Abstract 2862

Phase III Study of Crizotinib vs Pemetrexed or Docetaxel Chemotherapy in Patients with Advanced *ALK*-Positive NSCLC (PROFILE 1007)

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on behalf of all PROFILE 1007 investigators

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Disclosures

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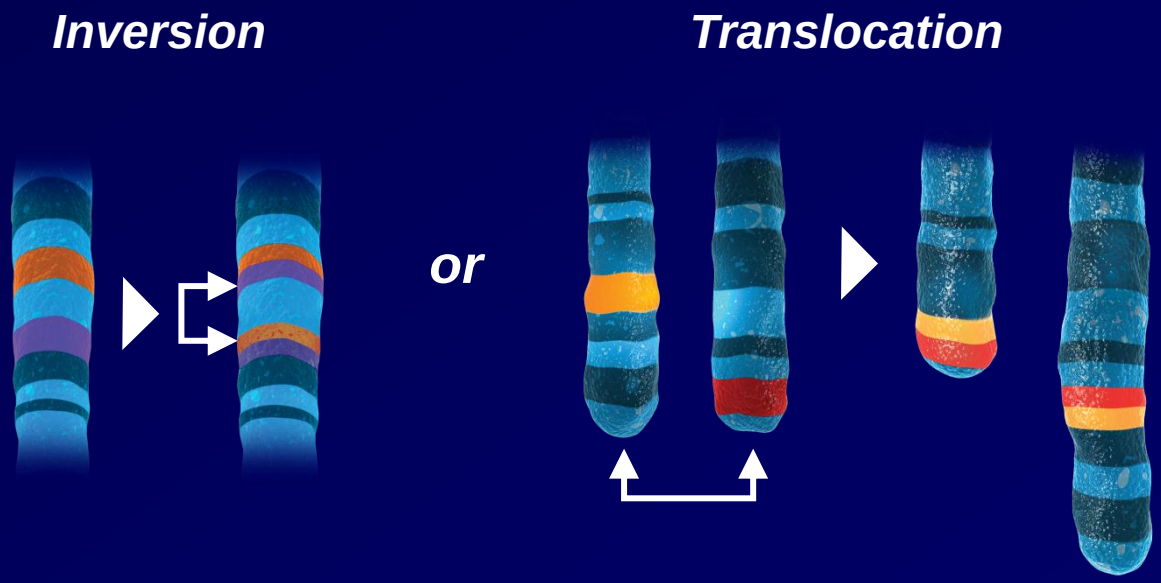
- Research funding from AstraZeneca and Novartis

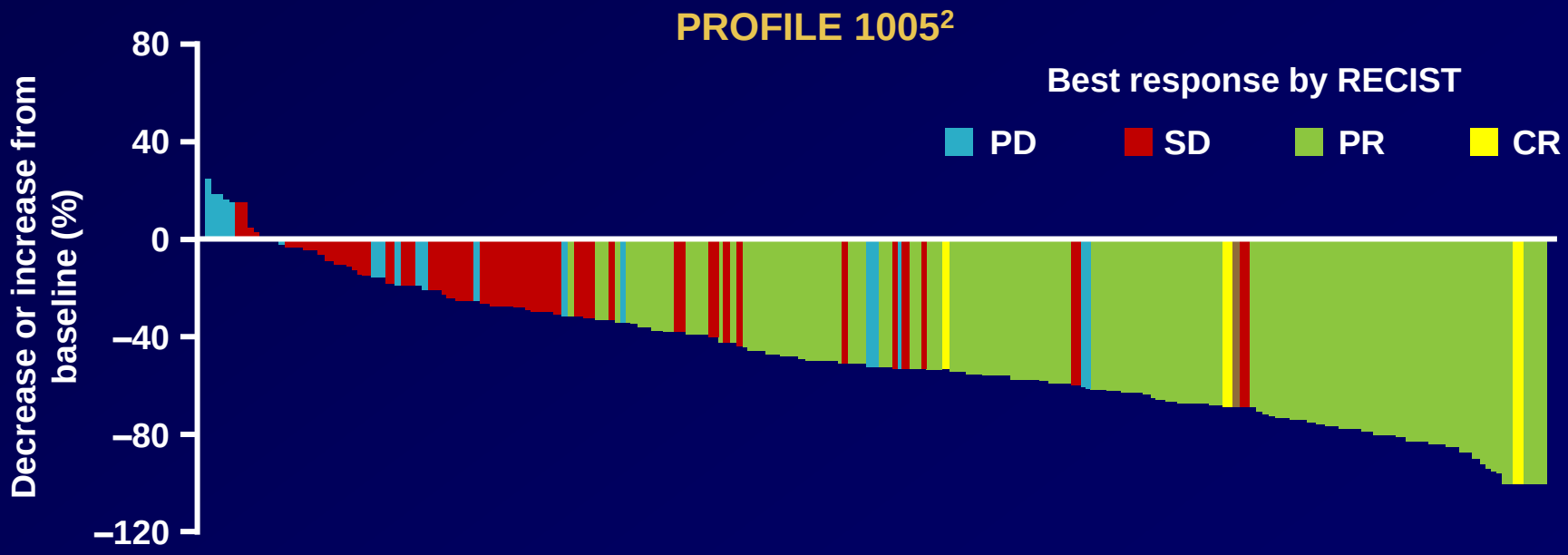
ALK Rearrangements in NSCLC

- ALK (anaplastic lymphoma kinase) is a tyrosine kinase target in several different cancers, including NSCLC
- In NSCLC, *ALK* is activated by chromosomal rearrangement, leading to constitutive kinase activation and oncogene addiction



Crizotinib: First-in-Class ALK Inhibitor

- Crizotinib is an orally available, small-molecule tyrosine kinase inhibitor (TKI) targeting ALK, ROS1, and MET
- Crizotinib has marked clinical activity in advanced *ALK*+ NSCLC (ORR ~60%, median PFS 8–10 months)[1,2]



