Comparative effectiveness of patients with ALK+ non small cell lung cancer (Alectinib clinical trial data vs Ceritinib real world data)

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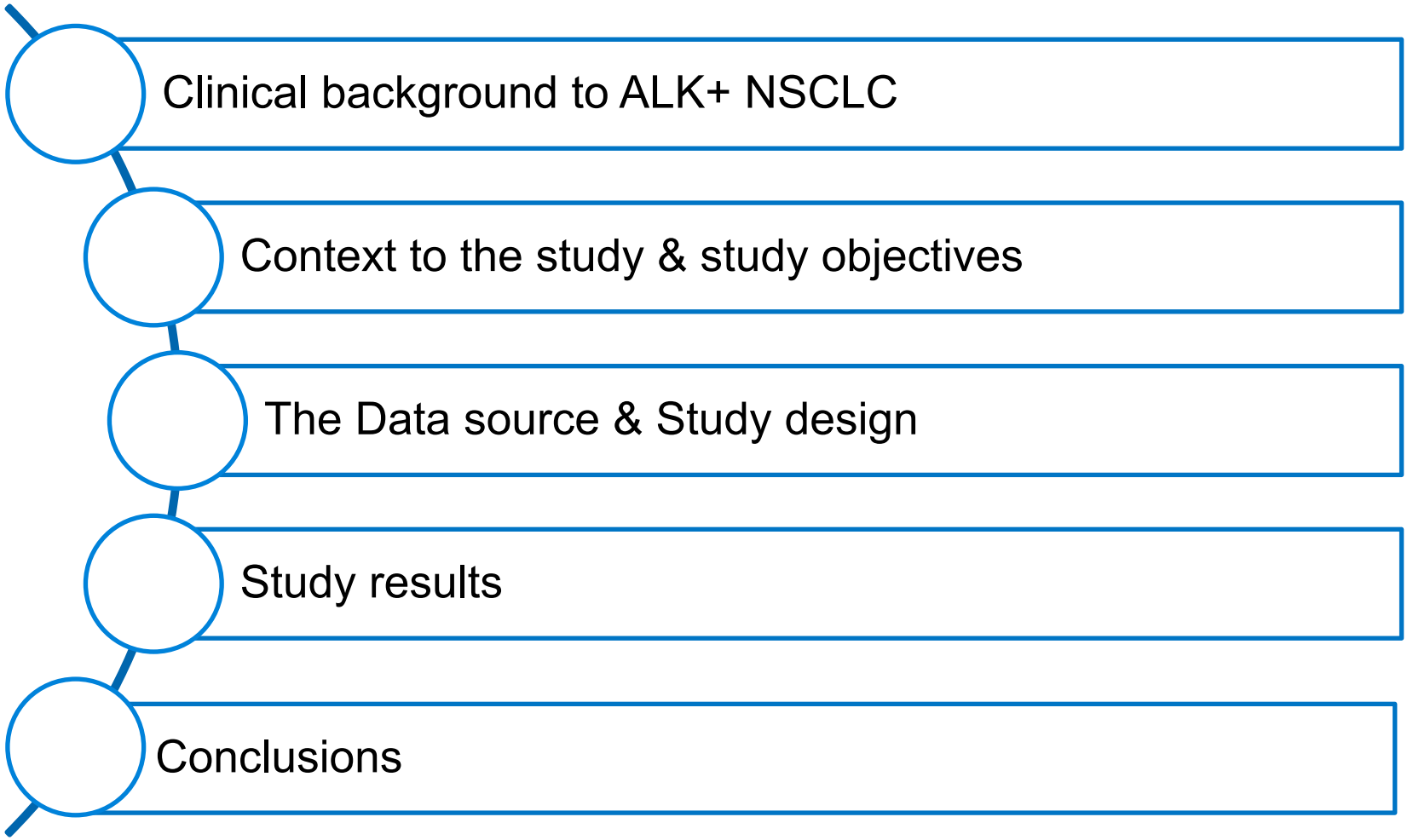
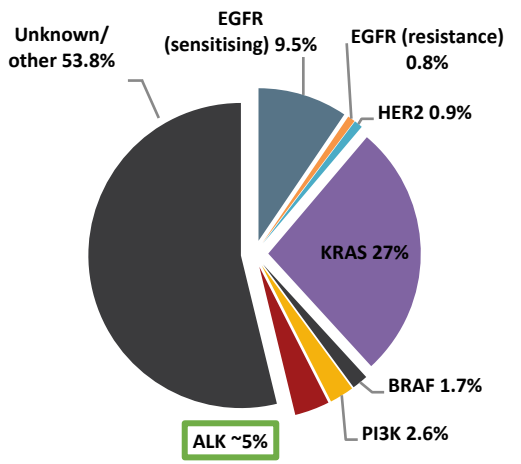
Outline of presentation



Highly segmented ALK+ NSCLC landscape with multiple approvals

- ALK+ NSCLC occurs in approximately **5% of patients** with advanced NSCLC and tends to occur more frequently amongst **women and light or non-smokers** [1,2,7]
- First approved ALK inhibitor **Crizotinib**, available in 2011
- The **majority of ALK+ NSCLC** patients experience **disease progression** on **crizotinib** within the **first year**[3]
- **Brain metastases are frequent** sites of **disease progression**:
- **Ceritinib and Alectinib** were approved in the crizotinib-failure setting[4,5, 6]
  - Regulatory approval based on single-arm phase II studies

Figure - ALK+ NSCLC accounts for around 5% of all NSCLC cases[4,8-9]

