**SUPPLEMENTARY INFORMATION CHAPTER 3**

**Supplementary Table 1.** Efficacy of osimertinib 80 mg or 160 mg daily for patients with *EGFR*ex20+ NSCLC in several trials.

| Clinical trial | Patient (No.) | ORR (%) | DCR (%) | PFS (months) | Reference |
|---|---|---|---|---|---|
| **Retrospective** | 80 mg/d: 6 | 67.7 | 100.0 | 6.2 | [21] |
| **NCT03414814** | 80 mg/d: 15 | 0 | 46.7 | 3.5 | [46] |
| **UMIN000031929** | 80 mg/d: 12 | 0 | 58.3 | 3.8 | [22] |
| **Retrospective** | 80 mg/d: 20 | 5.0 | 71.0 | 3.6 | [23] |
| | 160 mg/d: 1 | | | | |
| **Retrospective** | 80 mg/d: 53 | 6.5 | 53.2 | 2.3 | [20] |
| | 160 mg/d: 9 | | | | |
| **ECOG-ACRIN 5162 trial** | 160 mg/d: 20 | 25.0 | 85.0 | 9.7 | [26] |

**Supplementary Table 2. Efficacy of osimertinib 160 mg for 21 patients with NSCLC *EGFR*ex20+ within the study of Piotrowska et al., 2020[26].**

| | Best response | | | | |
|---|---|---|---|---|---|
| ***EGFR* exon 20 variant (No.)** | **CR** | **PR** | **SD** | **PD** | **Location** |
| **A767_V769dup (5)** | 1 | 0 | 4 | 0 | Near loop |
| **V769_D770insASV (1)** | 0 | 0 | 1 | 0 | Near loop |
| **D770_N771insG (2)** | 0 | 1 | 0 | 1 | Near loop |
| **D770_N771insNPH (1)** | 0 | 1 | 0 | 0 | Near loop |
| **D770_N771insSVD (1)** | 0 | 0 | 1 | 0 | Near loop |
| **N771_P772insH (1)** | 0 | 0 | 1 | 0 | Near loop |
| **N771_H773dup (1)** | 0 | 0 | 1 | 0 | Near loop |
| **P772_H773ARG (1)** | 0 | 1 | 0 | 0 | Near loop |
| **P772_H773insF (1)** | 0 | 0 | 1 | 0 | Near loop |
| **H773_V774insAH (1)** | 0 | 0 | 1 | 0 | Far loop |
| **H773_V774insPH (1)** | 0 | 1 | 0 | 0 | Far loop |
| **Unknown (5)** | 0 | 0 | 3 | 3 | n.a. |
| **TOTAL (21)** | **1** | **4** | **13** | **4** | |

**Supplementary Table 3. The *EGFR*ex20+ mutation variants and co-occurring alterations harbored by patients with NSCLC in the POSITION20 study and the response to treatment.**

| ***EGFR* exon 20 variants (No.)** | **Best response** | **Location** | **Co-occurring alterations** |
|---|---|---|---|
| **A763_Y764insFQEA** | PR | Helical region | N/A |
| **A767_V769dup** | SD | Near loop | None |
| **A767_V769dup** | PR | Near loop | N/A |
| **A767_V769dup** | PR | Near loop | N/A |
| **S768_D770dup** | SD | Near loop | TP53; RB1 |
| **S768_D770dup** | PR | Near loop | None |
| **S768_V769delinsIL** | SD | Near loop | N/A |
| **S768I & p.V774M** | PR | Near loop – point mutations | N/A |
| **D770_N771insG** | SD | Near loop | TP53 |
| **D770_N771insG** | SD | Near loop | None |
| **D770_P772dup** | SD | Near loop | None |
| **N771_P772insH** | SD | Near loop | N/A |
| **N771_P772insH** | SD | Near loop | None |
| **N771_P772insV** | NE | Near loop | N/A |
| **N771_H773dup** | SD | Near loop | None |
| **N771_H773dup** | NE | Near loop | N/A |
| **N771_H773dup** | SD | Near loop | N/A |
| **N771D** | SD | Near loop – point mutation | N/A |
| **P772_H773dup** | PD | Near loop | None |
| **P772_H773dup** | SD | Near loop | TP53 |
| **P772_H773insR** | NE | Near loop | TP53 |
| **P772_H773insQPNP** | NE | Near loop | N/A |
| **H773_V774delinsLM** | PR | Far loop | TP53 |
| **H773_V774insY** | PR | Far loop | None |
| **D777E** | SD | Far loop – point mutation | None |

