**MS# CD-16-1237R: Supplemental Tables**

**Supplemental Table 1. Adverse Events (All Grades) by Dosing Regimen:** Listed are adverse events that were reported in at least 10% of the patients (n=119) in either dosing regimen and that were deemed by the investigators to be related to study drug. Intermittent = Schedules A and C from ALKA-372-001 study; continuous = Schedule B (ALKA-372-001) and STARTRK-1 studies.

|  |  |  |  |
| --- | --- | --- | --- |
| **Adverse Event Term****n (%)**  | **Intermittent****(n=25)** | **Continuous****(n=94)** | **Total****(n=119)** |
| **Fatigue/Asthenia**  | 12 (48) | 43 (46) | 55 (46) |
| **Dysgeusia**  | 6 (24) | 44 (47) | 50 (42) |
| **Paresthesia**  | 14 (56) | 20 (21) | 34 (29) |
| **Nausea**  | 15 (60) | 18 (19) | 33 (28) |
| **Myalgia**  | 9 (36) | 18 (19) | 27 (23) |
| **Diarrhea**  | 7 (28) | 16 (17) | 23 (19) |
| **Vomiting** | 9 (36) | 11 (12) | 20 (17) |
| **Arthralgia**  | 6 (24) | 13 (14) | 19 (16) |
| **Dizziness** | 2 (8) | 17 (18) | 19 (16) |
| **Constipation**  | 1 (4) | 13 (14) | 14 (12) |
| **Weight Increased** | 0 | 12 (13) | 12 (10) |
| **Blood creatinine increased** | 0 | 11 (12) | 11 (9) |
| **Muscular weakness** | 1 (4) | 9 (10) | 10 (8) |
| **Anemia** | 0 | 9 (10) | 9 (8) |
| **Somnolence** | 4 (16) | 4 (4) | 8 (7) |
| **Musculoskeletal pain** | 4 (16) | 2 (2) | 6 (5) |
| **Headache** | 3 (12) | 3 (3) | 6 (5) |
| **Pain in extremity** | 3 (12) | 3 (3) | 6 (5) |
| **Oropharyngeal pain** | 3 (12) | 1 (1) | 4 (3) |
| **Paresthesia oral** | 3 (12) | 1 (1) | 4 (3) |
| **Hypotension** | 3 (12) | 0 | 3 (3) |

**Supplemental Table 2. Study ALKA-372-001 (Adverse Events by Dose):** Listed are adverse events that were deemed by the investigators to be related to study drug.

|  |  |  |  |
| --- | --- | --- | --- |
| **Adverse Event** **n (%)** | **Schedule A (n=19)** | **Schedule B (n=29)** | **Schedule C (n=6)** |
| **100 mg/m2 (n=3)** | **200 mg/m2 (n=3)** | **400 mg/m2 (n=4)** | **800 mg/m2 (n=3)** | **1200 mg/m2 (n=3)** | **1600 mg/m2 (n=3)** | **200** **mg/m2 (n=3)** | **400 mg/m2 (n=14)** | **600** **mg (n=12)** | **400 mg/m2 (n=3)** | **800 mg/m2 (n=3)** |
| **Fatigue/Asthenia** | 1 (33) | 2 (67) | 1 (25) | 1 (33) | 2 (67) | 1 (33) | 0 | 5 (36) | 4 (33) | 2 (67) | 2 (67) |
| **Dysgeusia** | 1 (33) | 1 (33) | 1 (25) | 1 (33) | 0 | 0 | 1 (33) | 6 (43) | 8 (67) | 1 (33) | 1 (33) |
| **Paresthesia** | 0 | 3 (100) | 3 (75) | 3 (100) | 2 (67) | 1 (33) | 0 | 5 (36) | 2 (17) | 2 (67) | 0 |
| **Nausea** | 2 (67) | 2 (67) | 3 (75) | 2 (67) | 2 (67) | 1 (33) | 0 | 3 (21) | 2 (17) | 2 (67) | 1 (33) |
| **Myalgia** | 1 (33) | 2 (67) | 0 | 1 (33) | 2 (67) | 1 (33) | 1 (33) | 6 (43) | 2 (17) | 2 (67) | 0 |
| **Diarrhea** | 0 | 2 (67) | 1 (25) | 0 | 2 (67) | 1 (33) | 0 | 3 (21) | 3 (25) | 1 (33) | 0 |
| **Vomiting** | 0 | 2 (67) | 1 (25) | 3 (100) | 1 (33) | 1 (33) | 0 | 0 | 4 (33) | 0 | 1 (33) |
| **Arthralgia** | 0 | 2 (67) | 1 (25) | 1 (33) | 0 | 0 | 0 | 3 (21) | 1 (8) | 2 (67) | 0 |
| **Dizziness** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 (29) | 2 (17) | 1 (33) | 1 (33) |
| **Balance disorder** | 0 | 0 | 0 | 0 | 1 (33) | 0 | 1 (33) | 2 (14) | 2 (17) | 0 | 0 |
| **Musculoskeletal pain** | 0 | 1 (33) | 0 | 0 | 1 (33) | 0 | 0 | 2 (14) | 0 | 2 (67) | 0 |
| **Somnolence** | 0 | 1 (33) | 0 | 0 | 1 (33) | 0 | 0 | 2 (14) | 0 | 0 | 2 (67) |

