Randomized Phase II Trial Comparing the Efficacy and Safety of Nintedanib Versus Sorafenib in Caucasian Patients With Advanced Hepatocellular Carcinoma

Abstract 238

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Learning Objectives

- To describe the potential of nintedanib for the treatment of advanced HCC
- To evaluate the efficacy of nintedanib versus sorafenib, the standard systemic therapy for advanced HCC, in this phase II trial
- To compare the safety profile of nintedanib versus sorafenib in patients with advanced HCC

HCC, hepatocellular carcinoma

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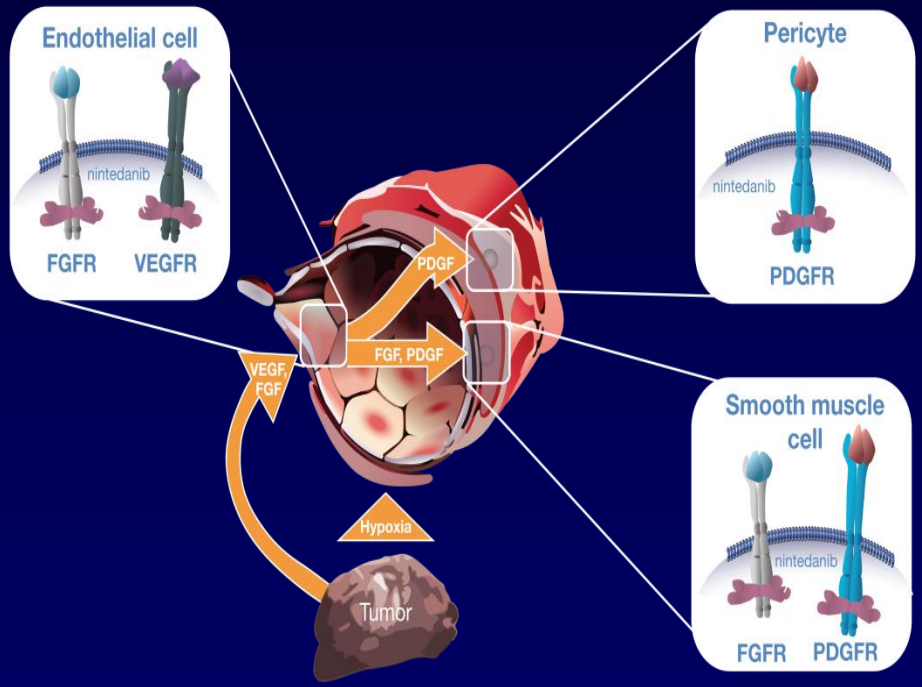
Characteristics of Nintedanib

- **Nintedanib is an oral, triple angiokinase inhibitor of VEGFR 1-3, PDGFR-α and -β, and FGFR 1-3, as well as RET, Flt3 and Src[1]**

  - **Nintedanib in combination with docetaxel has been approved in the European Union for treatment of patients with advanced NSCLC of adenocarcinoma tumor histology after first-line chemotherapy**
  - **Nintedanib has been approved by the FDA for treatment of patients with idiopathic pulmonary fibrosis**



1. Hilberg F, et al. *Cancer Res.* 2008;68(12):4774-4782.

FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; NSCLC, non-small cell lung cancer; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor

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Angiogenesis Inhibition in HCC

- HCC tumors are generally hypervascularized, suggesting that they may be vulnerable to angiogenesis inhibition
- Sorafenib – an inhibitor of VEGFR 1-3 and PDGFR-β, as well as Raf kinases – is a recommended first-line treatment for patients with advanced HCC[1]
  - However, the benefit of sorafenib in clinical trials was transient and disease progression occurred in all patients,[2,3] suggesting a continued need for new therapies
- This randomized, multicenter, open-label, phase II study (NCT01004003; 1199.37) evaluated the efficacy and safety of nintedanib versus sorafenib in predominantly Caucasian patients with advanced HCC

1. NCCN Guidelines: Hepatobiliary Cancers (2013). http://www.nccn.org. Accessed: November 13, 2014. 2. Llovet JM, et al. *N Engl J Med.* 2008;359(4):378-390. 3. Cheng AL, et al. *Eur J Cancer.* 2012;48(10):1452-1465.