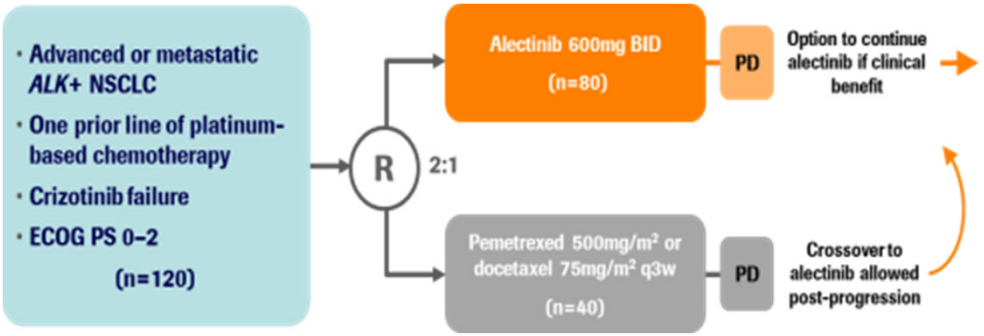


Sources: 1: Gridelli et al. Cancer Treatment Reviews 2014 40;300–306; 2: Pallis et al. Annals of Oncology 2014 00;1–13; 3: 1: Shaw et al. N Engl J Med 2014 370(13);1189-1197; 4: Mok et al. ASCO 2015 Chicago Illinois (Poster) 5 Scagliotti et al ESMO 2016 6: Ou et al. J Clin Oncol 2015 33; 7: Guerin et al. J Med Econ 2015 18(4);312-322; 8: Solomon et al. N Engl J Med 2014 371;2167-2177; 9: Khozin CDER 2014 NDA 205755; 10: Shaw, Alice T., et al. "Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial." The Lancet Oncology (2017). 11Wolf, J., Oh, I. J., Mazieres, J., de Castro, J., Revil, C., Kotb, A., ... & Novello, S. (2016). ALUR: a phase 3 study of alectinib versus chemotherapy in previously treated ALK+ non-small cell lung cancer (NSCLC).:

Evidence Requirements: HA vs HTA

European HTA

RCT Phase 3 Study of alectinib vs chemotherapy in crizotinib-failure[1]



Rapid Shift in Standard of Care with Ceritinib approval

Needed Comparative evidence vs Ceritinib

Comparative analysis of alectinib Phase 2 data with ceritinib data from US Flatiron Database

Sources: 1: Wolf, J., Oh, I. J., Mazieres, J., de Castro, J., Revil, C., Kotb, A., ... & Novello, S. (2016). ALUR: a phase 3 study of alectinib versus chemotherapy in previously treated ALK+ non-small cell lung cancer (NSCLC).:

Rationale

- In late-stage oncology settings accelerated access to novel targeted therapies has preceded availability of phase III data.
- Yet, comparative efficacy is needed to drive clinical & **economic** decisions
  - Endpoints: response rates (clinical) vs OS (economic)
- Direct, randomized H2H are the accepted standard, but not always available or feasible (Alectinib vs Ceritinib)
- Indirect treatment comparisons are commonly used but are limited in value as they do not use IPD
- Although external controls cannot replace a direct H2H randomized comparison, they provide some preliminary insights to comparative efficacy

Aim & Overview of Analyses (HTA focused)

- Aim: Comparative effectiveness (overall survival) of Alectinib (Phase 2 trial data) versus Ceritinib (US RWD)
- Methodology overview
  - Inclusion/exclusion trial criteria applied into real world database
  - Matching using propensity scores
  - Prognostic factors derived by literature review were included
  - Overall survival was calculated from initiation of treatment to follow-up end and/or death
  - KM curves were created and hazard ratios were estimated comparing Alectinib vs ceritinib
- External validation using Ceritinib trial data & Sensitivity analyses

The Alectinib Treatment Arm: Trial Population

	NP28673 (n=138)	NP28761 (n-87)
Study Location	Global	US & Canada
Study Design	Open-label, phase I/II, single arm	Open-label, phase II single arm
Patient Population	• Patients with aNSCLC • ≥18 years • ALK+ • Progression after crizotinib • Patients allowed to have multiple lines of previous treatment (incl. crizotinib) • No exposure to other Alki	
Enrolment period	June 2013-April 2014	Sept 2013-Aug 2014
Study Aims	Safety and efficacy	Safety and efficacy
Outcomes	• Primary: ORR • Secondary: OS (initiation of treatment), PFS	• Primary: ORR • Secondary: OS (initiation of treatment), PFS

