Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer

Valle J et al.

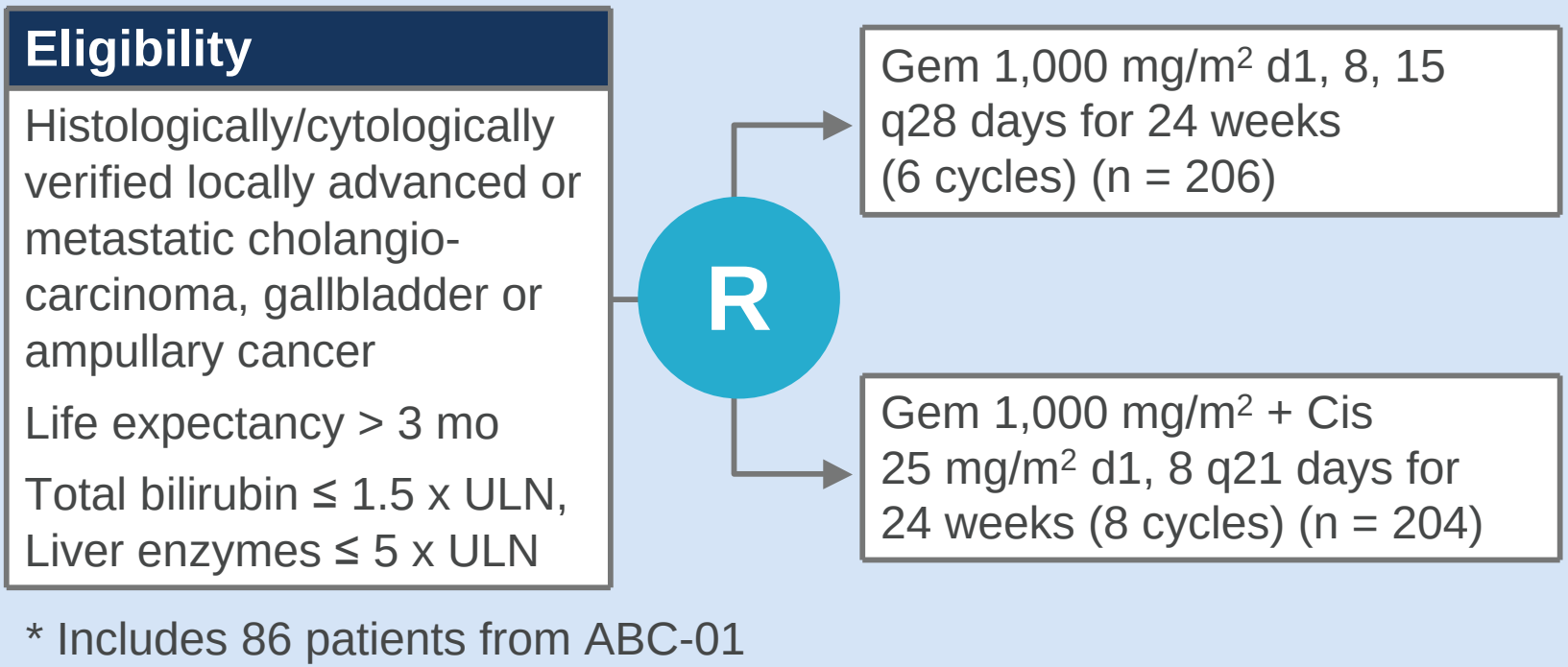
N Engl J Med 2010;362(14):1273-81.

Introduction

- Biliary tract cancers (BTC: cholangiocarcinoma, gall bladder cancer, ampullary cancer) are rare, lethal cancers with rising incidence for which no standard of care exists.
- Phase II trial ABC-01 demonstrated that cisplatin (Cis) and gemcitabine (Gem) was superior to Gem alone (*Br J Cancer* 2009;101:621).
  - 6-mo progression-free survival (PFS): 57.1% vs 47.7%
- Current study objective:
  - Prospectively evaluate the activity and safety of Gem and Cis vs Gem in patients with locally advanced or metastatic BTC.

Valle J et al. *N Engl J Med* 2010;362(14):1273-81.

ABC-02: A Phase III Multicenter Study (N = 410*)



* Includes 86 patients from ABC-01

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Disease Progression and Survival (Intent-to-Treat)

Clinical Variable	Number of Patients			
Tumor progression[1]	362 (278 deaths)			
Survival	**Gem (n = 206)**	**Cis + Gem (n = 204)**	**HR (95% CI)**	***p*-value**
Median overall survival (OS)	8.1 mo	11.7 mo	0.64 (0.52-0.80)	<0.001
Median PFS	5.0 mo	8.0 mo	0.63 (0.51-0.77)	<0.001

HR = hazard ratio

[1] The final analysis was event driven and performed 8 months after the last patient was enrolled.

