



Chemotherapy for HCC: A New Era

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(thanks to Greg Heestand for use of multiple slides)

Disclosures

- None

A Paradigm Shift

Progress in Treatment for Advanced HCC

2000	2007	2019
Supportive Care		
	Sorafenib	
		Lenvatinib
		Regorafenib
		Cabozantinib
		Nivolumab
		Pembrolizumab
		Ramucirumab

Courtesy: Greg Heestand

Before: LDT, and then sorafenib as a last resort

Now: Much more complicated discussion

Still dependent on liver function; CPS, specifically

Systemic Strategies for Hepatocellular Carcinoma

Strategy	Treatment	Median OS
Nonspecific	FOLFOX4	6.4 months ¹
Targeted	1 st -Line: <ul style="list-style-type: none"> • Sorafenib • Lenvatinib 	10.7-13.6 months ²⁻³
	2 nd -Line: <ul style="list-style-type: none"> • Regorafenib • Cabozantinib • Ramucirumab* 	8.5-10.6 months ⁴⁻⁶
Matched	To Be Determined	To Be Determined

¹Qin et al, *JCO* 2013.

²Llovet et al, *NEJM* 2008.

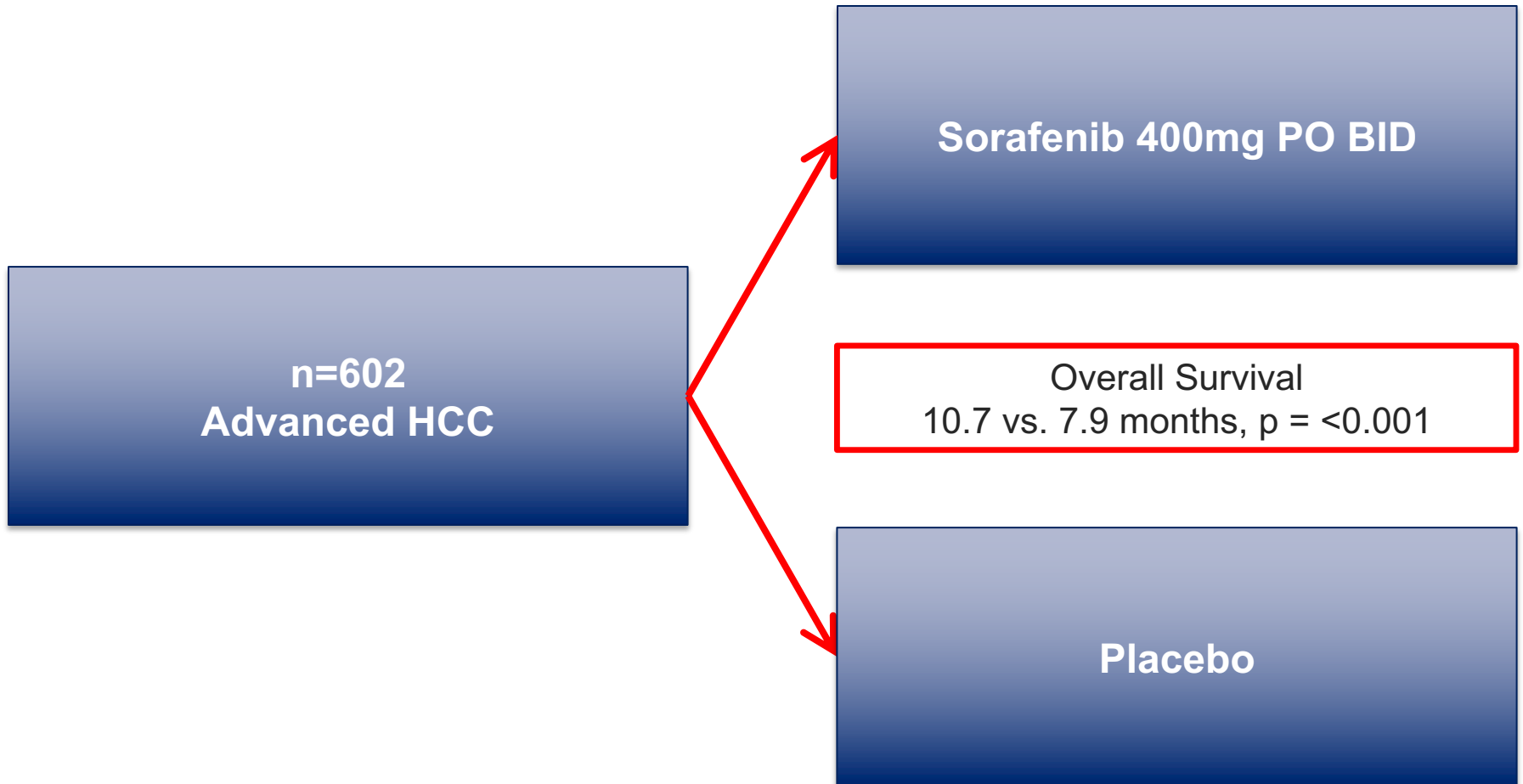
³Kudo et al, *Lancet* 2018.