OS, overall survival

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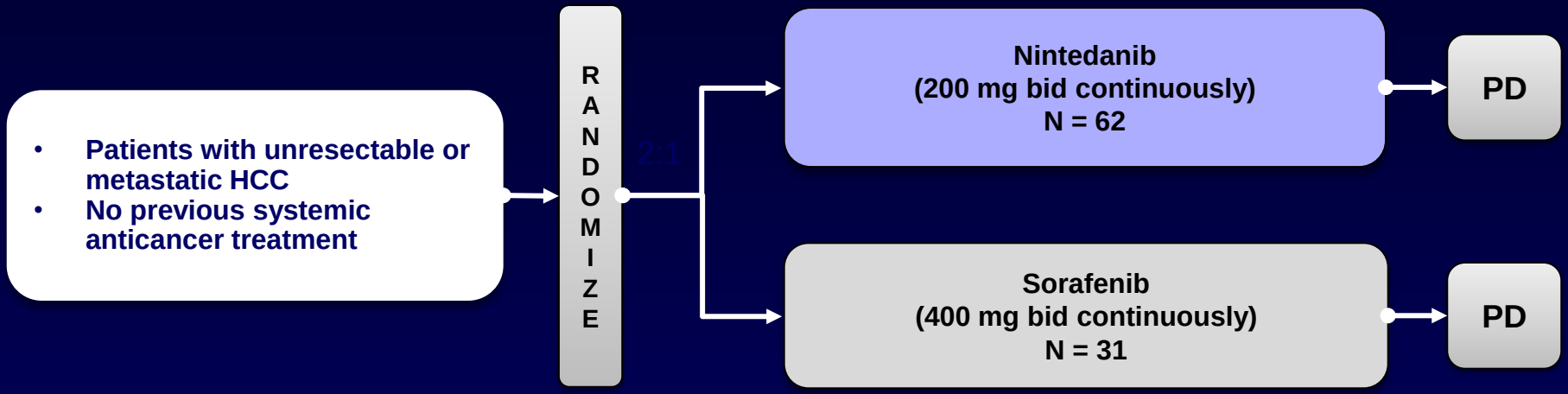
Study Design: Randomized, Open-Label, Parallel-Group Phase II Study



- Primary endpoint: TTP by central review according to RECIST 1.0
- Secondary endpoints: OS and PFS and objective response by central independent review according to RECIST
- Additional evaluations: Safety; TTP by investigator assessment (sensitivity analysis)
- Stratification factors: macrovascular invasion and/or extrahepatic spread versus no invasion or spread

bid, twice daily; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; TTP, time to progression; PD, disease progression.

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Key Eligibility Criteria

- Histologically/cytologically confirmed HCC not amenable to curative surgery or locoregional therapy
- ≥1 untreated, measurable lesion
- ECOG PS ≤2
- Child-Pugh score 5-6 (Class A)
- ALT or AST levels ≤2 × upper limit of normal
- >4 weeks since most recent local therapy
- No prior systemic therapy for HCC
- No history of other malignancy within the past 3 years and life expectancy ≥12 weeks

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECOG PS, Eastern Cooperative Oncology Group performance score;