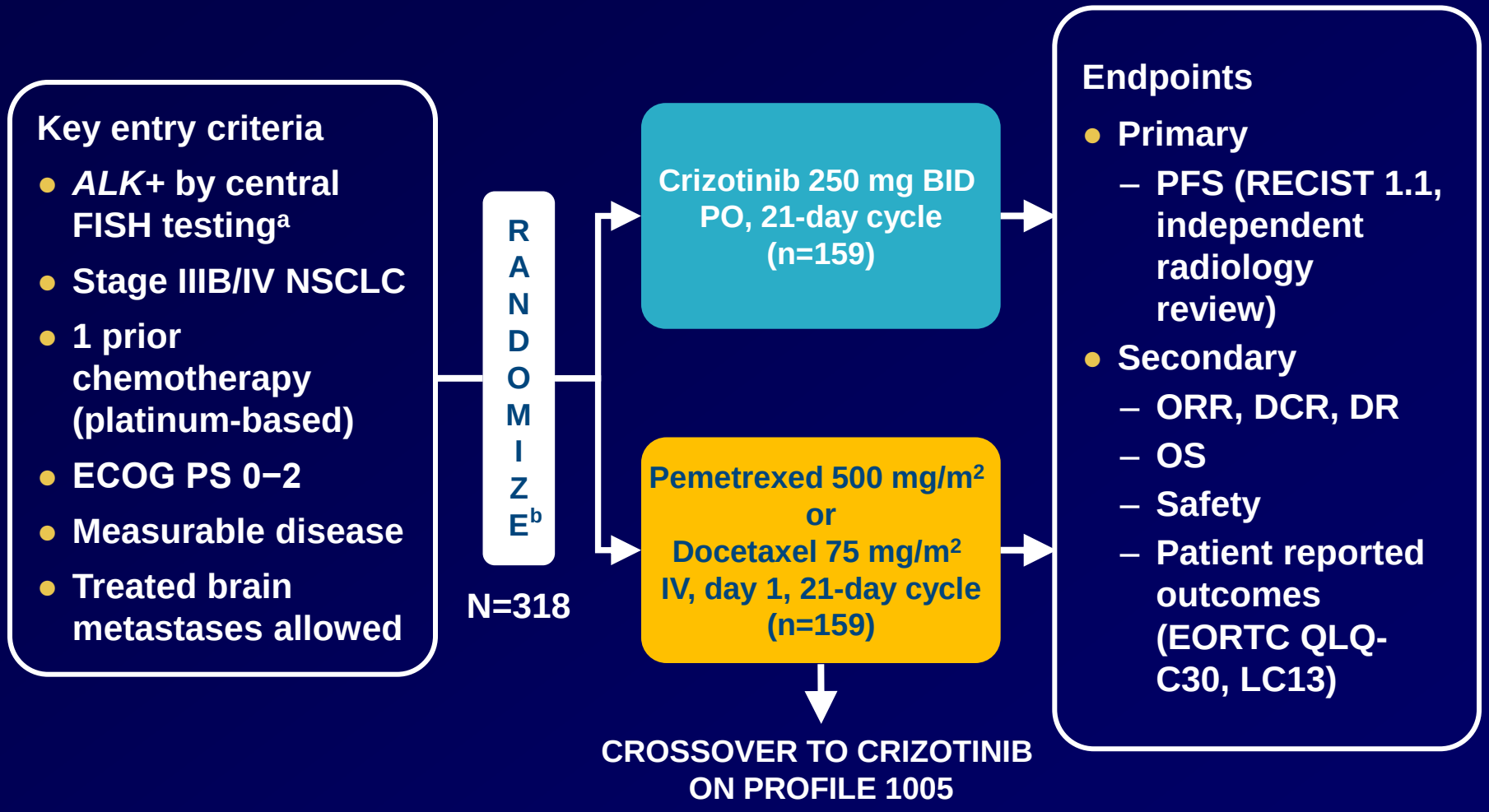
[1]Camidge DR, Bang Y-J, Kwak EW, et al. *Lancet Oncol* 2012; Epub ahead of print
[2]Kim D-W, Ahn M-J, Shi Y, et al. Poster presented at ASCO 2012 (Abstract 7533)

Study Rationale

- In *ALK*+ NSCLC, crizotinib is associated with significant clinical responses; however, the activity of standard chemotherapy is uncertain
- In unselected NSCLC, single-agent chemotherapy in the second-line setting has limited efficacy[1,2]
- We hypothesized that in a prospective randomized trial, crizotinib would have superior efficacy compared with standard second-line chemotherapy in advanced *ALK*+ NSCLC

[1]Shepherd FA, Dancey J, Ramlau R, et al, *J Clin Oncol* 2000;18:2095−2103
[2]Hanna N, Shepherd FA, Fossella FV, et al, *J Clin Oncol* 2004;22:1589−1597

Study Design



[a]*ALK* status determined using standard *ALK* break-apart FISH assay
[b]Stratification factors: ECOG PS (0/1 vs 2), brain metastases (present/absent), and prior EGFR TKI (yes/no)

PROFILE 1007: NCT00932893

Statistical Design

- Primary endpoint: PFS per independent radiology review
  - Sample size: 217 events (PD or death) needed to detect HR of 0.64 (or increase in median PFS from 4.5 to 7 months) at one-sided 2.5% significance level with 90% power
- Secondary endpoint: OS
  - Pre-specified interim OS analysis at time of final PFS analysis
  - 80% power to detect 44% increase in OS when 241 deaths occur

Participating Countries

105 sites in 21 countries

Study Conduct

- Accrual period: February 5, 2010 − February 23, 2012
- 347 patients randomized: 173 to crizotinib, 174 to chemotherapy[a]
  - pemetrexed: 99/174 (57%)
  - docetaxel: 72/174 (41%)
- Data cut-off: March 30, 2012
- Study treatment duration, median cycles started (range)
  - crizotinib: 11 (1−37)
  - chemotherapy: 4 (1−30)
- Duration of follow-up, median (95% CI)
  - crizotinib: 12.2 months (11.0−13.4)
  - chemotherapy: 12.1 months (10.6−13.6)
- Treatment could be continued beyond PD if ongoing clinical benefit

