BLA 125477 s34: Ramucirumab

FDA Opening Remarks

Oncologic Drugs Advisory Committee Meeting

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February 26, 2020

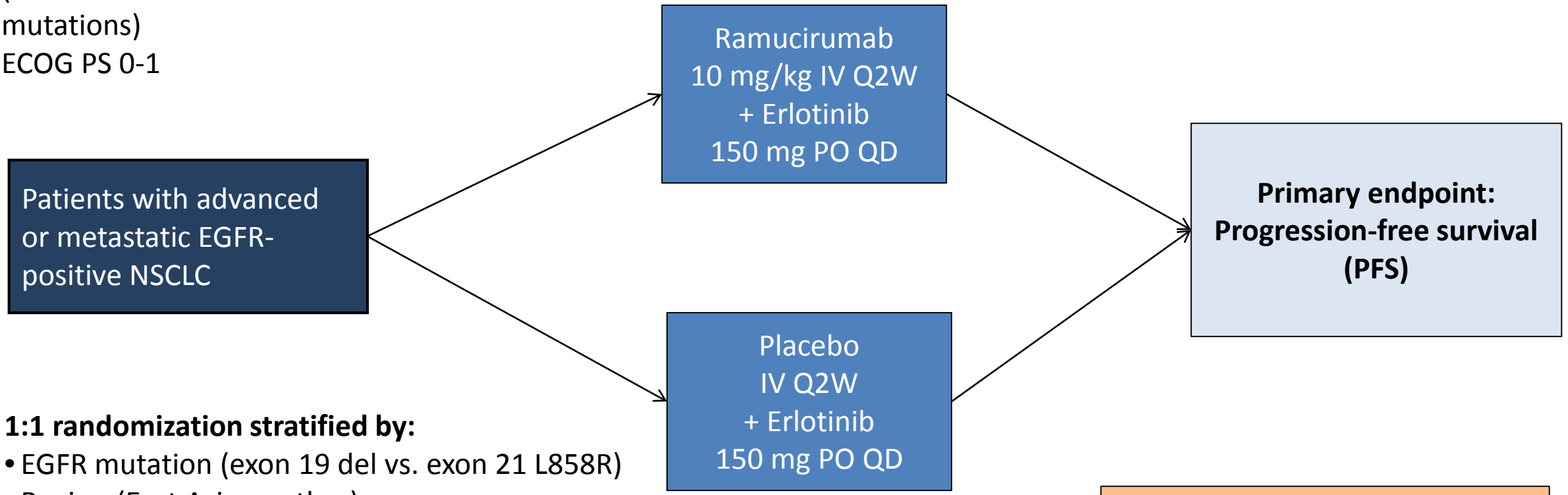
Proposed Indication

Ramucirumab, in combination with erlotinib, is indicated for first-line treatment of metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations.

Design of RELAY

Key Eligibility Criteria:

- Untreated, Stage IV, EGFR-positive NSCLC (exon 19 deletions or exon 21 L858R mutations)
- ECOG PS 0-1



1:1 randomization stratified by:

- EGFR mutation (exon 19 del vs. exon 21 L858R)
- Region (East Asia vs other)
- Gender (male vs. female)
- Test (Qiagen/Roche vs other)

Note: Post-progression cross-over was not allowed

ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; Q2W, every 2 weeks; PO, by mouth; QD, once daily

Primary Efficacy Results in RELAY

PFS by Investigator	Ramucirumab + Erlotinib N=224	Placebo + Erlotinib N=225
Number of Events, n (%)	122 (55)	158 (70)
Progression events, n (%)	118 (53)	157 (70)
Deaths, n (%)	4 (1.8)	1 (0.4)
Median PFS, months (95% CI)	19.4 (15.4, 21.6)	12.4 (11.0, 13.5)
Hazard ratio (95% CI)	0.59 (0.46, 0.76)	
p-value*	<0.0001	

*Based on the stratified log-rank test

PFS by blinded independent central review (BICR):

Median PFS 16.5 months vs 11.1 months, hazard ratio (HR) 0.67 (95% CI 0.52, 0.87)

