# Supplemental information

### **Supplemental Table 1**

### **Charlson score**

|  |  |  |
| --- | --- | --- |
| **Comorbidity index** | Status | Point |
| Myocardial infarction |  | 1 |
| Congestive heart insufficency |  | 1 |
| Peripheral vascular disease |  | 1 |
| Cerebrovascular disease |  | 1 |
| Dementia |  | 1 |
| Chronic lung disease |  | 1 |
| Connective tissue disease |  | 1 |
| Ulcus disease |  | 1 |
| Liver disease | Mild  Moderate or severe | 1  3 |
| Diabetes | Without end organ damage  With end organ damage | 1  2 |
| Hemiplegia |  | 2 |
| Kidney disease |  | 2 |
| Solid secondary tumor | Without metastases | 2 |
|  | With metastases | 6 |
| Leukemia |  | 2 |
| Malignant Lymphoma |  | 2 |
| AIDS |  | 6 |
|  |  |  |
| **Age risk** |  | Score |
| ≤49 |  | 0 |
| 50–59 |  | 1 |
| 60–69 |  | 2 |
| 70–79 |  | 3 |
| 80–89 |  | 4 |
| 90–99 |  | 5 |
|  |  |  |

Total score = comorbidity index + age risk

### **Supplemental Table 2**

### Classes of medications taken for hypertension, and medications with known cytochrome P450 or P-gp interaction in the treated set (n = 152)

|  |  |  |  |
| --- | --- | --- | --- |
| **Comedications** | **Patients,  n (%)** | **Cytochrome P450 interaction** | **P-glycoprotein interaction** |
| **Beta-receptor blockers** | **30 (19.7)** |  |  |
| Betaloc ZOK | 3 (2.0) | CYP2D6 [1], CYP3A4 [2] |  |
| Carvedilol | 1 (0.7) | CYP2D6 [3], CYP2C9 [4] | P-gp inhibitor [3] |
| Querto | 1 (0.7) | CYP2D6 [3], CYP2C9 [4] | P-gp inhibitor [3] |
| Nebivolol | 4 (2.6) | CYP2D6 [5] |  |
| **AT1-receptor antagonists** | **21 (13.8)** |  |  |
| Losartan | 1 (0.7) | CYP2C9 [5] |  |
| Lotar (losartan potassium) | 1 (0.7) | CYP2C9 [6] |  |
| **Combinations** | **5 (3.3)** |  |  |
| Sevikar [olmesartan-medoxomil and amlodipine] | 1 (0.7) | CYP3A4 [7] |  |
| **Calcium channel inhibitors** | **21 (13.8)** |  |  |
| Amlodipin (amlodipine) | 14 (9.2) | CYP3A4 [8] |  |
| Norvasc(amlodipine) | 2 (1.3) | CYP3A4 [8] |  |
| Carmen (lercanidipine hydrochloride) | 2 (1.3) | CYP3A4 [9] |  |
| Corifeo (lercanidipine) | 1 (0.7) | CYP3A4 [9] |  |
| Lercanidipine | 1 (0.7) | CYP3A4 [9] |  |
| Verapamila | 1 (0.7) | CYP3A4 [10] | P-gp inhibitor [10] |

Text in bold details the overall rates of comedication with the specified class of drug. Only the medications known to have cytochrome P450 and/or P-glycoprotein interactions are named in the table (i.e., of 30 patients receiving beta-blockers, nine patients were reported to have received beta-blockers with known cytochrome P450 interactions; 21 patients received beta-blockers without known cytochrome P450 interactions). aAlso shown to interact with CYP1A2, CYP2C8, CYP2C9, CYP2C18 in *in vitro* studies [10,11]. Abbreviations: AT1, angiotensin II type 1 receptor; P-gp, P-glycoprotein.

### **Supplemental Table 3**

### Details of disease progression in the <70 and ≥70 year old age groups

|  |  |  |  |
| --- | --- | --- | --- |
| **End of therapy – progression** | **Age <70 years, n (%)** | **Age ≥70 years, n (%)** | **Total, N (%)** |
| **Number of patients** | **86 (100.0)** | **68 (100.0)** | **152 (100.0)** |
| **End of therapy – progression detected** | | | |
| Yes | 59 (68.6) | 34 (51.5) | 93 (61.2) |
| No | 24 (27.9) | 32 (48.5) | 56 (36.8) |
| Missing | 3 (3.5) | 0 (0) | 3 (2.0) |
| **Local/distant progression at end of therapy (multiple answers possible)** | | | |
| Local | 46 (53.5) | 26 (39.4) | 72 (47.4) |
| Distant metastasis | 35 (40.7) | 18 (27.3) | 53 (34.9) |
| **Distant metastases: affected organ (multiple answers possible)** | | | |
| Bone | 8 (9.3) | 6 (9.1) | 14 (9.2) |
| Liver | 8 (9.3) | 2 (3.0) | 10 (6.6) |
| Brain | 10 (11.6) | 2 (3.0) | 12 (7.9) |
| Lymph nodes | 9 (10.5) | 6 (9.1) | 15 (9.9) |
| Pleura | 3 (3.5) | 2 (3.0) | 5 (3.3) |
| Peritoneum | 0 (0) | 1 (1.5) | 1 (0.7) |
| Adrenal gland | 5 (5.8) | 1 (1.5) | 6 (4.0) |
| Skin | 2 (2.3) | 0 (0) | 2 (1.3) |
| Other | 4 (4.7) | 5 (7.6) | 9 (5.9) |
| Missing | 0 (0) | 1 (1.5) | 1 (0.7) |