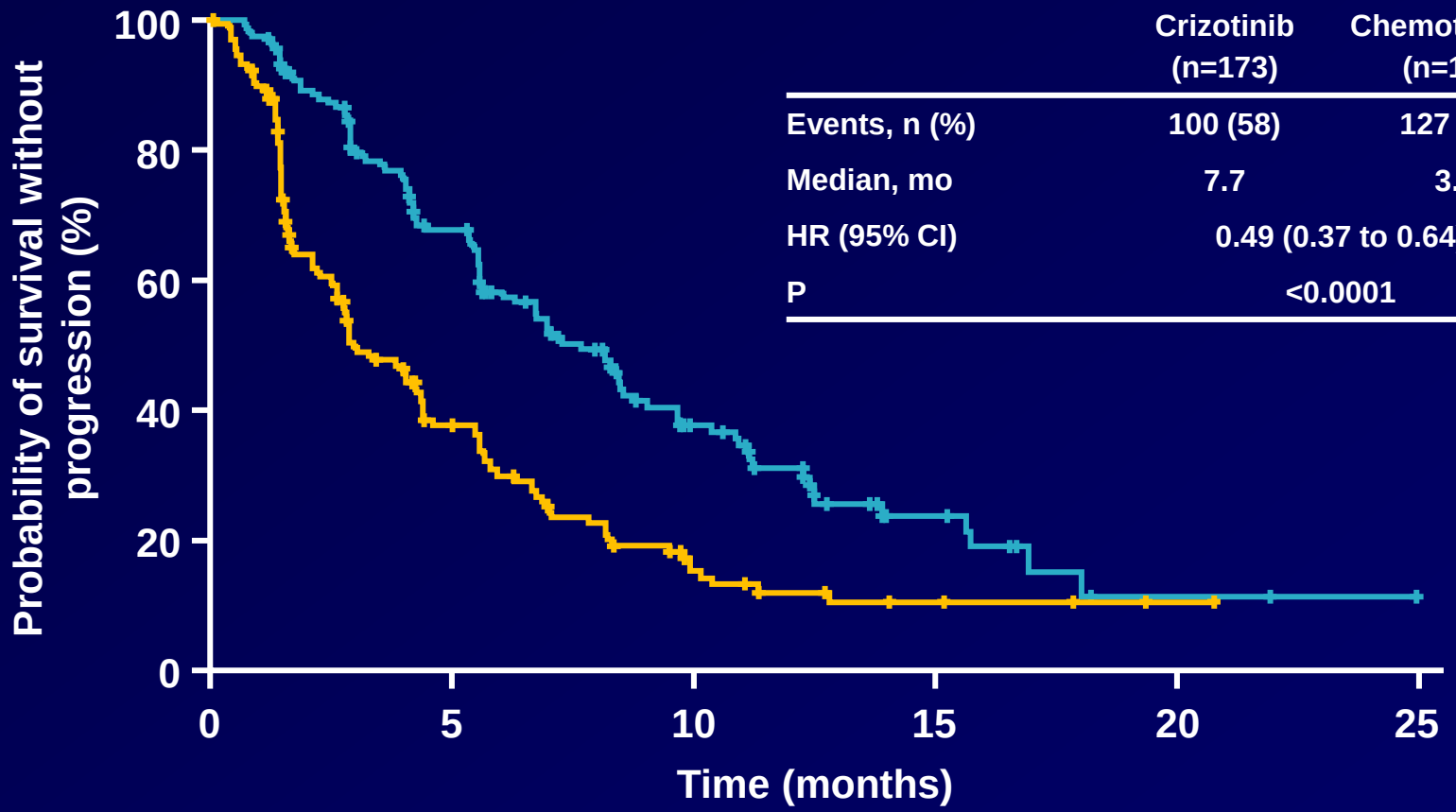
[a]3 patients randomized did not receive chemotherapy

Baseline Characteristics

		Crizotinib (n=173)	Chemotherapy (n=174)
Age, years	Median (range)	51 (22–81)	49 (24–85)
Sex, n (%)	Male	75 (43)	78 (45)
	Female	98 (57)	96 (55)
Race, n (%)	Caucasian	90 (52)	91 (52)
	Asian	79 (46)	78 (45)
	Other	4 (2)	5 (3)
Smoking,[a] n (%)	Never smoker	108 (62)	111 (64)
	Ex-smoker	59 (34)	54 (31)
	Current smoker	5 (3)	9 (5)
Histology,[b] n (%)	Adenocarcinoma	164 (95)	164 (94)
	Non-adenocarcinoma	5 (3)	7 (4)
ECOG PS,[a] n (%)	0	72 (42)	65 (37)
	1	84 (49)	95 (55)
	2	16 (9)	14 (8)
Brain metastases, n (%)	Present	60 (35)	60 (35)
	Absent	113 (65)	114 (66)

[a]Data missing for crizotinib (n=1); [b]data missing for 7 patients (crizotinib, n=4; chemotherapy, n=3)

