Summary—Conclusions

Disposition of subjects：

Totally, there were 256 subjects signed the informed consent and all of them were eligible for this study.

All 256 subjects were with at least one valid testing result (254 on Cobas, 256 on Super-ARMS, 255 on 3D PCR, and 256 on NGS) and included in full analysis set. Furthermore, 253 plasma samples (1 sample/1 subject) were retrospectively tested on the ddPCR platform.

Among these 256 subjects, 181 subjects were with T790M+ in plasma. For the other 75 subjects with T790M- in plasma, 11 subjects were with T790M+ in tissue, 10 subjects were with T790M- in tissue, and T790M status in tissue was unknown for 54 subjects.

The 64 subjects without T790M+ in either plasma or tissue discontinued from study due to treatment eligibility criteria not fulfilled. Also among 181 plasma T790M+ subjects, 14 subjects met treatment exclusion criterion and/or did not meet inclusion criterion and discontinued from study due to eligibility criteria not fulfilled. These 78 subjects discontinued from study and did not take study treatment.

In this way, 167 subjects with T790M+ in plasma were treated by AZD9291 and included in as-treated analysis set. Totally, 57 subjects were in treatment still and 48 subjects discontinued from treatment due to disease progression, 20 subjects due to investigator opinion: in patient's best interest to stop therapy, 18 subject due to non-first disease progression, 8 subjects due to death, 5 subjects due to AE/SAE, 5 subjects due to subject decision, 4 subjects due to start of additional anti-cancer therapy, 1 subject due to investigator decision, and 1 subject due to withdrawal of consent. Totally, 65 subjects completed or withdrew from study due to death, 3 subjects due to lost to follow-up, 1 due to withdrawal of consent, and 98 subjects due to study completion (18 months after the last patient was enrolled according to protocol). During study, 4 subjects switched to other anticancer therapy, disease progression was recorded for 109 subjects, and death without disease progression was recorded for 13 subjects.

All 11 plasma T790M-/tissue T790M+ subjects were treated by AZD9291. Totally, 6 subjects were in treatment still, and 2 subjects discontinued from treatment due to disease progression, 1 subject due to death, 1 subject due to investigator opinion: in patient's best interest to stop therapy, and 1 subject due to severe non-compliance to protocol. Totally, 8 subjects withdrew from study due to study completion and 3 subjects due to death. During study, no subject switched to other anticancer therapy, disease progression was records for 5 subjects, and no death without disease progression was recorded.

Demographic information of subjects：

The mean age was 58.54 years with range from 37.7 years to 84.0 years and 62.5% were females. All subjects were Asian and 48 (19.8%) of them used Nicotine formerly (46) and currently (2). Most of them (213, 88.4%) were of WHO status 1 (Restricted Activity) and 20 (8.3%) subjects were in normal activity. No subject was of WHO status higher than 2. The mean body weight was 60.4 kg with range from 33 to 105 kg. The demographic characteristics were similar for subjects with T790M positive status and T790M negative status.

Concordance Results：

For T790M, referred to Cobas, the concordance was 91.3% for Super-ARMS, 66.8% for 3D PCR, 82.7% for NGS, and 86.1% for ddPCR.

For T790M, referred to Super-ARMS, the concordance was 91.3% for Cobas, 71.0% for 3D PCR, 88.3% for NGS, and 88.1% for ddPCR.

For T790M, referred to 3D PCR, the concordance was 71.0% for Super-ARMS, 66.8% for Cobas, 76.5% for NGS, and 72.2% for ddPCR.

For T790M, referred to NGS, the concordance was 88.3% for Super-ARMS, 76.5% for 3D PCR, 82.7% for Cobas, and 85.8% for ddPCR.

Efficacy Results:

- Progression Free Survival (PFS)

Among As-treated Analysis Set, disease progression was recorded for 109 subjects, and death without disease progression was recorded for 13 subjects. See Table 1. Among 13 died subjects, 2 subjects' death were recorded after 98 days (equal to 2 treatment cycles duration, 6weeks +/- 7 days) from the last treatment dose and censored at last disease assessment date.

Totally, 120 events were recorded for PFS, the median PFS duration was 9.7 months from Kaplan-Meier Analysis with 95% CI from 8.4 to 11.2 months. The results were the comparable for subgroups with plasma T790M+ subjects via Cobas, Super-ARMS, 3D PCR, NGS, or ddPCR.

- Overall response rate

The best response rate was 56.3% with 95% CI from 48.4% to 63.9%. The results were the comparable for subgroups with plasma T790M+ subjects via Cobas, Super-ARMS, 3D PCR, NGS, or ddPCR. The ORR difference between subjects with RAF above and below cut-off values 0.2, 0.16, and 0.12 via NGS were explored.

- Overall survival

Totally, 65 events were recorded for overall survival, the median OS duration was not evaluable yet with 75% OS duration was 9.7 months. The results were the comparable for subgroups with plasma T790M+ subjects via Cobas, Super-ARMS, 3D PCR, NGS, or ddPCR.

Safety Results:

- Exposure and treatment duration

Totally, 110 subjects discontinued from treatment, the median treatment duration was 12.5 months. The results were the comparable for subgroups with plasma T790M+ subjects via Cobas, Super-ARMS, 3D PCR, NGS, or ddPCR.

Conclusion:

Totally, 256 subjects were included in analysis as Full Analysis Set.

With Cobas as reference platform, the concordance of plasma testing results was 91.3% for Super-ARMS, 66.8% for 3D PCR, 82.7% for NGS, and 86.1 for ddPCR.

With Cobas as reference platform, the sensitivity of plasma testing results was 94.7% for Super-ARMS, 90.5% for 3D PCR, 98.9% for NGS, and 98.9 for ddPCR.

With Cobas as reference platform, the specificity of plasma testing results was 89.3% for Super-ARMS, 52.5% for 3D PCR, 73.0% for NGS, and 78.5 for ddPCR.

With Cobas as reference platform, the positive predictive value of plasma testing results was 84.1% for Super-ARMS, 53.4% for 3D PCR, 68.6% for NGS, and 73.0 for ddPCR.

With Cobas as reference platform, the negative predictive value of plasma testing results was 96.6% for Super-ARMS, 90.2% for 3D PCR, 99.1% for NGS, and 99.2 for ddPCR.

Among 181 plasma T790M+ subjects, 167 subjects were treated by AZD9291 and included in as-treated analysis set. All 11 plasma T790M-/tissue T790M+ subjects were also treated by AZD9291.

The median PFS duration was 9.7 months from Kaplan-Meier Analysis with 95% CI from 8.4 to 11.2 months. The results were comparable for subgroups with plasma T790M+ subjects via Cobas, Super-ARMS, 3D PCR, NGS, or ddPCR.

The best response rate was 56.3% with 95% CI from 48.4 to 63.9%. The results were the comparable for subgroups with plasma T790M+ subjects via Cobas, Super-ARMS, 3D PCR, NGS, or ddPCR.

Totally, 65 events were recorded for overall survival, the median OS duration was not evaluable yet with 75% OS duration was 9.7 months. The results were the comparable for subgroups with plasma T790M+ subjects via Cobas, Super-ARMS, 3D PCR, NGS, or ddPCR.

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