APPENDIX

**Tissue Profiling For Detection of *NTRK* Fusions**

In patients from ALKA-372-001, local testing included fluorescence in situ hybridization (FISH) or immunohistochemistry (IHC). Molecular profiling of patients from STARTRK-1 was performed via local FISH, IHC, quantitative PCR or next-generation sequencing (NGS). In STARTRK-2, evidence of an activating fusion by high quality nucleic acid based-testing was required for inclusion in the integrated efficacy analysis. Trailblaze Pharos™ NGS central testing or local Clinical Laboratory Improvement Amendments (CLIA)-certified or equivalently accredited diagnostic laboratory nucleic acid-based methodologies (eg, NGS, Sanger sequencing, reverse transcription-PCR, or NanoString) were used. If patients were enrolled via a local test, independent central molecular NGS testing was performed post-enrolment via the Trailblaze Pharos™ assay if tumor sample was available.

**Supplementary data: CNS PFS**

In the overall efficacy-evaluable population, 53 of 121 patients (43.8%) had a CNS progression event or death; median CNS PFS was 26.7 months (95% CI, 18.7–37.1). Median CNS PFS was 10.1 months (95% CI, 5.9–26.7) in the subgroup of 26 patients with CNS metastases at baseline (investigator assessed); of the 17 (65.4%) patients with an event, 11 died, 5 had CNS disease progression and 1 had a first new lesion in the CNS. None of the 95 patients without baseline CNS metastases experienced symptomatic CNS progression: the 36 events contributing to CNS PFS were all deaths, and median CNS PFS was 30.7 months (95% CI, 20.9–46.4).

Table A1**.** Tumor histology of patients in the *NTRK* efficacy-evaluable population.

|  |  |
| --- | --- |
| **Histology, n (%)** | **Efficacy-evaluable population (*N* = 121)** |
| Salivary (MASC) | 24 (19.8) |
| Adenocarcinoma | 18 (14.9) |
| Colorectal carcinoma | 10 (8.3) |
| Papillary thyroid | 10 (8.3) |
| Sarcoma – other | 10 (8.3) |
| Spindle cell | 5 (4.1) |
| Breast (secretory) | 4 (3.3) |
| Pancreatic | 4 (3.3) |
| Cancer of unknown primary | 3 (2.5) |
| Neuroendocrine | 3 (2.5) |
| Thyroid – other | 3 (2.5) |
| Breast (non-secretory) | 2 (1.7) |
| GIST | 2 (1.7) |
| Head and neck – NOS | 2 (1.7) |
| Leiomyosarcoma | 2 (1.7) |
| NSCLC – NOS | 2 (1.7) |
| Squamous cell carcinoma | 2 (1.7) |
| Angiosarcoma | 1 (0.8) |
| Breast – NOS | 1 (0.8) |
| Cervical adenosarcoma | 1 (0.8) |
| Cholangiocarcinoma | 1 (0.8) |
| Chondrosarcoma | 1 (0.8) |
| Colon | 1 (0.8) |
| Endometrial sarcoma | 1 (0.8) |
| Endometrial stromal sarcoma | 1 (0.8) |
| Follicular dendritic cell sarcoma | 1 (0.8) |
| Inflammatory myofibroblastic tumor | 1 (0.8) |
| MPNST | 1 (0.8) |
| Neuroblastoma | 1 (0.8) |
| Non-CRC gastrointestinal – NOS | 1 (0.8) |
| Ovarian | 1 (0.8) |
| Paraganglioma | 1 (0.8) |
| Data cutoff August 31, 2020.  Abbreviations: CRC, colorectal carcinoma; GIST, gastrointestinal stromal tumor; MASC, mammary analogue of salivary gland; MPNST, malignant peripheral nerve sheath tumor; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; *NTRK*, neurotrophic tyrosine receptor kinase. | |

Table A2**.** Individual responses (BICR assessed) by *NTRK* gene fusion.

|  |  |  |  |
| --- | --- | --- | --- |
| ***NTRK* partner** | ***n*** | **ORR, *n* (%)** | **95% CI** |
| *ETV6–NTRK3* | 54 | 40 (74.1) | 60.4–85.0 |
| *TPM3–NTRK1* | 16 | 9 (56.3) | 29.9–80.3 |
| *TPR–NTRK1* | 7 | 5 (71.4) | 29.0–96.3 |
| *SQSTM1–NTRK1* | 3 | 2 (66.7) | NA |
| *EML4–NTRK3* | 4 | 3 (75.0) | 19.4–99.4 |
| *LMNA–NTRK1* | 6 | 3 (50.0) | 11.8–88.2 |
| *SEL1L-NTRK1* | 2 | 2 (100.0) | NA |
| *SQSTM1–NTRK2* | 4 | 1 (25.0) | NA |
| *PEAR1–NTRK1* | 2 | 0 (0.0) | NA |
| *PLEKHA6–NTRK1* | 1 | 1 (100.0) | NA |
| *RBPMS–NTRK3* | 1 | 1 (100.0) | NA |
| *SPECC1L-NTRK3* | 1 | 1 (100.0) | NA |
| *EPS15L1–NTRK1* | 1 | 1 (100.0) | NA |
| *CD74–NTRK1* | 1 | 1 (100.0) | NA |
| *CDC42BPA–NTRK1* | 1 | 1 (100.0) | NA |
| *IRFBP2-NTRK1* | 1 | 1 (100.0) | NA |
| *SQSTM1-NTRK3* | 1 | 1 (100.0) | NA |
| *STRN-NTRK3* | 1 | 1 (100.0) | NA |
| *AKAP13–NTRK3* | 1 | 0 (0.0) | NA |
| *ERC1–NTRK1* | 1 | 0 (0.0) | NA |
| *KIF7–NTRK3* | 1 | 0 (0.0) | NA |
| *TRIM33–NTRK1* | 1 | 0 (0.0) | NA |
| *PDIA3–NTRK1* | 1 | 0 (0.0) | NA |
| *FAM19A2–NTRK3* | 1 | 0 (0.0) | NA |
| *CGN–NTRK1* | 1 | 0 (0.0) | NA |
| *EPS15-NTRK1* | 1 | 0 (0.0) | NA |
| *SCAPER–NTRK3* | 1 | 0 (0.0) | NA |
| *MAMDC2-NTRK2* | 1 | 0 (0.0) | NA |
| *IQGAP-NTRK3* | 1 | 0 (0.0) | NA |
| *FOXB2-NTRK2* | 1 | 0 (0.0) | NA |
| *ZNF382-NTRK1* | 1 | 0 (0.0) | NA |
| Unknown | 1 | 0 (0.0) | NA |
| Data cutoff August 31, 2020.  Abbreviations: BICR, blinded independent central review; CI, confidence interval; NA, not available; *NTRK*, neurotrophic tyrosine receptor kinase; ORR, objective response rate. | | | |

Table A3. Overall efficacy (BICR assessed) of entrectinib in patients with *NTRK* fusion-positive solid tumors, by baseline BICR-assessed CNS metastases status.

|  |  |  |
| --- | --- | --- |
| **Efficacy parameter** | **Baseline CNS metastases**  **(*n* = 19)** | **No baseline  CNS metastases**  **(*n* = 102)** |
| Objective response ratea, *n* (%)  (95% CI) | 12 (63.2) (38.4–83.7) | 62 (60.8) (50.6–70.3) |
| Complete response | 1 (5.3) | 18 (17.6) |
| Partial response | 11 (57.9) | 44 (43.1) |
| Stable disease | 4 (21.1) | 9 (8.8) |
| Progressive disease | 2 (10.5) | 11 (10.8) |
| Non-CR/non-PDb | 0 (0.0) | 6 (5.9) |
| Missing or unevaluablec | 1 (5.3) | 14 (13.7) |
| Duration of responsea | *n* = 12 | *n* = 62 |
| Median, months (95% CI) | 15.2 (6.0–29.4) | 29.0 (13.0–NE) |
| Progression-free survivala |  |  |
| Median, months (95% CI) | 11.7 (5.1–30.3) | 13.8 (10.2–20.4) |
| Overall survival |  |  |
| Median, months (95% CI) | 19.9 (7.9–NE) | 37.1 (23.9–NE) |

Data cutoff August 31, 2020.   
Abbreviations: BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CR, complete response; NE, not estimable; *NTRK*, neurotrophic tyrosine receptor kinase; PD, progressive disease.   
aAs assessed by BICR.   
bPatients with non-measurable lesions. **c**Missing or unevaluable included patients with unevaluable on-study scans or who discontinued prior to obtaining adequate scans to evaluate or confirm response.