High ORR (Response rates) observed = 52%*

Shaw et a 2015

The Ceritinib Treatment Arm: RWD population from the US

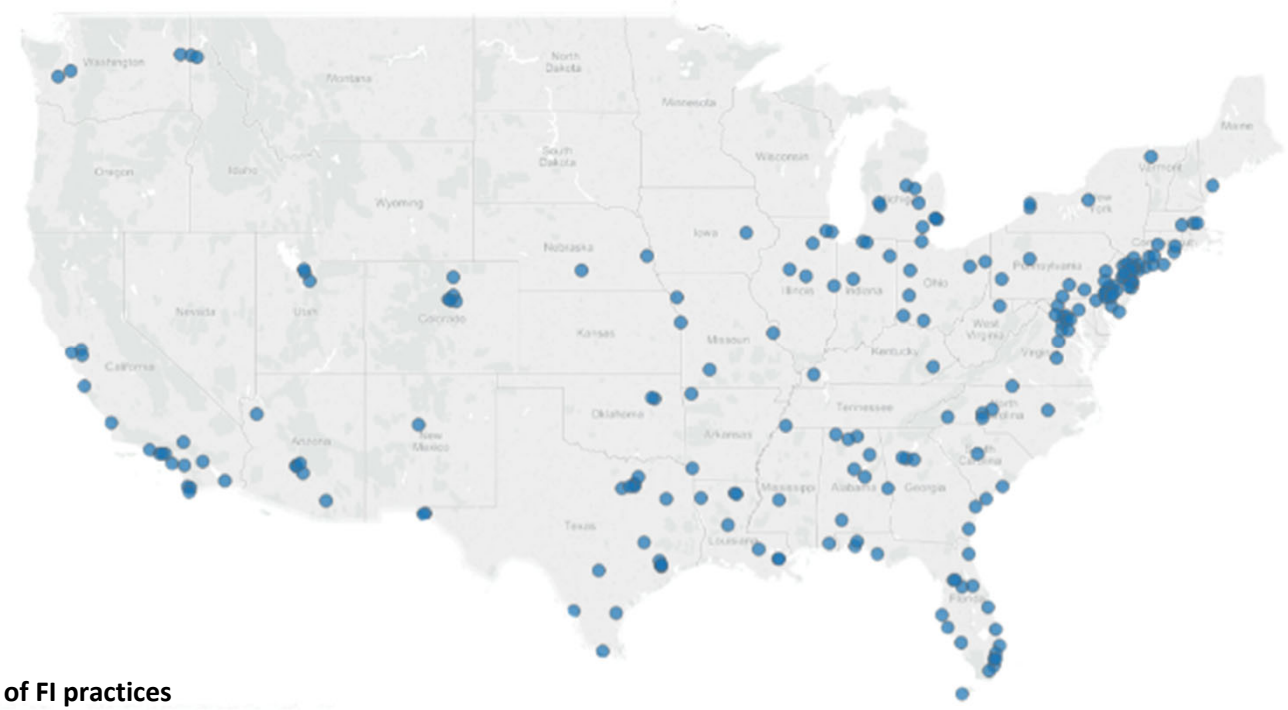
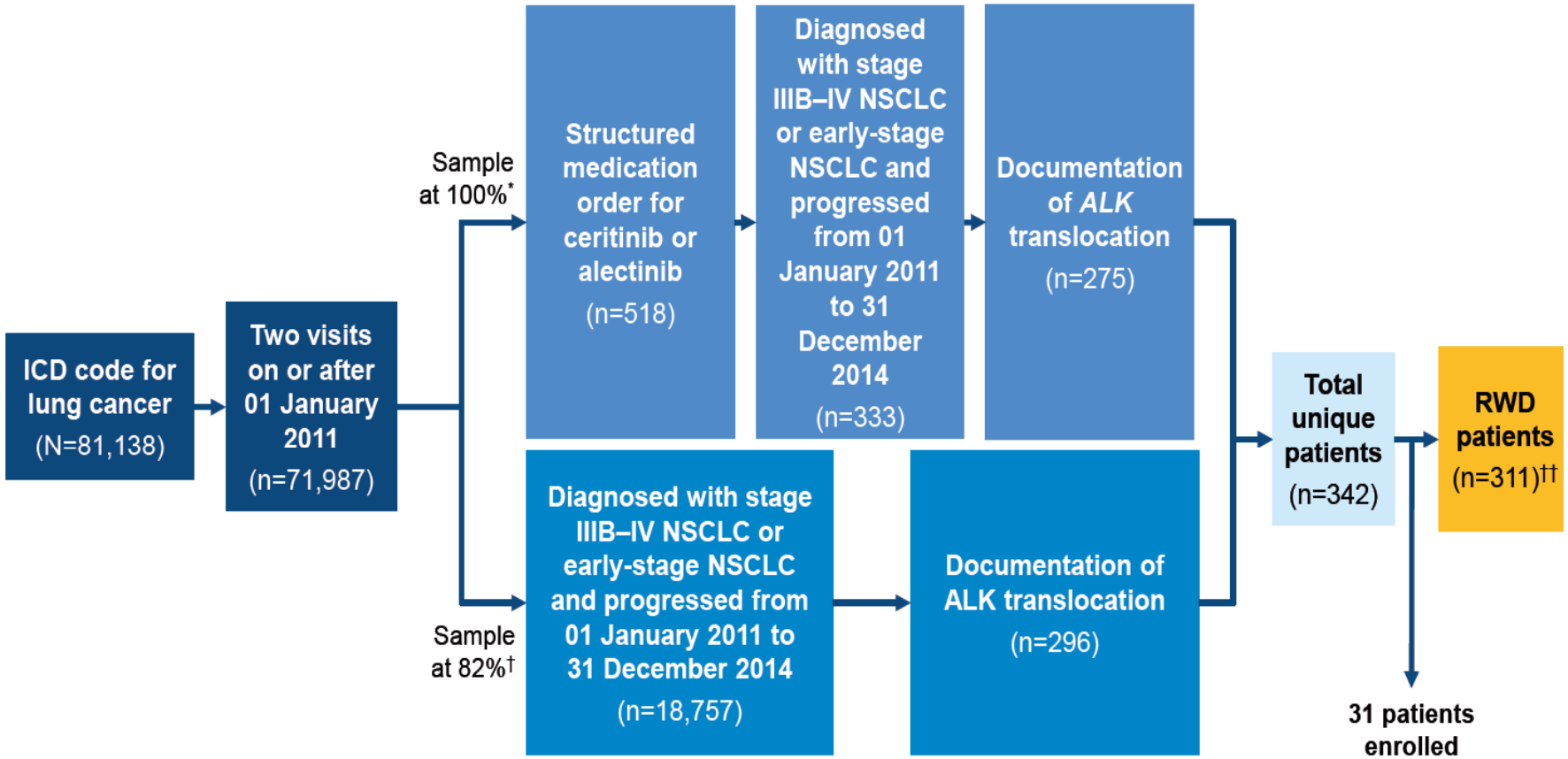


