Published in final edited form as:

Clin Cancer Res. 2021 March 15; 27(6): 1604–1611. doi:10.1158/1078-0432.CCR-20-4084.

Phase IB study of osimertinib in combination with navitoclax in EGFR-mutant NSCLC following resistance to initial EGFR therapy (ETCTN 9903)

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Abstract

Introduction: Osimertinib is an effective therapy in EGFR mutant NSCLC, but resistance invariably develops. Navitoclax is an oral inhibitor of BCL-2/BCL-xL that has exhibited synergy with osimertinib in preclinical models of EGFR-mutant NSCLC. In hematologic malignancies, BCL-2 family inhibitors in combination therapy effectively increase cellular apoptosis and decrease drug resistance.

Methods: This single arm phase IB study evaluated safety, tolerability and feasibility of osimertinib and navitoclax, including dose expansion in T790M+ patients at the recommended

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phase 2 dose (RP2D). Eligible pts had advanced *EGFR*-mutant NSCLC with prior TKI exposure. Five dose levels (DL) were planned with osimertinib from 40 – 80 mg PO daily and navitoclax from 150 – 325 mg PO daily.

Results: A total of 27 pts were enrolled (18 dose escalation, 9 expansion): median age 65, 67% female, 48% exon 19 del and 37% L858R, median 1 prior line of therapy. The most common adverse events were lymphopenia (37%), fatigue (22%), nausea (22%), and thrombocytopenia (37%). No DLTs were seen in dose escalation; osimertinib 80 mg, navitoclax 150 mg was chosen as the RP2D. Most patients (78%) received >95% of planned doses through 3 cycles. In expansion cohort, objective response rate (ORR) was 100% and median progression-free survival (PFS) was 16.8 months. A pro-apoptotic effect from navitoclax was demonstrated by early-onset thrombocytopenia.

Conclusions: Oral combination therapy with navitoclax and osimertinib was safe and feasible at RP2D with clinical efficacy. Early thrombocytopenia was common, supporting an target engagement by navitoclax. Further study of BCL-2/BCL-xL inhibition to enhance osimertinib activity is warranted.

Keywords

osimertinib; navitoclax; BCL-2; lung cancer; EGFR mutant

INTRODUCTION

Highly active oral targeted therapies have transformed the care of non-small cell lung cancer (NSCLC), with more than a dozen targeted therapies now approved as single agents for molecularly-defined subsets of advanced NSCLC. Although these drugs are highly effective and many have been shown to be superior first-line therapies in randomized trials, patients inevitably develop drug resistance at which point treatment options are more limited. Lung cancers harboring *EGFR* mutations represent the most common NSCLC genotype globally and are routinely treated with osimertinib (AZD9291), a third generation *EGFR* inhibitor, either in the first-line setting or following development of drug resistance due to an *EGFR* T790M mutation.[1] Given its activity and favorable toxicity profile, combinations of osimertinib with other targeted therapies are of clinical interest to improve outcomes for patients with advanced *EGFR*-mutant NSCLC.

Combination therapy with pro-apoptotic agents has emerged as a compelling strategy for increasing the activity of cancer therapeutics. Two leading agents are venetoclax (ABT-199/GDC-0199), a selective BCL-2 inhibitor approved for the treatment of hematologic malignancies (chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML)), and navitoclax (ABT-263), an inhibitor of BCL-xL, BCL-2, and other BCL-2 family proteins. In contrast to other known oncoproteins, BCL-2 does not stimulate cellular proliferation, but rather inhibits programmed cell death by protecting cells from a wide variety of pro-apoptotic stimuli, including cytokine withdrawal, irradiation, cytotoxic drugs, heat, and deregulated oncogenes.[2–4] In hematologic malignancies, BCL inhibition has demonstrated significant synergy with targeted therapies, including with ibrutinib and rituximab. Common toxicities observed include cytopenias, particularly neutropenia and

thrombocytopenia, and gastrointestinal side effects, including diarrhea and abdominal pain. [5–7]