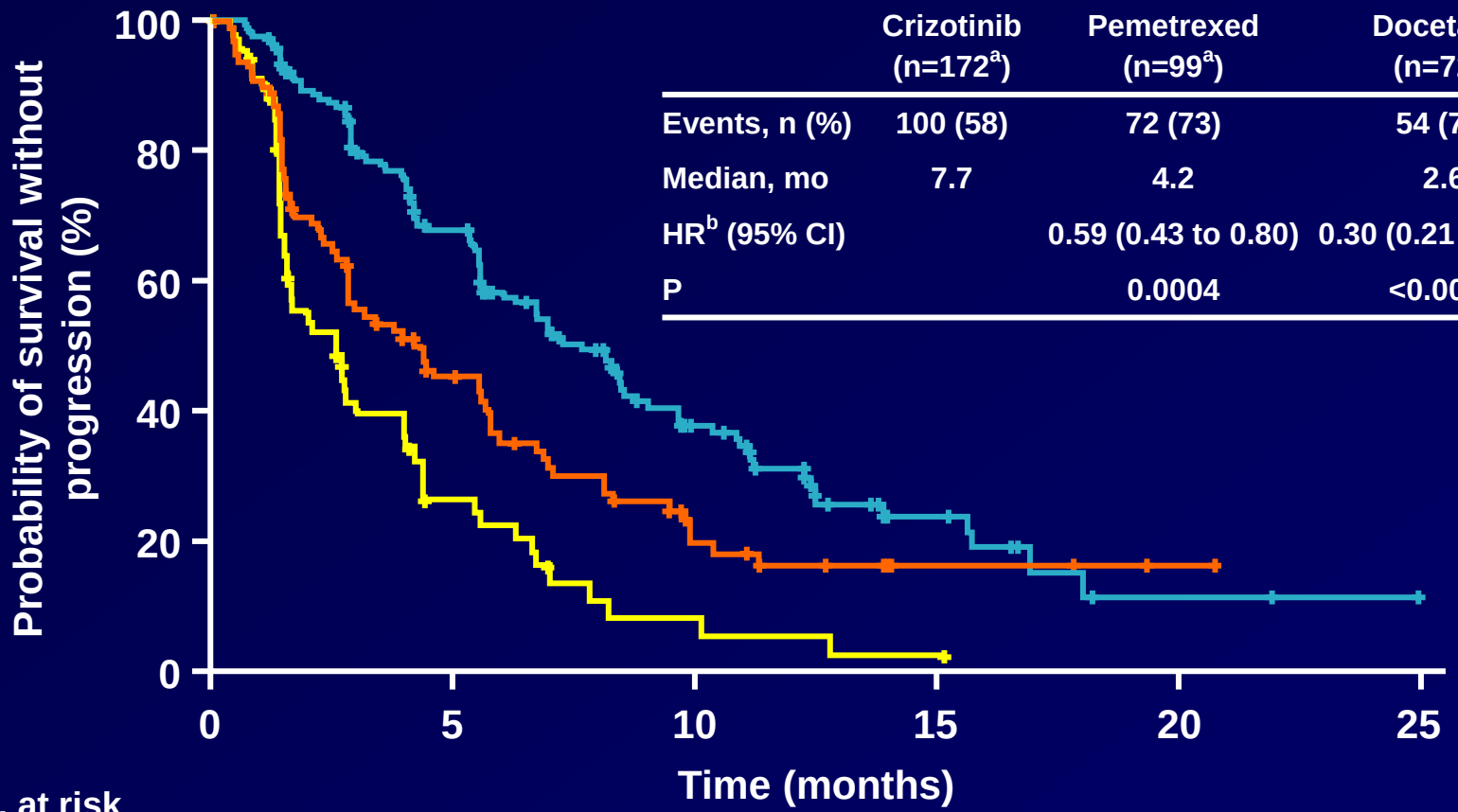
Primary Endpoint: PFS by Independent Radiologic Review (ITT Population)



	Crizotinib (n=173)	Chemotherapy (n=174)
Events, n (%)	100 (58)	127 (73)
Median, mo	7.7	3.0
HR (95% CI)	0.49 (0.37 to 0.64)	
P	<0.0001	

No. at risk						
Crizotinib	173	93	38	11	2	0
Chemotherapy	174	49	15	4	1	0

PFS of Crizotinib vs Pemetrexed or Docetaxel



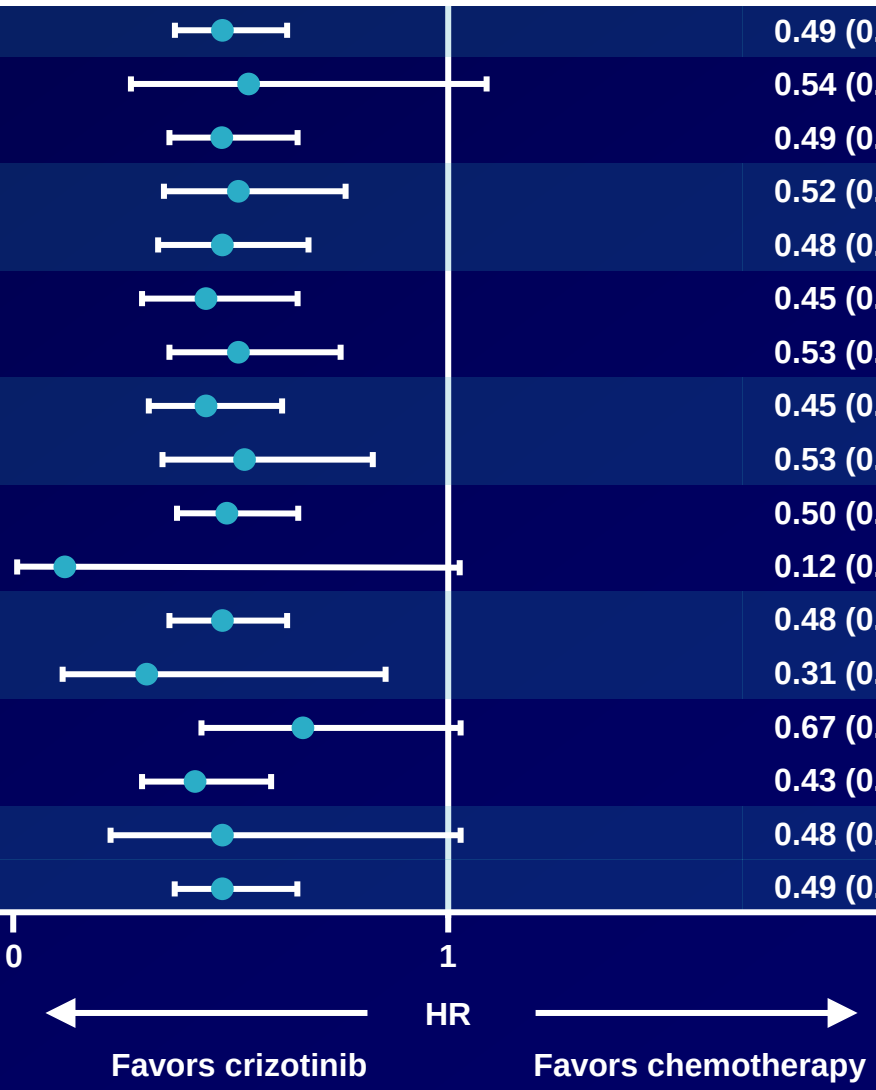
	Crizotinib (n=172[a])	Pemetrexed (n=99[a])	Docetaxel (n=72[a])
Events, n (%)	100 (58)	72 (73)	54 (75)
Median, mo	7.7	4.2	2.6
HR[b] (95% CI)		0.59 (0.43 to 0.80)	0.30 (0.21 to 0.43)
P		0.0004	<0.0001