⁴Bruix et al, *Lancet* 2017.

⁵Abou-Alfa et al, *NEJM* 2018.

⁶Zhu et al, *Lancet Oncology* 2019.

SHARP Trial: Sorafenib for Advanced HCC



Sorafenib is a really yucky drug

Other Small Molecule Inhibitors in Advanced HCC

- 2nd Line - Regorafenib versus placebo¹
 - Progression on sorafenib, Child-Pugh A
 - n=573, 2:1 randomization, HBV=38%
 - **OS 10.6 vs. 7.8 months, p<0.0001**
- 2nd Line - Cabozantinib versus placebo²
 - Progression on sorafenib, Child-Pugh A
 - n=707, 2:1 randomization, HBV=38%
 - **OS 10.2 vs. 8.0 months, p=0.005**

¹Bruix et al, *Lancet* 2017.

²Abou-Alfa et al, *NEJM* 2018.

Other Small Molecule Inhibitors in Advanced HCC

- 1st Line - Lenvatinib versus sorafenib
 - Trial design:
 - 1st-line, Child-Pugh A, no PV invasion
 - n=954, 1:1 randomization, HBV=50%
 - Lenvatinib dosing: 12 mg/day if ≥ 60 kg, 8 mg/day if < 60 kg
 - Sorafenib dosing: 400mg PO BID
 - OS 13.6 vs. 12.3 months – non-inferiority endpoint
 - PFS 7.4 vs. 3.7 months, $p < 0.0001$
 - RR 24.1% vs. 9.2%, $p < 0.0001$ (mRECIST by investigator)

HCC Treatment Options: Small Molecule Inhibitors

1st Line	2nd Line
Sorafenib	Regorafenib -If tolerated sorafenib
Lenvatinib	Cabozantinib

Ramucirumab (REACH-2)

- 2nd Line - ramucirumab versus placebo
 - Ramucirumab is a mAb VEGFR-2 antagonist
 - Trial design:
 - 2nd-line, Child-Pugh A
 - Prior sorafenib
 - AFP \geq 400
 - n=292, 2:1 randomization
 - HBV=42%
 - OS 8.5 vs. 7.3 months, p<0.0199
 - PFS 2.8 vs. 1.6 months, p<0.0001
 - RR 5% vs. 1%, p=0.1697

Nivolumab in Advanced HCC: Checkmate 040

- Nivolumab = mAb to PD-1
- Multicenter, open label, phase I/II study
- Dose escalation (n=48, 0.1-10mg/kg)
- Dose expansion (n=214, 3mg/kg)
 - Sorafenib untreated or intolerant - uninfected (n=56)
 - Sorafenib progression – uninfected (n=57)
 - HCV infected (n=50)
 - HBV infected (n=51)

Checkmate 040: Dose Expansion Efficacy (Table 4)

