# Brigatinib Versus Crizotinib in ALK Inhibitor–Naive Advanced ALK-Positive NSCLC: Final Results of Phase 3 ALTA-1L Trial

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# Brigatinib vs Crizotinib in ALKi-Naive Patients With Advanced *ALK*-Positive NSCLC (ALTA-1L): Background

- In patients with *ALK*-positive NSCLC, phase III PROFILE 1014 trial demonstrated significantly superior median PFS with first-line crizotinib vs platinum–pemetrexed doublet CT (10.9 vs 7.0 mos; $P < .001$)[1]
- Brigatinib: next-generation ALK/ROS1 inhibitor
  - Activity reported against ALK inhibitor–resistance mutations and *EGFR* mutations in in vitro and mouse models[2,3]
- Phase I/II trials evaluating brigatinib after crizotinib treatment have reported high rates of response systemically and in the CNS with a prolonged median PFS of ~ 16 mos[4,5]
- This article reports the final efficacy, safety, and exploratory results of the study

1. Solomon BJ, et al. N Engl J Med. 2014;371:216 7-2177. 2. Uchibori K, et al. Nat Commun. 2017;8:14768.
3. Huang WS, et al. J Med Chem. 2016;59:4948-4964. 4. Huber RM, et al. ASCO 2018. Abstract 9061.
5. Camidge DR, et al. J Clin Oncol. 2018;36:2693-2701.

# Brigatinib Exhibits a Pan-Inhibitory Preclinical Profile Against ALK Resistance Mutants

- Brigatinib overcomes mechanisms of resistance to first- and second-generation ALK inhibitors in preclinical models[1]
  - Potently inhibited all ALK resistance mutations tested, including G1202R, at clinically achievable levels
  - Significantly prolonged survival and reduced tumor burden in an ALK-dependent orthotopic brain tumor model in mice
- Brigatinib yielded promising clinical activity in crizotinib-treated ALK+ NSCLC patients in a phase 1/2 study[2]

| Effective Average Concentration ($C_{ave}$) in Patients* Exceeds $IC_{50}$ by at Least 2-fold | Yes / No |
|---|---|

| ALK Variant | TKI Activity, $IC_{50}$ (nM) | | | |
|---|---|---|---|---|
| | Crizotinib | Ceritinib | Alectinib | Brigatinib |
| Native | 107 | 37 | 25 | 14 |
| T1151Tins | 1109† | 283 | 201 | 114 |
| L1152R | 844† | 437† | 62 | 11 |
| L1152P | 721 | 451 | 48 | 20 |
| C1156Y | 529† | 195 | 67 | 45 |
| I1171N | 532† | 119 | 724† | 124 |
| F1174C | 238 | 109† | 31 | 58 |
| F1174L | 253† | 117 | 44 | 55 |
| F1174V | 257† | 121† | 46 | 64 |
| V1180L | 170 | 16 | 597 | 11 |
| L1196M | 589† | 67 | 133 | 41 |
| L1198F | 17 | 697 | 84 | 82 |
| G1202R | 617† | 354† | 695† | 184 |
| D1203N | 459† | 159 | 42 | 79 |
| S1206F | 199† | 39 | 34 | 43 |
| S1206Y | 179† | 42 | 19 | 36 |
| E1210K | 240 | 80 | 59 | 107 |
| G1269A | 509† | 29 | 56 | 9 |

*Effective $C_{ave}$ at steady-state concentrations at approved/recommended phase 2 doses (180 mg for brigatinib) corrected for functional effects of protein binding; †ALK mutations previously associated with clinical resistance[3,4]


(1) Zhang, et al. *Cancer Res*. 2015;75(15 suppl):abstract 781.
(2) Camidge, et al. *J Clin Oncol*. 2015;33(suppl):abstract 8062.
(3) Katayama, et al. *Clin Cancer Res*. 2015;21:2227-35.
(4) Friboulet, et al. *Cancer Discov*. 2014;4:662-73.

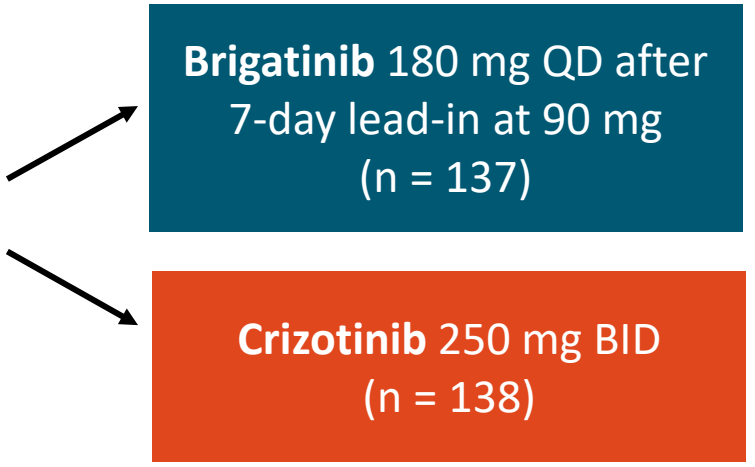

Adapted from Zhang, et al. Poster presented at AACR Annual Meeting, April 18–22, 2015, Philadelphia, PA, Abstract 781.

# ALTA-1L: Study Design

- Final analysis of multicenter, randomized, open-label phase III trial

*Stratified by BL brain mets (yes/no), prior CT for locally advanced or metastatic disease (yes/no)*

- Patients with stage IIIB/IV *ALK*-positive NSCLC,
- No previous ALK inhibitor,
- ≤ 1 previous systemic tx for locally advanced or metastatic NSCLC (N = 275)
- Asymptomatic or stable CNS mets allowed




***Until PD,* unacceptable toxicity, or other reasons for d/c***

*Crossover permitted to brigatinib arm on PD.