Figure: Distribution of FI practices

- An electronic health record database of US oncologists treating at the FI centers
- FI centers consists of community practices and academic affiliated hospitals
  - At each center the health record system is the “Flatiron IT” platform
  - All centers have a business associates agreement, which allows FI abstractors to process IPD and de-identify for research purposes
- Data available from medical chart consisting of unstructured and structured data elements

Source: [1] Flatiron Health INC., 2016.

311 ALK+ aNSCLC patients were extracted from the Flatiron EHR-derived database



IL = first-line; ALKi = ALK inhibitor; RWD = real-world data.
All patients (100%) in the Flatiron database with a structured ICD code for lung cancer and two visits to the Flatiron centre were searched for a structured order for crizotinib, ceritinib or alectinib. These patients also had advanced or metastatic disease along with an ALK mutation from unstructured data.
A sample (82%) of all patients with an ICD code for lung cancer and two visits to the Flatiron centre in the overall Flatiron database were selected for unstructured data processing of advanced or metastatic disease and a confirmed *ALK* mutation from unstructured data.

Figure Source: Davies J, Martinec M, Coudert M, Delmar P, Becker U, Crane G. Real World Anaplastic Lymphoma Kinase (ALK) Rearrangement Testing Patterns, Treatment Sequences and Survival of ALK-Inhibitor Treated Patients. Value in Health. 2016 Nov 1;19(7):A765.

Application of inclusion/exclusion criteria resulted in harmonized patient population

Characteristic	Alectinb (Trial) (N=183)	Ceritinib (RWD) (N=67)
Diagnosis	• Patients with stage IIIB or stage IV aNSCLC	• Patients with stage IIIB or stage IV aNSCLC
Age	≥18 years	≥18 years
Mutation	ALK	ALK
Prior Treatment Allowed	• Progression after crizotinib • Prior chemotherapy allowed	• Progression after crizotinib • Prior chemotherapy allowed
Prior Treatment Excluded	• Exposure to an ALKi other than crizotinib including ceritinib or ALKi under investigation	• Exposure to an ALKi other than crizotinib including, alectinib or ALKi under investigation
ECOG	≤2	≤2*

*ECOG is not recorded in clinical practice and was missing in 60% of the database. If an ECOG >2 was recorded the patient was excluded