Table A4. Intracranial efficacy (BICR assessed) in patients with *NTRK* fusion-positive solid tumors and BICR-assessed CNS metastases at baseline.

|  |  |  |
| --- | --- | --- |
| **Efficacy parameter** | **Patients with CNS metastases at baselinea** | |
| **Measurable disease**  **(*n* = 11)** | **All patientsb**  **(*N* = 19)** |
| Intracranial objective response rate, *n* (%) (95% CI) | 7 (63.6) (30.8–89.1) | 10 (52.6) (28.9–75.6) |
| Complete response | 3 (27.3) | 6 (31.6) |
| Partial response | 4 (36.4) | 4 (21.1) |
| Stable disease | 2 (18.2) | 2 (10.5) |
| Progressive disease | 1 (9.1) | 1 (5.3) |
| Non-CR/non-PD | 0 (0.0) | 5 (26.3) |
| Missing/unevaluable | 1 (9.1) | 1 (5.3) |
| Duration of intracranial response | *n* = 7 | *n* = 10 |
| Patients with event, *n* (%) | 4 (57.1) | 6 (60.0) |
| Median, months (95% CI) | 22.1 (7.4–NE) | 17.2 (7.4–NE) |
| Intracranial progression-free survival |  |  |
| Patients with event, *n* (%) | 6 (54.5) | 13 (68.4) |
| Median, months (95% CI) | 19.9 (5.9–NE) | 10.1 (6.3–26.7) |
| Data cutoff August 31, 2020. Intracranial objective response rate derived using RECIST v1.1 criteria applied only to CNS lesions. Abbreviations: BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CR, complete response; NE, not estimable; *NTRK*, neurotrophic tyrosine receptor kinase; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors.  aBICR assessed.  bIncludes patients with measurable and non-measurable CNS metastases. As per RECIST v1.1 non-measurable CNS disease could only be categorized as CR, non-CR/non-PD, or PD. | | |

Table A5. Intracranial efficacy (BICR assessed) in patients with *NTRK* fusion-positive solid tumors and BICR-assessed CNS metastases at baseline, according to prior brain radiotherapy status before start of treatment.

|  |  |  |
| --- | --- | --- |
| **Efficacy parameter** | **No prior brain radiotherapy or prior brain radiotherapy ≥6 months  (*n* = 9)** | **Prior brain radiotherapy <6 months  (*n* = 10)** |
| Intracranial objective response rate, *n* (%) (95% CI) | 5 (55.6)  (21.2–86.3) | 5 (50.0) (18.7–81.3) |
| Complete response | 3 (33.3) | 3 (30.0) |
| Partial response | 2 (22.2) | 2 (20.0) |
| Stable disease | 2 (22.2) | 0 |
| Progressive disease | 0 | 1 (10.0) |
| Non-CR/non-PD | 2 (22.2) | 3 (30.0) |
| Missing/unevaluable | 0 | 1 (10.0) |
| Duration of intracranial response | *n* = 5 | *n* = 5 |
| Patients with event, *n* (%) | 2 (40.0) | 4 (80.0) |
| Median, months (95% CI) | NE (7.4–NE) | 17.2 (5.0–NE) |
| Intracranial progression free survival |  |  |
| Patients with event, *n* (%) | 4 (44.4) | 9 (90.0) |
| Median, months (95% CI) | 10.1 (7.9–NE) | 10.3 (5.1–26.7) |

|  |
| --- |
| Data cutoff August 31, 2020.  Abbreviations: BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CR, complete response; NE, not estimable; *NTRK*, neurotrophic tyrosine receptor kinase; PD, progressive disease. |

Table A6. Baseline characteristics – safety-evaluable populations.

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristic | | *NTRK* fusion-positive  safety-evaluable population (*n* = 193) | Overall safety population (*N* = 626) |
| Age, years | Median (range) | 57.0 (21–88) | 54.0 (0–88) |
| Sex, *n* (%) | Female | 100 (51.8) | 344 (55.0) |
| Male | 93 (48.2) | 282 (45.0) |
| Race, *n* (%) | White | 112 (58.0) | 367 (58.6) |
| Asian | 49 (25.4) | 173 (27.6) |
| Black or African American | 7 (3.6) | 31 (5.0) |
| Other | 1 (0.5) | 10 (1.6) |
| Not reported | 24 (12.4) | 45 (7.2) |
| ECOG PS, *n* (%) |  | *n* = 193 | *n* = 583 |
| 0 | 73 (37.8) | 234 (40.1) |
| 1 | 98 (50.8) | 296 (50.8) |
| 2 | 19 (9.8) | 48 (8.2) |
|  | ≥3 | 3 (1.6) | 5 (0.9) |
| History of smoking, *n* (%) |  | *n* = 189 | *n* = 558 |
| Never smoker | 117 (61.9) | 339 (60.8) |
| Current / former smoker | 72 (38.1) | 219 (39.2) |
| Prior lines of systemic therapya, *n* (%) | 0 | 62 (32.1) | 181 (28.9) |
| 1 | 57 (29.5) | 179 (28.6) |
| ≥2 | 74 (38.3) | 266 (42.5) |
| Any previous therapyb, *n* (%) | Chemotherapy | 138 (71.5) | 459 (73.3) |
| Targeted therapy | 34 (17.6) | 162 (25.9) |
| Hormonal therapy | 14 (7.3) | 23 (3.7) |
| Immunotherapy | 21 (10.9) | 84 (13.4) |
| CNS metastases at baselinec, *n* (%) | Yes | 53 (27.5) | 205 (32.7) |
| No | 140 (72.5) | 421 (67.3) |
| Prior radiotherapy of the braind, *n* (%) |  | *n* = 53 | *n* = 205 |
| Yes | 39 (73.6) | 133 (64.9) |
| No | 14 (26.4) | 72 (35.1) |
| Time from end of prior radiotherapy  of the brain to first dosee, *n* (%) |  | *n* = 39 | *n* = 129 |
| <2 months | 12 (30.8) | 35 (27.1) |
| 2−<6 months | 9 (23.1) | 32 (24.8) |
| ≥6 months | 18 (46.2) | 62 (48.1) |
| Tumor categoryf, *n* (%) |  | *n* = 193 | *n* = 625 |
| NSCLC | 39 (20.2) | 320 (51.2) |
| Sarcoma | 37 (19.2) | 61 (9.8) |
| Salivary (MASC) | 30 (15.5) | 34 (5.4) |
| Thyroid | 16 (8.3) | 19 (3.0) |
| CNS primary | 15 (7.8) | 40 (6.4) |
| Colorectal | 12 (6.2) | 27 (4.3) |
| Breast | 12 (6.2) | 20 (3.2) |
| Neuroendocrine | 6 (3.1) | 11 (1.8) |
| Pancreatic | 6 (3.1) | 13 (2.1) |
| Head and neck | 5 (2.6) | 11 (1.8) |
| Cancer of unknown primary | 4 (2.1) | 5 (0.8) |
| Gynecologic | 3 (1.6) | 9 (1.4) |
| Cholangiocarcinoma | 1 (0.5) | 5 (0.8) |
| Neuroblastoma | 1 (0.5) | 22 (3.5) |
| Gastrointestinal – other | 1 (0.5) | 2 (0.3) |
| Gastroesophageal | 1 (0.5) | 2 (0.3) |
| Appendiceal | 1 (0.5) | 2 (0.3) |
| Penile | 1 (0.5) | 1 (0.2) |
| Prostate | 1 (0.5) | 3 (0.5) |
| Mesothelioma | 1 (0.5) | 2 (0.3) |
| Skin cancer | 0 | 6 (1.0) |
| Renal cell carcinoma | 0 | 3 (0.5) |
| Infantile fibrosarcomag | 0 | 2 (0.3) |
| Lymphoma | 0 | 2 (0.3) |
| Adrenal | 0 | 1 (0.2) |
| Brain | 0 | 1 (0.2) |
| Non-colon cancer GI | 0 | 1 (0.2) |
| Data cutoff August 31, 2020.  Abbreviations: CNS, central nervous system; CUP, cancer of unknown primary; ECOG PS, Eastern Cooperative Oncology Group performance status; GI, gastrointestinal; MASC, mammary analogue of secretory carcinoma; NSCLC, non-small cell lung cancer; *NTRK*, neurotrophic tyrosine receptor kinase; RECIST, Response Evaluation Criteria in Solid Tumors.  aTotal number of regimens received by a patient across all settings.  bPrevious therapy in any setting.  cCNS metastases status as assessed by investigator (RECIST v1.1).  dAmong patients with baseline CNS metastases as per investigator.  eAmong patients with baseline CNS metastases and prior radiotherapy of the brain.  fPatients may have had multiple sites of metastases at baseline.  gInfantile fibrosarcoma is considered separately from sarcomas because the efficacy-evaluable population only includes adults. | | | |

Table A7. Adverse events reported in ≥5% of patients regardless of causality.