- Primary endpoint: BIRC-assessed PFS (RECIST v1.1)
- Secondary endpoints: ORR, intracranial ORR, intracranial PFS, OS, DoR safety and QOL
- Exploratory end points: BIRC-assessed PFS and ORR in patients crossing over to brigatinib after PD on crizotinib, Molecular determinants (ALK-EML4 fusion variant and TP53 mutation status) of efficacy and emerging mutations over time



Slide credit: clinicaloptions.com

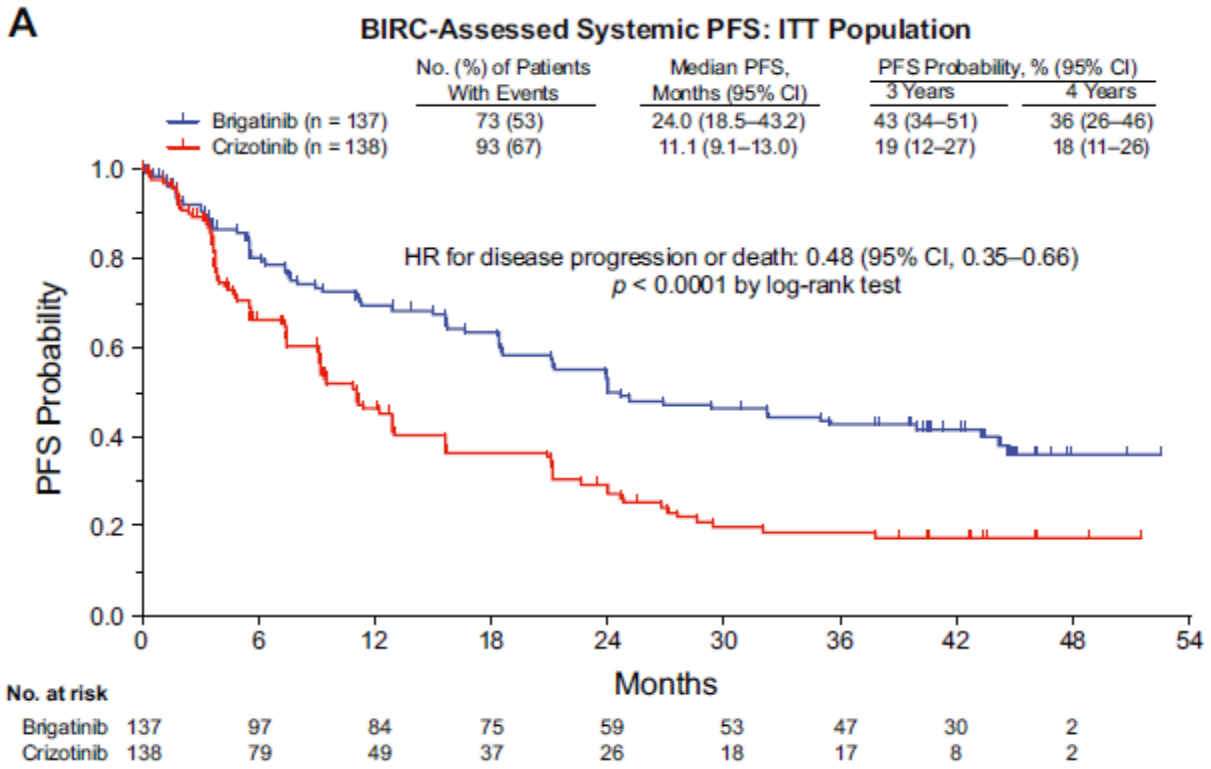
# ALTA-1L: Baseline Characteristics

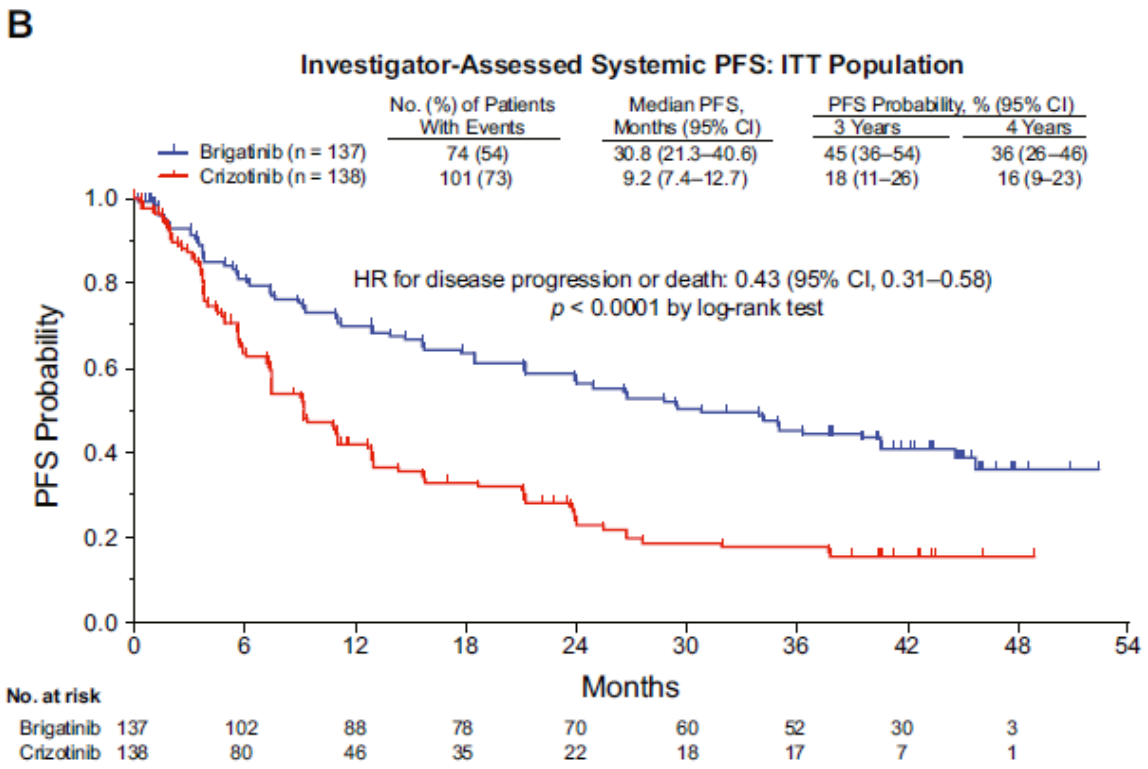
| Characteristic, % | Brigatinib (n = 137) | Crizotinib (n = 138) | All Patients (N = 275) |
|---|---|---|---|
| Median age, yrs (range) | 58 (27–86) | 60 (29–89) | 59 (27–89) |
| Female sex | 50 | 59 | 55 |
| Race | | | |
| ▪ White | 55 | 62 | 59 |
| ▪ Asian | 43 | 36 | 39 |
| ▪ Other | 1 | 2 | 2 |
| ECOG PS | | | |
| ▪ 0 | 42 | 43 | 43 |
| ▪ 1 | 53 | 52 | 53 |
| ▪ 2 | 4 | 4 | 4 |
| Disease stage at study entry | | | |
| ▪ IIIB | 6 | 9 | 7 |
| ▪ IV | 94 | 91 | 93 |