Interim Analyses of Overall Survival in RELAY

Overall Survival	DCO: January 23, 2019[1]		DCO: December 31, 2019[2]	
	Ramucirumab + Erlotinib N=224	Placebo + Erlotinib N=225	Ramucirumab + Erlotinib N=224	Placebo + Erlotinib N=225
Number of Events, n (%)	37 (17%)	42 (19%)	59 (26%)	66 (29%)
Hazard ratio (95% CI)	0.83 (0.53, 1.30)		0.92 (0.65, 1.32)	

DCO, data cut-off date

[1]26% of the deaths required for the final analysis were observed at this DCO
[2]42% of the deaths required for the final analysis were observed at this DCO

Ramucirumab plus Erlotinib Safety Profile

- In general, consistent with known toxicities of ramucirumab and erlotinib
- Compared to placebo plus erlotinib, higher incidence of Grade ≥3 adverse events (AEs) and serious adverse events (SAEs)
- Increased incidence of hypertension, bleeding, proteinuria, and severe infections

Efficacy Endpoints in Metastatic NSCLC

- For therapies which do not specifically target oncogenic driver mutations, approvals for first-line treatment of metastatic NSCLC have been supported by demonstrated improvement in overall survival (OS).

- PFS has been used as the primary approval endpoint for drugs that specifically target oncogenic driver mutations.

Issues

1. Uncertain effect on overall survival
    - Data cut-off date December 31, 2019
    - 42% of information required for final OS analysis
    - OS hazard ratio (HR) 0.92 (95% CI 0.65, 1.32)

Issues

2. Increased toxicity with combination therapy

- Increased incidence of Grade ≥3 AEs and SAEs
- Events of interest with increased incidence:
  - Hypertension
  - Bleeding
  - Proteinuria
  - Severe infections

Benefit/Risk Assessment Considerations

- Demonstrated improvement in PFS
- Uncertainty regarding effect on overall survival
- Additive toxicity

Question for ODAC

Is the benefit/risk profile of ramucirumab plus erlotinib favorable patients with untreated metastatic EGFR-positive non-small cell lung cancer?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BLA 125477 s34: Ramucirumab
FDA Presentation

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Division of Oncology 2
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February 26, 2020

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FDA Review Issue and Voting Question

Is the benefit/risk profile of ramucirumab plus erlotinib favorable for patients with untreated metastatic EGFR-positive non-small cell lung cancer?

Outline

- Overview of RELAY results
- FDA review issues
  - Improvement in median PFS with uncertainty of effect on OS
  - Increased toxicity with combination therapy
- Summary
- Discussion topic and question for ODAC

Regulatory History

- November 2014: Meeting
  - Discussion of design and plans for the RELAY study
- December 2014: Submission of RELAY protocol
- June 2019: Pre-supplemental BLA (sBLA) meeting
  - Recommended the Applicant wait for mature, pre-specified analysis of OS in the RELAY study before filing the sBLA
- July 2019: Supplement 34 submitted

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RELAY: Design

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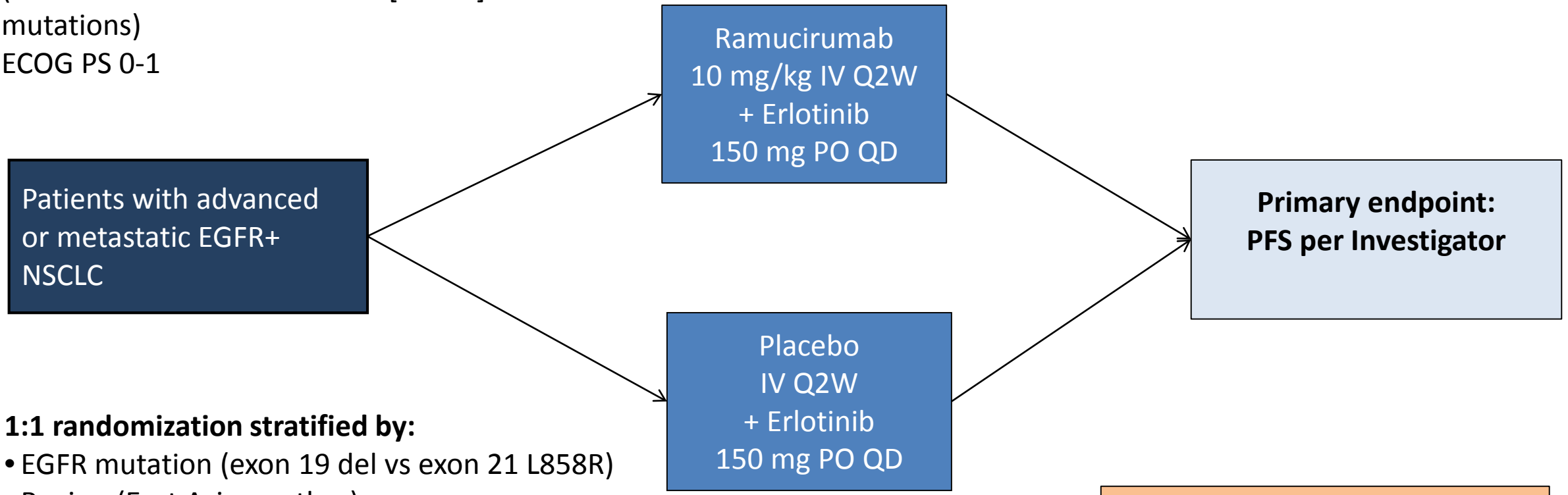