### **Supplemental Table 4**

### Patients with adverse drug reactions leading to treatment discontinuation

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Patients aged <70 years (n = 86) | | | | Patients aged ≥70 years (n = 66) | | | | | | | |
|  | **CTCAE Grade** | | | | | | **CTCAE Grade** | | | | | |
|  | 1 | 2 | 3 | 4 | | **Any Grade** | | 1 | 2 | 3 | 4 | **Any Grade** |
| Highest grade ADR leading to discontinuation by patient, n (%) | 2 (2.3) | 4 (4.7) | 6 (7.0) | - | | **12 (14.0)** | | 3 (4.6) | 5 (7.6) | 4 (6.1) | 1 (1.5) | **13 (19.7)** |
| ADRs leading to discontinuation  in two or more patients, n (%) | | | | | | | | | | | | |
| Diarrhea | 1 (1.2) | - | 1 (1.2) | - | | **2 (2.3)** | | - | 2 (3.0) | 3 (4.5) | - | **5 (7.6)** |
| Nausea | - | - | - | - | | - | | - | 1 (1.5) | 1 (1.5) | - | **2 (3.0)** |
| Maculo-papular rash | - | - | - | - | | - | | 1 (1.5) | 1 (1.5) | - | - | **2 (3.0)** |
| Vomiting | 1 (1.2) | 1 (1.2) | 1 (1.2) | - | | **3 (3.5)** | | 1 (1.5) | - | 1 (1.5) | - | **2 (3.0)** |
| Acneiform dermatitis | - | 1 (1.2) | - | - | | **1 (1.2)** | | 1 (1.5) | - | - | - | **1 (1.5)** |
| Stomatitis | - | - | 1 (1.2) | - | | **1 (1.2)** | | - | 1 (1.5) | - | - | **1 (1.5)** |
| Abbreviations: ADR, adverse drug reaction; CTCAE, Common Terminology Criteria for Adverse Events. | | | | | | | | | | | | |

**References**

1. U.S. Department of Health and Human Services Food and Drug Administration. Metroprolol succinate extended release tablets. Available at <https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/019962s032lbl.pdf>. 2006. Accessed 4 May 2021.

2. Berger B, Bachmann F, Duthaler U, et al. Cytochrome P450 enzymes involved in metoprolol metabolism and use of metoprolol as a CYP2D6 phenotyping probe drug. Front Pharmacol. 2018;9:774. <https://10.3389/fphar.2018.00774>.

3. European Medicines Agency Committee for Medicinal Products. Summary of Product Characteristics: Carvedilol. Available at <https://www.medicines.org.uk/emc/product/2548/smpc>. 2007, last updated 2020. Accessed 04 May 2021.

4. Parker BM, Rogers SL, Lymperopoulos A. Clinical pharmacogenomics of carvedilol: the stereo-selective metabolism angle. Pharmacogenomics. 2018;19(14):1089–93. <https://10.2217/pgs-2018-0115>.

5. European Medicines Agency Committee for Medicinal Products. Summary of Product Characteristics: Nebivolol. Available at <https://www.medicines.org.uk/emc/product/5828/smpc>. 2010, last updated 2021. Accessed 04 May 2021.

6. European Medicines Agency Committee for Medicinal Products. Summary of Product Characteristics: Losartan. Available at <https://www.medicines.org.uk/emc/product/6004/smpc#gref>. 2009, last updated 2021. Accessed 11 June 2021.

7. European Medicines Agency Committee for Medicinal Products. Summary of Product Characteristics: Losartan potassium. Available at <https://www.medicines.org.uk/emc/product/6004/smpc#gref>. 2009, last updated 2020. Accessed 11 June 2021.

8. European Medicines Agency Committee for Medicinal Products. Summary of Product Characteristics: Sevikar. Available at <https://www.medicines.org.uk/emc/product/6527/smpc#gref>. 2008, last updated 2020. Accessed 11 June 2021.

9. European Medicines Agency Committee for Medicinal Products. Summary of Product Characteristics: Amlodipine. Available at <https://www.medicines.org.uk/emc/product/4036/smpc#gref>. 2011, last updated 2018. Accessed 11 June 2021.

10. European Medicines Agency Committee for Medicinal Products. Summary of Product Characteristics: Lercanidipine HCl. Available at <https://www.medicines.org.uk/emc/product/5725/smpc#gref>. 2002, last updated 2019. Accessed 11 June 2021.

11. Fuhr U, Woodcock BG, Siewert M. Verapamil and drug metabolism by the cytochrome P450 isoform CYP1A2. Eur J Clin Pharmacol. 1992;42(4):463–4. <https://10.1007/BF00280138>.