| Characteristic, % | Brigatinib (n = 137) | Crizotinib (n = 138) | All Patients (N = 275) |
|---|---|---|---|
| Locally assessed *ALK* status per FDA-approved test | 90 | 81 | 86 |
| Brain mets | 29 | 30 | 29 |
| Prior RT to brain | 13 | 14 | 13 |
| Prior CT in locally advanced or metastatic setting | 26 | 27 | 27 |

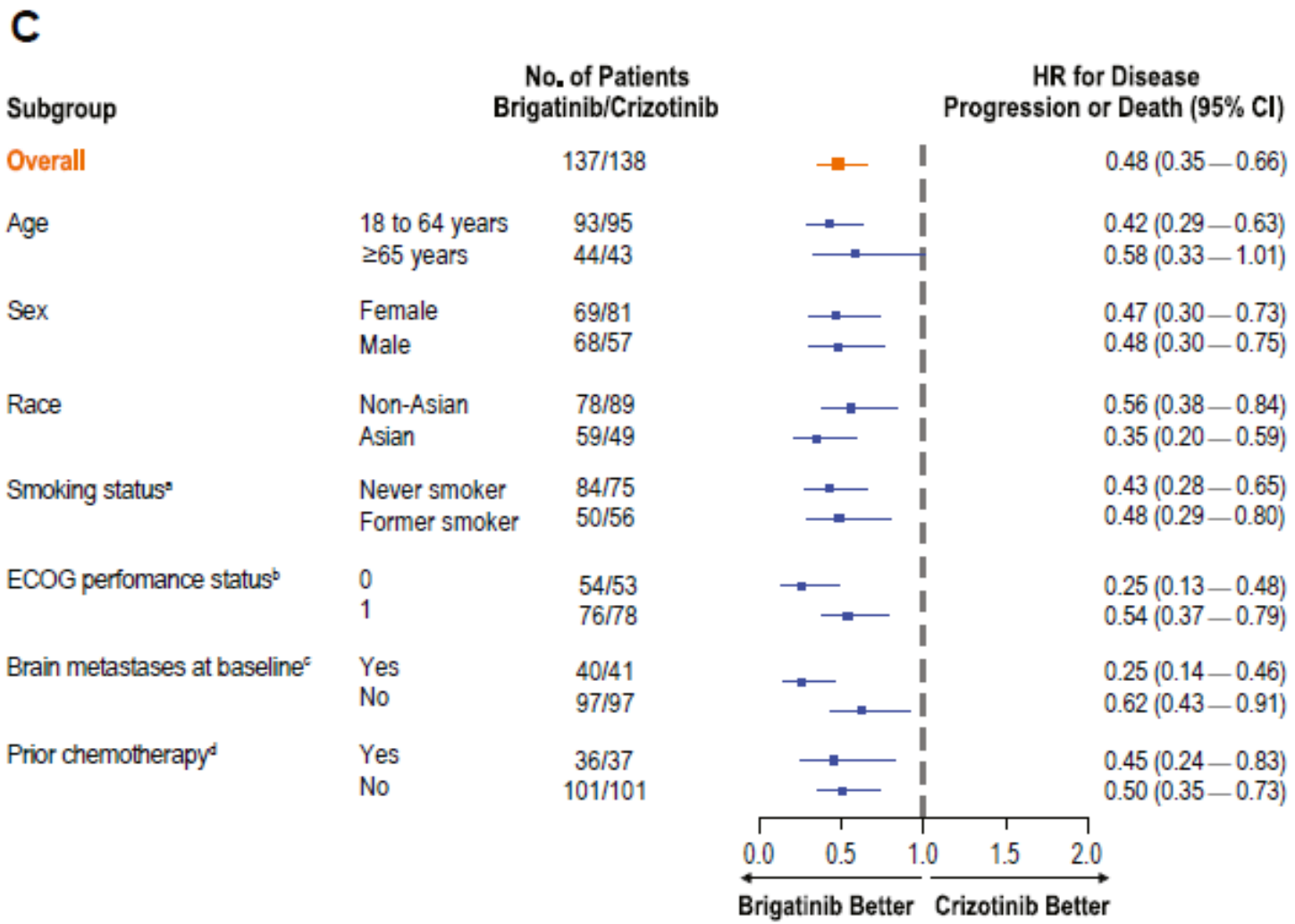
- Continuing on study treatment: brigatinib, n = 58 (42%); crizotinib, n = 16 (12%)
  - Median follow-up: brigatinib, 40.0 mos; crizotinib, 15.2 mos
  - 65 patients crossed over to brigatinib after d/c crizotinib due to PD