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RELAY: Statistical Plan and Assumptions

- Primary endpoint: PFS per RECIST v1.1 assessed by investigator
  - Difference to be detected: 4.5 months (HR: 0.71)
  - Power: 80%
  - Type I error: 0.05 (two-sided)

- Secondary endpoints: OS, ORR, DOR
  - Hierarchical testing plan for the primary and key secondary endpoints
    - OS will be tested only if PFS is significant.
  - Final OS analysis planned for 300 deaths, but power calculations and effect size assumptions for OS were not provided

RELAY: Primary Efficacy Results
PFS by Investigator

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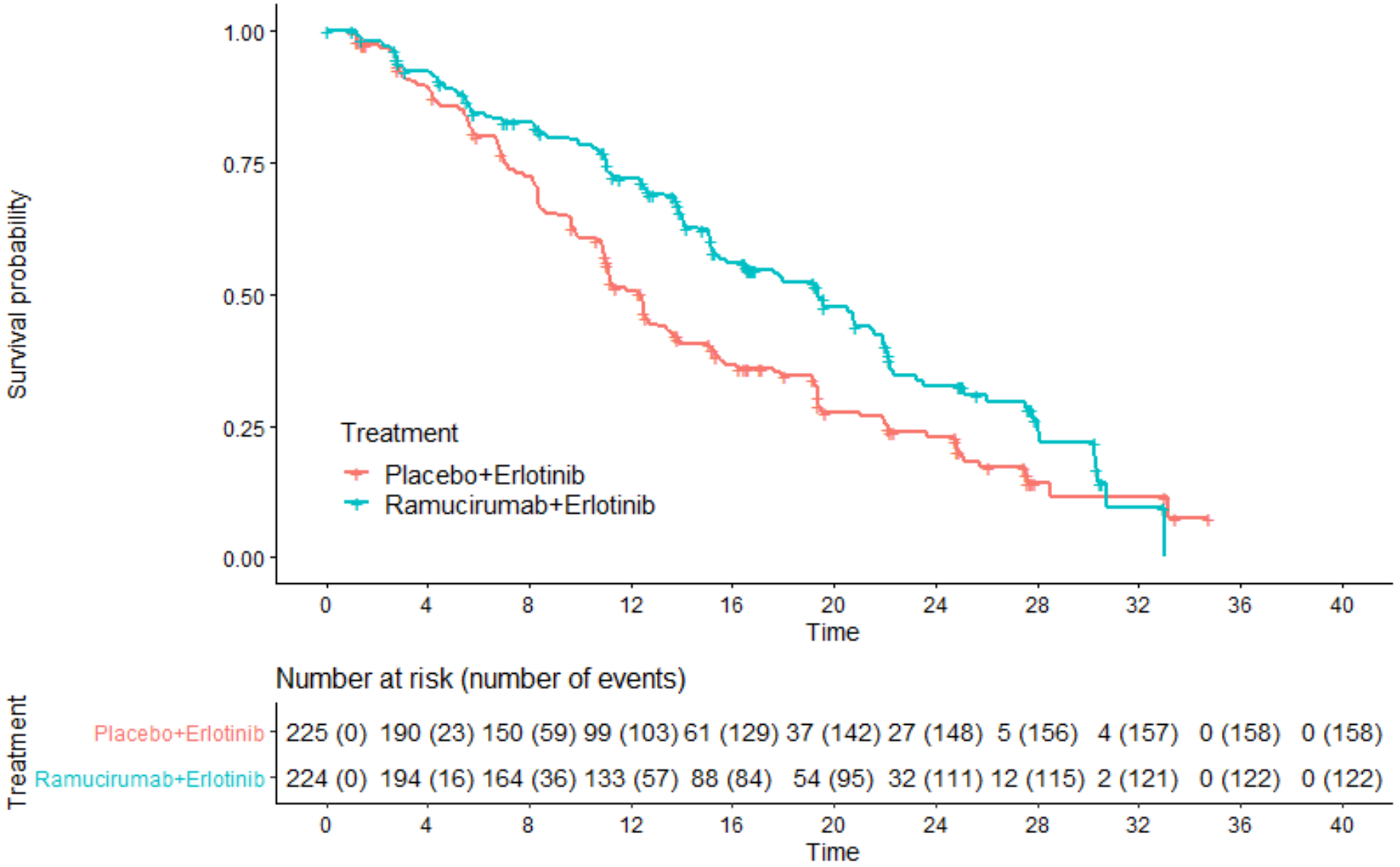
Kaplan-Meier Curves for Investigator-Assessed PFS