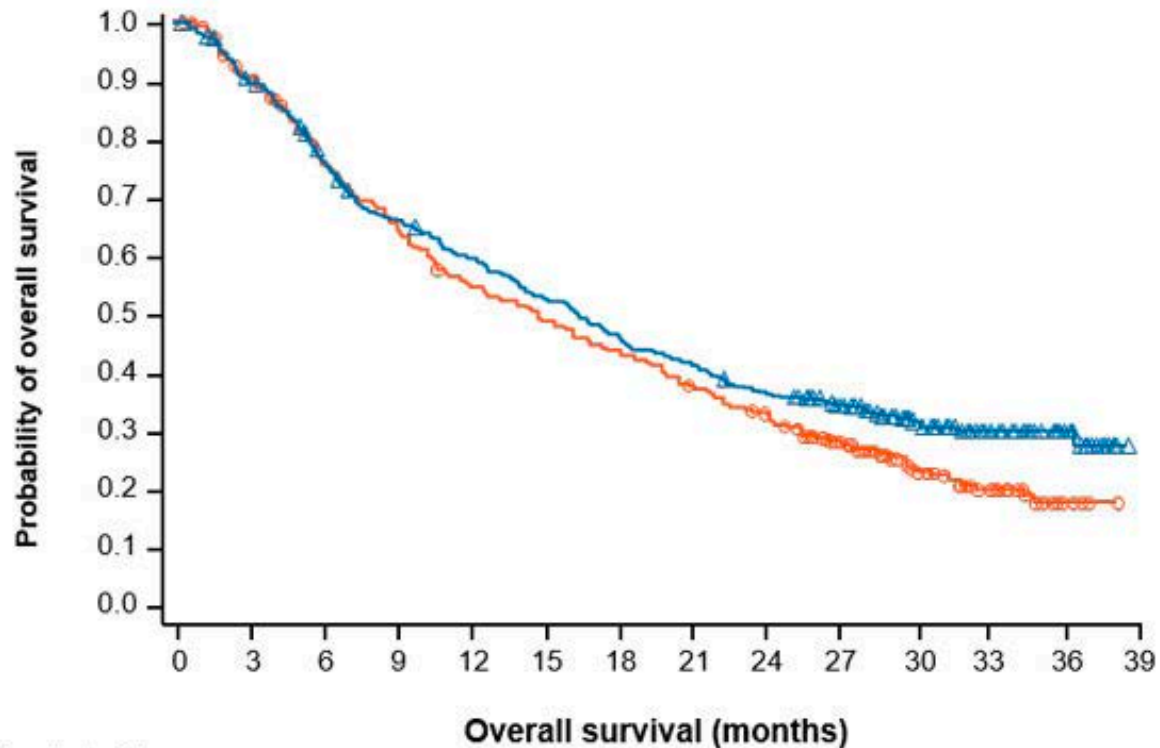
	Untreated Uninfected n=56	Treated Uninfected n=57	HCV n=50	HBV n=51	All n=214
OR	13 (23%)	12 (21%)	10 (20%)	7 (14%)	42 (20%)
CR	0	2 (4%)	0	1 (2%)	3 (1%)
PR	13 (23%)	10 (18%)	10 (20%)	6 (12%)	39 (18%)
SD	29 (52%)	23 (40%)	23 (46%)	21 (41%)	96 (45%)
PD	13 (23%)	18 (32%)	14 (28%)	23 (45%)	68 (32%)
OS					
9-month	82%	63%	81%	70%	74%
Median	NR	13.2mos	NR	NR	NR
PFS	5.4mos	4.0mos	4.0mos	4.0mos	4.0mos

Checkmate 040: 2nd Line Ipilimumab + Nivolumab

- Previous sorafenib treatment (n=148)
 - 88% progressed on sorafenib
 - 91% BCLC Stage C

	NIVO1/IPI3 Q3W (n = 50)	NIVO3/IPI1 Q3W (n = 49)	NIVO3 Q2/IPI1 Q6W (n = 49)
ORR, n (%)	16 (32)	15 (31)	15 (31)
Complete Response	4 (8)	3 (6)	0
Partial Response	12 (24)	12 (24)	15 (31)
Stable Disease	9 (18)	5 (10)	9 (18)
Progressive Disease	20 (40)	24 (49)	21 (43)
mOS, mo (95% CI)	23 (9–NA)	12 (8–15)	13 (7–33)