# ALTA-1L: BIRC-Assessed PFS (Primary Endpoint)



# ALTA-1L: BIRC-Assessed PFS by Prespecified Subgroup

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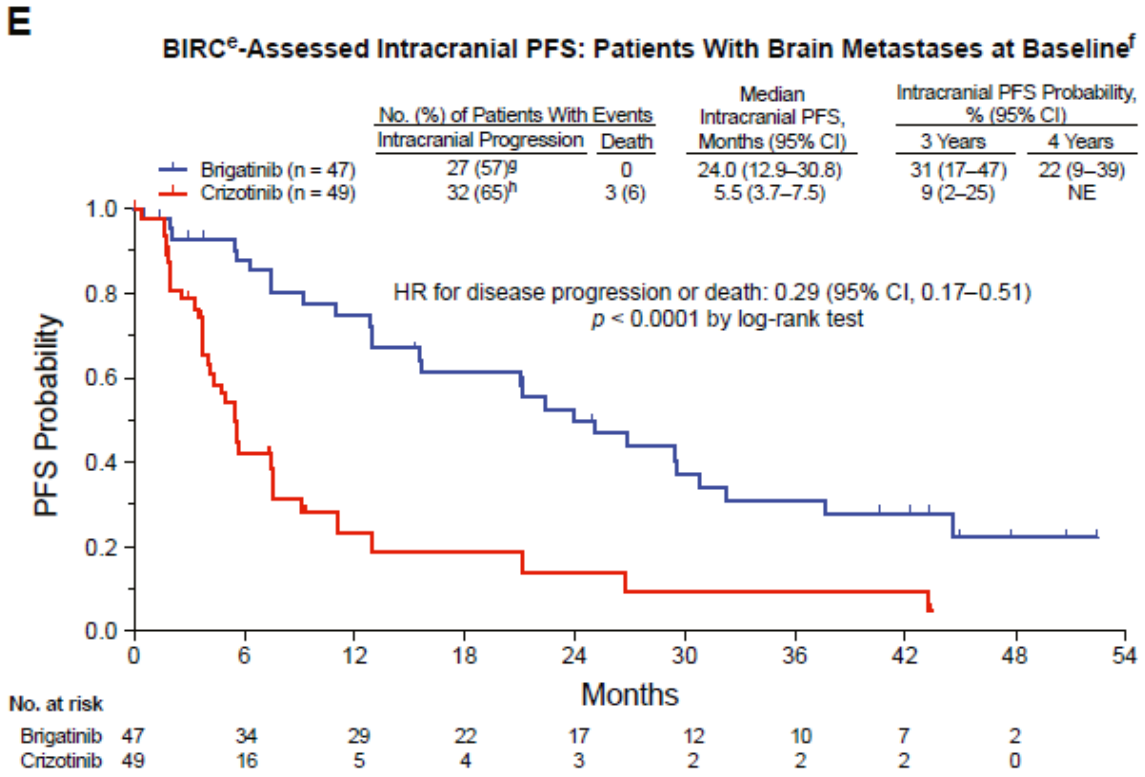
# ALTA-1L: BIRC-Assessed Intra cranial PFS



