Safety and preliminary clinical activity of NVL-520, a highly selective ROS1 inhibitor, in patients with advanced ROS1 fusion-positive solid tumors

Drilon, A.; Besse, B.; Camidge, D. R.; Ou, S. H.I.; Gadgeel, S. M.; Johnson, M. L.; Calles, A.; de Miguel, M. J.; Spira, A. I.; Felip, E.

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8 Oral

Safety and preliminary clinical activity of NVL-520, a highly selective ROS1 inhibitor, in patients with advanced ROS1 fusion-positive solid tumors

A. Drilon[1], B. Besse[2], D.R. Camidge[3], S.H.I. Ou[4], S.M. Gadgeel[5], M.L. Johnson[6], A. Calles[7], M.J. de Miguel[8], A.I. Spira[9], E. Felip[10], G. Lopes[11], A.J. van der Wekken[12], Y.Y. Elamin[13], J. Green[14], Y. Sun[15], J. Soglia[16], V.W. Zhu[14], J.J. Lin[17]. *[1]Memorial Sloan Kettering Cancer Center, Early Drug Development Service, New York, USA; [2]Institut Gustave Roussy, Cancer Medicine, Villejuif, France; [3]University of Colorado Cancer Center- Anschutz Medical Campus, Thoracic Oncology, Aurora, USA; [4]University of California Irvine Medical Center, Medicine, Orange, USA; [5]Henry Ford Cancer Institute, Internal Medicine, Detroit, USA; [6]Sarah Cannon Research Institute, Oncology, Nashville, USA; [7]Hospital Universitario Gregorio Marañón, Medical Oncology, Madrid, Spain; [8]START Madrid- HM CIOCC, Medical Oncology, Madrid, Spain; [9]NEXT Oncology - Virginia Cancer Specialists, Thoracic and Phase I Program, Fairfax, USA; [10]Hospital Vall d`Hebron, Oncology, Barcelona, USA; [11]Sylvester Comprehensive Cancer Center- University of Miami Miller School of Medicine, Medical Oncology- Thoracic Medical Oncology, Miami, USA; [12]University of Groningen and University Medical Centre Groningen, Pulmonary Oncology, Groningen, Netherlands; [13]MD Anderson Cancer Center, Thoracic Head & Neck Medical Oncology, Houston, USA; [14]Nuvalent Inc., Clinical Development, Cambridge, USA; [15]Nuvalent Inc., Biology, Cambridge, USA; [16]Nuvalent Inc., Translational Development, Cambridge, USA; [17]Massachusetts General Hospital, Medicine, Boston, USA*

Background: Oncogenic ROS1 fusions drive various malignancies, including 1–3% of non-small cell lung cancers (NSCLC). Rationally designed ROS1 tyrosine kinase inhibitors (TKIs) that surpass the limitations of FDA/EMA-approved (crizotinib/entrectinib) or other investigational agents are a medical need. The novel ROS1 TKI NVL-520 is highly selective and designed to avoid the neurologic toxicities associated with ROS1 TKIs that concurrently inhibit TRK (entrectinib/repotrectinib/taletrectinib). Furthermore, NVL-520 is brain-penetrant and targets a diverse array of ROS1 fusions and recalcitrant resistance mutations, including the ROS1 G2032R solvent-front mutation.

Materials and Methods: ARROS-1 (NCT05118789) is a global, tumor-agnostic, phase 1/2 trial of NVL-520. In the ongoing phase 1 dose escalation, patients are required to have a previously treated ROS1 fusion-positive solid tumor, including NSCLC treated with ≥1 prior ROS1 TKI. Primary objectives are to determine the recommended phase 2 dose (RP2D) and, if applicable, the maximum tolerated dose. Additional objectives include safety, pharmacokinetics (PK), pharmacodynamics, and preliminary activity. Response (RECIST v1.1) was investigator assessed. Data cut: June 13, 2022.