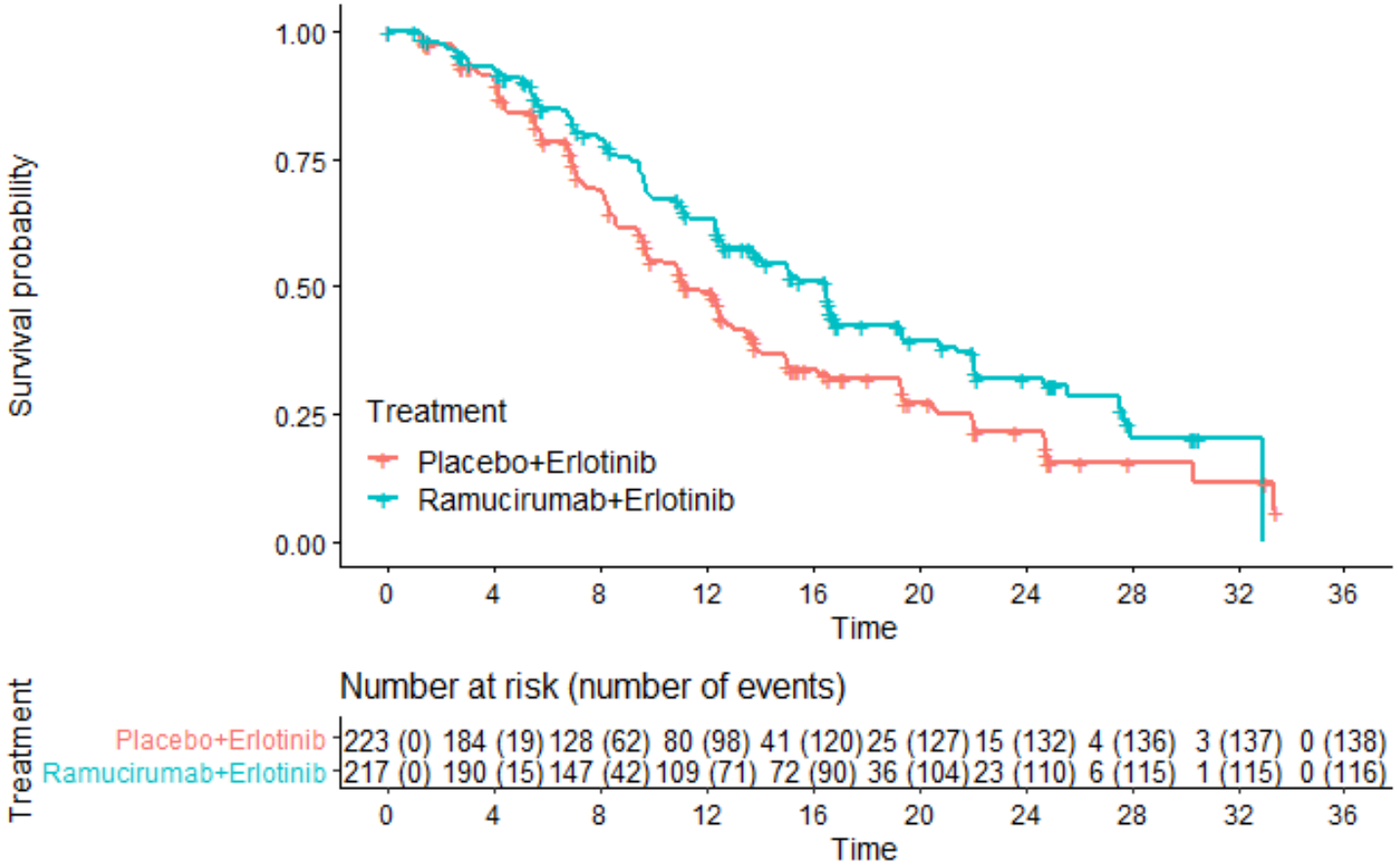
RELAY: PFS per BICR

- **PFS per BICR**
  - 5.4 month difference in median PFS (16.5 vs 11.1)
  - HR: 0.67

    (95% CI: 0.52, 0.87)