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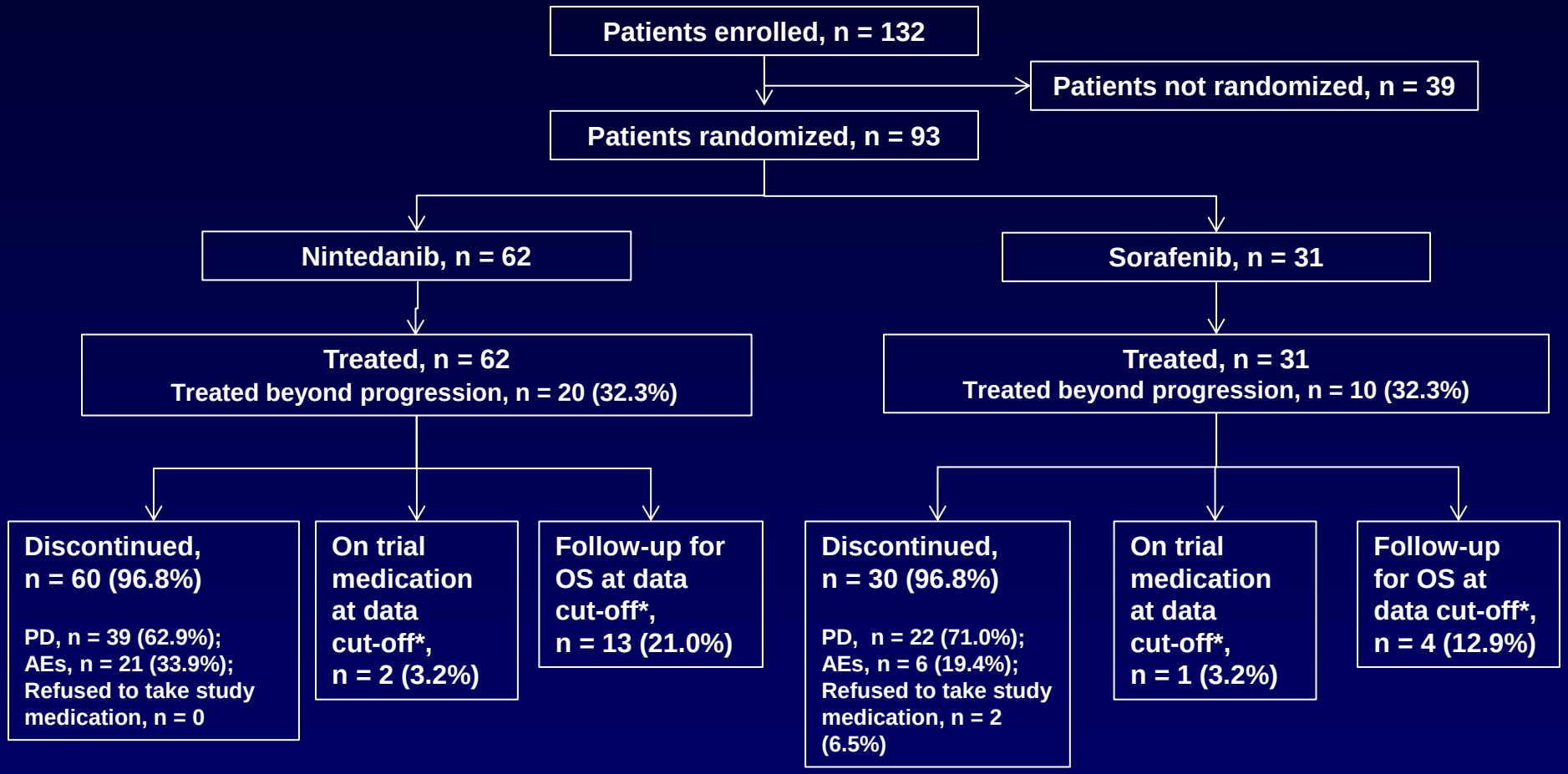
Patient Disposition



*At cutoff date: July 15, 2014. Treatment beyond RECIST progression was allowed at the investigator's discretion
AE, adverse event

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Baseline Characteristics

		Nintedanib (n = 62)	Sorafenib (n = 31)
Mean age, years (range)		65.4 (34-86)	63.1 (28-83)
Male, n (%)		48 (77.4)	26 (83.9)
Etiology of parenchymal liver disease, n (%)	Alcohol-related	10 (16.1)	3 (9.7)
	Hepatitis B	4 (6.5)	7 (22.6)
	Hepatitis C	13 (21.0)	8 (25.8)
	Unknown/Other	35 (56.5)	13 (41.9)
Child–Pugh score, n (%)	5	42 (67.7)	23 (74.2)
	6	19 (30.6)	8 (25.8)
	7*	1 (1.6)	0
Presence of EHS, n (%)		40 (64.5)	21 (67.7)
Presence of MVI, n (%)		22 (35.5)	9 (29.0)
Stratification group, n (%)	MVI, EHS, or both present	49 (79.0)	23 (74.2)
	MVI and EHS absent	13 (21.0)	8 (25.8)

*One patient in the nintedanib arm with a Child–Pugh score of 7 was a protocol deviation