Results: Twenty patients (19 NSCLC, 1 pancreatic cancer) have received NVL-520 orally at dose levels of 25–100 mg once daily. Patients received a median of 3 (range: 1–9) prior anticancer therapies, including any ROS1 TKI (100%); investigational ROS1 TKI (85%, including lorlatinib in 55%, repotrectinib in 40%); ≥2 ROS1 TKIs (75%); any chemotherapy (80%); ≥2 lines of chemotherapy (50%). At baseline, 55% had CNS metastases and 45% had ROS1 G2032R. No dose-limiting toxicities (DLTs), dose reductions, or drug-related treatment discontinuations have been reported. All treatment-related adverse events (TRAEs) were grade 1. The only TRAE in >1 patient was nausea (n = 2). NVL-520 PK analyses demonstrated dose-dependent exposure. Among 12 efficacy-evaluable patients with ROS1 + NSCLC treated at 25–75 mg QD, 6 confirmed partial responses (PRs) were achieved. Shrinkage or resolution of intracranial metastases were observed; no patients had intracranial progression. A PR was achieved in most (n = 5/7) ROS1 G2032R-mutant cancers, including lorlatinib or repotrectinib pre-treated tumors. Circulating tumor DNA analyses showed reductions of ROS1 variant allele frequency. The RP2D has not been identified and dose escalation continues.

Conclusions: NVL-520 has been well-tolerated up to 100 mg daily with favorable pharmacokinetics. Activity has been demonstrated in heavily pretreated patients (of whom 70% received ≥2 prior ROS1 TKIs plus chemotherapy), including those with brain metastases and the G2032R mutation.

Conflict of interest:
Ownership: Treeline Bio (AD) Nuvalent (JG, JS, YS, VZ) Turning Point Therapeutics, Elevation Oncology (SO).
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28 October 2022 15:00–16:30

PLENARY SESSION 7

Late breaking and Proffered Papers

9 Oral

NCI10329: Phase Ib Sequential Trial of Agents against DNA Repair (STAR) Study to investigate the sequential combination of the Poly (ADP-Ribose) Polymerase inhibitor (PARPi) olaparib (ola) and WEE1 inhibitor (WEE1i) adavosertib (ada) in patients (pts) with DNA Damage Response (DDR)-aberrant advanced tumors, enriched for BRCA1/2 mutated and CCNE1 amplified cancers

T.A. Yap[1,2], N. Ngoi[1], E.E. Dumbrava[1], D.D. Karp[1], J. Rodon Ahnert[1], S. Fu[1], D.S. Hong[1], A. Naing[1], S. Pant[1], S.A. Piha-Paul[1], V. Subbiah[1], A.M. Tsimberidou[1], D. Dufner[1], J. Rhudy[1], S. Gore[3], S.P. Ivy[4], Y. Yuan[5], S.N. Westin[6], G.B. Mills[7], F. Meric-Bernstam[1]. *[1]The University of Texas MD Anderson Cancer Center, Department of Investigational Cancer Therapeutics, Houston, USA; [2]The University of Texas MD Anderson Cancer Center, Khalifa Institute for Personalized Cancer Therapy, Houston, USA; [3]National Institutes of Health- National Cancer Institute, Cancer Therapy Evaluation Program CTEP, Bethesda, USA; [4]Cancer Therapy Evaluation Program CTEP, National Institutes of Health- National Cancer Institute, Bethesda, USA; [5]The University of Texas MD Anderson Cancer Center, Department of Biostatistics, Houston, USA; [6]The University of Texas MD Anderson Cancer Center, Department of Gynecologic Oncology and Reproductive Medicine, Houston, USA; [7]Knight Cancer Institute, Oregon Health Sciences University, Portland, USA*

Background: Combination PARPi plus WEE1i (PARPi + WEE1i) induces replication stress (RS), DNA damage, and abrogates the G2 cell cycle checkpoint. Concurrent PARPi + WEE1i administration effectively inhibits tumor growth but is poorly tolerated. Sequential PARPi+WEE1i administration in vivo mirrors concurrent dosing in cells with high basal RS, while normal cells with low basal RS are protected from DNA damage, improving tolerability while preserving efficacy (Fang et al., Cancer Cell 2019). Based on these compelling preclinical data, the NCI CTEP-sponsored STAR study investigated sequential ola+ada in pts with DDR aberrant advanced tumors (NCT04197713).