|  |  |  |
| --- | --- | --- |
| **MedDRA system organ class MedDRA preferred term, *n* (%)a** | ***NTRK* fusion-positive safety-evaluable population  (*n* = 193)** | **Overall safety population  (*N* = 626)** |
| **Overall number (%) of patients with ≥1 event** | 192 (99.5) | 621 (99.2) |
| **Nervous system disorders** | | |
| Dysgeusia | 71 (36.8) | 236 (37.7) |
| Dizziness | 69 (35.8) | 223 (35.6) |
| Headache | 29 (15.0) | 106 (16.9) |
| Paresthesia | 28 (14.5) | 113 (18.1) |
| Peripheral sensory neuropathy | 17 (8.8) | 55 (8.8) |
| Hyperesthesia | 16 (8.3) | 42 (6.7) |
| Neuropathy peripheral | 15 (7.8) | 46 (7.3) |
| Taste disorder | 14 (7.3) | 31 (5.0) |
| Cognitive disorder | 12 (6.2) | 39 (6.2) |
| Syncope | 11 (5.7) | 33 (5.3) |
| Ataxia | 10 (5.2) | 31 (5.0) |
| Somnolence | 8 (4.1) | 38 (6.1) |
| **Gastrointestinal disorders** | | |
| Diarrhea | 79 (40.9) | 237 (37.9) |
| Constipation | 76 (39.4) | 266 (42.5) |
| Nausea | 56 (29.0) | 213 (34.0) |
| Vomiting | 36 (18.7) | 159 (25.4) |
| Abdominal pain | 26 (13.5) | 80 (12.8) |
| Dysphagia | 18 (9.3) | 68 (10.9) |
| Dry mouth | 16 (8.3) | 43 (6.9) |
| Dyspepsia | 13 (6.7) | 41 (6.5) |
| Gastroesophageal reflux disease | 12 (6.2) | 40 (6.4) |
| Abdominal pain upper | 11 (5.7) | 28 (4.5) |
| Abdominal distension | 10 (5.2) | 37 (5.9) |
| **General disorders and administration site conditions** | | |
| Fatigue | 66 (34.2) | 246 (39.3) |
| Edema peripheral | 59 (30.6) | 178 (28.4) |
| Pyrexia | 27 (14.0) | 130 (20.8) |
| Gait disturbance | 19 (9.8) | 53 (8.5) |
| Asthenia | 17 (8.8) | 51 (8.1) |
| Pain | 11 (5.7) | 31 (5.0) |
| Edema | 10 (5.2) | 28 (4.5) |
| Peripheral swelling | 10 (5.2) | 29 (4.6) |
| **Respiratory, thoracic and mediastinal disorders** | | |
| Dyspnea | 41 (21.2) | 165 (26.4) |
| Cough | 33 (17.1) | 135 (21.6) |
| Pleural effusion | 13 (6.7) | 43 (6.9) |
| Hypoxia | 12 (6.2) | 32 (5.1) |
| Pulmonary embolism | 11 (5.7) | 26 (4.2) |
| Oropharyngeal pain | 10 (5.2) | 46 (7.3) |
| **Musculoskeletal and connective tissue disorders** | | |
| Myalgia | 35 (18.1) | 122 (19.5) |
| Arthralgia | 29 (15.0) | 122 (19.5) |
| Pain in extremity | 29 (15.0) | 80 (12.8) |
| Back pain | 17 (8.8) | 73 (11.7) |
| Muscular weakness | 15 (7.8) | 74 (11.8) |
| Muscle spasms | 11 (5.7) | 27 (4.3) |
| Musculoskeletal pain | 10 (5.2) | 34 (5.4) |
| **Investigations** | | |
| Weight increased | 67 (34.7) | 204 (32.6) |
| Blood creatinine increased | 64 (33.2) | 178 (28.4) |
| Alanine aminotransferase increased | 44 (22.8) | 114 (18.2) |
| Aspartate aminotransferase increased | 41 (21.2) | 115 (18.4) |
| Neutrophil count decreased | 16 (8.3) | 55 (8.8) |
| White blood cell count decreased | 16 (8.3) | 44 (7.0) |
| Blood alkaline phosphatase increased | 15 (7.8) | 30 (4.8) |
| Blood uric acid increased | 10 (5.2) | 15 (2.4) |
| **Infections and infestations** | | |
| Urinary tract infection | 38 (19.7) | 97 (15.5) |
| Upper respiratory tract infection | 17 (8.8) | 61 (9.7) |
| Pneumonia | 17 (8.8) | 55 (8.8) |
| **Metabolism and nutrition disorders** | | |
| Hyperuricemia | 23 (11.9) | 67 (10.7) |
| Dehydration | 17 (8.8) | 55 (8.8) |
| Hypocalcemia | 17 (8.8) | 41 (6.5) |
| Decreased appetite | 16 (8.3) | 82 (13.1) |
| Hypokalemia | 15 (7.8) | 48 (7.7) |
| Hyperglycemia | 15 (7.8) | 42 (6.7) |
| Hypoalbuminemia | 13 (6.7) | 41 (6.5) |
| Hyperkalemia | 12 (6.2) | 42 (6.7) |
| Hypomagnesemia | 11 (5.7) | 24 (3.8) |
| Hypophosphatemia | 10 (5.2) | 34 (5.4) |
| Hyponatremia | 10 (5.2) | 30 (4.8) |
| Hypernatremia | 9 (4.7) | 33 (5.3) |
| **Skin and subcutaneous tissue disorders** | | |
| Rash | 18 (9.3) | 55 (8.8) |
| Dry skin | 11 (5.7) | 39 (6.2) |
| Pruritus | 9 (4.7) | 46 (7.3) |
| **Blood and lymphatic system disorders** | | |
| Anemia | 62 (32.1) | 191 (30.5) |
| Neutropenia | 13 (6.7) | 35 (5.6) |
| **Eye disorders** | | |
| Vision blurred | 17 (8.8) | 59 (9.4) |
| Dry eye | 10 (5.2) | 26 (4.2) |
| Photophobia | 7 (3.6) | 31 (5.0) |
| **Psychiatric disorders** | | |
| Insomnia | 18 (9.3) | 50 (8.0) |
| Confusional state | 13 (6.7) | 46 (7.3) |
| Anxiety | 11 (5.7) | 32 (5.1) |
| **Vascular disorders** | | |
| Hypotension | 30 (15.5) | 90 (14.4) |
| Hypertension | 10 (5.2) | 38 (6.1) |
| **Injury, poisoning, and procedural complications** | | |
| Fall | 24 (12.4) | 60 (9.6) |
| **Renal and urinary disorders** | | |
| Acute kidney injury | 15 (7.8) | 28 (4.5) |
| Urinary incontinence | 11 (5.7) | 39 (6.2) |
| Urinary retention | 7 (3.6) | 34 (5.4) |
| **Ear and labyrinth disorders** |  |  |
| Vertigo | 12 (6.2) | 29 (4.6) |
| Data cutoff August 31, 2020. Data are n (%) of patients. Adverse events were encoded using MedDRA (version 21.0).  Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; *NTRK*, neurotrophic tyrosine receptor kinase.  aFor preferred term rows, multiple occurrences of the same adverse event in one individual are counted once at the highest grade for this patient, for the overall (first) row a patient contributes only with the adverse event occurring with the highest grade. | | |