- 79% concordance in assessment of progression between INV and BICR

KM Curves for PFS per BICR

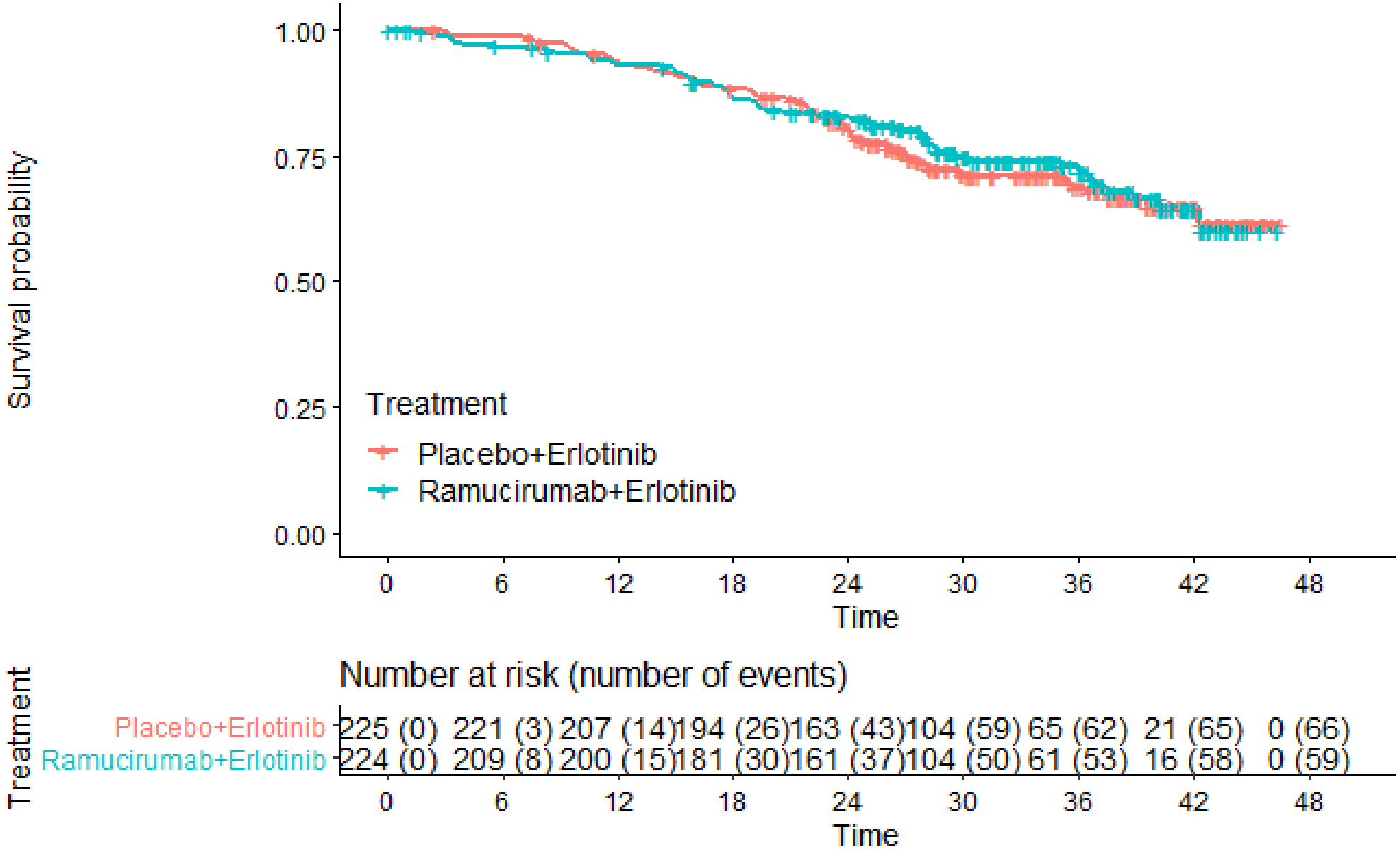


Key Secondary Endpoint: OS

- **OS at the time of the final PFS Analysis (DCO: 1/23/19)**
  - 79 deaths (26% information)
  - Median follow up 20.7 months, median OS not reached in either arm
  - **HR: 0.83 (95% CI: 0.53, 1.30)**, p-value = 0.421

- **Updated OS data provided on FDA request (DCO: 12/31/19)**
  - 125 deaths (42% information)
  - Median follow up 29.1 months, median OS not reached in either arm
  - **HR: 0.92 (95% CI: 0.65, 1.32)**

Kaplan-Meier Curves for OS (Updated)



Secondary Endpoint: ORR

Overall Response Rate	Ramucirumab + Erlotinib N=224	Placebo + Erlotinib N=225
Complete Responses, n (%)	3 (1.3)	2 (0.9)
Partial Responses, n (%)	168 (75)	166 (74)
ORR, % (95% CI)	76 (70, 82)	75 (68, 80)
Median DOR, months (range)	18.0 (13.9, 19.8)	11.1 (9.7, 12.3)

ORR, overall response rate
DOR, duration of response

Exploratory Endpoint: PFS2

- Progression-free survival 2 (PFS2) is defined as time from randomization to second disease progression.
- PFS2 is considered an exploratory endpoint.
- The endpoint is subject to measurement bias due to lack of consistent and structured radiological follow-up after the first progression event.
- Treatment effect on PFS2 can be confounded by the differential use of various post-progression anti-cancer therapies.

Exploratory Endpoints: PROs

- Two patient-reported outcomes (PROs) as exploratory endpoints: EQ-5D-5L and Lung Cancer Symptom Scale (LCSS)
  - Completion rates were high among patients remaining on study drug