**PR = partial response, N/A = not applicable, SD = stable disease, NE = non-evaluable, PD = progressive disease.**

**Supplementary Table 4.** Adverse events regardless of causality in ≥1 patient in the safety population

| **Adverse events** | **Safety population (N = 25)** *Number of patients (percent)* | | | | |
|---|---|---|---|---|---|
| | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** | **All grades** |
| Any adverse event | 25 (100) | 15 (60) | 8 (32) | 0 | 25 (100) |
| Diarrhoea | 14 (56) | 3 (12) | 1 (4) | 0 | 18 (72) |
| Dry skin* | 10 (40) | 1 (4) | 0 | 0 | 11 (44) |
| Fatigue | 9 (36) | 2 (8) | 0 | 0 | 11 (44) |
| Rash or acne* | 8 (32) | 1 (4) | 1 (4) | 0 | 10 (40) |
| Dyspnoea | 8 (32) | 1 (4) | 0 | 0 | 9 (36) |
| Paronychia | 9 (36) | 0 | 0 | 0 | 9 (36) |
| Anaemia | 6 (24) | 1 (4) | 1 (4) | 0 | 8 (32) |
| Coughing | 7 (28) | 0 | 0 | 0 | 7 (28) |
| Myalgia | 4 (16) | 2 (8) | 1 (4) | 0 | 7 (28) |
| Anorexia | 3 (12) | 3 (12) | 0 | 0 | 6 (24) |
| CPK increased | 3 (12) | 1 (4) | 2 (8) | 0 | 6 (24) |
| Back pain | 4 (16) | 1 (4) | 0 | 0 | 5 (20) |

| | | | | | |
|---|---|---|---|---|---|
| Dry eyes | 5 (20) | 0 | 0 | 0 | 5 (20) |
| Mucositis oral | 4 (16) | 1 (4) | 0 | 0 | 5 (20) |
| Nausea | 5 (20) | 0 | 0 | 0 | 5 (20) |
| Platelets decreased | 4 (16) | 1 (4) | 0 | 0 | 5 (20) |
| Constipation | 2 (8) | 1 (4) | 0 | 0 | 3 (12) |
| Dry mouth | 3 (12) | 0 | 0 | 0 | 3 (12) |
| Pruritus | 0 | 3 (12) | 0 | 0 | 3 (12) |
| Fissures | 3 (12) | 0 | 0 | 0 | 3 (12) |
| Pain joint | 3 (12) | 0 | 0 | 0 | 3 (12) |
| Urinary tract infection | 3 (12) | 0 | 0 | 0 | 3 (12) |
| Pain in extremity | 2 (8) | 0 | 0 | 0 | 2 (8) |
| Localized edema | 1 (4) | 1 (4) | 0 | 0 | 2 (8) |
| Alopecia | 2 (8) | 0 | 0 | 0 | 2 (8) |
| Dizziness | 2 (8) | 0 | 0 | 0 | 2 (8) |
| Conjunctivitis | 2 (8) | 0 | 0 | 0 | 2 (8) |
| Upper respiratory infection | 0 | 2 (8) | 0 | 0 | 2 (8) |
| Vomiting | 2 (8) | 0 | 0 | 0 | 2 (8) |
| Alanine aminotransferase increased | 1 (4) | 1 (4) | 0 | 0 | 2 (8) |
| Creatinine increased | 1 (4) | 1 (4) | 0 | 0 | 2 (8) |
| Headache | 2 (8) | 0 | 0 | 0 | 2 (8) |
| Skin induration | 1 (4) | 0 | 0 | 0 | 1 (4) |
| Fever | 1 (4) | 0 | 0 | 0 | 1 (4) |
| Palpitations | 1 (4) | 0 | 0 | 0 | 1 (4) |
| Gastritis | 1 (4) | 0 | 0 | 0 | 1 (4) |
| Malaise | 0 | 1 (4) | 0 | 0 | 1 (4) |
| Dysgeusia | 1 (4) | 0 | 0 | 0 | 1 (4) |
| Hypertension | 0 | 0 | 1 (4) | 0 | 1 (4) |
| Red face | 1 (4) | 0 | 0 | 0 | 1 (4) |
| Amnesia | 1 (4) | 0 | 0 | 0 | 1 (4) |
| Embolism | 0 | 1 (4) | 0 | 0 | 1 (4) |
| Lumbago | 1 (4) | 0 | 0 | 0 | 1 (4) |
| ECG QT corrected interval prolonged | 0 | 1 (4) | 0 | 0 | 1 (4) |
| Stomach pain | 0 | 1 (4) | 0 | 0 | 1 (4) |
| Dyspepsia | 1 (4) | 0 | 0 | 0 | 1 (4) |
| Thrush | 0 | 1 (4) | 0 | 0 | 1 (4) |
| Anxiety | 1 (4) | 0 | 0 | 0 | 1 (4) |
| Vascular access complication | 0 | 0 | 1 (4) | 0 | 1 (4) |
| Joint range of motion decreased | 1 (4) | 0 | 0 | 0 | 1 (4) |
| Aspartate aminotransferase increased | 1 (4) | 0 | 0 | 0 | 1 (4) |
| Leukopenia | 1 (4) | 0 | 0 | 0 | 1 (4) |
| Hepatotoxicity | 0 | 0 | 1 (4) | 0 | 1 (4) |
| Left ventricular systolic dysfunction | 0 | 0 | 1 (4) | 0 | 1 (4) |
| Hyponatraemia | 0 | 1 (4) | 0 | 0 | 1 (4) |
| Hypokalaemia | 1 (4) | 0 | 0 | 0 | 1 (4) |
| Hypomagnesaemia | 1 (4) | 0 | 0 | 0 | 1 (4) |