No. at risk						
Crizotinib	172	93	38	11	2	0
Pemetrexed	99	36	12	3	1	0
Docetaxel	72	13	3	1	0	

[a]As-treated population: excludes 1 patient in crizotinib arm who did not receive study treatment and 3 patients in chemotherapy arm who did not receive study treatment; [b]vs crizotinib

PFS Subgroup Analysis

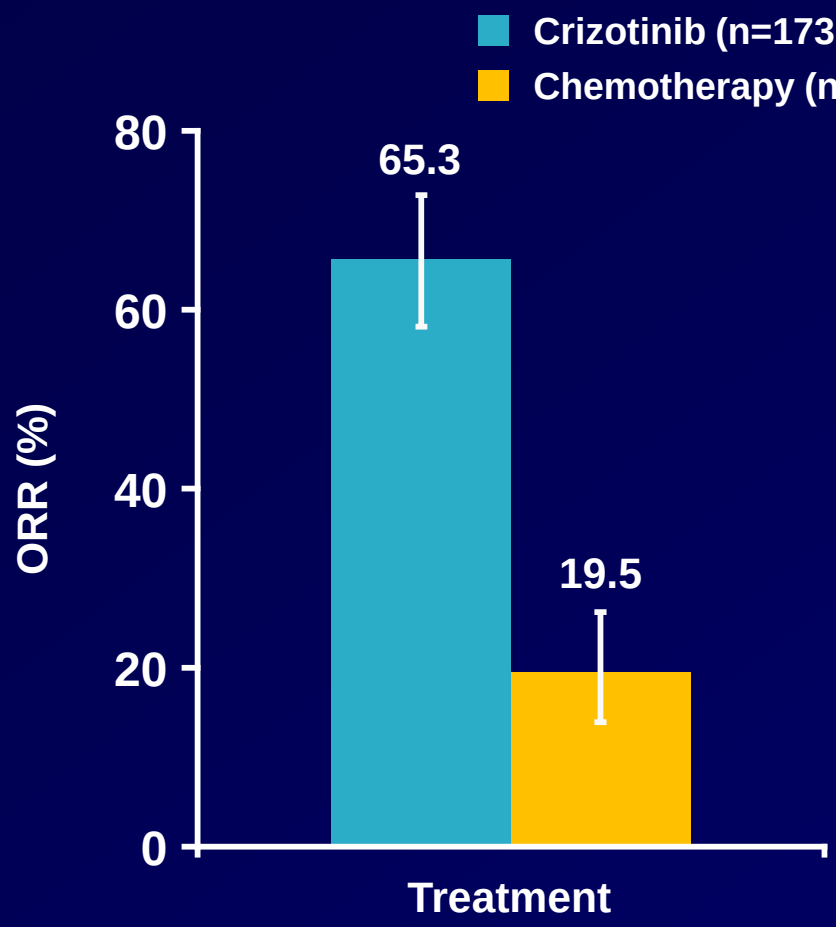
Subgroup	n[a]	HR (95% CI)
All patients	347	0.49 (0.37–0.64)
Age ≥65 years	50	0.54 (0.27–1.08)
Age <65 years	297	0.49 (0.37–0.65)
Male	153	0.52 (0.34–0.77)
Female	194	0.48 (0.34–0.68)
Non-Asian	190	0.45 (0.30–0.66)
Asian	157	0.53 (0.36–0.76)
Non-smoker	219	0.45 (0.32–0.63)
Smoker or ex-smoker	127	0.53 (0.34–0.83)
Adenocarcinoma	328	0.50 (0.38–0.66)
Non-adenocarcinoma	12	0.12 (0.01–1.02)
ECOG PS 0/1	313	0.48 (0.36–0.63)
ECOG PS 2	34	0.31 (0.12–0.86)
Brain metastases present	120	0.67 (0.44–1.03)
Brain metastases absent	227	0.43 (0.30–0.60)
Prior EGFR TKI	41	0.48 (0.22–1.03)
No prior EGFR TKI	306	0.49 (0.37–0.66)