In *EGFR*-mutant lung cancer, preclinical studies demonstrated that models with a low level of the proapoptotic protein BIM had a sub-optimal response to EGFR TKI.[8] Moreover, lung cancer cell lines with TKI resistance, in particular those harboring T790M after prior TKI exposure, demonstrated reduced apoptotic response to EGFR inhibition over time. In this setting, the addition of navitoclax demonstrated increased apoptotic activity in combination with a third-generation TKI similar to osimertinib.[9] This preclinical works supports the hypothesis that impairing the activity of anti-apoptotic proteins could shift this balance in favor of apoptosis and achieve more dramatic tumor response. It is therefore hypothesized that the addition of navitoclax to osimertinib in T790M-positive lung cancers could improve the apoptotic response, resulting in deeper and more durable regressions. To investigate this hypothesis, we performed a phase Ib trial of osimertinib and navitoclax in pre-treated *EGFR* mutant NSCLC.

PATIENTS AND METHODS

Patients:

Between March 2016 and April 2019, we enrolled 27 patients to a single arm, multi-institution phase I trial. This study was approved by the institutional review board of all the participating centers, and this trial was conducted in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki. Patients were required to provide informed written consent before any study-related procedures. This protocol is also registered with clinicaltrials.gov (identifier [NCT02520778](https://clinicaltrials.gov/ct2/show/study/NCT02520778)). This first-in-human combination study enrolled patients with previously treated advanced NSCLC harboring an activating *EGFR* mutation who had progressed on a prior EGFR directed tyrosine kinase inhibitor. In the dose escalation portion of the study, patients were eligible regardless of the specific resistance mechanism to prior EGFR TKI treatment. Dose expansion was limited to patients whose tumor had an *EGFR* T790M mutation based on local testing and were osimertinib-naïve. Fresh or archival tissue submission was optional in dose escalation, but was required for those enrolled to the dose expansion portion of the study. The study was developed prior to the adoption of osimertinib as first-line therapy, thus treatment-naïve patients were not allowed. Patients with brain metastases could be enrolled after completing local treatment and could not be on corticosteroids. All patients were required to have measurable disease by RECIST 1.1 criteria and ECOG performance status 0–1.[10] Women of child-bearing age were required to have a negative serum pregnancy test within 7 days prior to enrollment. Adequate organ function and bone marrow reserve was required (absolute neutrophil count > 1500, platelets > 100,000, total bilirubin < 1.5 mg/dL, ALT/AST < 3 times the upper limit of normal, and creatinine < 2 mg/dL (or creatinine clearance > 50 ml/min).

Exclusion criteria included a significant cardiovascular event within 6 months (myocardial infarct, thrombotic or thromboembolic event), underlying bleeding disorders, history of a clinically significant bleeding event or non-chemotherapy induced thrombocytopenic-associated bleeding. Uncontrolled brain metastases or leptomeningeal disease was not

permitted. Patients receiving anticoagulation or anti-platelet therapy were excluded due to risk of thrombocytopenia with navitoclax. Excluded agents included heparin or low molecular weight heparin, warfarin, clopidogrel, ibuprofen and other NSAIDs, tirofiban, and other anticoagulants, drugs, or herbal supplements that affect platelet function.

There was no limit on prior therapy, although prior treatment with a third-generation T790M directed tyrosine kinase inhibitor was only permitted for patients enrolled on the dose escalation portion of trial. A 7-day washout was required between last dose of EGFR TKI and study enrollment. HIV positive patients on antiretroviral therapy were not permitted due to the possibility of drug interactions.

Study Design/Treatment Plan:

The study was designed as a single arm phase IB study that included dose escalation of both osimertinib and navitoclax, conducted with a standard 3+3 design, followed by expansion at the recommended phase 2 dose (RP2D). Osimertinib and navitoclax were supplied by the Pharmaceutical Management Branch of the Cancer Therapy Evaluation Program (CTEP), NCI under a collaborative agreement with AstraZeneca and AbbVie. In the dose escalation cohort, cycle 1 started with a 3 day lead-in of navitoclax only, prior to starting osimertinib on cycle 1 day 4 for PK analysis of single-agent navitoclax prior to combination therapy. Osimertinib was initially dosed at 40mg daily, an active dose, and then increased to 80 mg daily in dose level 2 and subsequent dose levels. Navitoclax was initially dosed at 150mg daily, below the single agent MTD of 325mg daily, and then increased to 200mg daily and higher starting from dose level 3. At doses above 150mg, a navitoclax lead-in dose of 150 mg daily for 7 days was included prior to escalation to permit stabilization of platelet levels, which are known to drop during this lead-in period.[11, 12] In the dose expansion cohort, both agents started together on C1D1.