**Supplemental Table 3. Study STARTRK-1 (Adverse Events by Dose):** Listed are adverse events that were deemed by the investigators to be related to study drug.

|  |  |
| --- | --- |
| **Adverse Event****n (%)** | **Continuous Daily Dosing (n=65)** |
| **100 mg/m2 (n=5)** | **200 mg/m2 (n=5)** | **400 mg/m2 (n=10)** | **600 mg (n=33)** | **800 mg (n=12)** |
| **Fatigue/Asthenia** | 1 (20) | 2 (40) | 6 (60) | 17 (52) | 8 (67) |
| **Dysgeusia** | 0 | 2 (40) | 7 (70) | 13 (39) | 7 (58) |
| **Nausea** | 0 | 2 (40) | 3 (30) | 8 (24) | 0 |
| **Paresthesia** | 1 (20) | 0 | 5 (50) | 5 (15) | 2 (17) |
| **Constipation** | 0 | 2 (40) | 2 (20) | 8 (24) | 0 |
| **Weight increased** | 0 | 0 | 0 | 11 (33) | 1 (8) |
| **Blood creatinine increased** | 0 | 0 | 2 (20) | 5 (15) | 4 (33) |
| **Dizziness** | 0 | 1 (20) | 4 (40) | 4 (12) | 2 (17) |
| **Diarrhea** | 0 | 1 (20) | 2 (20) | 5 (15) | 2 (17) |
| **Anemia** | 0 | 0 | 1 (10) | 6 (18) | 2 (17) |
| **Arthralgia** | 0 | 0 | 2 (20) | 4 (12) | 3 (25) |
| **Myalgia** | 0 | 0 | 2 (20) | 6 (18) | 1 (8) |
| **Peripheral sensory neuropathy** | 0 | 0 | 0 | 7 (21) | 1 (8) |
| **Edema peripheral** | 0 | 0 | 2 (20) | 5 (15) | 0 |
| **Vomiting** | 0 | 1 (20) | 1 (10) | 3 (9) | 2 (17) |