Table A8**.** Treatment-related adverse events, by highest grade, reported in ≥10% of patients or with ≥1 grade 3 or 4 event.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **MedDRA system organ class**  **Preferred term, *n* (%)a** | | ***NTRK* fusion-positive safety-evaluable population (*n* = 193)** | | | | | | | | | | **Overall safety-evaluable population  (*n* = 626)** | | | | | | |
| **Patients** | | **Grade 1** | | **Grade 2** | | | **Grade 3** | | | **Grade 4** | | **Grade 1** | **Grade 2** | | **Grade 3** | | **Grade 4** | |
| **Overall number (%) of patients with ≥1 event** | | **29  (15.0)** | | **66  (34.2)** | | | **71  (36.8)** | | | **4  (2.1)** | | **127  (20.3)** | **211  (33.7)** | | **213  (34.0)** | | **20  (3.2)** | |
| **Nervous system disordersb** | | | | | | | | | | | |  | |  | |  | |  |
| Dysgeusia | | 54 (28.0) | | 14 (7.3) | | | 0 | | | 0 | | 194 (31.0) | 30 (4.8) | | 1 (0.2) | | 0 | |
| Dizziness | | 29 (15.0) | | 14 (7.3) | | | 5 (2.6) | | | 0 | | 113 (18.1) | 49 (7.8) | | 6 (1.0) | | 0 | |
| Paresthesia | | 20 (10.4) | | 3 (1.6) | | | 0 | | | 0 | | 86 (13.7) | 11 (1.8) | | 2 (0.3) | | 0 | |
| Peripheral sensory neuropathy | | 9 (4.7) | | 4 (2.1) | | | 1 (0.5) | | | 0 | | 29 (4.6) | 12 (1.9) | | 5 (0.8) | | 0 | |
| Cognitive disorder | | 4 (2.1) | | 3 (1.6) | | | 2 (1.0) | | | 0 | | 19 (3.0) | 9 (1.4) | | 5 (0.8) | | 0 | |
| Syncope | | 0 | | 0 | | | 2 (1.0) | | | 0 | | 2 (0.3) | 1 (0.2) | | 4 (0.6) | | 0 | |
| Thalamic infarction | | 0 | | 0 | | | 1 (0.5) | | | 0 | | 0 | 0 | | 1 (0.2) | | 0 | |
| Hyperesthesia | | 13 (6.7) | | 1 (0.5) | | | 0 | | | 0 | | 37 (5.9) | 1 (0.2) | | 1 (0.2) | | 0 | |
| Neuropathy peripheral | | 7 (3.6) | | 4 (2.1) | | | 0 | | | 0 | | 21 (3.4) | 10 (1.6) | | 1 (0.2) | | 0 | |
| Disturbance in attention | | 5 (2.6) | | 1 (0.5) | | | 0 | | | 0 | | 22 (3.5) | 2 (0.3) | | 1 (0.2) | | 0 | |
| Ataxia | | 2 (1.0) | | 4 (2.1) | | | 0 | | | 0 | | 8 (1.3) | 12 (1.9) | | 3 (0.5) | | 0 | |
| Dysarthria | | 2 (1.0) | | 2 (1.0) | | | 0 | | | 0 | | 9 (1.4) | 4 (0.6) | | 2 (0.3) | | 0 | |
| Amnesia | | 2 (1.0) | | 1 (0.5) | | | 0 | | | 0 | | 11 (1.8) | 1 (0.2) | | 1 (0.2) | | 0 | |
| Myoclonus | | 0 | | 0 | | | 0 | | | 0 | | 0 | 0 | | 1 (0.2) | | 0 | |
| **Gastrointestinal disorders** | | | | | | | | | | | |  | |  | |  | |  |
| Diarrhea | | 39 (20.2) | 17 (8.8) | | | 4 (2.1) | | | 0 | | | 115 (18.4) | | 35 (5.6) | | 12 (1.9) | | 0 |
| Constipation | | 35 (18.1) | 15 (7.8) | | | 0 | | | 0 | | | 111 (17.7) | | 45 (7.2) | | 1 (0.2) | | 0 |
| Nausea | | 28 (14.5) | 4 (2.1) | | | 0 | | | 0 | | | 112 (17.9) | | 13 (2.1) | | 2 (0.3) | | 0 |
| Vomiting | | 17 (8.8) | 3 (1.6) | | | 1 (0.5) | | | 0 | | | 75 (12.0) | | 7 (1.1) | | 3 (0.5) | | 0 |
| Anorectal disorder | | 0 | 0 | | | 0 | | | 0 | | | 0 | | 0 | | 0 | | 1 (0.2) |
| Pancreatitis | | 0 | 0 | | | 0 | | | 0 | | | 0 | | 0 | | 0 | | 1 (0.2) |
| **General disorders and administration site conditionsb** | | | | | | | | | | | |  | |  | |  | |  |
| Fatigue | | 27 (14.0) | 17 (8.8) | | | 9 (4.7) | | | 0 | | | 94 (15.0) | 69 (11.0) | | 17 (2.7) | | 0 | |
| Edema peripheral | | 25 (13.0) | 9 (4.7) | | | 1 (0.5) | | | 0 | | | 71 (11.3) | 28 (4.5) | | 2 (0.3) | | 0 | |
| Asthenia | | 8 (4.1) | 2 (1.0) | | | 2 (1.0) | | | 0 | | | 22 (3.5) | 7 (1.1) | | 3 (0.5) | | 0 | |
| Edema | | 3 (1.6) | 1 (0.5) | | | 2 (1.0) | | | 0 | | | 13 (2.1) | 5 (0.8) | | 2 (0.3) | | 0 | |
| Edema localized | | 1 (0.5) | 1 (0.5) | | | 1 (0.5) | | | 0 | | | 2 (0.3) | 1 (0.2) | | 1 (0.2) | | 0 | |
| Pyrexia | | 4 (2.1) | 0 | | | 0 | | | 0 | | | 11 (1.8) | 4 (0.6) | | 2 (0.3) | | 0 | |
| Pain | | 2 (1.0) | 1 (0.5) | | | 0 | | | 0 | | | 5 (0.8) | 3 (0.5) | | 1 (0.2) | | 0 | |
| Peripheral swelling | | 3 (1.6) | 1 (0.5) | | | 0 | | | 0 | | | 6 (1.0) | 3 (0.5) | | 1 (0.2) | | 0 | |
| Generalized edema | | 0 | 1 (0.5) | | | 0 | | | 0 | | | 2 (0.3) | 5 (0.8) | | 3 (0.5) | | 0 | |
| **Investigations** | | | | | | | | | | | |  | |  | |  | |  |
| Blood creatinine increased | | 32 (16.6) | 16 (8.3) | | | 2 (1.0) | | | 0 | | | 79 (12.6) | 51 (8.1) | | 3 (0.5) | | 0 | |
| Weight increased | | 23 (11.9) | 14 (7.3) | | | 16 (8.3) | | | 0 | | | 57 (9.1) | 64 (10.2) | | 50 (8.0) | | 0 | |
| AST increased | | 21 (10.9) | 7 (3.6) | | | 3 (1.6) | | | 1 (0.5) | | | 61 (9.7) | 11 (1.8) | | 8 (1.3) | | 2 (0.3) | |
| ALT increased | | 21 (10.9) | 5 (2.6) | | | 3 (1.6) | | | 1 (0.5) | | | 53 (8.5) | 12 (1.9) | | 11 (1.8) | | 2 (0.3) | |
| Neutrophil count decreased | | 5 (2.6) | 6 (3.1) | | | 4 (2.1) | | | 0 | | | 8 (1.3) | 16 (2.6) | | 19 (3.0) | | 2 (0.3) | |
| White blood cell count decreased | | 8 (4.1) | 5 (2.6) | | | 1 (0.5) | | | 0 | | | 19 (3.0) | 14 (2.2) | | 3 (0.5) | | 0 | |
| Blood uric acid increased | | 3 (1.6) | 0 | | | 0 | | | 1 (0.5) | | | 6 (1.0) | 0 | | 0 | | 1 (0.2) | |
| Electrocardiogram QT prolonged | | 2 (1.0) | 0 | | | 1 (0.5) | | | 0 | | | 9 (1.4) | 2 (0.3) | | 3 (0.5) | | 0 | |
| Ejection fraction decreased | | 0 | 0 | | | 1 (0.5) | | | 0 | | | 0 | 4 (0.6) | | 2 (0.3) | | 0 | |
| Lymphocyte count decreased | | 1 (0.5) | 3 (1.6) | | | 0 | | | 0 | | | 7 (1.1) | 3 (0.5) | | 4 (0.6) | | 0 | |
| Blood creatine PK increased | | 2 (1.0) | 0 | | | 0 | | | 0 | | | 7 (1.1) | 1 (0.2) | | 2 (0.3) | | 0 | |
| Platelet count decreased | | 3 (1.6) | 0 | | | 0 | | | 0 | | | 7 (1.1) | 1 (0.2) | | 0 | | 1 (0.2) | |
| Amylase increased | | 0 | 0 | | | 0 | | | 0 | | | 2 (0.3) | 2 (0.3) | | 3 (0.5) | | 0 | |
| Weight decreased | | 2 (1.0) | 1 (0.5) | | | 0 | | | 0 | | | 3 (0.5) | 2 (0.3) | | 1 (0.2) | | 0 | |
| Lipase increased | | 0 | 0 | | | 0 | | | 0 | | | 2 (0.3) | 0 | | 2 (0.3) | | 1 (0.2) | |
| Blood creatine PK MB increased | | 0 | 0 | | | 0 | | | 0 | | | 0 | 0 | | 0 | | 1 (0.2) | |
| Neutrophil percentage decreased | | 0 | 0 | | | 0 | | | 0 | | | 0 | 0 | | 1 (0.2) | | 0 | |
| Troponin T increased | | 0 | 0 | | | 0 | | | 0 | | | 0 | 0 | | 1 (0.2) | | 0 | |
| **Musculoskeletal and connective tissue disorders** | | | | | | | | | | | |  | |  | |  | |  |
| Myalgia | | 16 (8.3) | 4 (2.1) | | | 1 (0.5) | | | 0 | | | 69 (11.0) | 18 (2.9) | | 3 (0.5) | | 0 | |
| Muscular weakness | | 7 (3.6) | 2 (1.0) | | | 1 (0.5) | | | 0 | | | 25 (4.0) | 10 (1.6) | | 4 (0.6) | | 0 | |
| Osteoarthritis | | 0 | 0 | | | 1 (0.5) | | | 0 | | | 2 (0.3) | 1 (0.2) | | 1 (0.2) | | 0 | |
| Arthralgia | | 7 (3.6) | 3 (1.6) | | | 0 | | | 0 | | | 47 (7.5) | 15 (2.4) | | 2 (0.3) | | 0 | |
| Facet joint syndrome | | 0 | 0 | | | 0 | | | 0 | | | 0 | 0 | | 1 (0.2) | | 0 | |
| Lumbar spinal stenosis | | 0 | 0 | | | 0 | | | 0 | | | 0 | 0 | | 1 (0.2) | | 0 | |
| Spinal stenosis | | 0 | 0 | | | 0 | | | 0 | | | 0 | 0 | | 1 (0.2) | | 0 | |
| Synovial cyst | | 0 | 0 | | | 0 | | | 0 | | | 0 | 0 | | 1 (0.2) | | 0 | |
| **Metabolism and nutrition disorders** | | | | | | | | | | | |  | |  | |  | |  |
| Hyperuricemia | | 10 (5.2) | 2 (1.0) | | | 1 (0.5) | | | 3 (1.6) | | | 27 (4.3) | 3 (0.5) | | 2 (0.3) | | 6 (1.0) | |