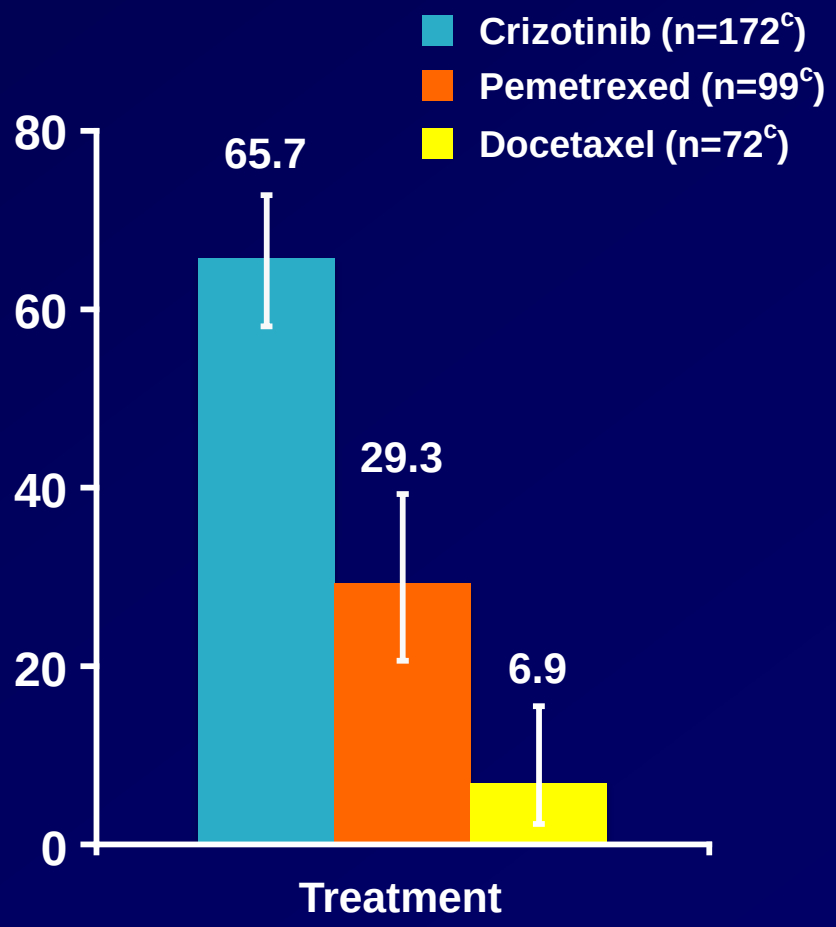


[a]Data missing for smoking status (n=1) and tumor histology (n=7)

ORR[a] by Independent Radiologic Review

ORR ratio: 3.4 (95% CI: 2.5 to 4.7); P<0.0001

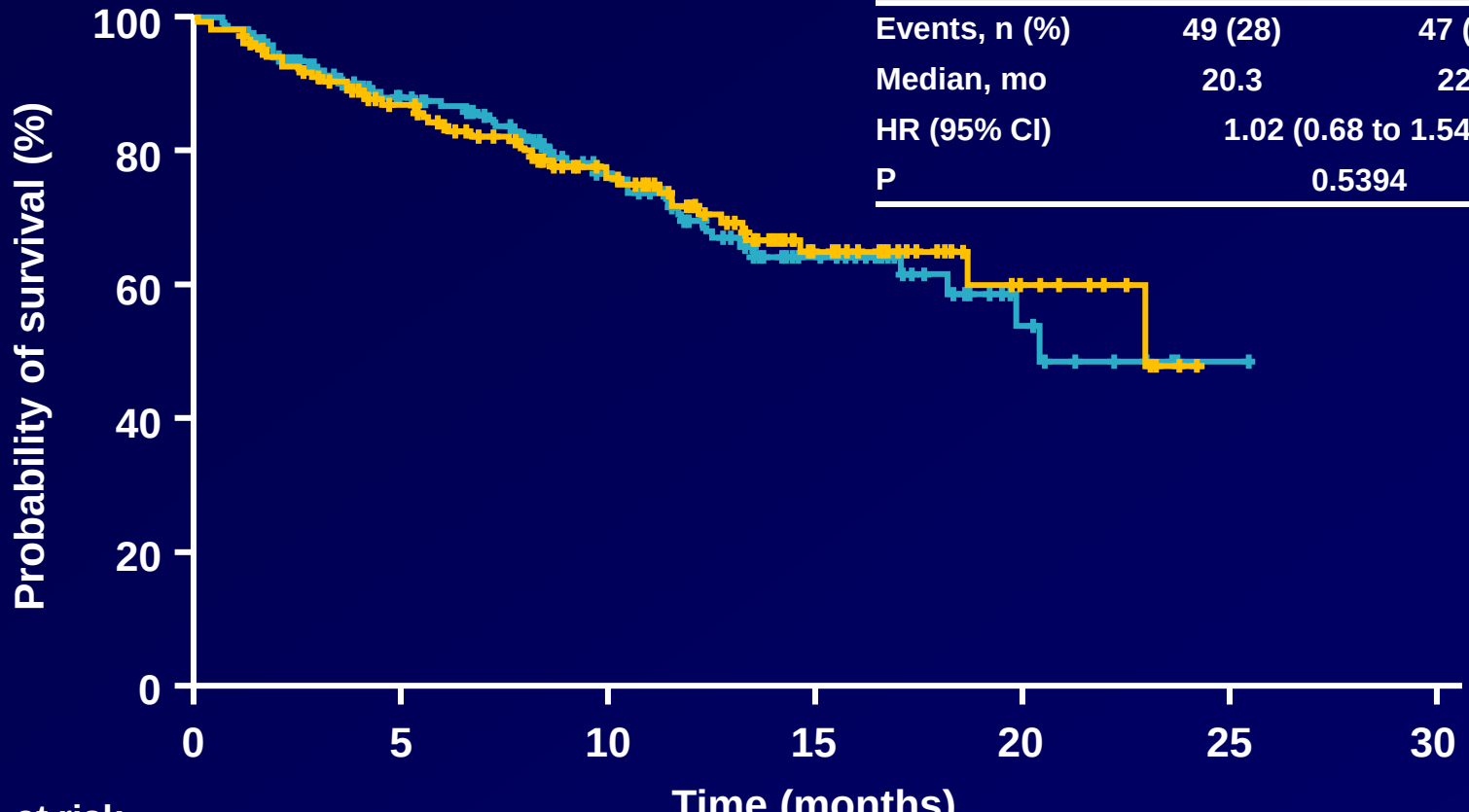




[a]RECIST v1.1; [b]ITT population; [c]as-treated population

Interim Analysis of OS

	Crizotinib (n=173)	Chemotherapy[a] (n=174)
Events, n (%)	49 (28)	47 (27)
Median, mo	20.3	22.8
HR (95% CI)	1.02 (0.68 to 1.54)[b]	
P	0.5394	



No. at risk							
Crizotinib	173	129	83	37	11	1	0
Chemotherapy	174	129	84	34	10	0	

[a]111 patients crossed over to crizotinib outside PROFILE 1007
[b]HR adjusted for crossover using rank-preserving structural failure time method: 0.83 (0.36 to 1.35)

Common AEs of Any Cause in ≥15% of Patients
≥5% difference between groups[a]