Materials and Methods: Pts with advanced cancer with actionable DDR variants were enrolled. Prior PARPi was allowed. Dose escalation followed Bayesian Optimal Interval Design; Dose Level (DL) 1: ola 300 mg BID days (D) 1–5, 15–19 + ada 250 mg QD D8–12, 22–26; DL 2: ola 300 mg BID D1–5, 15–19 + ada 300 mg QD D8–12, 22–26; Q28 days. Primary objectives were safety and recommended phase 2 dose (RP2D). Secondary objectives were antitumor activity, PK, PD and biomarkers of response/resistance. Serial tumor and blood sampling were obtained for tumor whole exome and RNA sequencing, RAD51-IF, multiplex IHC and ctDNA NGS.

Results: 13 pts (M:F 2:11; ECOG PS 0:1: 4/9; mean age: 50y (35–72) with breast (n = 5), ovarian (n = 5), colorectal, gastric, prostate (n = 1) cancers were enrolled. Actionable genomic alterations included *BRCA1/2* (n = 8), *CCNE1* amplification (n = 3), *ARID1A* (n = 2), *ATM* (n = 1), P*ALB2* (n = 1). 10/13 pts had ≥3 lines of prior systemic therapy; 7/13 had progressed on prior PARPi. 3/13 pts were treated with sequential ola+ada at DL 1, 10/13 at DL 2. Common toxicities: grade (G) 1/2 nausea (10/13), anemia (7/13), fatigue (7/13), vomiting (7/13), and diarrhea (4/13). No DLTs occurred. Non-DLT ≥G3 myelosuppression occurred in 2/13 pts who were heavily pre-treated (≥5 prior lines). Dose reduction occurred in only 1/13 pts even with long term follow-up. 3/12 evaluable pts had RECIST1.1 PR and/or GCIG CA125 response, and 5/12 pts had SD ≥4 mths for 66.7% (8/12) disease control rate; 4 of these 8 pts had progressed on prior PARPi. RECIST1.1 PRs were seen in *BRCA2*m ER+ breast cancer pt (–57%,17 wks) and *BRCA2*m PARPi-resistant ovarian cancer pt (–50%; 26 wks) who had *BRCA2*m reversion at baseline. A *CCNE1* amp ovarian cancer pt had GCIG CA125 response and SD 20 wks. Translational analyses are ongoing.

Conclusion: The novel sequential dosing schedule of ola + ada is well tolerated at full monotherapy dosing of each drug, with antitumor activity in pts with post-PARPi DDR aberrant tumors. RP2D was ola 300 mg BID D1–5, 15–19 + ada 300 mg OD D8–12, 22–26; Q28 days. Planned expansion cohorts include (1) pts with *BRCA1/2* m tumors with intrinsic PARPi resistance and (2) pts with DDR mutated tumors with acquired PARPi resistance.

Conflict of interest:
Ownership: T.A.Y holds stocks in Seagen.
Advisory Board: T.A.Y has received fees for consulting from AbbVie, AstraZeneca, Acrivon, Adagene, Almac, Aduro, Amphista, Artios, Athena, Atrin, Avoro, Axiom, Baptist Health Systems, Bayer, Beigene, Boxer, Bristol Myers Squibb, C4 The rapeutics, Calithera, Cancer Research UK, Clovis, Cybrexa, Diffusion, EMD Serono, F-Star, Genmab, Glenmark, GLG, Globe Life Sciences, GSK, Guidepoint, Idience, Ignyta, I-Mab, ImmuneSensor, Institut Gustave Roussy, Intellisphere, Jansen, Kyn, MEI pharma, Mereo, Merck, Natera, Nexys, Novocure, OHSU, OncoSec, Ono Pharma, Pegascy, PER, Pfizer, Piper-Sandler, Prolynx, Repare, resTORbio, Roche, Schrodinger, Theragnostics, Varian, Versant, Vibliome, Xinthera, Zai Labs and ZielBio.
Board of Directors: N/A.
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Other Substantive Relationships: N/A.