Dose limiting toxicity (DLT) was assessed during cycle 1 in patients who had received at least 75% of the planned doses in cycle 1 (unless held due to DLT). DLT was defined grade 3 non-hematologic toxicity, except nausea, vomiting, or diarrhea resolving to at least grade 1 within 48 hours. Grade 3 rash was considered a DLT only if not improved within 72 hours with maximal medical management. Additional DLTs included febrile neutropenia, grade 4 neutropenia, anemia, or thrombocytopenia; thrombocytopenic bleeding, pneumonitis grade 2, or delay in starting cycle 2 of 14 days due to toxicity of any grade related to one or more protocol drugs. Dose reductions were made independently for each drug based on attribution. If toxicity resulted in one study drug discontinuation, the other drug was permitted to continue. All toxicities were assessed using Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Toxicity assessments were completed through October 2019.

Analysis plan:

The primary endpoints in this phase IB trial were to assess toxicity during dose escalation and feasibility during dose expansion. Feasibility was specifically assessed as ability for patients to tolerate combination dosing (osimertinib and navitoclax) for at least 12 weeks (3 cycles). All patients who started therapy were included in the toxicity assessment with

toxicities reported through data lock in October 2019. Data were initially locked in October 2019; additional clinical outcomes data, including survival, were collected through June 2020.

Measurable disease was required for study enrollment. Baseline computerized tomography scans were done within 4 weeks of starting study treatment in all patients and repeated after every 2 cycles. Response Evaluation Criteria in Solid Tumors (RECIST 1.1) was used for assessment of tumor response. All responding patients were required to have their response confirmed 4 to 6 weeks after the first documentation of response. Progression free survival was calculated from the date of the cycle 1 of study treatment.

Planned sample size included up to 30 patients in the dose escalation portion and 20 patients in the dose expansion. The dose expansion at RP2D was planned to assess a response rate as compared to historical controls for T790M positive patients.

Correlative Analysis:

Fresh or archival tissue was required from all enrolled patients in the dose expansion cohort for central T790M testing and next-generation sequencing (NGS) using Oncopanel at Dana-Farber Cancer Institute.[13] Tissue submission was optional for those with prior local T790M testing results in the dose escalation cohort. Analysis of circulating tumor DNA (ctDNA) using digital droplet PCR (ddPCR) was performed at the Belfer Center for Applied Cancer Science at Dana-Farber Cancer Institute, as described previously.[14] Each specimen was tested separately for EGFR T790M and the known sensitizing mutation (L858R or exon 19 deletion). Plasma ctDNA samples were collected as baseline, day 1 of each cycle, and at the end-of-study visit. Patients who had no detectable *EGFR* mutations in plasma at baseline were excluded from further plasma analysis.

Since osimertinib induces CYP3A4 and navitoclax is a CYP3A4 substrate, enzyme induction may reduce navitoclax plasma concentrations. Therefore, pharmacokinetic studies were performed to assess for this possible drug-drug interaction.[15, 16] Samples for analysis of navitoclax were collected on Day 3 of Cycle 1 after a 3 day lead-in of single agent navitoclax prior to dosing and at 1, 2, 3, 4, 6 and 8 hours after dosing and again on Cycle 2, Day 1 after 25 days of combination therapy. Samples for osimertinib and active metabolites were obtained at the same time as navitoclax sampling in Cycle 2. Navitoclax, osimertinib and active metabolites AZ5104, AZ7550 were measured by validated LC MS/MS assays and Cmax and AUC were calculated with non-compartmental analyses using Phoenix 64 WinNonlin and dose adjusted.[11, 17]

RESULTS:

Patient Characteristics:

A total of 27 patients with a median age of 65 years (range 40–83 years) were enrolled on trial. Most patients were female (67%), with 48% exon 19 del and 37% L858R. Most patients received one prior systemic lung cancer treatment (14 patients, 52%); 7 patients received 2 prior lines of therapy, and 6 patients had received 3 or more prior therapies. All patients had received at least one EGFR TKI (24 erlotinib, 6 afatinib, 6 osimertinib, 1

rociletinib), two patients received immunotherapy, two patients received bevacizumab, two patients received investigation TKI therapy (MET inhibitor, MEK inhibitor, and AXL inhibitor), and 10 patients received prior chemotherapy. Nineteen patients had histologic assessment at time of study enrollment; most were adenocarcinoma, except one adenocarcinoma with rhabdoid features, one adenosquamous, one small cell transformation (dose escalation), and three NSCLC NOS. Demographic information is detailed in Table 1.