Checkmate 459: 1st-Line Nivolumab vs. Sorafenib



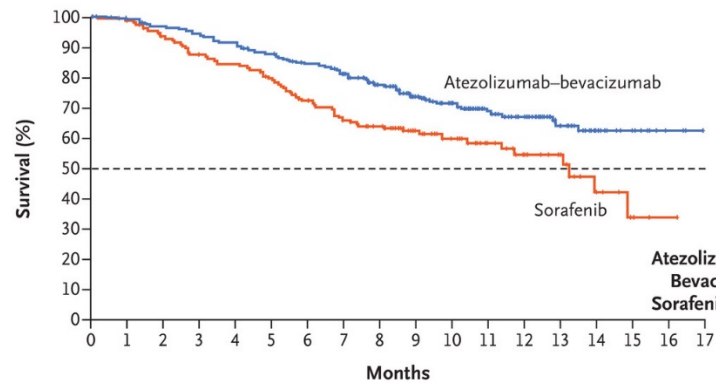
Number of patients at risk

Nivolumab 240 mg	371	326	271	235	211	187	165	146	129	104	63	39	17	0
Sorafenib 400 mg	372	328	274	232	196	174	155	133	115	80	47	30	7	0

IMbrave150: A New Era

- 1st-Line.
Atezolizumab/
Bevacizumab
vs. Sorafenib
 - n=501
 - 2:1 random.
 - Hep B = 48%

A Overall Survival



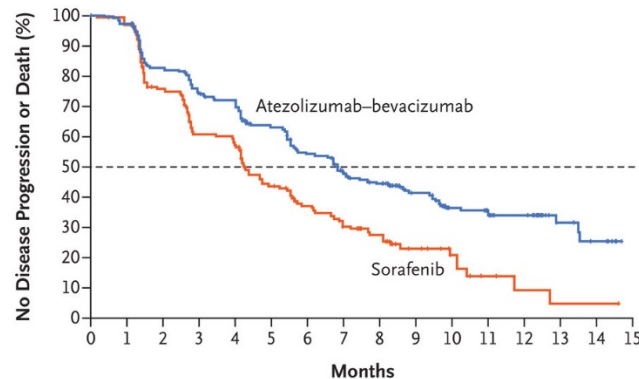
No. of Events/ No. of Patients (%)	Median Overall Survival (95% CI) <i>mo</i>	Overall Survival at 6 Mo %	
Atezolizumab- Bevacizumab	96/336 (28.6)	NE	84.8
Sorafenib	65/165 (39.4)	13.2 (10.4–NE)	72.2