Alectinib & Ceritinib patients were blended into one study cohort

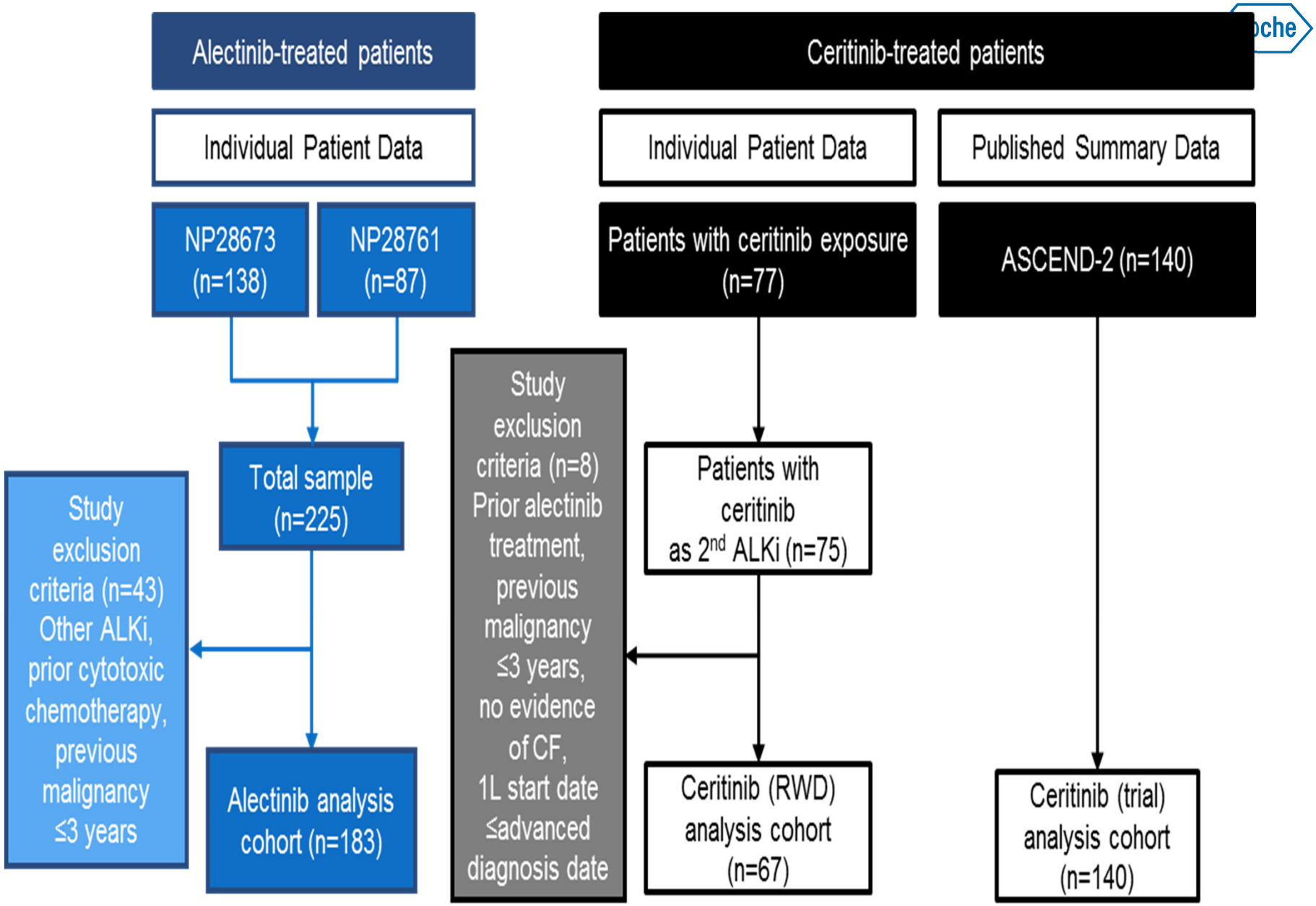


Figure Source: Davies J, Martinec M, Martina R, Delmar P, Coudert M, Bordogna W, Golding S, Crane G. 98PRetrospective indirect comparison of alectinib phase II data vs ceritinib real-world data in ALK+ NSCLC after progression on crizotinib. Annals of Oncology. 2017 Apr 1;28(suppl_2).

Alectinib and Ceritinib patients still in imbalanced in terms age, prior treatment, & CNS metastasis

Characteristic	Alectinib (n=183)	Ceritinib (n=67)	P-value
Age (years)*			
Mean (SD)	52.53 (11.18)	59.81 (11.44)	< 0.0001
Median (IQR)	53 (44 - 60.5)	61 (53 - 67)	< 0.0001
< 65	160 (87.43%)	41 (61.19%)	< 0.0001
Gender			
Female	98 (53.55%)	37 (55.22%)	0.89
Race			
White	133 (72.68%)	49 (73.13%)	1.0
Stage at diagnosis			
Stage IIIB	13 (7.10%)	8 (11.94%)	0.30
Lines prior *			
1	51 (27.87%)	38 (56.72%)	< 0.0001
2	66 (36.07%)	20 (29.85%)	
3+	66 (36.07%)	9 (13.43%)	
CNS Metastasis*			
Yes	112 (61.20%)	23 (34.33%)	0.0002

*Baseline: initiation of treatment

Patient populations well balanced after weighting and trimming

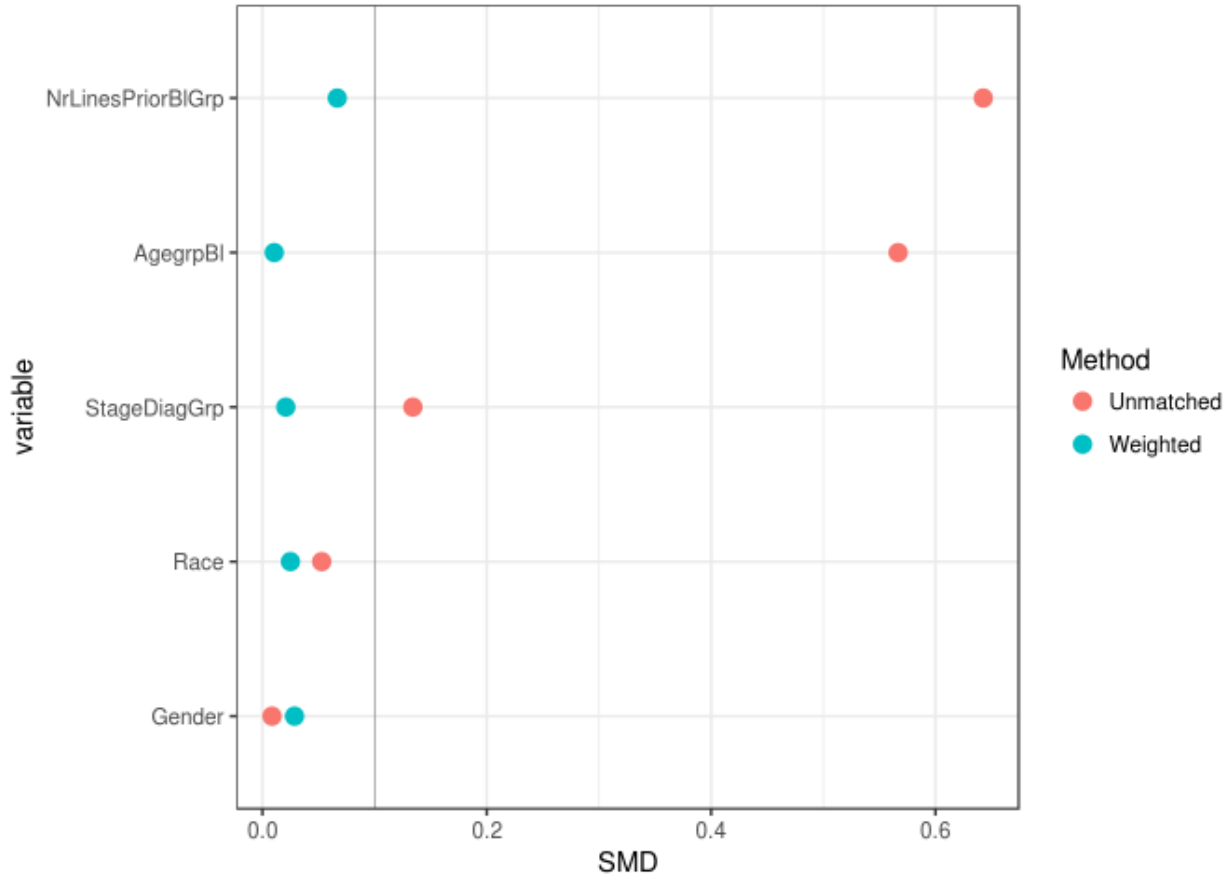
Characteristic	Alectinib (N=183)	Ceritinib (N=64)
Age (years)¥		
<65	146 (80%)	53 (79%)
≥65	37 (20%)	14 (21%)
Gender¥		
Female	86 (47%)	34 (51%)
Male	97 (53%)	33 (49%)
Race¥		
White	134 (73%)	48 (72%)
Other	49 (27%)	19 (28%)
Stage at Diagnosis¥		
Stage IIIB	15 (8%)	5 (8%)
Stage IV	168 (92%)	62 (92%)
Prior Lines¥		
1	66 (36%)	25 (37%)
2	62 (34%)	24 (36%)
≥3	55 (30%)	18 (27%)