Twelve patients, 5 of 18 from dose escalation and 7 of 9 from dose expansion cohorts, had adequate tissue submitted for central tumor sequencing. All 12 had confirmed *EGFR* mutations (6 Exon 19 deletion, 4 L858R, 1 L861Q, and 1 with both G719S and S768I). Eight (67%) had *EGFR* T790M on central testing. An additional 6 patients had T790M based on local testing only without tissue submitted for central confirmation. Eight of 12 (67%) with central testing had at least one additional oncogene or tumor suppressor gene alteration in addition to mutation(s) in *EGFR*. Seven of 12 (58%) had concomitant *TP53* mutations, and one patient had both *TP53* and *RBI* alterations. Three of 12 (25%) had CTNNB1 mutations, two of 12 (17%) had *PI3KCA* mutations, and 1 of 12 (8%) had *APC* or *CDKN2A* mutations.

Safety and Feasibility:

Eighteen patients were treated during the dose escalation portion of the study; nine patients were treated during dose expansion (Supplemental table 1). In dose escalation, four patients were enrolled in dose level 1, seven at dose level 2, and seven at dose level 3. One patient at each dose level was non-evaluable for safety and feasibility due to either disease progression (n=1) or poor compliance (n=2). Among 15 DLT evaluable patients, no DLTs were seen, however 3 of 7 pts (43%) in dose level 3 (osimertinib 80 mg + navitoclax 200 mg) required dose reductions during cycle 1 suggesting dose expansion at DL3 would not be well tolerated. For dose levels 1 and 2, three patients had navitoclax dose reductions and no patients required osimertinib dose reductions during cycles 1 or 2. For dose expansion, one patient dose reduced both navitoclax and osimertinib after cycle 1, one patient dose reduced navitoclax after cycle 2, and one patient discontinued navitoclax after cycle 2 due to VTE (Supplemental Table 1). Toxicities requiring dose reduction at dose level 3 included diarrhea (grade 3), fatigue (grade 3), generalized muscle weakness (grade 3), and abdominal bloating (grade 2).

DL2 (osimertinib 80 mg + navitoclax 150 mg) was selected as the recommended phase 2 dose (RP2D) for further study. In dose expansion, nine patients with *EGFR* T790M resistance and no prior 3rd-generation TKI were enrolled before study enrollment was discontinued due to slow enrollment and with the approval of osimertinib as first-line therapy. Feasibility of combination dosing over the initial 3 months of therapy was studied in these nine patients. Seven of nine patients (78%) received >95% of planned doses through 3 cycles (Figure 1). Two patients developed venous thromboemboli; one patient developed a pulmonary embolus after cycle 2 and one patient had a deep vein thrombosis after cycle 9. Both patients started anticoagulation and discontinued navitoclax, per protocol, due to the potential for increased bleeding risk, but continued osimertinib on study.

Most toxicities were grade 2; no grade 4 or 5 treatment related toxicities were observed. The most common treatment-related adverse events at any DL were fatigue (26% grade 2–3), leukopenia/lymphopenia (37% grade 2–3), thrombocytopenia (37% grade 2–3), diarrhea (33% grade 2–3) and nausea (22% grade 2). Grade 3 toxicities included cytopenias (neutropenia 3.7%, lymphopenia 11%, thrombocytopenia 11%), diarrhea (18.5%), electrolyte imbalances (hyponatremia 3.7%, hypocalcemia 3.7%, hypophosphatemia 3.7%), fatigue (3.7%), muscle weakness (3.7%) and QT prolongation (3.7%). Thrombocytopenia was not associated with bleeding events. The most common reason for study discontinuation was progressive disease; three patients discontinued navitoclax due to initiation of anticoagulation. Dose reductions for navitoclax were required for hypokalemia, fatigue, thrombocytopenia, diarrhea, and intolerable bloating (grade 2). Treatment related toxicities of at least grade 2 are summarized in Table 2, grade 1 toxicities are included in Supplemental Table 2.