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Gem and Cis vs Gem Hazard Ratio (Intent-to-Treat)

Subgroup	Number of Patients	HR* (95% CI)
ABC trial group		
01	86	0.65 (0.42-1.01)
02	324	0.64 (0.50-0.83)
Extent of disease		
Locally advanced	104	0.47 (0.29-0.74)
Metastatic	306	0.74 (0.57-0.95)
Previous therapy		
No	100	0.65 (0.41-1.01)
Yes	310	0.64 (0.49-0.82)
All patients	410	0.64 (0.52-0.80)

* Hazard ratio of <1 favors Gem and Cis

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Select Grade 3/4 Adverse Events

Adverse Event	Gem (n = 199)	Cis + Gem (n = 198)	*p*-value
Any Grade 3/4 event	**68.8%**	**70.7%**	**0.69**
Fatigue	16.6%	18.7%	0.58
Leukopenia	9.5%	15.7%	0.07
Neutropenia	16.6%	25.3%	0.03
Thrombocytopenia	6.5%	8.6%	0.44
Infection	19.1%	18.2%	0.82
Any abnormal liver function	27.1%	16.7%	0.01

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Summary and Conclusions

- Gem and Cis significantly improves OS and PFS compared to Gem alone.
  - Median OS: 11.7 mo vs 8.1 mo
  - Reduced risk of death by 36% (HR = 0.64, $p < 0.001$)
  - Median PFS: 8 mo vs 5 mo
  - Reduced risk of disease progression by 37% (HR = 0.63, $p < 0.001$)
- Adverse events were similar in the two treatment arms.
  - Liver function was significantly worse in patients receiving Gem compared to Gem and Cis. Authors feel this probably reflects better control of disease in the combined therapy group.
- Cis + Gem is an appropriate option for the treatment of patients with advanced biliary cancer.

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Faculty Comments

DR AJANI: This is a good study in an uncommon tumor, for which few, if any, Phase III studies are done, and it demonstrates that adding cisplatin to gemcitabine improves survival. It is game changing in that patients with advanced extrahepatic biliary cancers should receive gemcitabine/cisplatin or, perhaps, gemcitabine/oxaliplatin.

DR ALBERTS: This was a landmark study. Until this study was performed, there had never been a completed Phase III trial in biliary tract cancers. This study not only has changed how we treat patients, but also shows that in a rare disease, such as biliary tract cancers, with a concerted effort it is possible to conduct a randomized Phase III trial and have meaningful outcomes that do change the standard of care.

Efficacy and Safety of Sorafenib in Asian-Pacific Patients with Advanced Hepatocellular Carcinoma: A Double-Blind, Placebo-Controlled Phase III Trial

Cheng A-L et al.
Lancet Oncol 2009;10(1):25-34.