EHS, extrahepatic spread; MVI, macrovascular invasion

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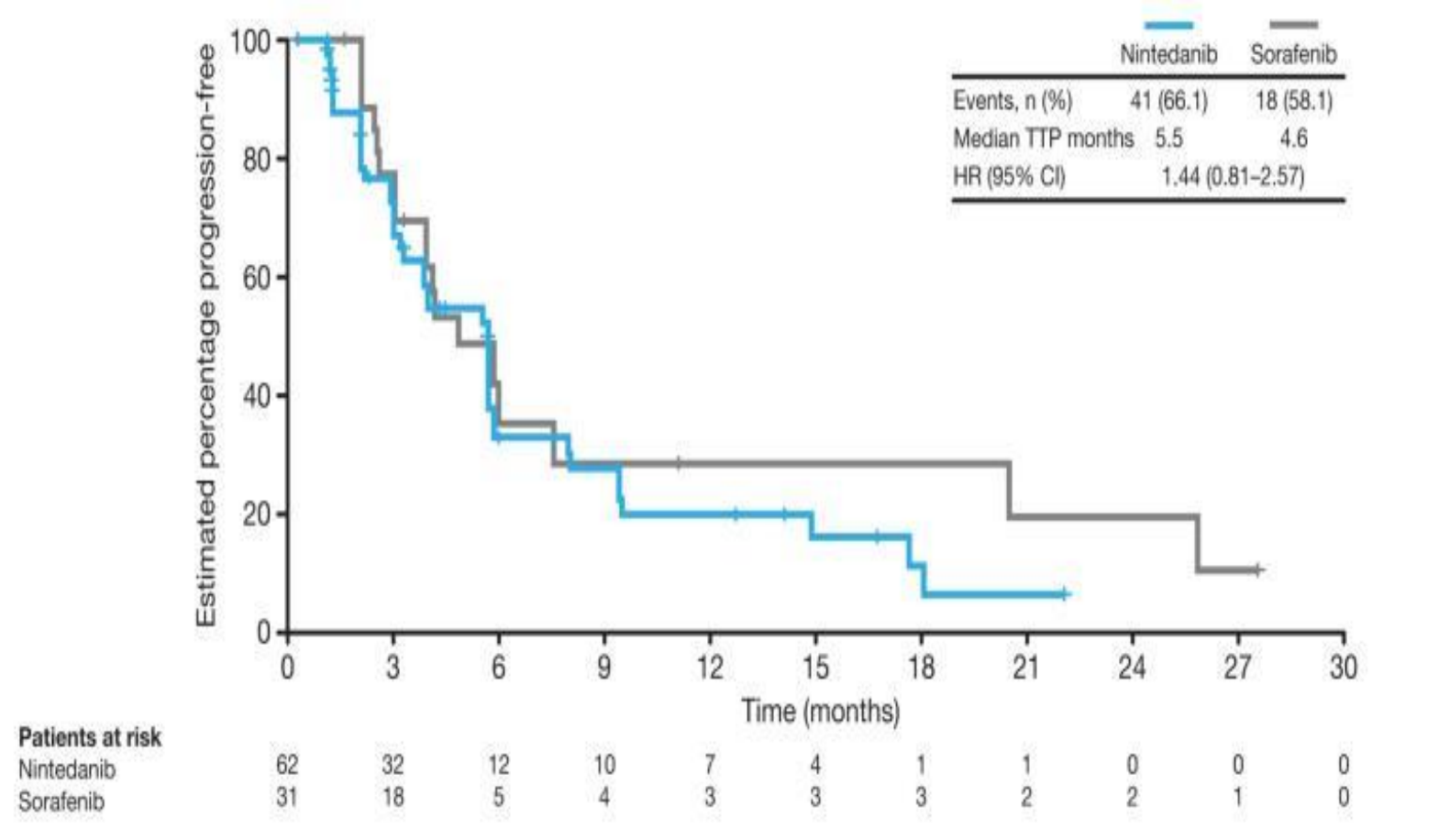
Primary Endpoint: Time-to-Progression (TTP) (Central Review)