¥ Standardized mean difference <10%

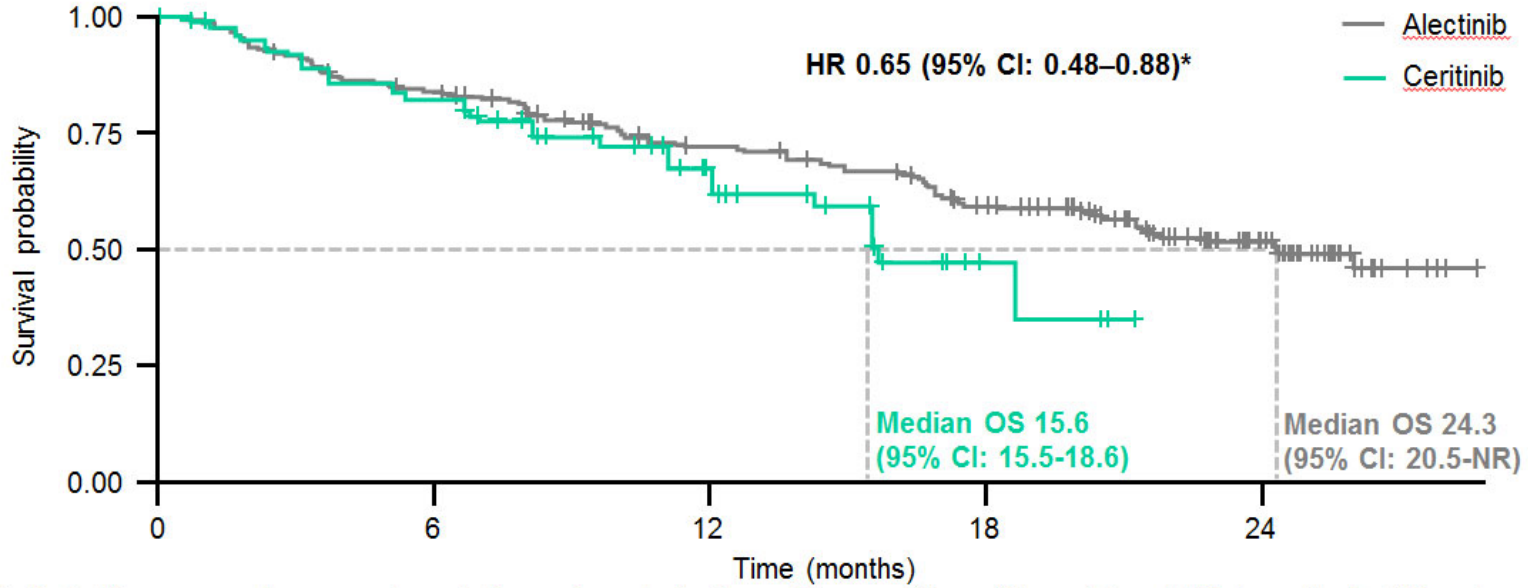
- Propensity scores applied to re-weight the populations
- CNS mets – removed due to differences in collection methodology trial vs RWD setting

After IPTW matching the populations are well balanced

Source	trimmed	n	freq
CT	Kept	183	100%
RWD	Kept	64	95.5%
RWD	Trimmed	3	4.5%



Alectinib patients had longer observed survival



*adjusted for age, gender, race, stage at diagnosis, and prior lines of therapy. CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival.

Treatment group	Median OS in months (95% CI)
Alectinib (weighted)*	24.3 (20.5 - NR)
Ceritinib (weighted)*	15.6 (15.5-18.6)