| Hypophosphatemia | | 1 (0.5) | 2 (1.0) | | | 2 (1.0) | | | 0 | | | 4 (0.6) | 5 (0.8) | | 4 (0.6) | | 0 | |
| Increased appetite | | 4 (2.1) | 0 | | | 1 (0.5) | | | 0 | | | 15 (2.4) | 4 (0.6) | | 1 (0.2) | | 0 | |
| Hypokalemia | | 2 (1.0) | 0 | | | 1 (0.5) | | | 0 | | | 12 (1.9) | 0 | | 1 (0.2) | | 0 | |
| Hyponatremia | | 3 (1.6) | 0 | | | 1 (0.5) | | | 0 | | | 6 (1.0) | 0 | | 3 (0.5) | | 0 | |
| Fluid retention | | 1 (0.5) | 0 | | | 1 (0.5) | | | 0 | | | 2 (0.3) | 1 (0.2) | | 1 (0.2) | | 0 | |
| Hypocalcemia | | 1 (0.5) | 0 | | | 1 (0.5) | | | 0 | | | 3 (0.5) | 0 | | 1 (0.2) | | 1 (0.2) | |
| Hypermagnesemia | | 0 | 0 | | | 1 (0.5) | | | 0 | | | 2 (0.3) | 0 | | 1 (0.2) | | 0 | |
| Tumor lysis syndrome | | 0 | 0 | | | 1 (0.5) | | | 0 | | | 0 | 0 | | 1 (0.2) | | 0 | |
| Dehydration | | 2 (1.0) | 3 (1.6) | | | 0 | | | 0 | | | 3 (0.5) | 6 (1.0) | | 3 (0.3) | | 0 | |
| Hyperkalemia | | 2 (1.0) | 0 | | | 0 | | | 0 | | | 7 (1.1) | 0 | | 1 (0.2) | | 0 | |
| Hypertriglyceridemia | | 2 (1.0) | 0 | | | 0 | | | 0 | | | 5 (0.8) | 1 (0.2) | | 1 (0.2) | | 1 (0.2) | |
| Hypoalbuminemia | | 1 (0.5) | 0 | | | 0 | | | 0 | | | 6 (1.0) | 0 | | 1 (0.2) | | 0 | |
| Hyperglycemia | | 1 (0.5) | 0 | | | 0 | | | 0 | | | 5 (0.8) | 0 | | 1 (0.2) | | 0 | |
| Hyperamylasemia | | 0 | 0 | | | 0 | | | 0 | | | 0 | 0 | | 1 (0.2) | | 0 | |
| Hypervolemia | | 0 | 0 | | | 0 | | | 0 | | | 0 | 0 | | 1 (0.2) | | 0 | |
| **Blood and lymphatic system disorders** | | | | | | | | | | | |  | |  | |  | |  |
| Anemia | | 14 (7.3) | 9 (4.7) | | | 10 (5.2) | | | 0 | | | 38 (6.1) | 36 (5.8) | | 24 (3.8) | | 0 | |
| Neutropenia | | 5 (2.6) | 2 (1.0) | | | 4 (2.1) | | | 0 | | | 10 (1.6) | 6 (1.0) | | 13 (2.1) | | 0 | |
| Lymphopenia | | 2 (1.0) | 0 | | | 1 (0.5) | | | 0 | | | 8 (1.3) | 0 | | 1 (0.2) | | 0 | |
| **Skin and cutaneous tissue disorder** | | | | | | | | | | | |  | |  | |  | |  |
| Rash maculo-papular |  | 2 (1.0) | 0 | | | 1 (0.5) | | | 0 | | | 10 (1.6) | 1 (0.2) | | 2 (0.3) | | 0 | |
| Rash |  | 7 (3.6) | 2 (1.0) | | | 0 | | | 0 | | | 28 (4.5) | 5 (0.8) | | 4 (0.6) | | 0 | |
| Pruritus |  | 3 (1.6) | 3 (1.6) | | | 0 | | | 0 | | | 20 (3.2) | 6 (1.0) | | 1 (0.2) | | 0 | |
| Pain of skin |  | 7 (3.6) | 0 | | | 0 | | | 0 | | | 15 (2.4) | 1 (0.2) | | 1 (0.2) | | 0 | |
| Erythema |  | 1 (0.5) | 0 | | | 0 | | | 0 | | | 4 (0.6) | 0 | | 1 (0.2) | | 0 | |
| Urticaria |  | 1 (0.5) | 0 | | | 0 | | | 0 | | | 4 (0.6) | 0 | | 1 (0.2) | | 0 | |
| **Eye disorders** | | | | | | | | | | | |  | |  | |  | |  |
| Diplopia | | 0 | 1 (0.5) | | | 1 (0.5) | | | 0 | | | 2 (0.3) | 4 (0.6) | | 1 (0.2) | | 0 | |
| **Psychiatric disorders** | | | | | | | | | | | |  | |  | |  | |  |
| Confusional state | | 5 (2.6) | 2 (1.0) | | | 1 (0.5) | | | 0 | | | 18 (2.9) | 6 (1.0) | | 1 (0.2) | | 0 | |
| Anxiety | | 0 | 0 | | | 1 (0.5) | | | 0 | | | 2 (0.3) | 2 (0.3) | | 1 (0.2) | | 0 | |
| Delirium | | 0 | 0 | | | 0 | | | 0 | | | 0 | 1 (0.2) | | 1 (0.2) | | 0 | |
| Mental status changes | | 0 | 0 | | | 0 | | | 0 | | | 0 | 0 | | 2 (0.3) | | 0 | |
| Agitation | | 0 | 0 | | | 0 | | | 0 | | | 0 | 0 | | 1 (0.2) | | 0 | |
| Disorientation | | 0 | 0 | | | 0 | | | 0 | | | 0 | 0 | | 1 (0.2) | | 0 | |
| Mood altered | | 0 | 0 | | | 0 | | | 0 | | | 0 | 0 | | 1 (0.2) | | 0 | |
| **Vascular disorders** | | | | | | | | | | | |  | |  | |  | |  |
| Hypotension | | 1 (0.5) | 2 (1.0) | | | 2 (1.0) | | | 0 | | | 13 (2.1) | 9 (1.4) | | 3 (0.5) | | 0 | |
| Orthostatic hypotension | | 0 | 0 | | | 1 (0.9) | | | 0 | | | 6 (1.0) | 1 (0.2) | | 1 (0.2) | | 0 | |
| Hypertension | | 0 | 1 (0.5) | | | 0 | | | 0 | | | 0 | 1 (0.2) | | 2 (0.3) | | 0 | |
| **Renal and urinary disorders** | | | | | | | | | | | |  | |  | |  | |  |
| Chronic kidney disease | | 0 | 1 (0.5) | | | 2 (1.0) | | | 0 | | | 1 (0.2) | 2 (0.3) | | 2 (0.3) | | 0 | |
| Urinary retention | | 2 (1.0) | 0 | | | 1 (0.5) | | | 0 | | | 7 (1.1) | 1 (0.2) | | 1 (0.2) | | 0 | |
| Acute kidney injury | | 3 (1.6) | 1 (0.5) | | | 0 | | | 0 | | | 5 (0.8) | 2 (0.3) | | 1 (0.2) | | 0 | |
| Lymphedema | | 0 | 0 | | | 0 | | | 0 | | | 0 | 0 | | 1 (0.2) | | 0 | |
| **Cardiac disordersb** | | | | | | | | | | | |  | |  | |  | |  |
| Cardiac failure | | 0 | 0 | | | 2 (1.0) | | | 0 | | | 0 | 2 (0.3) | | 5 (0.8) | | 1 (0.2) | |
| Cardiac failure congestive | | 0 | 0 | | | 2 (1.0) | | | 0 | | | 0 | 0 | | 4 (0.6) | | 0 | |
| Left ventricular dysfunction | | 0 | 1 (0.5) | | | 1 (0.5) | | | 0 | | | 0 | 1 (0.2) | | 1 (0.2) | | 0 | |
| Acute coronary syndrome | | 0 | 0 | | | 0 | | | 0 | | | 0 | 0 | | 1 (0.2) | | 0 | |
| Myocarditis | | 0 | 0 | | | 0 | | | 0 | | | 0 | 0 | | 0 | | 1 (0.2) | |
| **Ear and labyrinth disorders** | |  | | |  | | |  | | |  |  | |  | |  | |  |
| Vertigo | | 7 (3.6) | 1 (0.5) | | | 1 (0.5) | | | 0 | | | 17 (2.7) | 3 (0.5) | | 1 (0.2) | | 0 | |
| **Immune system disorders** | |  | | |  | | |  | | |  |  | |  | |  | |  |
| Anaphylactic reaction | | 0 | 0 | | | 1 (0.5) | | | 0 | | | 0 | 0 | | 1 (0.2) | | 0 | |
| Drug hypersensitivity | | 0 | 0 | | | 0 | | | 0 | | | 0 | 0 | | 1 (0.2) | | 0 | |
| **Injury, poisoning and procedural complications** | | | | | | | | | | | |  | |  | |  | |  |
| Fall | | 3 (1.6) | 1 (0.5) | | | 0 | | | 0 | | | 14 (2.2) | 1 (0.2) | | 1 (0.2) | | 0 | |
| Foot fracture | | 0 | 1 (0.5) | | | 0 | | | 0 | | | 0 | 1 (0.2) | | 1 (0.2) | | 0 | |
| Tibia fracture | | 0 | 0 | | | 0 | | | 0 | | | 0 | 1 (0.2) | | 2 (0.3) | | 0 | |
| Femur fracture | | 0 | 0 | | | 0 | | | 0 | | | 0 | 1 (0.2) | | 1 (0.2) | | 0 | |
| **Respiratory, thoracic and mediastinal disorders** | | | | | | | | | | | |  | |  | |  | |  |
| Dyspnea | | 6 (3.1) | 3 (1.6) | | | 0 | | | 0 | | | 17 (2.7) | 6 (1.0) | | 1 (0.2) | | 0 | |
| Hypoxia | | 1 (0.5) | 1 (0.5) | | | 0 | | | 0 | | | 1 (0.2) | 1 (0.2) | | 1 (0.2) | | 1 (0.2) | |
| Pulmonary edema | | 0 | 0 | | | 0 | | | 0 | | | 0 | 0 | | 1 (0.2) | | 1 (0.2) | |
| Respiratory failure | | 0 | 0 | | | 0 | | | 0 | | | 0 | 0 | | 0 | | 1 (0.2) | |
| **Infections and infestations** | |  | | |  | | |  | | |  |  | |  | |  | |  |
| Urinary tract infection | | 0 | 2 (1.0) | | | 0 | | | 0 | | | 1 (0.2) | 5 (0.8) | | 1 (0.2) | | 0 | |
| Pneumonia | | 0 | 0 | | | 0 | | | 0 | | | 0 | 4 (0.6) | | 0 | | 1 (0.2) | |
| Data cutoff August 31, 2020. Data are n (%) of patients. Adverse events were encoded using MedDRA (version 21.0).  Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; MB, myocardial band; MedDRA, Medical Dictionary for Regulatory Activities; *NTRK,* neurotrophic tyrosine receptor kinase; PK, phosphokinase. aFor preferred term rows, multiple occurrences of the same adverse event in one individual are counted once at the highest grade for this patient, for the overall (first) row a patient contributes only with the adverse event occurring with the highest grade.  bFive grade 5 adverse events (all *n* = 1: cardiac arrest; sudden death; cerebrovascular accident; atrioventricular block; ventricular fibrillation) were reported, for which relationship with treatment could not be ruled out. | | | | | | | | | | | | | | | | | | |