According to RECIST 1.0

CI, confidence interval; HR, hazard ratio

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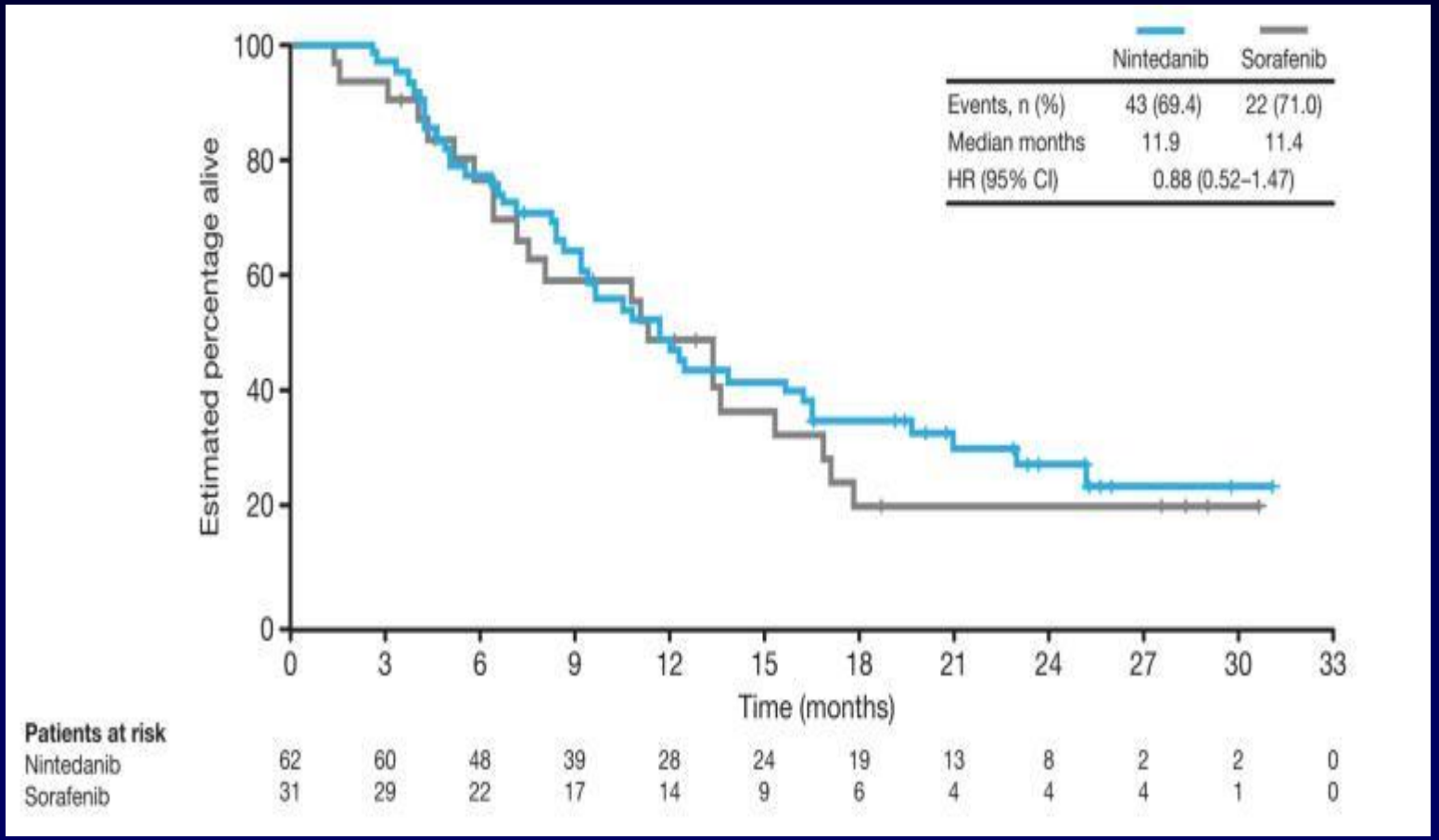
Overall Survival