Pharmacokinetics and pharmacodynamics:

Navitoclax drug levels were studied to confirm active dosing at the levels studied (100mg–200mg daily). The plasma concentrations achieved were similar to those observed in prior reports (see Supplement).[11] There was no evidence of a clinically significant drug-drug interaction based on pharmacokinetic assessments during cycle 1 (navitoclax alone) and cycle 2 (navitoclax plus osimertinib) (see Supplement).

Platelet counts were assessed at day 3 after starting navitoclax. All 27 patients (100%) experienced platelet decline at day 3 at all dose levels with a median decrease of 70%. Platelet counts recovered within the first two weeks of combination therapy with osimertinib and the majority remained stable throughout the duration of therapy (Figure 2).

Efficacy analysis:

All 27 patients enrolled on trial were considered evaluable for response. For dose escalation (n=18), partial response was the best response observed in 2 patients (11%), stable disease in 12 patients (67%), and progressive disease in four patients (22%). Both patients in dose escalation with responses were treated on dose level 3, osimertinib-naïve, and T790M positive. One patient received first line erlotinib and the other patient received first line combination therapy with erlotinib and bevacizumab. No responses were observed in the patients with prior osimertinib treatment. There was no clear correlation between T790M status and response in dose escalation (Supplemental Table 1). All patients with prior osimertinib exposure developed disease progression within the first 2 cycles. In the dose expansion phase (n=9), the objective response rate (ORR) was 100%, including one complete response (11%) and eight partial responses (89%) (Figure 3). Dose levels and best response are also in Supplemental Table 1.

At the time of data analysis, 20 patients had progressed while seven patients remain free from progression. The median progression free survival (PFS) was 7.6 months, (95% confidence interval (CI), 1.9–12.6 months) with a 6-month PFS rate of 51.6% (95% CI, 31.6%–61.4%). For the expansion cohort, median PFS was 16.8 months (95% CI, 3.5 to NR, Figure 1). The 12 month PFS rate was 76.2% (95% CI, 33.2%–93.5%).

Correlative Biomarker Studies:

Droplet digital PCR (ddPCR) was performed on plasma ctDNA at baseline and subsequently on day 1 of each cycle starting with cycle 1. Of 27 patients, eight (29.6%) had no detectable *EGFR* mutations (including exon 19 or L858R) in plasma at baseline; of the remaining 19 patients, 16 had plasma evaluable for ctDNA analysis at multiple time points, including 9 in dose escalation and 7 in dose expansion. Plasma ctDNA response was measured as change in allele frequency (AF) of the *EGFR* driver mutation between baseline and treatment dosing. By cycle 2, 14 patients (87.5%) demonstrated a decrease in plasma ctDNA (del19 and L8585R) (2). In addition, of the 10 patients who had detectable T790M in plasma, 60% demonstrated a decrease in plasma T790M by cycle 2. All 7 evaluable patients in the dose expansion cohort demonstrated a complete ctDNA response with no detectable *EGFR* mutation after 2 cycles (Figure 4).

DISCUSSION:

This phase Ib trial of osimertinib and navitoclax demonstrated that combination therapy was feasible with preliminary clinical activity demonstrated in an expansion cohort. Our study evaluated the combination of osimertinib and navitoclax in the setting of acquired resistance to first or second generation *EGFR* TKIs with required presence of T790M in the expansion cohort. In the expansion cohort of T790M positive patients, the ORR was 100% with one patient achieving a CR. Most patients in the expansion cohort (7 of 9, 78%) were able to maintain combination dosing at the RP2D through the first 3 months of therapy, with a median PFS of 16.8 months (12-month PFS rate 76.2%), which compares favorably with the known efficacy of osimertinib in the setting of T790M-positive acquired resistance.[18] The clearance of circulating tumor DNA in patients in the expansion cohort also supports the on-target effect of this combination approach.