Table A9**.** Serious treatment-related adverse events.

|  |  |  |
| --- | --- | --- |
| **MedDRA system organ class**  **MedDRA preferred terma** | ***NTRK* fusion-positive  safety-evaluable population  (*n* = 193)** | **Overall safety population**  **(*n* = 626)** |
| **Overall number (%) of patients with ≥1 event** | 24 (12.4) | 72 (11.5) |
| **Total number of events** | 41 | 113 |
| **Nervous system disorders, *n* (%)** |  |  |
| Dizziness | 3 (1.6) | 3 (0.5) |
| Cognitive disorder | 2 (1.0) | 6 (1.0) |
| Dysarthria | 1 (0.5) | 2 (0.3) |
| Balance disorder | 1 (0.5) | 1 (0.2) |
| Cerebellar ataxia | 1 (0.5) | 1 (0.2) |
| Cerebrovascular accident | 1 (0.5) | 1 (0.2) |
| Epilepsy | 1 (0.5) | 1 (0.2) |
| Somnolence | 1 (0.5) | 1 (0.2) |
| Thalamic infarction | 1 (0.5) | 1 (0.2) |
| Ataxia | 0 | 2 (0.3) |
| Syncope | 0 | 1 (0.2) |
| Limbic encephalitis | 0 | 1 (0.2) |
| **Cardiac disorders, *n* (%)** |  |  |
| Cardiac failure congestive | 2 (1.0) | 4 (0.6) |
| Cardiac failure | 1 (0.5) | 5 (0.8) |
| Cardiac arrest | 1 (0.5) | 1 (0.2) |
| Atrioventricular block | 1 (0.5) | 1 (0.2) |
| Ventricular fibrillation | 1 (0.5) | 1 (0.2) |
| Acute coronary syndrome | 0 | 1 (0.2) |
| Sinus arrythmia | 0 | 1 (0.2) |
| Myocarditis | 0 | 1 (0.2) |
| **General disorders and administration site conditions, *n* (%)** | |  |
| Edema peripheral | 2 (1.0) | 2 (0.3) |
| Sudden death | 1 (0.5) | 1 (0.2) |
| Pyrexia | 0 | 4 (0.6) |
| Fatigue | 0 | 1 (0.2) |
| **Metabolism and nutrition disorders, *n* (%)** |  |  |
| Fluid retention | 1 (0.5) | 1 (0.2) |
| Tumor lysis syndrome | 1 (0.5) | 1 (0.2) |
| Dehydration | 0 | 1 (0.2) |
| Hyperkalemia | 0 | 1 (0.2) |
| Hypertriglyceridemia | 0 | 1 (0.2) |
| Hypervolemia | 0 | 1 (0.2) |
| Hyponatremia | 0 | 1 (0.2) |
| **Psychiatric disorders, *n* (%)** |  |  |
| Confusional state | 1 (0.5) | 1 (0.2) |
| Mental status changes | 0 | 2 (0.3) |
| Delirium | 0 | 1 (0.2) |
| **Vascular disorders, *n* (%)** |  |  |
| Hypotension | 2 (1.0) | 3 (0.5) |
| Orthostatic hypotension | 0 | 1 (0.2) |
| **Respiratory, thoracic and mediastinal disorders, *n* (%)** | |  |
| Dyspnea | 2 (1.0) | 3 (0.5) |
| Hypoxia | 1 (0.5) | 2 (0.3) |
| Pulmonary edema | 0 | 2 (0.3) |
| Respiratory failure | 0 | 1 (0.2) |
| **Eye disorders, *n* (%)** |  |  |
| Diplopia | 1 (0.5) | 1 (0.2) |
| Vision blurred | 0 | 1 (0.2) |
| **Investigations, *n* (%)** |  |  |
| Blood creatinine increased | 1 (0.5) | 2 (0.3) |
| ALT increased | 1 (0.5) | 1 (0.2) |
| AST increased | 1 (0.5) | 1 (0.2) |
| Blood alkaline phosphatase increased | 1 (0.5) | 1 (0.2) |
| Blood bilirubin increased | 1 (0.5) | 1 (0.2) |
| Electrocardiogram QT prolonged | 1 (0.5) | 1 (0.2) |
| Ejection fraction decreased | 0 | 1 (0.2) |
| **Endocrine disorders, *n* (%)** |  |  |
| Hypogonadism | 1 (0.5) | 1 (0.2) |
| **Immune system disorders, *n* (%)** |  |  |
| Anaphylactic reaction | 1 (0.5) | 1 (0.2) |
| **Gastrointestinal disorders, *n* (%)** |  |  |
| Vomiting | 0 | 2 (0.3) |
| Anorectal disorder | 0 | 1 (0.2) |
| Diarrhea | 0 | 1 (0.2) |
| Dysphagia | 0 | 1 (0.2) |
| Pancreatitis | 0 | 1 (0.2) |
| **Injury, poisoning and procedural complications, *n* (%)** | |  |
| Femur fracture | 0 | 2 (0.3) |
| Fall | 0 | 1 (0.2) |
| Fracture | 0 | 1 (0.2) |
| Stress fracture | 0 | 1 (0.2) |
| Tendon fracture | 0 | 1 (0.2) |
| **Musculoskeletal and connective tissue disorders, *n* (%)** | |  |
| Muscular weakness | 0 | 1 (0.2) |
| Osteoarthritis | 0 | 1 (0.2) |
| Periostitis | 0 | 1 (0.2) |
| Spinal stenosis | 0 | 1 (0.2) |
| **Infections and infestations, *n* (%)** |  |  |
| Pneumonia | 0 | 1 (0.2) |
| Urinary tract infection | 0 | 1 (0.2) |
| **Renal and urinary disorders, *n* (%)** |  |  |
| Acute kidney injury | 0 | 1 (0.2) |
| Urinary retention | 0 | 1 (0.2) |
| **Skin and subcutaneous tissue disorders, *n* (%)** | |  |
| Rash | 0 | 1 (0.2) |
| Data cutoff August 31, 2020. Data are n (%) of patients. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; *NTRK*, neurotrophic tyrosine receptor kinase.  aFor preferred term rows, multiple occurrences of the same adverse event in one individual are counted once at the highest grade for this patient, for the overall (first) row a patient contributes only with the adverse event occurring with the highest grade. | | |

**October 2018 cutoff:**

Data from an earlier clinical data cutoff (October 31, 2018) were used to support the European approval of entrectinib. The key efficacy and safety data from this cutoff are presented in **Appendix Tables A9–A14** and **Figure A5**.