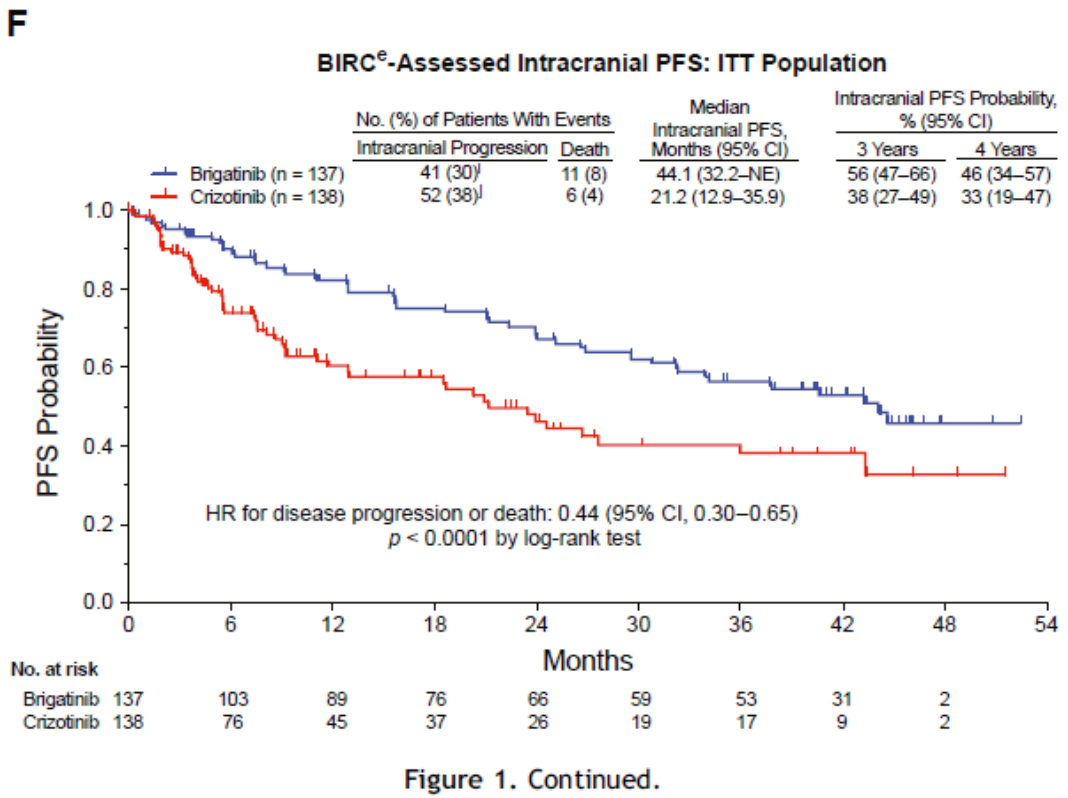
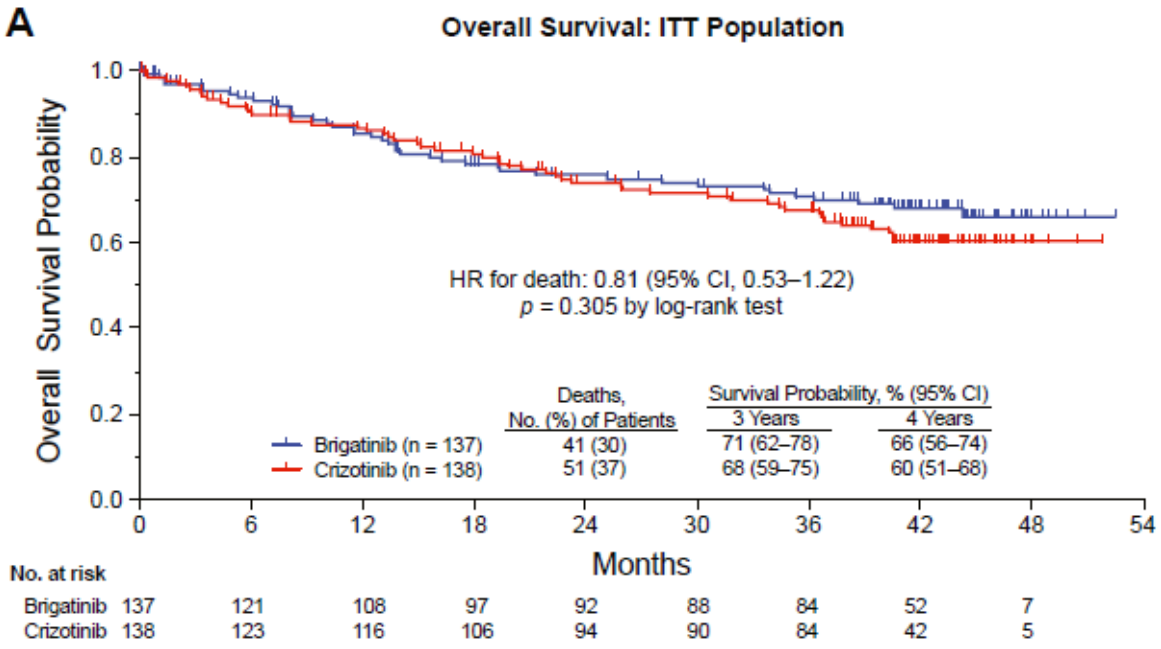
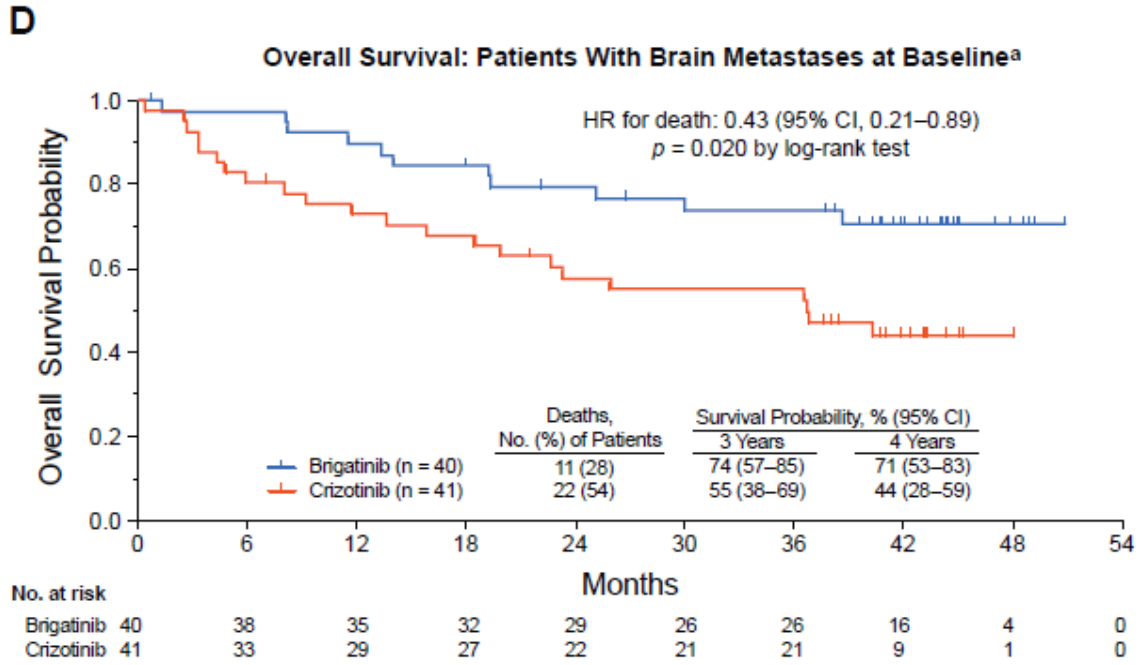




Figure 1. Continued.