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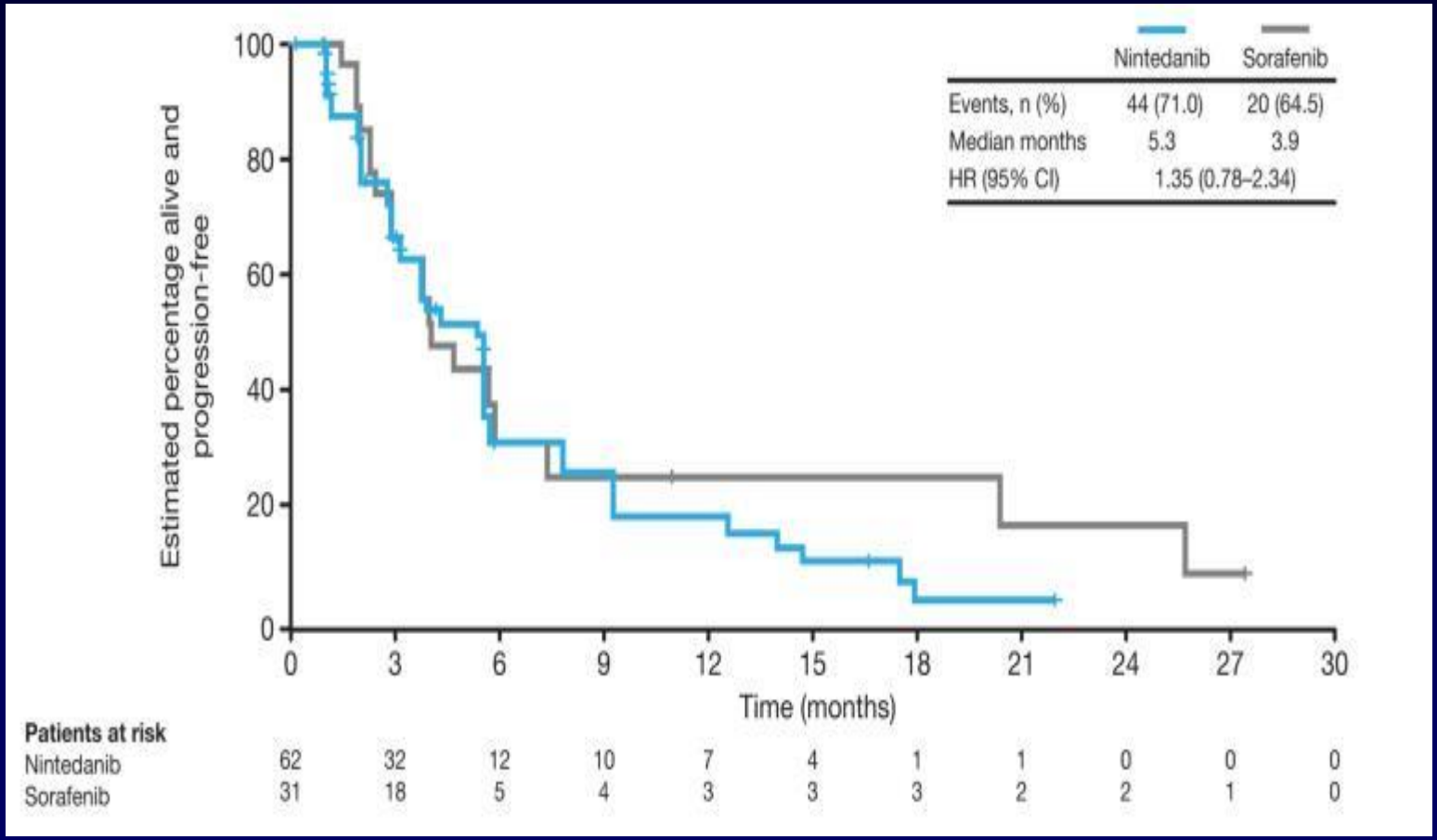
Progression-Free Survival (Central Review)



According to RECIST 1.0

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Best Overall Tumor Response (Central Review)

RECIST response, n (%)	Nintedanib (n = 62)	Sorafenib (n = 31)
Disease control	51 (82.3)	28 (90.3)
Objective response	1 (1.6)	2 (6.5)
Complete response	0	0
Partial response	1 (1.6)	2 (6.5)
Stable disease	50 (80.6)	26 (83.9)
Disease progression	8 (12.9)	1 (3.2)
Not evaluable/unknown	3 (4.8)	2 (6.5)