**Supplemental Table 4. Adverse Events at the RP2D (600 mg once daily, continuous daily dosing):** Listed are adverse events that were reported in at least 10% of the patients (n=45) who received entrectinib at the RP2D (600 mg) on either Phase 1 trial (ALKA-372-001 or STARTRK-1) and that were deemed by the investigators to be related to study drug.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Adverse Event Term****n (%)** | **Grade 1** | **Grade 2** | **Grade 3** | **All Grades****(n=45)** |
| **Fatigue/Asthenia** | 13 (29) | 7 (16) | 1 (2) | 21 (47) |
| **Dysgeusia**  | 21 (47) | 0 | 0 | 21 (47) |
| **Weight increased** | 3 (7) | 6 (13) | 2 (4) | 11 (24) |
| **Nausea** | 8 (18) | 2 (4) | 0 | 10 (22) |
| **Constipation** | 7 (16) | 2 (4) | 0 | 9 (20) |
| **Diarrhea** | 7 (16) | 0 | 1 (2) | 8 (18) |
| **Dysphagia** | 7 (16) | 1 (2) | 0 | 8 (18) |
| **Myalgia** | 6 (13) | 2 (4) | 0 | 8 (18) |
| **Paresthesia** | 7 (16) | 0 | 0 | 7 (16) |
| **Peripheral sensory neuropathy** | 2 (4) | 3 (7) | 2 (4) | 7 (16) |
| **Vomiting** | 6 (13) | 1 (2) | 0 | 7 (16) |
| **Anemia** | 3 (7) | 0 | 3 (7) | 6 (13) |
| **Dizziness** | 5 (11) | 1 (2) | 0 | 6 (13) |
| **Arthralgia** | 4 (9) | 1 (2) | 0 | 5 (11) |
| **Blood creatinine increased** | 2 (4) | 3 (7) | 0 | 5 (11) |
| **Edema peripheral** | 5 (11) | 0 | 0 | 5 (11) |

**Supplemental Table 5. Pharmacokinetics of Entrectinib Following Continuous Dosing**

|  |  |  |
| --- | --- | --- |
| **Daily Dose** | **Median Tmax, range** | **Mean (CV%)** |
| **Cmax (nM)** | **AUC0-24 (nM·h)** |
| **100 mg/m2** | 4 hours (2 – 8) | 1140 (19.6) | 20400 (24.4) |
| **200 mg/m2** | 4 hours (2 – 6) | 2120 (39.5) | 33600 (45.6) |
| **400 mg/m2** | 4 hours (2 – 6) | 4400 (44.5) | 82600 (43.2) |
| **600 mg fixed dose** | 4 hours (2 – 8) | 2470 (52.1) | 43300 (57.4) |

**Supplemental Table 6. Molecular Characteristics:** The molecular profile of 119 patients with advanced solid tumors who received entrectinib on either Phase 1 trial (ALKA-372-001 or STARTRK-1) are summarized.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **ALKA-372-001 (n=54)** | **STARTRK-1 (n=65)** | **TOTAL****(n=119)** |
| **TRK Molecular Alterations, n (%)**  | **11 (20)** | **18 (28)** | **29 (24)** |
| Gene rearrangement (fusion) | 1 (2)  | 3 (5) | 4 (3) |
| Amplification/overexpression | 6 (11) | 3 (5) | 9 (8) |
| Other mutations\* | 4 (7) | 6 (9) | 10 (8) |
|  Unknown# | 0 | 6 (9) | 6 (5) |
| **ROS1 Molecular Alterations, n (%)** | **20 (37)** | **21 (32)** | **41 (34)** |
| Gene rearrangement (fusion) | 15 (28) | 13 (20) | 28 (24) |
| Amplification/overexpression | 0 | 1 (2) | 1 (1) |
| Other mutations\* | 5 (9) | 4 (6) | 9 (8) |
|  Unknown# | 0 | 3 (5) | 3 (3) |
| **ALK Molecular Alterations, n (%)**  | **21 (39)** | **22 (34)** | **43 (36)** |
| Gene rearrangement (fusion) | 16 (30) | 12 (18) | 28 (24) |
| Amplification/overexpression | 0 | 2 (3) | 2 (2) |
| Other mutations\* | 5 (9) | 5 (8) | 10 (8) |
|  Unknown# | 0 | 3 (5) | 3 (3) |
| **No Molecular Alterations, n (%)** | **2 (4)** | **4 (6)** | **6 (5)** |

\*Other mutations: deletions and single point mutations, including *NTRK R686C*, *NTRK R326G*, *ROS1 S884F*, *ALK A1200V, ALK F1245V,* and others not specified

#Unknown: data not available or not otherwise specified