	Crizotinib (n=172), n (%)		Chemotherapy (n=171), n (%)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Vision disorder[b]	103 (60)	0 (0)	16 (9)	0 (0)
Diarrhea	103 (60)	0 (0)	33 (19)	1 (1)
Nausea[c]	94 (55)	2 (1)	64 (37)	1 (1)
Vomiting[c]	80 (47)	2 (1)	30 (18)	0 (0)
Constipation	73 (42)	4 (2)	39 (23)	0 (0)
Elevated transaminases[b]	66 (38)	27 (16)	25 (15)	4 (2)
Edema[b]	54 (31)	0 (0)	27 (16)	0 (0)
Upper respiratory infection[b]	44 (26)	0 (0)	22 (13)	1 (1)
Dysgeusia	44 (26)	0 (0)	16 (9)	0 (0)
Dizziness[b]	37 (22)	1 (1)	14 (8)	0 (0)
Fatigue	46 (27)	4 (2)	57 (33)	7 (4)
Alopecia	14 (8)	0 (0)	35 (21)	0 (0)
Dyspnea[b,d]	23 (13)	7 (4)	32 (19)	1 (1)
Rash	15 (9)	0 (0)	29 (17)	0 (0)

[a]Not adjusted for differential treatment duration; [b]clustered term; [c]antiemetic use significantly higher in chemo arm vs crizotinib arm (67% vs 20%); patients in chemo arm also received more dexamethasone (94% vs 25%); [d]grade 5 dyspnea (n=1; <1%) reported in each treatment arm

Grade 3/4 AEs of Any Cause in ≥3% of Patients

	n (%)	
	Crizotinib (n=172)	Chemotherapy (n=171)
Elevated transaminases[a]	27 (16)	4 (2)
Pulmonary embolism[a]	9 (5)	3 (2)
Dyspnea[a]	7 (4)	5 (3)
Pneumonia	6 (4)	3 (2)
Hypokalemia	6 (4)	0 (0)
ECG QTc prolonged	6 (4)	0 (0)[b]
Neutropenia[a]	23 (13)	33 (19)
Febrile neutropenia	1 (1)	16 (9)
Anemia[a]	4 (2)	9 (5)
WBC decreased	2 (1)	8 (5)
Fatigue	4 (2)	7 (4)

[a]Clustered term; [b]no on-treatment assessments

Grade 5 AEs of Any Cause and Permanent Discontinuations Due to AEs

	n (%)	
	Crizotinib (n=172)	Chemotherapy (n=171)
Total deaths	25 (15)[a]	7 (4)
Cause		
Disease progression	14 (8)	3 (2)
Study-treatment-related	3 (2)	1 (1)
Arrhythmia	1 (1)	0 (0)
ILD or pneumonitis	2 (1)	0 (0)
Sepsis	0 (0)	1 (1)
Other[b]	8 (5)	3 (2)
Unknown cause	1 (1)	0 (0)
Permanent discontinuations	30 (17)	23 (13)
Study-treatment-related	11 (6)	17 (10)

ARDS, acute respiratory distress syndrome; ILD, interstitial lung disease

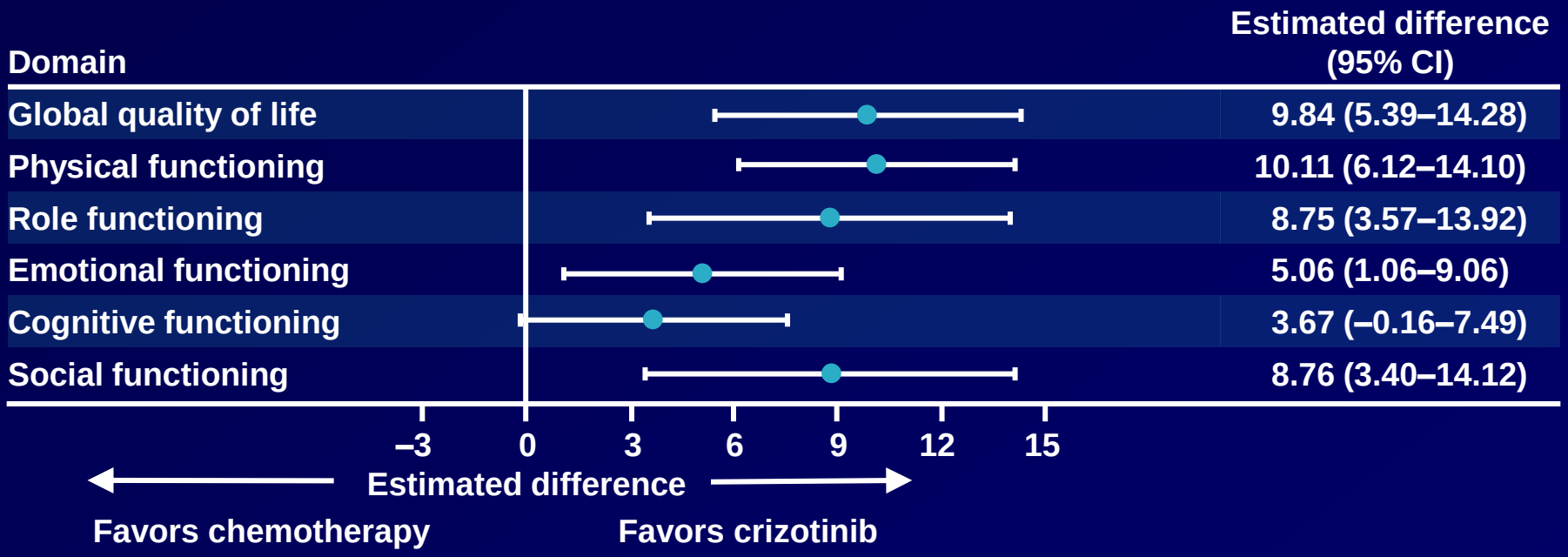
[a]One death attributed to two causes (ARDS and sepsis)