In addition, dosing at the RP2D of osimertinib 80 mg daily and navitoclax 150 mg daily was well-tolerated. Both drugs are known to be associated with thrombocytopenia. Although significant platelet decreases occurred early in the treatment course, no bleeding or other adverse events were associated with severe thrombocytopenia; platelet counts typically recovered and stabilized for the duration of therapy. In fact, the rapid onset of thrombocytopenia on this treatment prior to the introduction of osimertinib is an indication of the intended target engagement of navitoclax, which was seen even at the lower doses used in this combination. Two patients developed thromboemboli in the expansion cohort. One of these patients had a prior history of a provoked lower extremity DVT preceding his cancer diagnosis and was off anticoagulation. These events were not attributed to navitoclax by the investigators and active malignancy along is known to increase the risk of thrombotic events. Given that thrombocytopenia was not prolonged or associated with bleeding events, it may be reasonable to consider inclusion of patients on anticoagulation in future studies.

Osimertinib is typically well-tolerated as a single agent and our study demonstrates that overlapping toxicities, such as thrombocytopenia and gastrointestinal adverse events were manageable. In April 2018, after initial design of this study, osimertinib was approved as first line therapy due to improved progression free survival compared to erlotinib or gefitinib in the first line setting.[19–21] Osimertinib is now most commonly used as a first-line agent.

The safety and feasibility of osimertinib plus navitoclax in this study supports further study of this regimen as an oral combination approach to be tested in the first-line setting.

Other BCL-2 family inhibitors have also demonstrated activity in combination therapy in both hematologic malignancies and solid tumors. Venetoclax, a BCL-2 inhibitor, has been utilized in combination with ibrutinib, a BTK inhibitor, for hematologic malignancies, including mantle cell lymphoma and chronic lymphocytic leukemia.[6, 22] Additionally, a phase 1b trial of metastatic breast cancer demonstrated clinical activity of venetoclax combined with tamoxifen, supporting preclinical data suggesting that tamoxifen may sensitize breast cancer cells to apoptosis.

In conclusion, we found the combination of osimertinib plus navitoclax to be feasible in this first-in-human study with compelling clinical activity seen at the RP2D, supporting further studies of oral anti-apoptotic agents and EGFR TKI combinations. There remains compelling need for combination approaches leveraging oral therapies that could further improve outcomes in oncogene-addicted NSCLC while maintaining the favorable quality of life afforded by these agents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding disclosure: This study was approved by the National Cancer Institute-Cancer Therapy Evaluation Program (NCI-CTEP) and funded by National Cancer Institute grant UM1 CA186709 (G.I.S.), an NCI-CTEP UM1 CA 186709 Biomarker Supplement (G.R.O. and C.P.P.), the Dana-Farber Cancer Institute-Brigham and Women's Hospital UM1 CA 186709 Biomarker/Molecular Characterization Hub (L.S.), as well as National Institute of Health grant NIH R35 - R35CA220497 (P.A.J.), and Damon Runyon Cancer Research Foundation grant CI-86-16 (G.R.O.). Additional funding in part from the Expect Miracles Foundation (C.P.P.) and the Robert and René Belfer Foundation (C.P.P.).

Appendix

Conflicts of Interest:

Author	COI Statement
Erin M.Bertino MD	Dr. Bertino reports personal fees from Pfizer, non-financial support from Merck, non-financial support from Lilly, grants from Ohio State Intramural Research Program, outside the submitted work.
Ryan D. Gentzler MD MS	Dr. Gentzler reports grants from NIH, during the conduct of the study; personal fees from AstraZeneca, personal fees from Pfizer, personal fees from Blueprint Medicines, grants from Pfizer, grants from Merck, grants from Bristol Myers Squibb, grants from Helsinn, grants from Takeda, grants from Jounce, outside the submitted work;.
Sarah Clifford MPH	Ms. Clifford reports other from Foundation Medicine, Inc., outside the submitted work.
Jill Kolesar PharmD MS	Dr. Kolesar reports grants from NCI, during the conduct of the study.
Alona Muzikansky MA	Ms. Muzikansky has nothing to disclose.
Eric B. Haura MD	Dr. Haura reports personal fees from Amgen, personal fees from Janssen, outside the submitted work.

