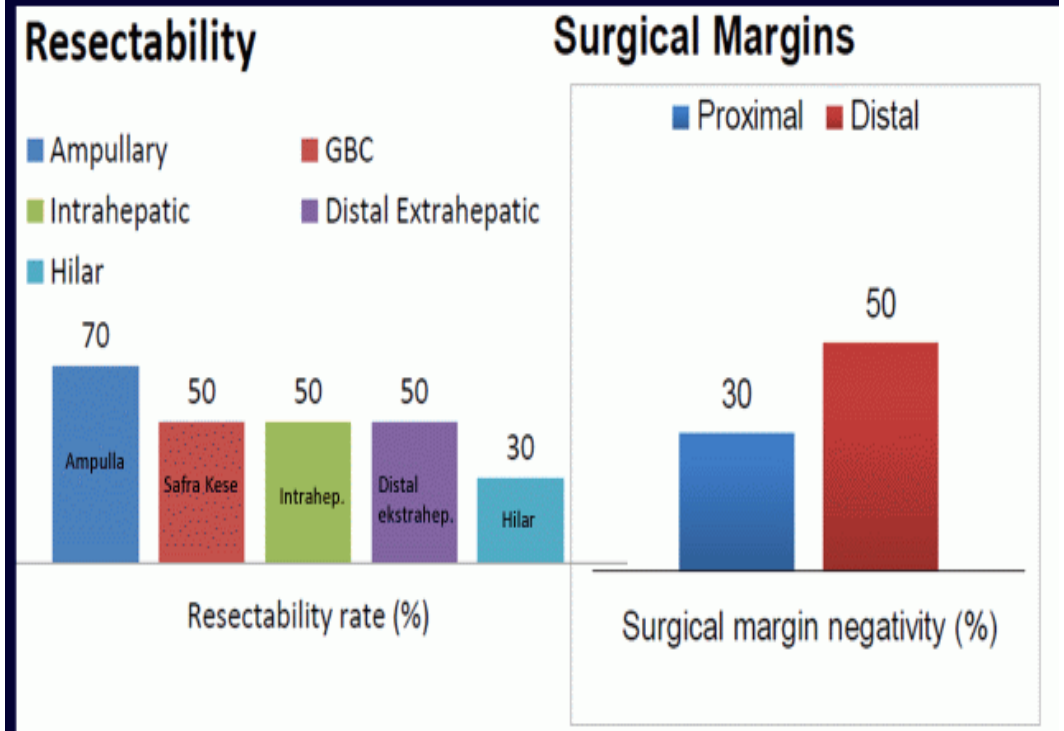


SAFRA YOLLARI KANSERLERİ

- ❑ **Kolanjiyokanser**
  - ✓ intrahepatik (IHCC) (5-10%)
  - ✓ Ekstrahepatik (EHCC)
    - -Perihiler (Klatskin) (60-70%)
    - -Distal (20-30%)
- ❑ **Safra kesesi tm**

Biliary tract cancers are a very heterogeneous disease. And within the biliary tree, you have cholangiocarcin

Rezektabilite



World J Gastroenterol 2012 June 7; 18(21): 2591-2596

Safta yolları kanserlerinde adjuvan tedavi çalışmaları:

Table 1. Summary of adjuvant treatments.

Study	Number and Type of Patients	Study Arms	RFS	OS
Primrose et al. [15] randomised, controlled, multicentre, phase III BILICAP trial	447 CCA or muscle-invasive gallbladder cancer	Cap: 1250 mg/m^2 twice a day on days 1 to 14 of a 3-week cycle for 24 weeks (8cycles) vs. Obs	Cap: 24.6 months (95% CI, 18.9 to 36.7 months) Obs: 17.6 months (95% CI, 12.8 to 27.6 months) HR 0.76 (95% CI, 0.58 to 0.99; $p = 0.039$)	Cap: 51.1 months (95% CI, 34.6 to 59.1 months) Obs: 36.4 months (95% CI, 29.7 to 44.5 months) HR: 0.81 (95% CI, 0.63 to 1.04; $p = 0.097$)
Edeline et al. [14] multicentre, open-label, randomised phase III PRODIGE 12-ACCORD 18 trial	196 resected BTC	Gem 1000 mg/m^2 on day 1 and oxaliplatin 85 mg/m^2 on day 2 for 12 cycles vs. Surveillance	GemOx: 30.4 months (95% CI, 15.4 to 43.0 months) Surveillance: 18.5 months (95% CI, 12.6 to 38.2 months) HR 0.71 (95% CI, 0.62 to 1.25; $p = 0.48$)	GemOx: 24-months OS 69% 48-months OS 51% 72-months OS 51% Surveillance: 24-months OS 76% 48-months OS 52% 72-months OS 48%
Ebata et al. [13] randomised phase III BCAT trial	225 resected BTC	Gem 1000 mg/m^2 on days 1,8, and 15 every 4 weeks (6 cycles) vs. Obs	Gem: 36.0 months Obs: 39.9 months HR 0.93 (95% CI, 0.66 to 1.32; $p = 0.693$)	Gem: 62.3 months Obs: 63.8 months HR 1.01 (95% CI, 0.70 to 1.45; $p = 0.964$)
Kobayashi et al. [16] multicentre, randomised phase II KHBO 1208 trial	70 BTC after major hepatectomy	Gem 1000 mg/m^2 on days 1 and 8 every 2 weeks vs. S1 80 mg/m^2/day for 28 days every 6 weeks	1-year 51.4% vs. 62.9% 2-year 31.4% vs. 51.4%	1-year 80% vs. 97.1% HR 0.48 (CI 90%, 0.24-0.93) 2-year 60% vs. 80%
Nakachi et al. [17] open-label, multicentre, randomised phase III ASCOT trial	350 resected BTC	S1: 40–60 mg/day related to BSA (body surface area) vs. Obs	n.a	3-year OS n.a vs. 47%

Cancers **2020, 12, 1237; doi:10.3390/cancers12051237**

Metastatik hastalıkta 1. sıra tedaviler

Table 2. Summary of first-line treatments in advanced settings.