10 Oral

CBX-12-101: A first-in-human study of CBX-12, an alphalex peptide drug conjugate (PDC) in patients with advanced or metastatic solid tumors

F. Meric-Bernstam[1], J.P. Eder[2], A. Vandross[3], M. Gara[4], S. Gayle[4], P. Pearson[4], A. DeCillis[4], A. Tolcher[5]. *[1]University of Texas, MD Anderson Cancer Center, Houston, USA; [2]Yale University, Smilow Cancer Center, New Haven, USA; [3]NEXT Oncology, Medical Oncology, Austin, USA; [4]Cybrexa Therapeutics, Inc, Biology, New Haven, USA; [5]NEXT Oncology, Clinical Research, San Antonio, USA*

Background: Tumor-targeted drug delivery technologies are urgently needed to overcome lack of tumor selectivity, a major drawback of conventional chemotherapy. The acidic intercellular microenvironment in solid tumors traps weak acid/base chemotherapy agents, preventing necessary intracellular concentrations in tumor cells. An alphalex conjugate, which contains a pH-low insertion peptide (pHLIP), a linker, and a payload, was designed to overcome these limitations. Unlike antibody drug conjugates, alphalex PDCs target tumors in an antigen-agnostic manner. At pH ≥7.0, the peptide is unstructured. In the low-pH tumor microenvironment the peptide forms an alpha helix and inserts directionally into the tumor cell membrane delivering the linker and payload intracellularly where the linker is cleaved releasing the payload in the cytosol. CBX-12 consists of the pH-sensitive peptide, a self-immolating linker, and the topoisomerase 1 (TOP1) inhibitor exatecan.

Method: In a Phase 1 trial, cohorts of patients were treated with escalating doses of CBX-12 in a 3 + 3 design on three dosing schedules: Daily × 5 every 3 weeks (Schedule A), daily × 3 every 3 weeks (Schedule B) or once weekly (Schedule C). NCT04902872. The primary objectives are safety, tolerability, and to determine the MTD and/or RP2D. Secondary and exploratory objectives include evaluation of plasma PK and intratumoral levels of CBX-12 and exatecan, anti-tumor activity per RECIST v1.1, and measurement of anti-drug antibodies.

Results: As of 28 June 2022, 24 patients have been treated in the following schedules/cohorts (dose: n): A1 (0.25 mg/kg: 1), A2 (0.50 mg/kg: 3), B1 (20 mg/m^2: 3), B2 (30 mg/m^2: 3), B3 (45 mg/m^2: 7), B4 (60 mg/m^2: 2), C1(20 mg/m^2: 5). The most common treatment-related AEs (TRAEs) were nausea (11), diarrhea (8), vomiting (8), anemia (8), and WBC/ANC decrease and fatigue (7 each), dehydration (4), AST increased (3) and alopecia (3). The most common Gr3/4 TRAEs (Gr: n) were ANC decrease (Gr3:2, Gr4:3), anemia (Gr3:4), platelet (Plt) count decrease (Gr4:3), and WBC decrease (Gr3:1, Gr4:2). One patient in Cohort A2 had DLTs of ANC and Plt decrease. Two patients in Cohort B4 had DLTs including febrile neutropenia (2), ANC and Plt decrease (2) and sepsis (1). The best response for 14 response-evaluable patients were 1 CR (ovarian), 1 PR (breast) and 9 SD. The preliminary PR2D in Part B is 45 mg/m^2. Dose escalation continues in Part C. Plasma CBX-12 and free exatecan concentrations increased in a dose-