  - Trial was not designed to compare differences in patient-reported symptoms and Quality of Life (QoL)

- FDA disagrees with the applicant's conclusion
  - Hazard ratios do not favor ramucirumab and erlotinib arm (HRs > 1 in 8 of 13 symptoms/scores; however, most confidence intervals cross 1)
  - Patient-reported symptoms observed corroborate the clinician reported events (blood in sputum, pain, shortness of breath)
  - LCSS primarily measures patients' symptoms and QoL, and does not capture tolerability of therapy

RELAY: Safety

- The combination of ramucirumab plus erlotinib resulted in increased toxicity compared to placebo plus erlotinib
  - ↑ Grade ≥3 adverse events (AEs)
  - ↑ Serious adverse events (SAEs)
  - ↑ Hypertension, bleeding, proteinuria and severe infections
    - 22% vs 2% required ≥3 antihypertensives
  - ↑ Deaths due to AE (6 vs 0)

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First-line NSCLC approvals

- Over the last decade, approvals of first-line treatments for metastatic NSCLC therapies *not targeting oncogenic driver mutations* have been based on demonstration of an improvement in **overall survival**.

- Approvals of first-line treatments for metastatic NSCLC therapies that specifically target oncogenic driver mutations have been based on demonstration of improvement in **progression-free survival.**

- While RELAY enrolled patients with NSCLC with an oncogenic driver mutation, all patients received erlotinib and the investigational agent *ramucirumab does not specifically target a driver mutation.*