# ALTA 1L – Overall survival

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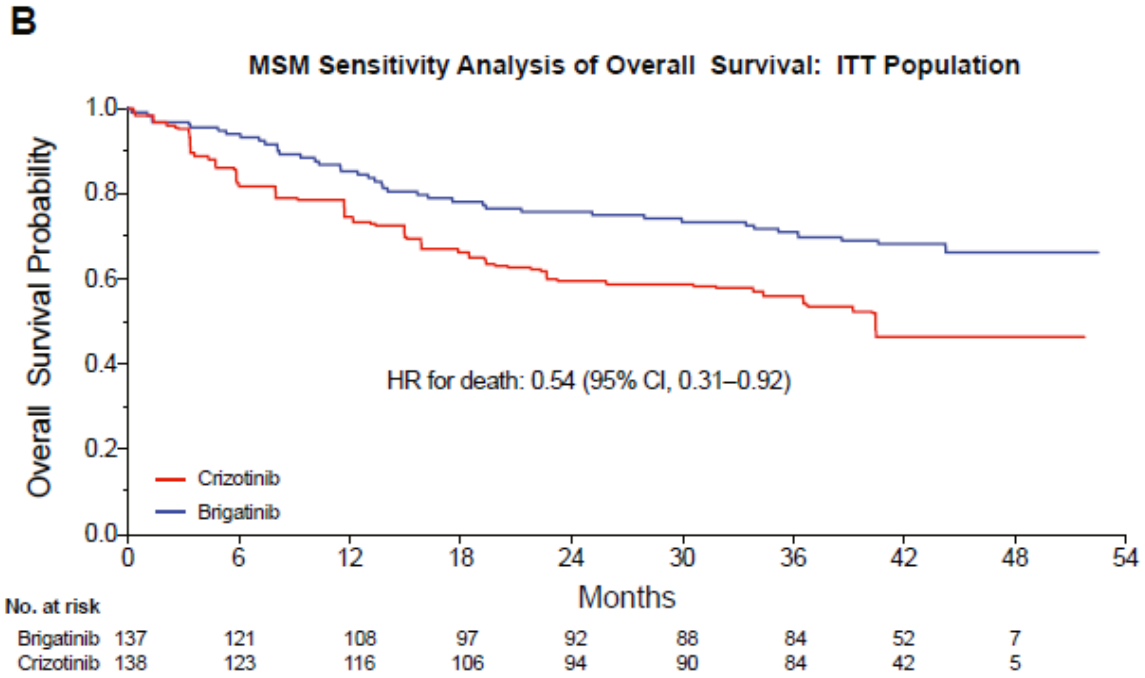
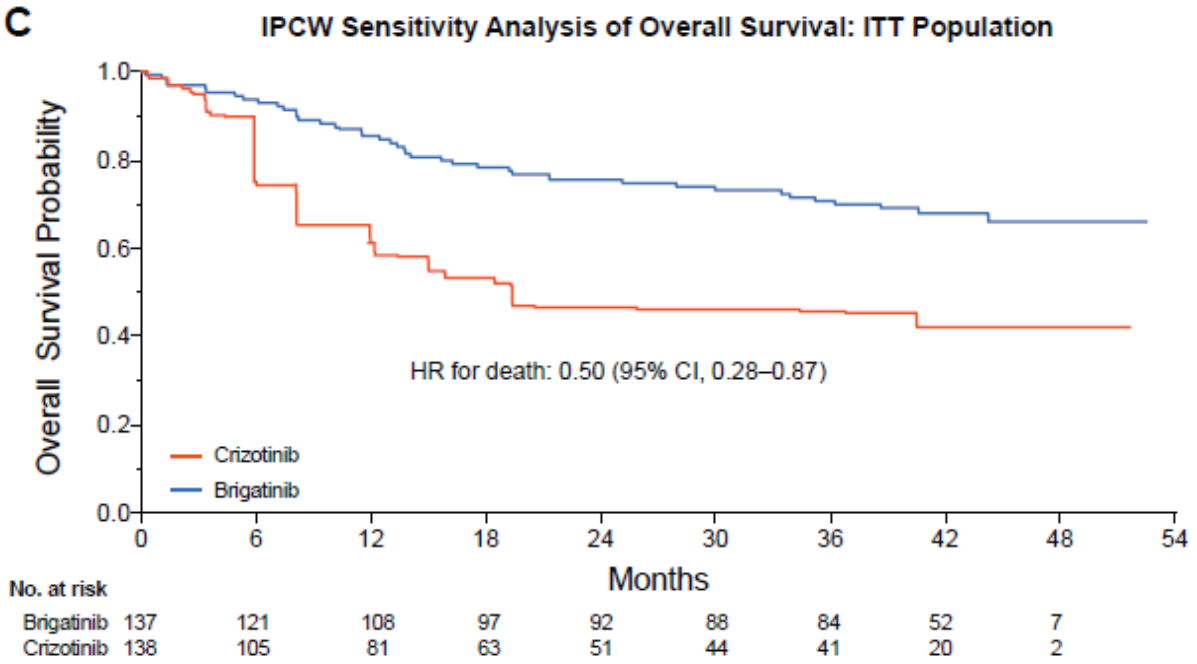
# ALTA 1L – Overall survival

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# Exploratory analyses: OS by molecular variant and TP53