Author	COI Statement
Zofia Piotrowska MD MHS	Dr. Piotrowska reports personal fees from Jazz Pharmaceuticals, personal fees from Blueprint Medicines, personal fees from Eli Lilly, personal fees from InCyte, personal fees from Genentech, grants and personal fees from Spectrum, grants and personal fees from Takeda, personal fees from Guardant Health, personal fees from C4 Therapeutics, grants and personal fees from AstraZeneca, grants and personal fees from Novartis, personal fees from AbbVie, grants from Tesaro, grants from Cullinan, outside the submitted work.
D. Ross Camidge MD PhD	Dr. Camidge reports personal fees and institutional trial fees from AstraZeneca and Abbvie outside the submitted work
Thomas E. Stinchcombe MD	Dr. Stinchcombe has nothing to disclose.
Christine Hann MD PhD	Dr. Hann reports personal fees from Abbvie/Stemcentrx, Ascentage, AstraZeneca, BMS, Genentech/Roche and Research Funding from AstraZeneca, Abbvie, Amgen, BMS, Merrimack outside of the submitted work.
Jyoti Malhotra MD MPH	Dr. Malhotra reports personal fees from Astra Zeneca, personal fees from Blueprint Medicines, grants from Beyond Spring Pharmaceutical, grants from Bristol Myers Squibb, grants from Biohaven pharma, grants from Celldex, outside the submitted work.
Liza C. Villaruz MD	Dr. Villaruz reports research support from the National Cancer Institute, Genentech, Astrazeneca, Exelixis, Rain, and GSK.
Cloud Paweletz PhD	Dr. Paweletz reports grants from NATIONAL CANCER INSTITUTE, during the conduct of the study; grants from Daiichi Sankyo, grants from Bicycle Therapeutics, grants from AstraZeneca, grants from Intellia Therapeutics, grants from Transcenta, grants from Bicara Therapeutics, other from Dropworks, other from XSphera Biosciences, outside the submitted work;.
Christie Lau	Ms. Lau has nothing to disclose.
Lynette Sholl	Dr. Sholl reports research funding to her institution from Roche Genentech. She reports personal consulting fees from EMD Serono, Foghorn Therapeutics, and AstraZeneca, and has served on an advisory board for LOXO Oncology.
Naoko Takebe MD PhD	Dr. Takebe has nothing to disclose.
Jeffrey A. Moscow MD	Dr. Moscow has nothing to disclose.
Geoffrey I. Shapiro MD PhD	G.I.S. has received research funding from Eli Lilly, Merck KGaA/EMD-Serono, Merck, and Sierra Oncology. He has served on advisory boards for Pfizer, Eli Lilly, G1 Therapeutics, Roche, Merck KGaA/EMD-Serono, Sierra Oncology, Bicycle Therapeutics, Fusion Pharmaceuticals, Cybrexa Therapeutics, Astex, Almac, Ipsen, Bayer, Angiox, Daiichi Sankyo, Seattle Genetics, Boehringer Ingelheim, ImmunoMet, Asana, Artios, Atrin, Concarlo Holdings, Syros and Zentalis. In addition, he holds a patent entitled, "Dosage regimen for sapacitabine and seliciclib," also issued to Cyclacel Pharmaceuticals, and a pending patent, entitled, "Compositions and Methods for Predicting Response and Resistance to CDK4/6 Inhibition," together with Liam Cornell.
Pasi A. Jänne MD PhD	P.A.J. has received consulting fees from AstraZeneca, Boehringer-Ingelheim, Pfizer, Roche/Genentech, Takeda Oncology, ACEA Biosciences, Eli Lilly and Company, Araxes Pharma, Ignyta, Mirati Therapeutics, Novartis, LOXO Oncology, Daiichi Sankyo, Sanofi Oncology, Voronoi, SFJ Pharmaceuticals, Takeda Oncology, Transcenta, and Biocartis; receives post-marketing royalties from DFCI owned intellectual property on EGFR mutations licensed to Lab Corp; has sponsored research agreements with AstraZeneca, Daiichi-Sankyo, PUMA, Boehringer Ingelheim, Eli Lilly and Company, Revolution Medicines and Astellas Pharmaceuticals; and has stock ownership in LOXO Oncology and Gatekeeper Pharmaceuticals.
Geoffrey R. Oxnard MD	Dr. Oxnard reports other from Roche, other from Foundation Medicine, outside the submitted work.