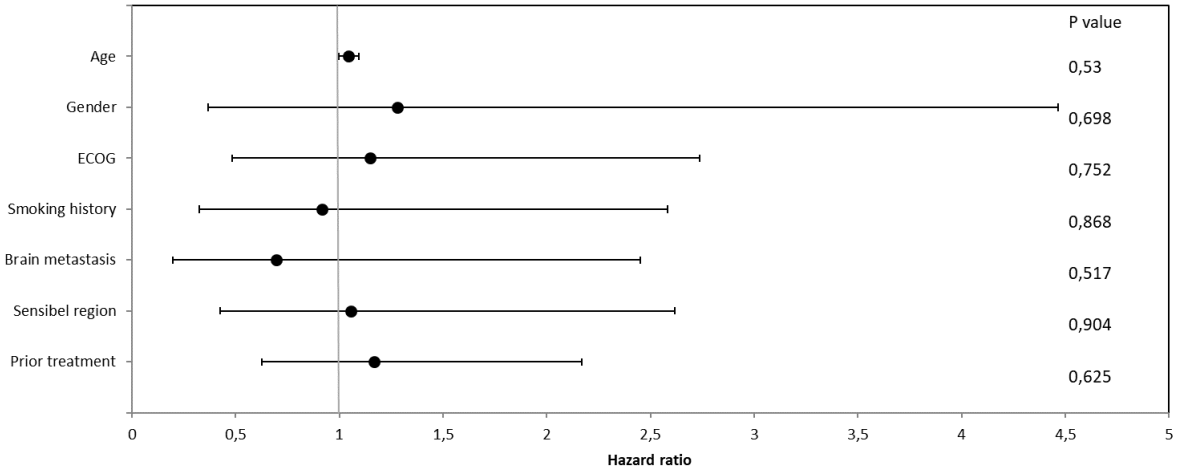
All the adverse events (including adverse events that were considered by the investigators to be related to osimertinib treatment) that were considered and observed by the investigators that were observed in at least ≥1 patient are recorded.

* This category is a grouped term

**Supplementary Table 5.** Serious adverse events (safety population).

| **Serious adverse events (SAE)** *SAEs occurring in ≥1 patient* | **Number of patients (percent)** | **Relation to treatment** |
|---|---|---|
| Seizures | 1 (4) | Unrelated |
| Pneumonitis | 1 (4) | Probably |
| Haematuria | 1 (4) | Unrelated |
| Fractures (fall stairs) | 1 (4) | Unrelated |
| Hyponatraemia | 1 (4) | Unrelated |
| Hypokalaemia due to diarrhoea | 1 (4) | Possible |
| Thoracic pain | 1 (4) | Unrelated |
| Dyspnoea | 1 (4) | Unrelated |
| Dehydration | 1 (4) | Possible |

All the SAEs occurring in ≥1 patient are recorded. Unrelated: no relation between the treatment of osimertinib 16mg once daily and the SAE. Probably: relation between the treatment of osimertinib 160mg once daily and the SAE not completely excludable. Possible: known relation between the treatment of osimertinib 160mg once daily and the SAE.




**Supplementary Figure 1.** Forest plot for progression free survival (PFS). Univariate results are expressed as unstratified hazard ratios for the risk of progression with 95% confidence intervals. Multivariate analysis was not performed due to of small number of events and the lack of statistical results in the univariate analysis.