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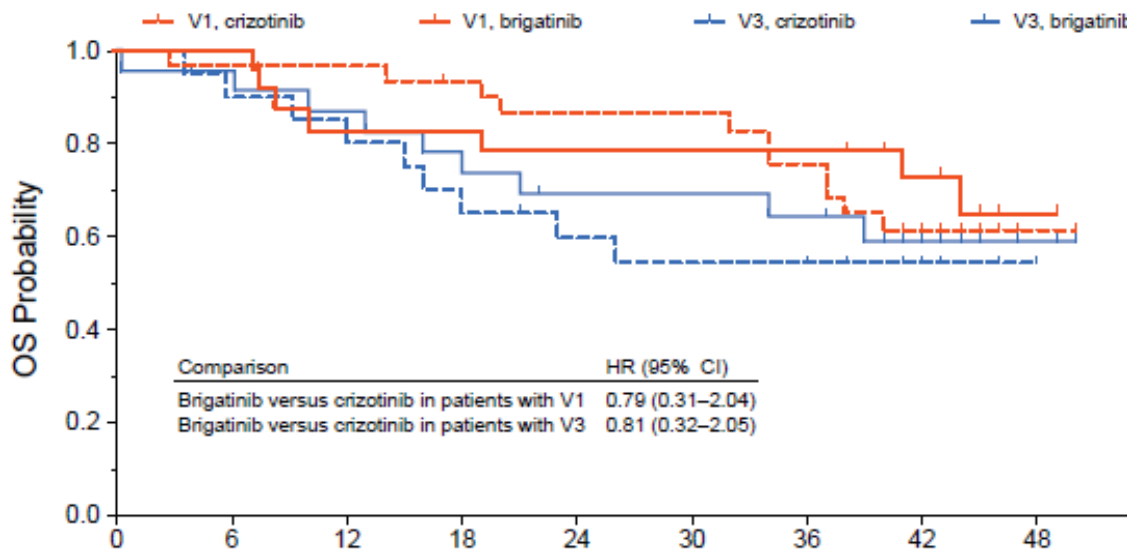
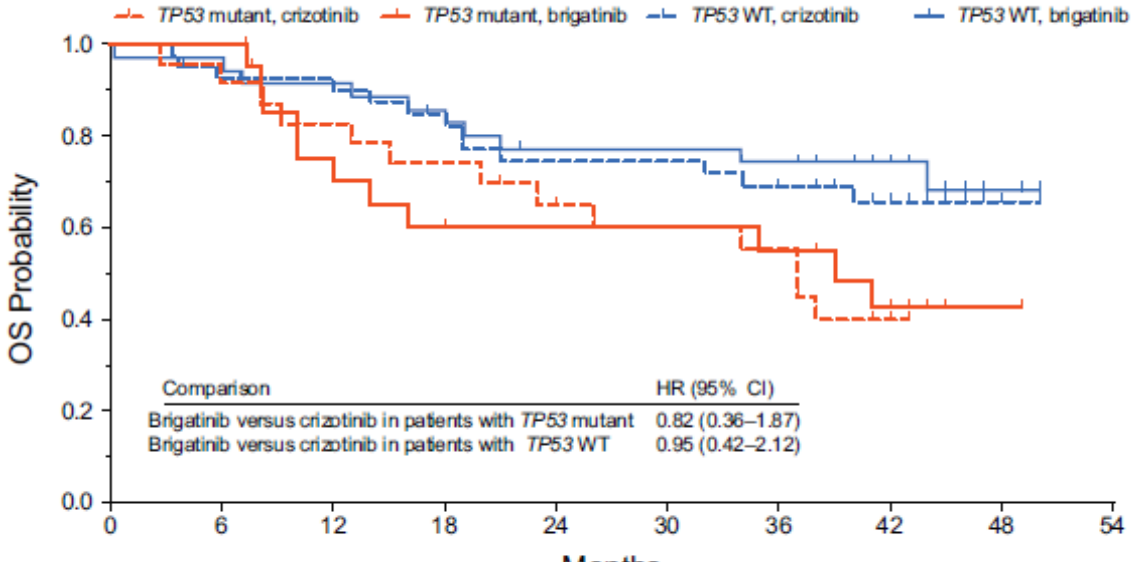



| No. at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Crizotinib, V1 | 30 | 29 | 29 | 27 | 25 | 25 | 21 | 11 | 1 |
| Crizotinib, V3 | 21 | 18 | 17 | 14 | 11 | 10 | 10 | 6 | 1 |
| Brigatinib, V1 | 25 | 25 | 19 | 19 | 18 | 18 | 18 | 10 | 2 |
| Brigatinib, V3 | 23 | 22 | 20 | 18 | 14 | 14 | 13 | 9 | 3 |

E




| No. at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Crizotinib, WT | 41 | 37 | 36 | 32 | 28 | 28 | 25 | 17 | 2 |
| Crizotinib, mutant | 23 | 21 | 19 | 17 | 14 | 12 | 11 | 2 | 0 |
| Brigatinib, WT | 35 | 34 | 32 | 30 | 26 | 26 | 25 | 15 | 4 |
| Brigatinib, mutant | 22 | 22 | 15 | 12 | 11 | 11 | 10 | 6 | 1 |

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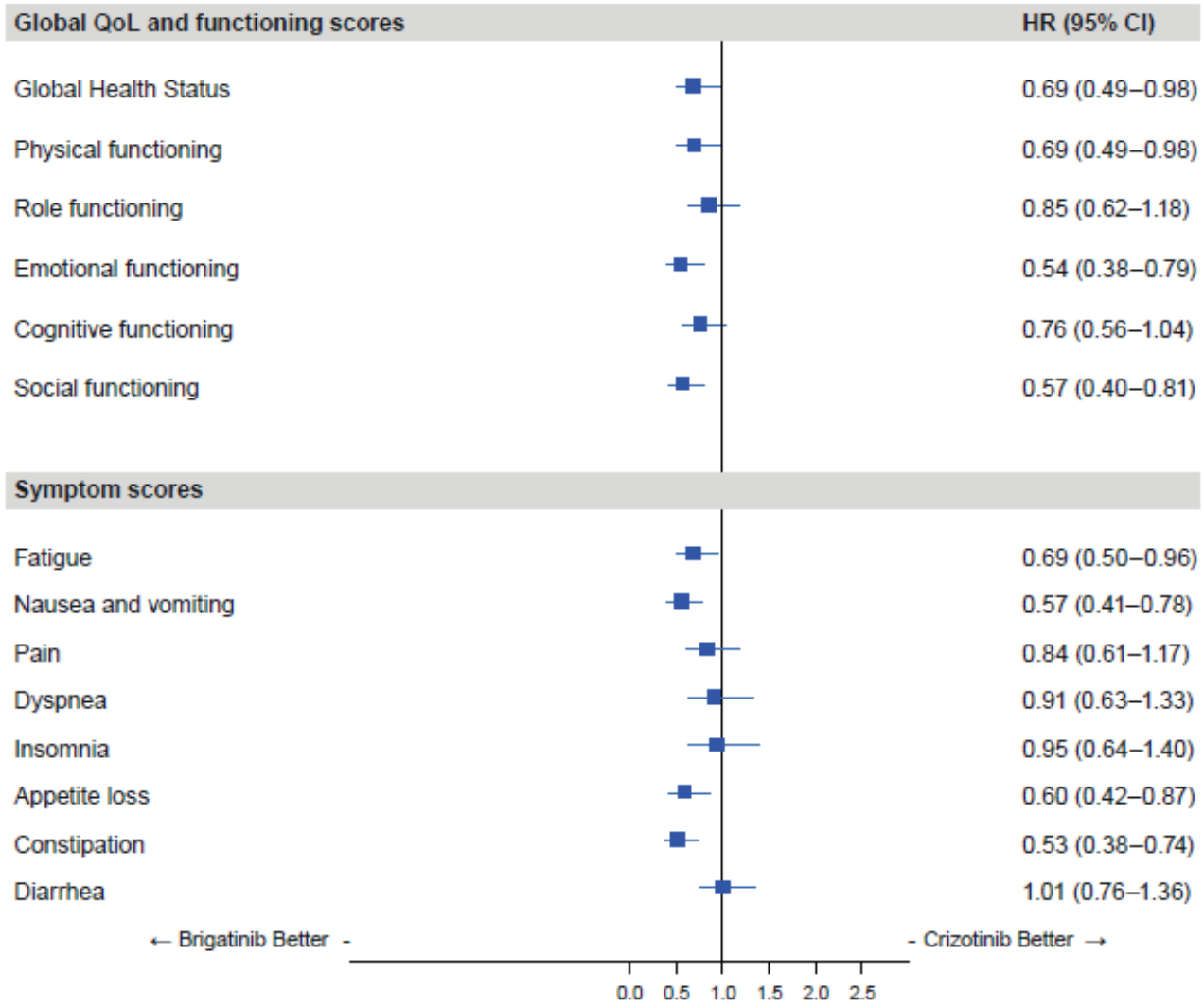
# Global QOL and functional scores




