Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer

Valle J et al.

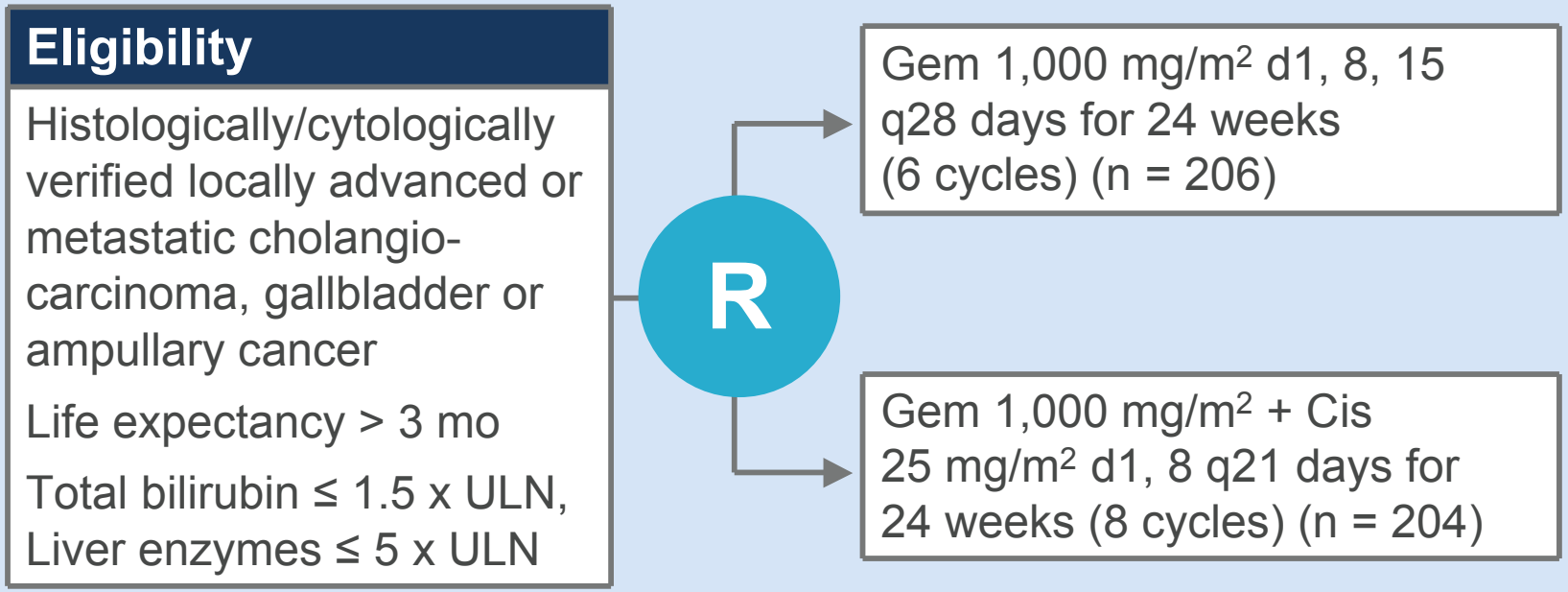
N Engl J Med 2010;362(14):1273-81.

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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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.

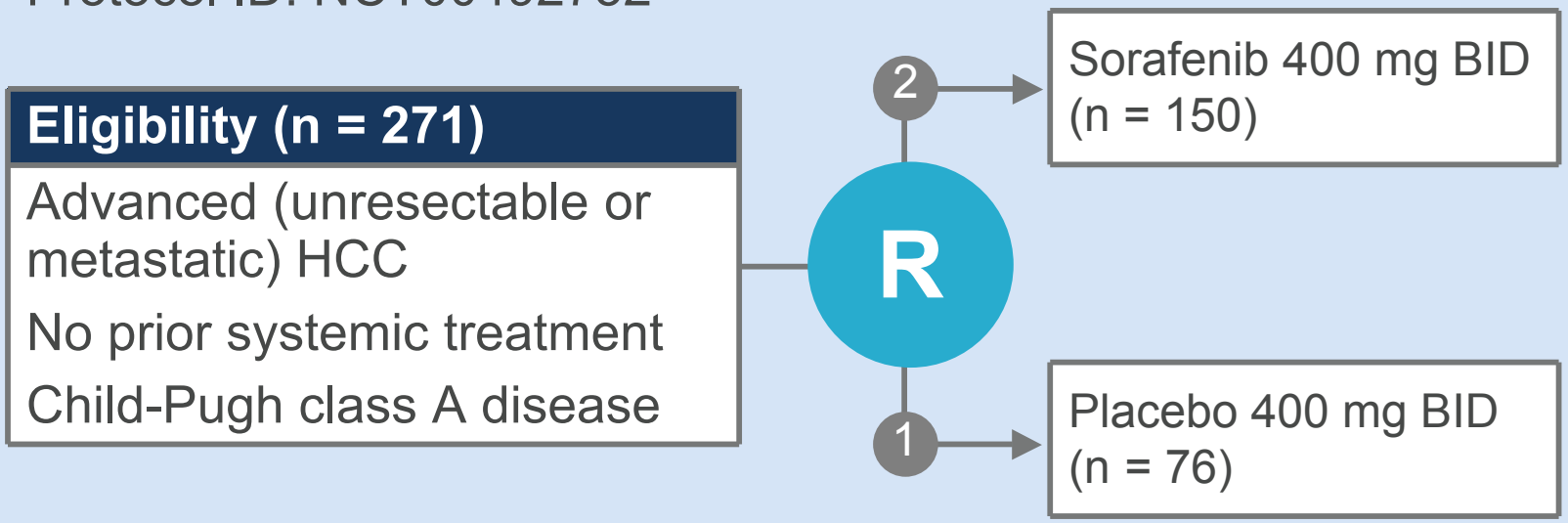
Introduction

- 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

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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.