Available Therapy: First line EGFR-positive NSCLC

	Approval Endpoint	Overall Survival
Afatinib vs chemotherapy	**Median PFS 11 mo vs 6.9 mo HR: 0.58 (95% CI: 0.43, 0.78)**	HR 0.88 (95% CI: 0.66, 1.17)
Gefitinib vs chemotherapy*	**Median PFS: 9.7 mo vs 5.2 mo HR 0.37 (95% CI: 0.25, 0.54)**	HR 1.04 (95% CI: 0.65, 1.68)
Erlotinib vs chemotherapy	**Median PFS: 10.4 mo vs 5.2 mo HR 0.34 (95% CI: 0.23, 0.49)**	HR 0.93 (95% CI: 0.64, 1.35)
Dacomitinib vs gefitinib	**Median PFS: 14.7 mo vs 9.2 mo HR 0.59 (95% CI: 0.47, 0.74)**	HR 0.76 (95% CI: 0.58, 0.99)
Osimertinib vs erlotinib/gefitinib	**Median PFS: 18.9 mo vs 10.2 mo HR 0.46 (95% CI: 0.37, 0.57)**	HR 0.63 (95% CI: 0.45, 0.88)**

*Gefitinib was approved based on the totality of data from a single arm trial and the IPASS study

**Published Data: Medians 38.6 mo vs 31.8 mo, [HR 0.80 (95% CI: 0.64, 1.00), p=0.046]

Source: USPI for erlotinib, afatinib, gefitinib, and osimertinib; published data

Overall Survival Results

Overall Survival	DCO: January 23, 2019[1]		DCO: December 31, 2019[2]	
	Ramucirumab + Erlotinib N=224	Placebo + Erlotinib N=225	Ramucirumab + Erlotinib N=224	Placebo + Erlotinib N=225
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Additional follow up is the only reliable way to assess the effect on OS

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RELAY: Summary of Adverse Events

Adverse Event Category	Ramucirumab + Erlotinib N = 221 (%)	Placebo + Erlotinib N = 225 (%)
Patients with ≥1 AE	100%	100%
Patients with ≥1 Grade 3 AE	72%	54%
Patients with ≥1 SAE	29%	21%
All deaths	17%	19%
Patients who died due to AE on study treatment or within 30 days of discontinuation	3%	0

RELAY: Selected Adverse Events

	Ramucirumab + Erlotinib N=221 (%)		Placebo + Erlotinib N=225 (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Infections	81%	18%	76%	7%
Bleeding/ hemorrhage	55%	1%	26%	0
Hypertension*	45%	24%	12%	5%
Proteinuria	34%	3%	8%	0

*Of the patients treated with ramucirumab plus erlotinib, 22% required ≥3 antihypertensives compared to 2% of patients treated with placebo plus erlotinib.

RELAY: Treatment-Emergent Laboratory Results

	Ramucirumab + Erlotinib N=221 (%)		Placebo + Erlotinib N=225 (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Increased ALT	74%	11%	60%	13%
Increased AST	71%	6%	47%	4%
Anemia	42%	5%	25%	2%
Thrombocytopenia	41%	3%	12%	3%
Neutropenia	33%	7%	21%	4%

ALT, alanine aminotransferase
AST, aspartate aminotransferase

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RELAY: Summary

- Efficacy Results
  - Investigator assessed median PFS: 19.4 vs 12.4 (HR=0.59)
  - BICR assessed median PFS: 16.5 vs 11.1 (HR= 0.67)
  - Uncertain effect on OS (HR=0.92, 95% CI: 0.65, 1.32)

- Increased toxicity
  - Severe infections
  - Hypertension (requiring ≥ 3 anti-hypertensives)
  - Bleeding (mostly grade 1 - 2)
  - TEAE laboratory abnormalities (AST, ALT, cytopenias)

TEAE, treatment emergent adverse events

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Discussion Topic

Discuss whether the results of the RELAY trial, with a demonstrated improvement in PFS, support a positive benefit/risk assessment given the uncertain effect on OS and the increased toxicity associated with the addition of ramucirumab to erlotinib.

Voting Question

Is the benefit/risk profile of ramucirumab plus erlotinib favorable for patients with untreated metastatic EGFR-positive non-small cell lung cancer?


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BACK UP SLIDES SHOWN

Predicted Probability of OS Effect

- What is the probability of an OS HR > 1?
  - FDA Analysis: Probability that HR > 1 is **30%-63%** (varies based upon assumptions)
  - Applicant Analysis: Probability that HR > 1 is **15%**

- Limitations:
  - The model is highly sensitive to the distribution/parameter assumptions, with uncertainty and sensitivity increasing with longer looks into the future.
  - Best at forecasting OS trends at proximal timepoints.

Additional follow up is the only reliable way to assess the effect on OS