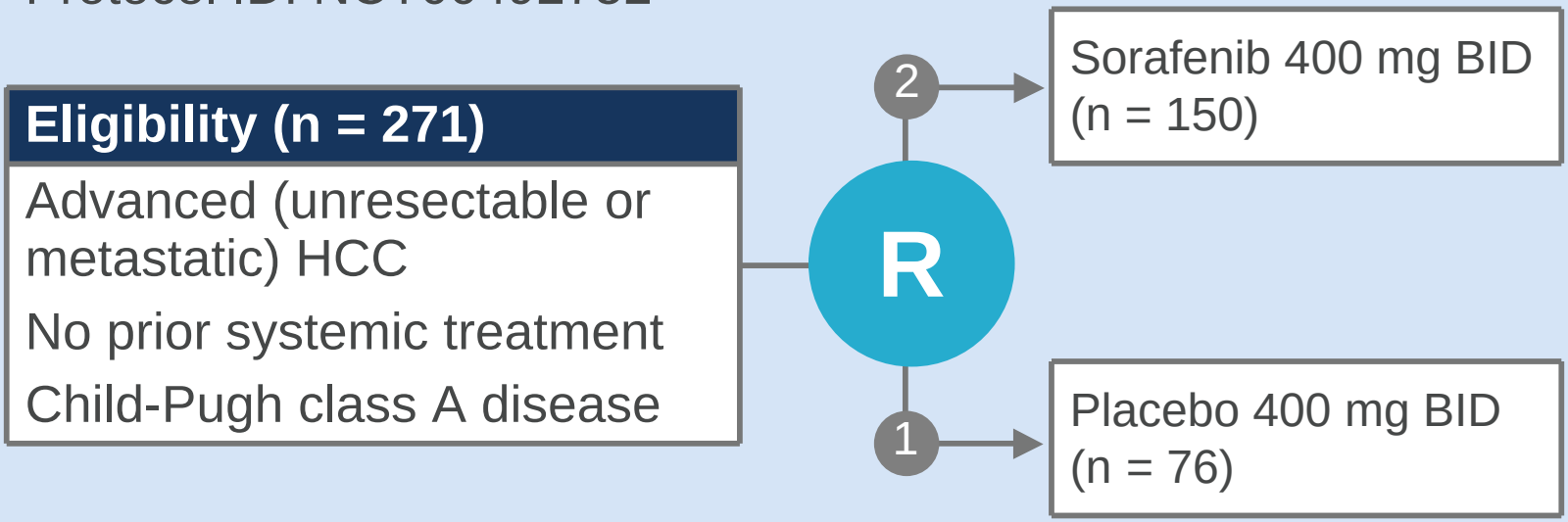
Introduction

- The Asia-Pacific region is a high-risk population for the development of hepatocellular carcinoma (HCC).
  - Greater than 75% of HCC cases worldwide occur in the Asia-Pacific region (*Int J Cancer* 2001;94:290).
  - Hepatitis virus B infection is a significant risk factor for HCC in this region (*Lancet* 2003;362:1907).
- Phase III, placebo-controlled SHARP trial demonstrated sorafenib is efficacious in patients from North America and Europe with advanced HCC (*NEJM* 2008;359:378).
  - Median overall survival: 10.7 mo vs 7.9 mo ($p<0.001$)
- Current study objective:
  - Assess the safety and efficacy of sorafenib in patients from the Asia-Pacific region with advanced HCC.

Cheng A-L et al. *Lancet Oncol* 2009;10(1):25-34.

Phase III, Placebo-Controlled Trial of Sorafenib for Advanced HCC in Asian-Pacific Patients

Protocol ID: NCT00492752



Patients stratified by the presence of macroscopic vascular lesion and/or extrahepatic spread, ECOG performance score (PS) and geographical region (China, Taiwan or South Korea)

Cheng A-L et al. *Lancet Oncol* 2009;10(1):25-34.

Baseline Patient Characteristics

Patient Characteristic	Sorafenib (n = 150)	Placebo (n = 76)
ECOG PS		
0	25.3%	27.6%
1	69.3%	67.1%
2	5.3%	5.3%
Extrahepatic spread		
No	31.3%	31.6%
Yes	68.7%	68.4%
Hepatitis virus status		
HBV infection	70.7%	77.6%
HCV infection	10.7%	3.9%

Cheng A-L et al. *Lancet Oncol* 2009;10(1):25-34.

Efficacy Results (Intent-to-Treat)

	Sorafenib (n = 150)	Placebo (n = 76)	HR (*p*-value)
Median overall survival (OS)	6.5 mo	4.2 mo	0.68 (0.014)
Median time-to-progression (TTP)	2.8 mo	1.4 mo	0.57 (0.0005)
Complete response (CR)	0%	0%	—
Partial response (PR)	3.3%	1.3%	—
Stable disease (SD)	54.0%	27.6%	—
Disease control rate (DCR)*	35.3%	15.8%	—

* Defined as proportion of patients with CR, PR or SD maintained for ≥4 weeks; HR = hazard ratio

Cheng A-L et al. *Lancet Oncol* 2009;10(1):25-34.

Select Adverse Events (Safety Population)

Drug-Related Adverse Event*	Sorafenib (n = 149)		Placebo (n = 75)	
	All	Grade 3/4	All	Grade 3/4
Hand-foot skin reaction	45.0%	10.7%	2.7%	0%
Diarrhea	25.5%	6.0%	5.3%	0%
Alopecia	24.8%	—	1.3%	—
Fatigue	20.1%	3.4%	8.0%	1.3%
Rash/desquamation	20.1%	0.7%	6.7%	0%
Hypertension	18.8%	2.0%	1.3%	0%

* Observed in ≥10% of patients in any study group

Cheng A-L et al. *Lancet Oncol* 2009;10(1):25-34.

Summary and Conclusions

- Sorafenib is effective for the treatment of advanced HCC in patients from the Asia Pacific region.
  - OS, TTP and DCR were significantly prolonged with sorafenib.
  - Multivariate analyses suggested that sorafenib provided benefit to all subpopulations analyzed (data not shown).
- Overall efficacy results of sorafenib were comparable with those reported in the SHARP trial.
  - Survival HR: 0.68 vs 0.69 in SHARP trial
- Sorafenib was well-tolerated with predominately Grade 1/2 adverse events reported.

Cheng A-L et al. *Lancet Oncol* 2009;10(1):25-34.

Faculty Comments

DR AJANI: Although the magnitude of benefit is less than observed in the SHARP trial, this is the second randomized study to demonstrate the benefit of sorafenib in patients with hepatocellular carcinoma. In contrast to SHARP, this study was with an Asian patient population who had much more advanced disease. I believe there is a difference in the biology of hepatocellular carcinoma, based on the antecedent liver disease. Differences exist in terms of the type of hepatitis, alcohol-related issues and obesity, which play out in the aggressiveness of the disease. This study confirms not only that sorafenib is a solid drug in hepatocellular carcinoma, but also that it works across the spectrum of the disease, whether there is a different biology or different carcinogenic drivers.