- The median time to worsening in GHS/QoL for
  - Brigatinib was 26.7 months
  - Crizotinib was 8.3 months
  - (HR= 0.69, 95% CI: 0.49–0.98, log-rank p = 0.047)

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# ALTA-1L: Safety

- **ILD/pneumonitis:**
  - Brigatinib, 6%; crizotinib, 2%
  - In brigatinib arm, 3% observed within 14 days of starting treatment
  - Grade 3 or higher 3% and <1% patients, respectively.
  - Patients crossing over to Brigatinib from Crizotinib 6% had ILD or pneumonitis with 2% having grade 3

**Table 2. Safety Overview and Treatment-Emergent Adverse Events of Grade 3 or Higher Reported in at Least 2% of Patients in Either Treatment Arm**

| Patients with ≥1 event, n (%) | Brigatinib (n = 136) | Crizotinib (n = 137) |
|---|---|---|
| Overview of adverse events | | |
| Any-grade adverse event | 136 (100) | 137 (100) |
| Grade 3-4 adverse event | 95 (70) | 77 (56) |
| Adverse events leading to death (grade 5) | 11 (8) | 11 (8) |
| Treatment-related | 0 | 0 |
| Adverse event leading to treatment discontinuation | 18 (13) | 12 (9) |
| Adverse event leading to dose reduction | 60 (44) | 34 (25) |
| Adverse event leading to dose interruption | 98 (72) | 65 (47) |
| Grade ≥3 adverse events reported in ≥2% of patients in either treatment arm | | |
| Blood creatine phosphokinase increased[a] | 36 (26) | 2 (1) |
| Lipase increased[b] | 21 (15) | 11 (8) |
| Hypertension | 19 (14) | 6 (4) |
| Amylase increased[b] | 8 (6) | 2 (1) |
| Pneumonia | 7 (5) | 5 (4) |
| Alanine aminotransferase increased | 6 (4) | 14 (10) |
| Aspartate aminotransferase increased | 6 (4) | 9 (7) |
| Neoplasm progression | 4 (3) | 4 (3) |
| Anemia | 4 (3) | 1 (1) |
| Blood alkaline phosphatase increased | 4 (3) | 1 (1) |
| Dyspnea | 3 (2) | 6 (4) |
| Pulmonary embolism | 3 (2) | 5 (4) |
| Diarrhea | 3 (2) | 4 (3) |
| Nausea | 3 (2) | 4 (3) |
| Hypophosphatemia | 3 (2) | 3 (2) |
| Gamma-glutamyl transferase increased | 3 (2) | 3 (2) |
| Headache | 3 (2) | 0 |
| Neutropenia | 2 (1) | 4 (3) |
| Pleural effusion | 2 (1) | 3 (2) |
| Vomiting | 2 (1) | 3 (2) |
| Neutrophil count decreased | 1 (1) | 7 (5) |
| Decreased appetite | 1 (1) | 4 (3) |
| Urinary tract infection | 1 (1) | 3 (2) |
| Upper abdominal pain | 1 (1) | 3 (2) |
| Noncardiac chest pain | 0 | 3 (2) |

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# ALTA-1L: Conclusions

- In ALK inhibitor–naive patients with *ALK*-positive NSCLC, final analysis confirmed significantly improved PFS with brigatinib vs crizotinib
  - Median PFS: 24 vs 11.1 mos (HR: 0.48; log-rank *P* = <0 .0001)
  - PFS benefit observed across most subgroups except those aged 65 yrs or older
  - Intracranial PFS was better in patients receiving Brigatinib, including those with BL brain metastases (31% vs 9%; log-rank p < 0.0001 )and ITT (57% vs. 38%)
- No clear pattern of emerging mutations was identified in patients who progressed on brigatinib
- More treatment discontinuations and dose interruptions were noted with Brigatinib
- Investigators concluded that brigatinib a promising first-line treatment option for patients with *ALK*-positive NSCLC especially for those with brain metastases at baseline

# Thank you