Fist Line				
Study	**Number and Type of Patients**	**Study Arms**	**PFS**	**OS**
Valle et al. [12] Phase III ABC-02 trial	410 locally advanced or metastatic CCA, gallbladder cancer, or ampullary cancer	GemCis: cisplatin 25 mg/m^2 followed by Gem 1000 mg/m^2 (on days 1 and 8, every 3 weeks for 8 cycles) vs. Gem alone 1000 mg/m^2 (on days 1, 8, and 15, every 4 weeks for six cycles) for up to 24 weeks.	8.0 vs. 5.0 months	11.7 vs. 8.1 months HR (0.64; 95% confidence interval, 0.52 to 0.80; $p < 0.001$)
Shroff et al. [25] open-label, single-arm, Phase II trial	60 advance BTC	GAP: Gem 1000 mg/m^2, cisplatin, 25 mg/m^2, and nab-paclitaxel, 125 mg/m^2, on days 1 and 8 of 21-day cycles	11.8 months (95% CI, 6.0 to 15.6)	19.2 months (95% CI, 13.2 months to not estimable)
Phelip et al. [29] Phase II/III trial PRODIGE38-AMEBICA trial	intra or extra hepatic or hilar or gallbladder carcinoma	FOLFIRINOXm Oxali 85 mg/m2, IRI 180 mg/m^2 (IV 90 min), folinic acid 400 mg/m^2 (IV 2 h), 5 FU 2400 mg/m^2 (46 h) every 2 weeks vs. GemCIs: cisplatin 25 mg/m^2 followed by Gem 1000 mg/m^2 (on days 1 and 8) every 3 weeks	n.a	n.a
Berger et al. [30] Phase II NIFE trial	locally advanced, non-resectable or metastatic BTC	Nal-IRI: nal-IRI mg/m^2 (46 h infusion), 5-FU 2400 mg/m^2 (46 h infusion), leucovorin 400 mg/m^2 (0.5 h infusion) on day 1 every 2 weeks Vs. GemCis: cisplatin 25 mg/m^2 followed by Gem 1000 mg/m^2 (on days 1 and 8) every 3 weeks	n.a	n.a

Safra Yolu Kanserlerinde 2. sıra tedaviler

After First-Line

Study	Number and Type of Patients	Study Arms	PFS	OS
Lamarca et al. [21] randomised phase III, multi-centre, open-label ABC-06 trial	162 locally advanced/metastatic BTC patients previously-treated with CisGem chemotherapy	ASC+ mFOLFOX6: Oxali 85 mg/m^2, folinic acid 350 mg/m^2, 5-FU 400 mg/m^2 (bolus) and 2400 mg/m^2 (infusion) every 2 weeks for 12 cycles vs. ASC		mOS: 6.2 vs. 5.3 months HR: 0.69 (95% CI 0.50–0.97; $p = 0.031$) 6-months OS: 50.6% vs. 35.5% 12-months OS: 25.9% vs. 11.4%
Zheng et al. [33] randomised, Phase II study	64 advanced BTC patients progressed after CisGem	XELIRI: IRI 180 mg/m^2 on day 1, cap 1000 mg/m^2 twice daily on days 1–10 every 2 weeks vs. Irinotecan: IRI 180 mg/m^2 every 2 weeks	3.7 vs. 2.4 months	9-month OS: 60.9% vs. 32.0%, mOS 10.1 vs. 7.3 months DCR: 63.3% vs. 50.0%
Guion-Dusserre et al. [34]	13 metastatic intrahepatic CCA patients who were refractory to GemOx	FOLFIRI + bevacizumab: IRI 180 mg/m^2 (IV 90 min), folinic acid 400 mg/m^2 (IV 2h), 5-FU 2400 mg/m^2 (46h), bevacizumab (5 mg/kg) every 2 weeks	8 months (95% CI: 7–16 months)	20 months (95% CI: 8–48 months) DCR: 84.5% (95% CI: 42%–100%) ORR: 38.4% (95% CI: 12.5%–89%)
Sebbagh et al. [35] retrospective trial	52 recurrent/advanced BTC patients after progression to GemOx	FOLFIRI (after GemOx in fist line): IRI 180 mg/m^2 (IV 90 min), folinic acid 400 mg/m^2 (IV 2h), 5-FU 2400 mg/m^2 (46h)	Fist-line GemOx: 4.8 months Second-line FOLFIRI: 3.2 months	21.9 months
Chakrabarti et al. [36] Phase II trial	27 advanced BTC previously treated	FTD/TPI 35 mg/m^2/day	3.8 months (95% CI, 2.0 to 5.8 months)	6.1 months (95% CI, 4.4 to 11.4 months)

SKY Kanserleri 2020

- Safra kesesi ve yolları kanserlerinde, son 10 yılda çok az pozitif sonuçları olan çalışma yayınlanmıştır. Günümüzde , ilk planda adjuvan tedavide Kapesitabinin etkinliği ön plandadır ve önerilmektedir.
- Metastatik hastalıkta , 1. sıra tedavide Gemcitabine-Cisplatin rejimi etkinliği gösterilmiştir.
- 2. sıra tedavide , mFOLFOX6 ile ilk pozitif verileriler elde edilmiş ve günümüzde kullnılmaktadır.
- Hedef tedavi ajanları, spesifik genomik değişikliklere göre belli hastalarda önerilebilir , çalışmaları devam etmektedir.

Teşekkür ederim