Stratified hazard ratio for death, 0.58
(95% CI, 0.42–0.79)
P<0.001

No. at Risk

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

B Survival without Disease Progression



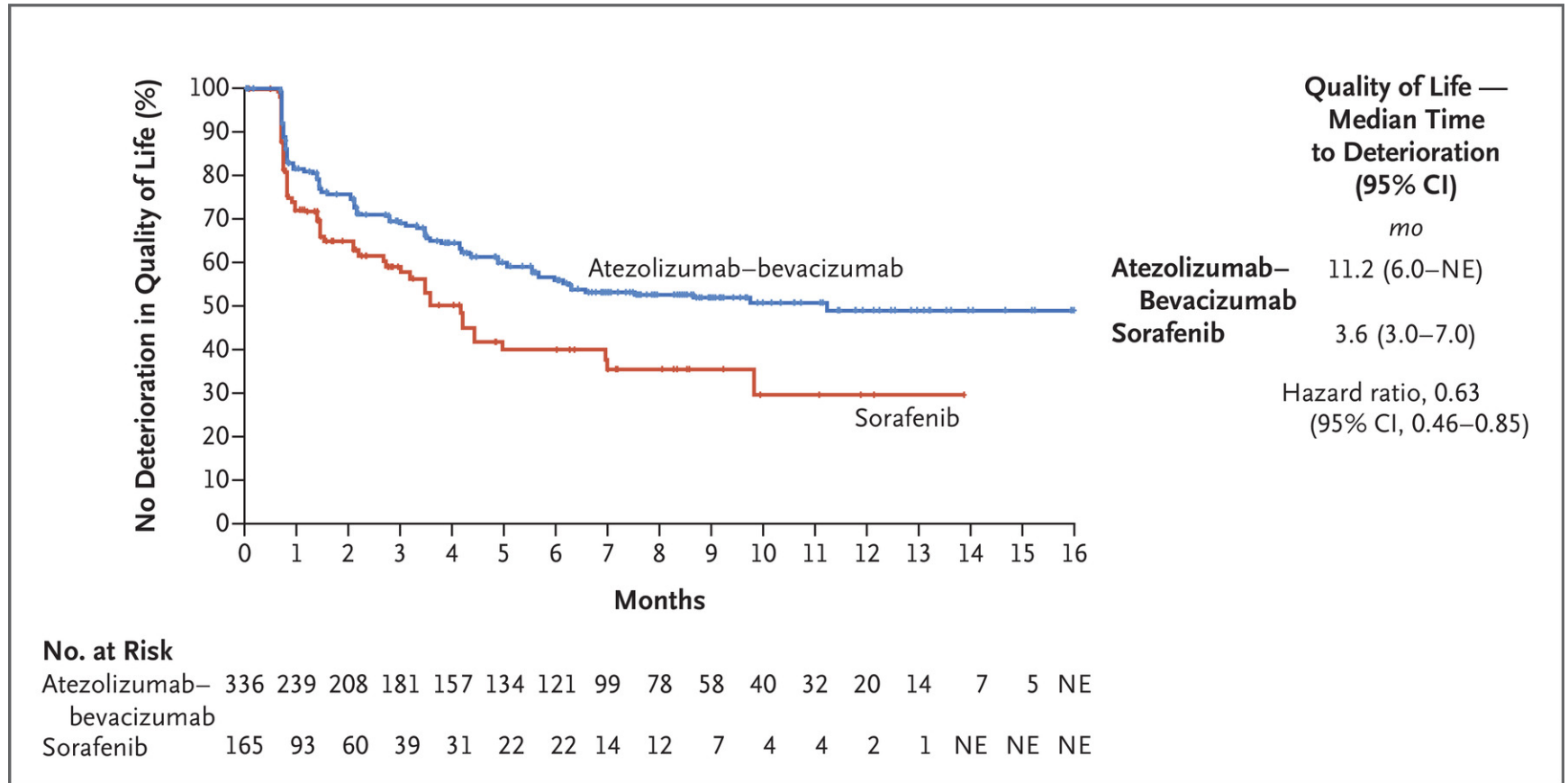
No. of Events/ No. of Patients (%)	Median Progression- free Survival (95% CI) <i>mo</i>	Progression- free Survival at 6 Mo %	
Atezolizumab- Bevacizumab	197/336 (58.6)	6.8 (5.7–8.3)	54.5
Sorafenib	109/165 (66.1)	4.3 (4.0–5.6)	37.2

Stratified hazard ratio for progression or death,
0.59 (95% CI, 0.47–0.76)
P<0.001

No. at Risk

Atezolizumab- bevacizumab	336	322	270	243	232	201	169	137	120	74	50	46	34	11	7	NE
Sorafenib	165	148	109	84	80	57	44	34	27	15	9	4	2	1	1	NE

IMbrave150: The Advanced HCC Game Changer!



Again, though, remember CPS/comorbid conditions

Summary: Advanced HCC Treatment Options

1 st Line	2 nd Line
Atezolizumab + Bevacizumab	Regorafenib -If tolerated sorafenib
Sorafenib	Cabozantinib
Lenvatinib	Ramucirumab -If AFP \geq 400
Nivolumab	Nivolumab
	Pembrolizumab

In Summary

- A New Era
- Oncologists now play a major role in therapy for HCC
- Targeted and Immuno therapies play a major role
- Combinations offer even greater treatment possibilities

Thank You