**Table A10.** Oct 2018 cutoff: overall efficacy (BICR assessed) of entrectinib in patients with *NTRK* fusion-positive solid tumors, by baseline investigator-assessed CNS metastases status.

|  |  |  |  |
| --- | --- | --- | --- |
| **Efficacy parameter** | **Efficacy-evaluable population**  **(*N* = 74)** | **Baseline CNS metastasesa**  **(*n* = 19)** | **No baseline CNS metastasesa**  **(*n* = 55)** |
| Objective response rate, *n* (%)  (95% CI) | 47 (63.5) (51.5–74.4) | 11 (57.9) (33.5–79.8) | 36 (65.5) (51.4–77.8) |
| Complete response | 5 (6.8) | 0 | 5 (9.1) |
| Partial response | 42 (56.8) | 11 (57.9) | 31 (56.4) |
| Stable disease | 9 (12.2) | 4 (21.1) | 5 (9.1) |
| Progressive disease | 6 (8.1) | 1 (5.3) | 5 (9.1) |
| Non-CR/non-PDb | 3 (4.1) | 0 | 3 (5.5) |
| Missing or unevaluablec | 9 (12.2) | 3 (15.8) | 6 (10.9) |
| Objective response rate, *n/N* (%)  Patients with no prior lines  of systemic therapy | 16/20 (80.0) | NA | NA |
| Patients with ≥1 prior lines  of systemic therapy | 31/54 (57.4) | NA | NA |
| Duration of response | *n* = 47 | *n* = 11 | *n* = 36 |
| Median, months (95% CI) | 12.9 (9.3–NE) | 6.0 (4.2–NE) | 12.9 (9.3–NE) |
| Progression-free survival |  |  |  |
| Median, months (95% CI) | 11.2 (8.0–15.7) | 6.7 (4.5–NE) | 13.7 (10.1–16.0) |
| Time to CNS progression or death  Median, months (95% CI) | 16.8 (14.3–NE) | 7.6 (5.6–14.3) | 20.9 (16.0–NE) |
| Patients with event, *n* (%) | 27 (36.5) | 12 (63.2) | 15 (27.3) |
| CNS progression | 3 (4.1) | 3 (15.8) | 0 |
| Death | 24 (32.4) | 9 (47.4) | 15 (27.3) |
| Overall survival |  |  |  |
| Median, months (95% CI) | 23.9 (16.0–NE) | 14.3 (5.9–NE) | NE (16.8–NE) |

Data cutoff October 31, 2018. Median survival follow-up: 14.2 months. Median duration of treatment: 8.6 months (IQR 4.8–14.7). Median time to response: 0.95 months.  
Abbreviations: BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CR, complete response; NA, not available; NE, not estimable; *NTRK*, neurotrophic tyrosine receptor kinase; PD, progressive disease.   
aCNS metastases status determined by investigator.

bPatients with non-measurable lesions.   
cMissing or unevaluable included patients with unevaluable on-study scans or who discontinued prior to obtaining adequate scans to evaluate or confirm response.

**Table A11.** Oct 2018 cutoff: overall efficacy (BICR assessed) of entrectinib in patients with *NTRK* fusion-positive solid tumors,by tumor type.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Tumor category** | ***n*** | **Baseline CNS metastasesa *n* (%)** | **Objective response rate**  ***n* (%)  (95% CI)** | **Duration of response  median, months (95% CI)** | **Progression-free survival**  **median, months**  **(95% CI)** | **Overall survival**  **median, months  (95% CI)** |
| Sarcoma | 16 | 2 (12.5) | 9 (56.3)  (29.9–80.3) | 9.3 (4.6–15.0) | 10.1 (6.5–11.2) | 16.8 (10.6–20.9) |
| NSCLC | 13 | 9 (69.2) | 9 (69.2)  (38.6–90.9) | NE (5.6–NE) | 14.9 (4.7–NE) | 14.9  (5.9–NE) |
| Salivary (MASC) | 13 | 1 (7.7) | 12 (92.3)  (64.0–99.8) | NE (6.0–NE) | NE (7.7–NE) | NE  (NE–NE) |
| Thyroid cancer | 7 | 4 (57.1) | 3 (42.9)  (9.9–81.6) | 7.9 (5.6–NE) | 11.8 (6.5–NE) | NE  (8.7–NE) |
| Colorectal carcinoma | 7 | 0 (0) | 2 (28.6)  (3.7–71.0) | 15.1 (NE–NE) | 2.4 (1.0–16.0) | 16.0(2.4–NE) |
| Breast cancer | 6 | 2 (33.3) | 5 (83.3)  (35.9–99.6) | 12.9 (4.2–NE) | 10.1 (5.1–NE) | 23.9  (5.1–23.9) |
| Neuroendocrine tumors | 4 | 0 (0) | 2 (50.0)  (6.8–93.2) | NE (NE–NE) | NE  (0.9–NE) | NE  (NE–NE) |
| Pancreatic cancer | 3 | 0 (0) | 2 (66.7)  (9.4–99.2) | 10.0 (7.1–12.9) | 8.0 (6.2–17.5) | 13.4  (11.2–NE) |
| Gynecologic | 2 | 0 (0) | 1 (50.0)  (1.3–98.7) | NE (NE–NE) | NE  (13.7–NE) | NE  (NE–NE) |
| Cholangiocarcinoma | 1 | 0 (0) | 1 (100.0)  (2.5–100.0) | 9.3 (NE–NE) | 12.0 (NE–NE) | NE  (NE–NE) |
| Adenocarcinoma of upper GI tract | 1 | 0 (0) | 1 (100.0)  (2.5–100.0) | NE (NE–NE) | NE (NE–NE) | NE  (NE–NE) |
| Neuroblastoma | 1 | 1 (100.0) | 0 (0.0) | — | 0.1 (NE–NE) | 0.1  (NE–NE) |

Data cutoff October 31, 2018.   
Abbreviations: BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; GI, gastrointestinal; MASC, mammary analogue secretory carcinoma; NE, not estimable; NSCLC, non-small cell lung cancer.   
aCNS metastases status determined by investigator.

Table A12. Oct 2018 cutoff: intracranial efficacy (BICR assessed) in patients with *NTRK* fusion-positive solid tumors and BICR-assessed CNS metastases at baseline.

|  |  |  |
| --- | --- | --- |
| **Efficacy parameter** | **Patients with CNS metastases at baselinea** | |
| **Measurable disease**  **(*n* = 8)** | **All patientsb**  **(*N* = 16)** |
| Intracranial objective response rate, *n* (%) (95% CI) | 5 (62.5) (24.5–91.5) | 8 (50.0) (24.7–75.4) |
| Complete response | 1 (12.5) | 4 (25.0) |
| Partial response | 4 (50.0) | 4 (25.0) |
| Stable disease | 1 (12.5) | 1 (6.3) |
| Progressive disease | 1 (12.5) | 1 (6.3) |
| Non-CR/non-PD | 0 | 5 (31.3) |
| Missing/unevaluable | 1 (12.5) | 1 (6.3) |
| Duration of intracranial response | *n* = 5 | *n* = 8 |
| Patients with event, *n* (%) | 2 (40.0) | 4 (50.0) |
| Median, months (95% CI) | NE (5.0–NE) | 8.0 (6.7–NE) |
| Intracranial progression-free survival |  |  |
| Patients with events, *n* (%) | 4 (50.0) | 10 (62.5) |
| Median, months (95% CI) | 10.1 (2.8–NE) | 8.9 (5.9–14.3) |
| Data cutoff October 31, 2018. Intracranial objective response rate derived using RECIST v1.1 criteria applied only to CNS lesions. Time to intracranial response ranged from 27 to 234 days, with 50.0% of patients responding by their first tumor assessment at 4 weeks. Abbreviations: BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CR, complete response; NE, not estimable; *NTRK*, neurotrophic tyrosine receptor kinase; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors.  aBICR assessed.  bIncludes patients with measurable and non-measurable CNS metastases. As per RECIST v1.1 non-measurable CNS disease could only be categorized as CR, non-CR/non-PD, or PD. | | |