[b]Crizotinib: ARDS, cognitive disorder, dyspnea, pneumonia, pulmonary embolism, respiratory failure, sepsis, and sudden death; chemotherapy: dyspnea, pericardial effusion, and tumor hemorrhage

Patient Reported Outcomes

Symptoms and Quality of Life[a]

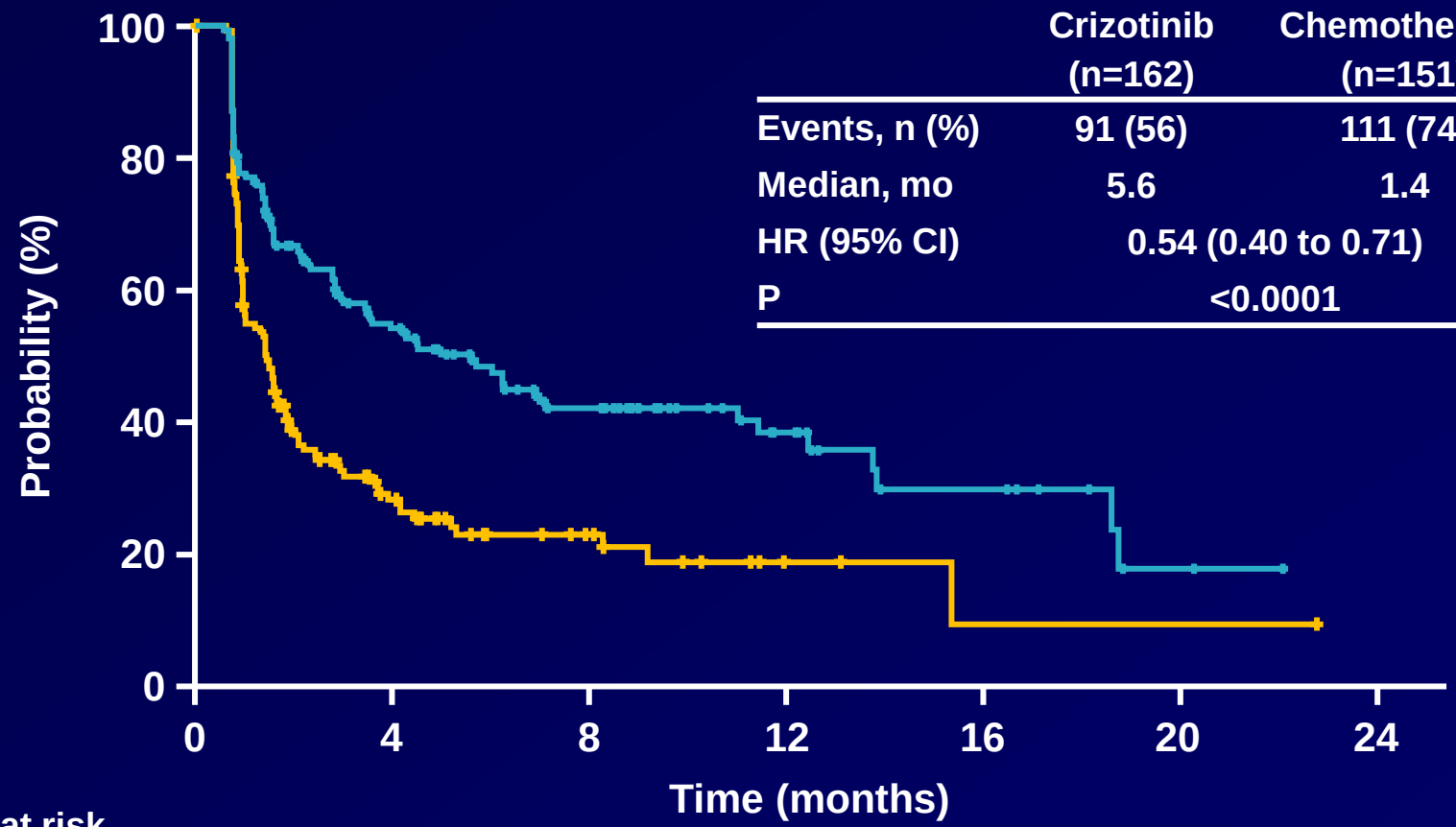
- **SYMPTOMS:** Greater improvement from baseline in cough, dyspnea, fatigue, alopecia, insomnia, and pain with crizotinib (statistically significant: all P<0.0001)[b]
- **QUALITY OF LIFE:** Greater improvement from baseline in global quality of life in patients treated with crizotinib (statistically significant: P<0.0001)[b]



[a]EORTC QLQ-C30 and QLQ-LC13; [b]based on a repeated measures mixed-effects model with an intercept, treatment, treatment by time interaction, and subscale baseline score; not adjusted for multiplicity of testing

Patient Reported Outcomes

Time to Deterioration in Lung Cancer Symptoms[a]



	Crizotinib (n=162)	Chemotherapy (n=151)
Events, n (%)	91 (56)	111 (74)
Median, mo	5.6	1.4
HR (95% CI)	0.54 (0.40 to 0.71)	
P	<0.0001	

No. at risk							
Crizotinib	162	71	40	17	9	2	0
Chemotherapy	151	30	13	3	1	1	0

[a]Composite of chest pain, cough, and dyspnea

Summary and Conclusion (1)

- **PROFILE 1007 is the first randomized phase III trial in advanced *ALK*+ NSCLC comparing crizotinib with standard chemotherapy**
- **Crizotinib significantly prolongs PFS and improves ORR compared with single-agent chemotherapy in advanced previously treated *ALK*+ NSCLC**
- **No statistically significant difference in OS was observed between crizotinib and chemotherapy, but interim analysis was immature and may have been confounded by crossover**

Summary and Conclusion (2)

- Crizotinib has a distinct side effect profile when compared with single-agent chemotherapy and is generally tolerable and manageable
- Compared with chemotherapy, crizotinib is associated with significantly greater improvement from baseline in both lung cancer symptoms and quality of life
- These results establish crizotinib as the standard of care for patients with advanced previously treated *ALK*+ NSCLC

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