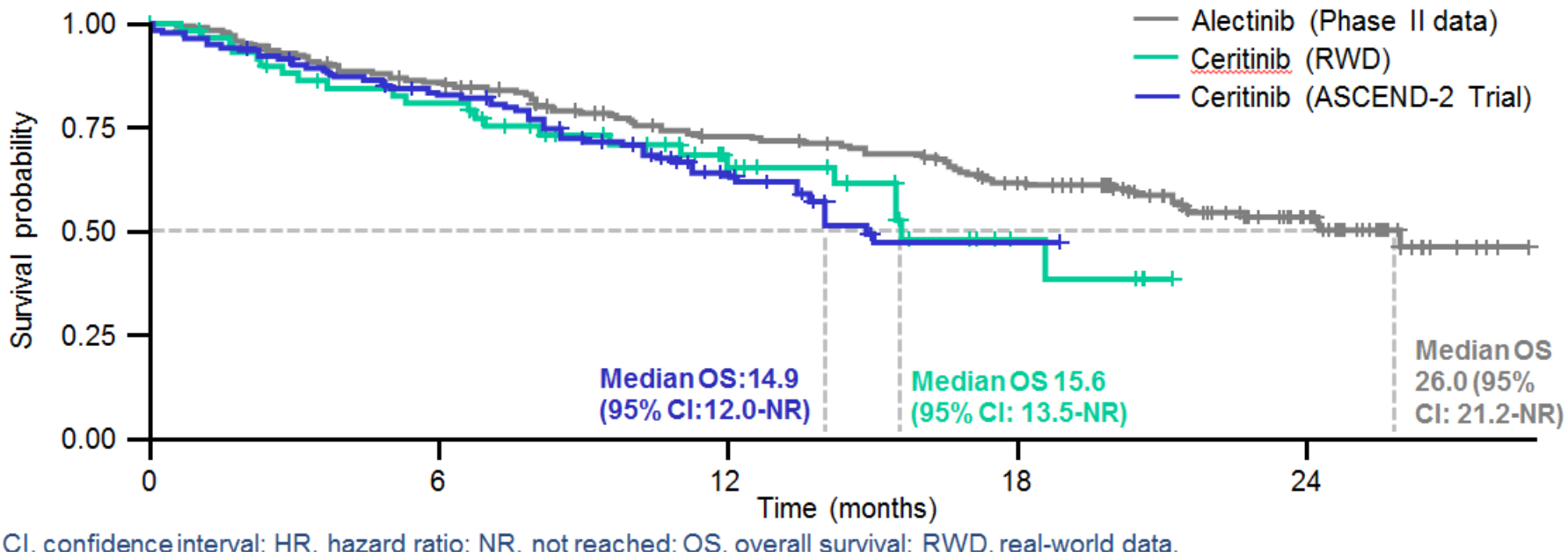
*Weights standardized (standardized using mean weight; the sum of weights is equal to patient counts)

Source: Davies J, Martinec M, Martina R, Delmar P, Coudert M, Bordogna W, Golding S, Crane G. 98PRetrospective indirect comparison of alectinib phase II data vs ceritinib real-world data in ALK+ NSCLC after progression on crizotinib. Annals of Oncology. 2017 Apr 1;28(suppl_2).

Comparison with Ceritinib trial data: Sensitivity Analysis with Ascend-2

- Individual patient data (IPD) from the Ceritinib trials (Ascend-2) are not publically available.
- Rates of OS at multiple time points were digitized from published Kaplan-Meier curves
  - Consistent with the National Institute for Health and Care Excellence technical support guidelines
- OS was defined similarly across the trial cohorts and observational cohort
  - Time from treatment initiation to death due to any cause
  - Patients without a death event were censored at the last day on which they were known to be event-free

Survival in Ceritinib RWD Arm Reflects the Survival in Ceritinib Trial



CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival; RWD, real-world data.

Cohort	Median OS (Months)	95% CI
Alectinib	25.95	21.22 -NR
RWD Ceritinib	15.63	12.02-NR
Trial Ceritinib	14.91	13.45-NR

Figure Source: Davies J, Martinec M, Martina R, Delmar P, Coudert M, Bordogna W, Golding S, Crane G. 98PRetrospective indirect comparison of alectinib phase II data vs ceritinib real-world data in ALK+ NSCLC after progression on crizotinib. Annals of Oncology. 2017 Apr 1;28(suppl_2).

Additional Sensitivity Analysis

Cohort	Ceritinib (n)	Alectinib (n)	aHR (95% CI)	p-value
Exclude patients with follow-up time in top 10% percentile	57	164	0.64 (0.47-0.88)	0.006
Impute missing covariates (Race & Stage at diag.)	69	183	0.56 (0.42-0.75)	<0.001
Include CNS mets as prognostic factor	64	151	0.67 (0.49-0.91)	0.01
Not include Stage as prognostic Factor	67	183	0.58 (0.43-0.77)	<0.001
Patients with 1-3 lines of treatment	63	146	0.66 (0.48-0.90)	0.009
Age as continuous*	64	169	0.65 (0.48-0.88)	0.006
Include Asian race category	64	174	0.66 (0.49-0.90)	0.01
1 to 1 PS matching (GenMatch)	67	183	0.54 (0.48-0.62)	< 0.001
1 to 1 PS matching (GenMatch, ATC)	67	183	0.52 (0.43-0.63)	< 0.001

Alectinib was associated with significantly prolonged OS compared to Ceritinib

Conclusions

- **Alectinib was associated with significantly prolonged OS compared to Ceritinib in the real world**
  - **Consistent through sensitivity analyses**
- **Ceritinib RWD OS was similar to the OS observed in ASCEND 2. Availability of RWD allowed for this comparison.**
- **Alectinib was associated with prolonged OS compared to ceritinib real world and ASCEND 2**

- ***Strengths***
  - Utilized IPD for comparison (best available in the crizotinib-failure setting, at the moment)
  - Verified trends with independent data source
  - Propensity scoring robust methodology that can provide preliminary insights to comparative efficacy when direct head-to-head comparisons are not available[1].
  - In absence of head-to-head trial data RWD provided a acceptable data source to build a comparison
- ***Limitations***
  - Small sample size and limited follow-up of available data
  - Potential unmeasured confounding of ECOG
  - CNS mets missing as prognostic variable

Sources: [1] Austin, PC. 2014. [2] De Marinis et al., 2014. [3] Gridelli et al., 2015. [4] Moro-Sibilot et al., 2014. [5] Pan et al., 2013. [6] Flatiron Health INC, 2016. [7] Sun et al., 2010. [8] Zietemann & Duell., 2010

Application

- Are we able **to discuss RWE** in a reimbursement dossier submission ?
- Is a “RWE **bridging strategy” acceptable** from phase II and phase III results ?
- Are we able to **obtain relevant RWE** (comparative effectiveness) from the US and use it in Europe?