Table A13**.** Oct 2018 cutoff: treatment-related adverse events, by highest grade, reported in ≥10% of patients or with ≥1 grade 3 or 4 event.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **MedDRA system organ class**  **MedDRA preferred term, *n* (%)a** | ***NTRK* fusion-positive safety-evaluable population (*n* = 113)** | | | |
| **Patients** | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| **Overall number (%) of patients with ≥1 event** | **19 (16.8)** | **37 (32.7)** | **37 (32.7)** | **4 (3.5)** |
| **Nervous system disorders** | | | | |
| Dysgeusia | 36 (31.9) | 8 (7.1) | 0 | 0 |
| Dizziness | 20 (17.7) | 9 (8.0) | 2 (1.8) | 0 |
| Paresthesia | 12 (10.6) | 2 (1.8) | 0 | 0 |
| Peripheral sensory neuropathy | 4 (3.5) | 2 (1.8) | 1 (0.9) | 0 |
| Cognitive disorder | 1 (0.9) | 0 | 1 (0.9) | 0 |
| Syncope | 0 | 0 | 3 (2.7) | 0 |
| Thalamic infarction | 0 | 0 | 1 (0.9) | 0 |
| **Gastrointestinal disorders** | | | | |
| Constipation | 22 (19.5) | 8 (7.1) | 0 | 0 |
| Diarrhea | 20 (17.7) | 8 (7.1) | 2 (1.8) | 0 |
| Nausea | 14 (12.4) | 3 (2.7) | 0 | 0 |
| **General disorders and administration site conditionsb** | | | | |
| Fatigue | 24 (21.2) | 10 (8.8) | 7 (6.2) | 0 |
| Edema peripheral | 15 (13.3) | 3 (2.7) | 1 (0.9) | 0 |
| Edema localized | 1 (0.9) | 1 (0.9) | 1 (0.9) | 0 |
| **Investigations** | | | | |
| Weight increased | 7 (6.2) | 6 (5.3) | 8 (7.1) | 0 |
| Blood creatinine increased | 11 (9.7) | 10 (8.8) | 1 (0.9) | 0 |
| AST increased | 15 (13.3) | 3 (2.7) | 2 (1.8) | 1 (0.9) |
| ALT increased | 13 (11.5) | 4 (3.5) | 1 (0.9) | 1 (0.9) |
| Blood uric acid increased | 0 | 0 | 0 | 1 (0.9) |
| **Musculoskeletal and connective tissue disorders** | | | | |
| Myalgia | 9 (8.0) | 3 (2.7) | 0 | 0 |
| Muscular weakness | 6 (5.3) | 1 (0.9) | 1 (0.9) | 0 |
| Osteoarthritis | 0 | 0 | 1 (0.9) | 0 |
| **Metabolism and nutrition disorders** | | | | |
| Hyperuricemia | 1 (0.9) | 1 (0.9) | 0 | 3 (2.7) |
| Hypophosphatemia | 1 (0.9) | 2 (1.8) | 2 (1.8) | 0 |
| Hypokalemia | 0 | 0 | 1 (0.9) | 0 |
| Hyponatremia | 1 (0.9) | 0 | 1 (0.9) | 0 |
| Hypermagnesemia | 0 | 0 | 1 (0.9) | 0 |
| **Blood and lymphatic system disorders** | | | | |
| Anemia | 8 (7.1) | 2 (1.8) | 8 (7.1) | 0 |
| Neutropenia | 2 (1.8) | 2 (1.8) | 2 (1.8) | 0 |
| Lymphopenia | 2 (1.8) | 0 | 1 (0.9) | 0 |
| **Eye disorders** | | | | |
| Diplopia | 0 | 1 (0.9) | 1 (0.9) | 0 |
| **Psychiatric disorders** | | | | |
| Confusional state | 5 (4.4) | 0 | 1 (0.9) | 0 |
| **Vascular disorders** | | | | |
| Hypotension | 1 (0.9) | 1 (0.9) | 2 (1.8) | 0 |
| Orthostatic hypotension | 0 | 0 | 1 (0.9) | 0 |
| **Renal and urinary disorders** | | | | |
| Urinary retention | 1 (0.9) | 0 | 1 (0.9) | 0 |
| **Cardiac disordersb** | | | | |
| Cardiac failure | 0 | 0 | 1 (0.9) | 0 |
| Cardiac failure congestive | 0 | 0 | 1 (0.9) | 0 |
| **Immune system disorders** |  |  |  |  |
| Anaphylactic reaction | 0 | 0 | 1 (0.9) | 0 |
| Data cutoff October 31, 2018. Data are n (%) of patients. Median treatment duration: 6.4 months (IQR, 2.7–11.0). Median dose intensity: 95.0% (IQR, 69.9–100.0). Dose reductions / drug interruptions / discontinuations due to TRAEs: 28.3% / 29.2% / 6.2% of patients. The most common all-cause AEs leading to dose reductions were dizziness (5.3%), fatigue (4.4%), and anemia (4.4%). Data are n (%) of patients. Adverse events were encoded using MedDRA (version 21.0).  Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; *NTRK,* neurotrophic tyrosine receptor kinase.  aFor preferred term rows, multiple occurrences of the same adverse event in one individual are counted once at the highest grade for this patient, for the overall row a patient contributes only with the adverse event occurring with the highest grade.  bTwo grade 5 adverse events (one cardiac arrest and one sudden death) were reported, for which relationship with treatment could not be ruled out. | | | | |

Table A14**.** Oct 2018 cutoff: serious adverse events related to study treatment.

|  |  |
| --- | --- |
| **MedDRA system organ class**  **MedDRA preferred terma** | ***NTRK* fusion-positive  safety-evaluable population  (*n* = 113)** |
| **Total number of patients with ≥1 event** | 16 (14.2) |
| **Overall number of events** | 22 |
| **Nervous system disorders, *n* (%)** |  |
| Cognitive disorder | 1 (0.9) |
| Cerebellar ataxia | 1 (0.9) |
| Dizziness | 1 (0.9) |
| Syncope | 1 (0.9) |
| Thalamic infarction | 1 (0.9) |
| **Cardiac disorders, *n* (%)** |  |
| Cardiac arrest | 1 (0.9) |
| Cardiac failure – congestive | 1 (0.9) |
| **General disorders and administration site conditions, *n* (%)** | |
| Edema | 1 (0.9) |
| Edema – peripheral | 1 (0.9) |
| Sudden death | 1 (0.9) |
| **Metabolism and nutrition disorders, *n* (%)** | |
| Hyperuricemia | 1 (0.9) |
| **Psychiatric disorders, *n* (%)** |  |
| Confusional state | 1 (0.9) |
| **Vascular disorders, *n* (%)** |  |
| Hypotension | 2 (1.8) |
| **Respiratory, thoracic and mediastinal disorders, *n* (%)** | |
| Dyspnea | 2 (1.8) |
| **Eye disorders, *n* (%)** |  |
| Diplopia | 1 (0.9) |
| **Investigations, *n* (%)** |  |
| Blood creatinine increased | 1 (0.9) |
| **Endocrine disorders, *n* (%)** |  |
| Hypogonadism | 1 (0.9) |
| **Immune system disorders, *n* (%)** |  |
| Anaphylactic reaction | 1 (0.9) |
| Data cutoff October 31, 2018. Data are n (%) of patients.  Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; *NTRK*, neurotrophic tyrosine receptor kinase.  aFor preferred term rows, multiple occurrences of the same adverse event in one individual are counted once at the highest grade for this patient, for the overall row a patient contributes only with the adverse event occurring with the highest grade. | |

Figure A1. Summary of efficacy- and safety-evaluable patient populations enrolled in the integrated analysis. CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non–small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; RECIST, Response Evaluation Criteria in Solid Tumors; TRK, tropomyosin receptor kinase.

Figure A2. Best individual patient responses to entrectinib treatment in patients with *NTRK* fusion-positive solid tumors, by *NTRK* gene (BICR assessed). Patients with missing SLD change were excluded from the plot. Data cutoff August 31, 2020. BICR, blinded independent central review; *NTRK*, neurotrophic tyrosine receptor kinase; SLD, sum of longest diameter.

Figure A3. Best individual patient responses to entrectinib treatment in patients with *NTRK* fusion-positive solid tumors, by fusion partner (BICR assessed). Patients with missing SLD change were excluded from the plot. Data cutoff August 31, 2020.BICR, blinded independent central review; *NTRK*, neurotrophic tyrosine receptor kinase; SLD, sum of longest diameter.

Figure A4. Time-to-event analyses for time to CNS progression (death censored) in all patients (grey) and in patients with (red) or without (blue) baseline CNS metastases by investigator assessment. Data cutoff August 31, 2020. CNS, central nervous system; mets, metastases.

Figure A5. Oct 2018 cutoff: responses and time on entrectinib treatment in patients with *NTRK* fusion-positive solid tumors, by tumor type (BICR assessed). A, Duration of response for responding patients; B, Progression-free survival per BICR; C, Overall survival in patients with *NTRK* fusion-positive solid tumors (*N* = 74); D, Time-to-event analyses for time to CNS progression (death censored) in all patients (grey) and in patients with (red) or without (blue) baseline CNS metastases by investigator assessment. In the overall efficacy-evaluable population, 3 of 74 patients (4.1%; all with baseline CNS disease), experienced CNS progression. Median time to CNS progression (only scan-confirmed CNS progression counted as an event) was not estimable. None of the patients without baseline CNS disease had experienced symptomatic, scan-confirmed CNS progression by data cutoff. Data cutoff October 31, 2018. BICR, blinded independent central review; CNS, central nervous system; *NTRK,* neurotrophic tyrosine receptor kinase.