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Translational Relevance: 150 word limit

EGFR mutant NSCLC represents a unique subset of lung cancers with sensitivity to EGFR targeted therapy. Although initial responses are often clinically significant, they are not durable due to drug resistance. This trial evaluated utilization of navitoclax, an oral BCL-2/BCL-xL inhibitor, with osimertinib, a third-generation EGFR TKI, in EGFR mutant NSCLC. This combination is relevant to ongoing studies of pro-apoptotic agents and distinct from many osimertinib combinations as it is intended to increase the effectiveness of osimertinib in a TKI-sensitive population. In addition, the trial was one of very few oral combinations being studied for this purpose. Our study demonstrates the tolerability and feasibility of this combination as well as compelling efficacy in T790M-positive NSCLC, with durable responses and complete clearance of ctDNA. The trial closed to enrollment early when osimertinib became a first-line agent, but our data now are being used to advance a first-line combinations study.

Figure 1: Feasibility of combination therapy and progression-free survival. Swimmers plot demonstrating progression-free survival for each subject in the expansion phase including duration of each individual therapy. 7 of 9 continued navitoclax and 9 of 9 continued osimertinib until progression. 5 of 9 patients have ongoing progression-free survival as indicated by arrows.

Figure 2: Platelet count trends by dose level.

Graph of platelet counts from serial complete blood counts (CBC) collected at baseline, day 3, and then weekly after first dose of navitoclax. Platelet counts demonstrate pro-apoptotic effect of navitoclax on platelets across a range of doses, including dose level 1 (A), dose level 2 (B), dose level 3 (C), expansion cohort (D).

Figure 4: Circulating tumor DNA (ctDNA) analyses.

(A) Scatterplot of baseline EGFR allele frequency (AF). Of 27 patients enrolled, ddPCR detected EGFR exon 19 deletion or L858R driver mutation in 19 patients (70.4%) in pre-treatment plasma. Exon 19 deletion was detected in 12 patients (44.4%) and L858R in 7 patients (25.9%). Eight patients did not have detectable EGFR mutation by ddPCR. (B) Percent change in allele frequency (AF) from baseline to cycle 2 in all patients. In the expansion cohort, 100% (7 of 7) had clearance of detectable EGFR mutation in plasma.

Table 1:

Patient demographics

Patients, N	27
Men, N (%)	9 (33)
Women, N (%)	18 (67)
Age in years, median (min-max)	65 (40–83)
Prior Systemic Therapy, N (%)	
Erlotinib	24
Afatinib	5
Osimertinib	6
Immunotherapy	2
Chemotherapy	10
Bevacizumab	2
Other clinical trial therapy	4
EGFR mutation	
L858R	10 (37)
Exon 19 del	13 (48)
Other – L861Q, G719S, S768I	4 (15)
T790M	15 (55.5%)

Table 2:

Treatment-related Grade 2 Adverse Events

Toxicity	Grade 2 N (%)	Grade 3 N (%)
Neutropenia	2 (7.4)	1 (3.7)
Thrombocytopenia	7 (25.9)	3 (11.1)
Leukopenia/lymphopenia	7 (25.9)	3 (11.1)
White blood cell decreased	6 (22.2)	1 (3.7)
Anemia	1 (3.7)	
Diarrhea	4 (14.8)	5 (18.5)
Nausea	6 (22.2)	
Vomiting	2 (7.4)	
Flatulence	1 (3.7)	
Gastroesophageal reflux disease	1 (3.7)	
Dysgeusia	1 (3.7)	
Dyspepsia	2 (7.4)	
Alanine aminotransferase increase	1 (3.7)	
Hypoalbuminemia	1 (3.7)	
Hyponatremia		1 (3.7)
Hypocalcemia		1 (3.7)
Hypophosphatemia		1 (3.7)
Allergic reaction	1 (3.7)	
Rash maculo-papular	1 (3.7)	
Rash pustular	1 (3.7)	
Dehydration	1 (3.7)	
Dizziness	1 (3.7)	
Dry skin	2 (7.4)	
Paronychia	1 (3.7)	
Electrocardiogram QT corrected interval prolonged		1 (3.7)
Fatigue	6 (22.2)	1 (3.7)
Generalized muscle weakness		1 (3.7)
Pleural effusion	1 (3.7)	
Vaginal hemorrhage	1 (3.7)	
Weight loss	1 (3.7)	