Special thanks to

- Walter Bogdana (Clinical Science)
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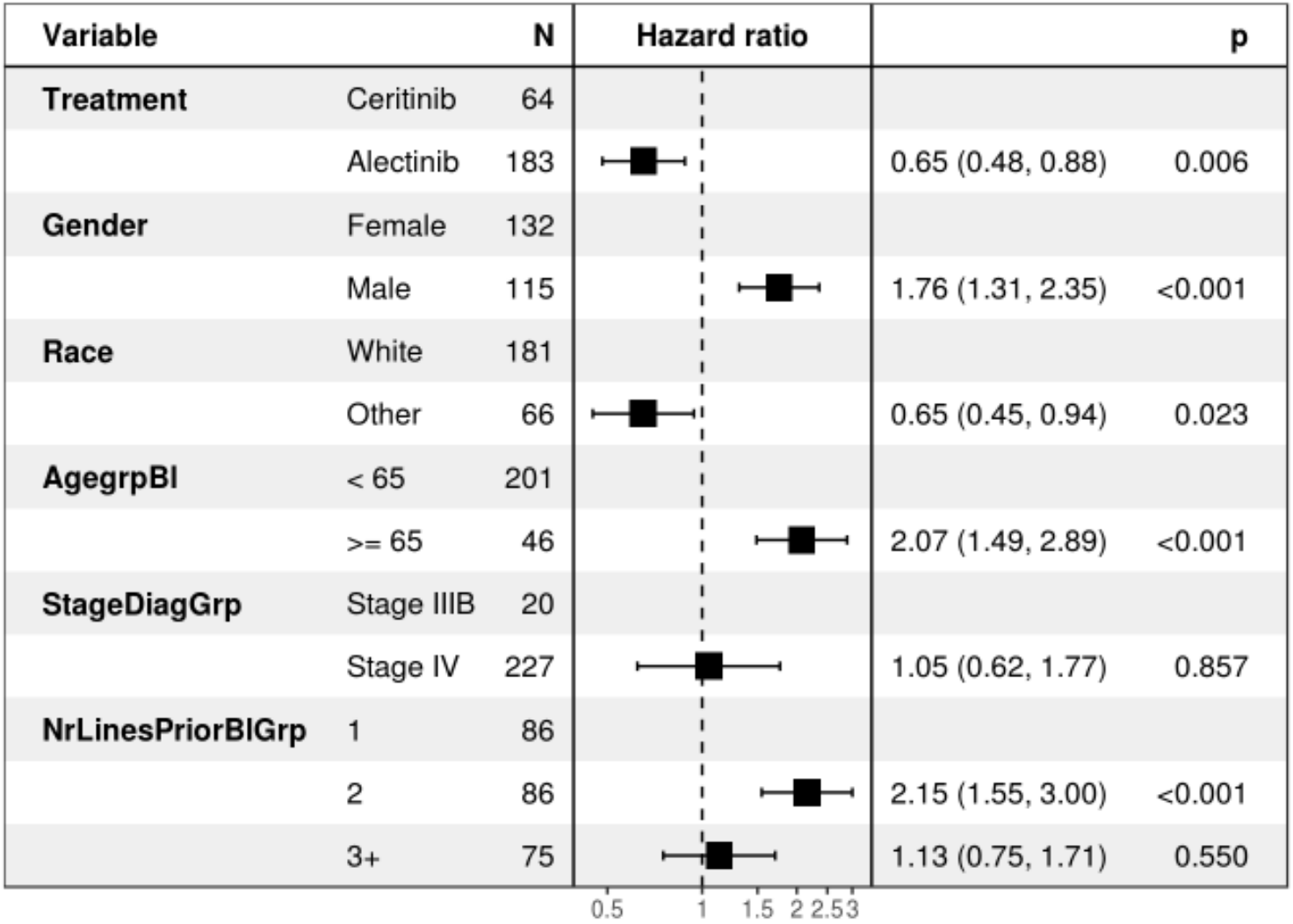
- Carlotta Pasina (IPSL)
- Raphale Lorieau-Thibault (Roche SAS)

And acknowledgements to study team

Doing now what patients need next

Lower Risk of Death among patients treated with Alectinib



Variable		N	Hazard ratio	p
Treatment	Ceritinib	64		
	Alectinib	183	0.65 (0.48, 0.88)	0.006
Gender	Female	132		
	Male	115	1.76 (1.31, 2.35)	<0.001
Race	White	181		
	Other	66	0.65 (0.45, 0.94)	0.023
AgegrpBl	< 65	201		
	>= 65	46	2.07 (1.49, 2.89)	<0.001
StageDiagGrp	Stage IIIB	20		
	Stage IV	227	1.05 (0.62, 1.77)	0.857
NrLinesPriorBlGrp	1	86		
	2	86	2.15 (1.55, 3.00)	<0.001
	3+	75	1.13 (0.75, 1.71)	0.550

- Proportional hazards assumption assessed with Schoenfeld residuals
- 64 patients after trimming (PS value inside common range)