Tumor response by independent central review according to RECIST version 1.0

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Overall Summary of AEs

Patients with AEs, n (%)		Nintedanib (n = 62)	Sorafenib (n = 31)
Any AE*		62 (100)	31 (100)
Drug-related AE		54 (87.1)	30 (96.8)
AE leading to dose reduction		12 (19.4)	13 (41.9)
AE leading to drug discontinuation		28 (45.2)	7 (22.6)
Any serious AE		34 (54.8)	14 (45.2)
Worst CTCAE grade	Grade 1	8 (12.9)	1 (3.2)
	Grade 2	12 (19.4)	2 (6.5)
	Grade 3	26 (41.9)	24 (77.4)
	Grade 4	7 (11.3)	1 (3.2)
	Grade 5**	9 (14.5)	3 (9.7)

*Median duration of nintedanib or sorafenib treatment was similar (164.5 vs 165.0 days); **All deaths were related to disease progression except for one in the nintedanib arm, which was due to interstitial lung diseaset; CTCAE, Common Terminology Criteria for Adverse Events

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Most Frequent AEs (≥20% in Either Study Arm)

Patients with AEs, n (%)	Nintedanib (n = 62)	Sorafenib (n = 31)
Diarrhea	44 (71.0)	21 (67.7)
Fatigue*	38 (61.3)	17 (54.8)
Nausea	30 (48.4)	9 (29.0)
Vomiting	24 (38.7)	9 (29.0)
Decreased appetite	23 (37.1)	13 (41.9)
Abdominal pain	16 (25.8)	9 (29.0)
Upper abdominal pain	16 (25.8)	4 (12.9)
Rash	6 (9.7)	7 (22.6)
Alopecia	3 (4.8)	11 (35.5)
Palmar–plantar erythrodysesthesia syndrome	1 (1.6)	11 (35.5)

By preferred term

*Group term includes fatigue, lethargy, asthenia and malaise

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AEs of Grade ≥3 (≥5% in Either Study Arm)

Patients with AEs, n (%)	Nintedanib (n = 62)	Sorafenib (n = 1)
Diarrhea	8 (12.9)	1 (3.2)
Fatigue*	7 (11.3)	2 (6.5)
Increased AST	7 (11.3)	1 (3.2)
Increased ALT	5 (8.1)	2 (6.5)
Hepatic encephalopathy	5 (8.1)	1 (3.2)
Anemia	4 (6.5)	1 (3.2)
Malignant neoplasm progression	2 (3.2)	3 (9.7)
Thrombocytopenia	1 (1.6)	3 (9.7)
Skin reaction	1 (1.6)	2 (6.5)
Palmar–plantar erythrodysesthesia syndrome	0	7 (22.6)

By preferred term

*Group term includes fatigue, lethargy, asthenia and malaise; ALT, alanine aminotransferase; AST, aspartate aminotransferase

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AEs Frequently Associated With VEGF/VEGFR Inhibitors

Patients with AEs, n (%)	Nintedanib (n = 62)		Sorafenib (n = 31)	
	All grades	Grade ≥3	All grades	Grade ≥3
Bleeding	18 (29.0)	5 (8.1)	7 (22.6)	0
Specific liver-related investigations (tailored)*	15 (24.2)	11 (17.7)	8 (25.8)	4 (12.9)
Rash	13 (21.0)	2 (3.2)	12 (38.7)	4 (12.9)
Hypertension	9 (14.5)	2 (3.2)	3 (9.7)	1 (3.2)
Cutaneous serious skin reactions	3 (4.8)	0	6 (19.4)	2 (6.5)
Thromboembolic events**	1 (1.6)	1 (1.6)	4 (12.9)	2 (6.5)
GI perforations	0	0	1 (3.2)	1 (3.2)

By group term

*Reported events included increased aspartate aminotransferase, increased blood bilirubin, increased alanine aminotransferase, jaundice, hyperbilirubinaemia, increased hepatic enzyme and increased transaminases; **No arterial thromboembolism events were reported

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Conclusions

- Nintedanib showed similar efficacy to sorafenib with respect to TTP by central review, OS, PFS, and OR by central review
- A manageable safety profile was observed with nintedanib
  - Diarrhea, fatigue, nausea, vomiting, and upper abdominal pain were reported more frequently with nintedanib than with sorafenib
  - Decreased appetite, abdominal pain, rash, alopecia, and palmar–plantar erythrodysesthesia syndrome were more frequent with sorafenib than with nintedanib
- Further studies of nintedanib in patients with advanced HCC are warranted

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