



Research Paper

First-in-human study of the safety, pharmacokinetics, and pharmacodynamics of first-in-class fatty acid synthase inhibitor TVB-2640 alone and with a taxane in advanced tumors

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ARTICLE INFO

Article History:

Received 1 December 2020

Revised 24 February 2021

Accepted 25 February 2021

Available online xxx

Keywords:

Breast cancer

Gynecological cancers

Lung cancer

Biomarkers

Drug mechanisms

Pharmacology

Small molecule agents

Clinical trials

ABSTRACT

Background: We conducted a first-in-human dose-escalation study with the oral FASN inhibitor TVB-2640 to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D), as monotherapy and with a taxane.

Methods: This completed open-label outpatient study was conducted at 11 sites in the United States and United Kingdom. Patients with previously-treated advanced metastatic solid tumors and adequate performance status and organ function were eligible. TVB-2640 was administered orally daily until PD. Dose escalation initially followed an accelerated titration design that switched to a standard 3 + 3 design after Grade 2 toxicity occurred. Disease-specific cohorts were enrolled at the MTD. Statistical analyses were primarily descriptive. Safety analyses were performed on patients who received at least 1 dose of study drug. (ClinicalTrials.gov identifier NCT02223247)

Findings: The study was conducted from 21 November 2013 to 07 February 2017. Overall, 136 patients received TVB-2640, 76 as monotherapy (weight-based doses of 60 mg/m² to 240 mg/m² and flat doses of 200 and 250 mg) and 60 in combination, (weight-based doses of 60 mg/m² to 100 mg/m² and flat dose of 200 mg) (55 paclitaxel, 5 docetaxel). DLTs with TVB-2640 were reversible skin and ocular effects. The MTD/RP2D was 100 mg/m². The most common TEAEs (n,%) with TVB-2640 monotherapy were alopecia (46; 61%), PPE syndrome (35; 46%), fatigue (28; 37%), decreased appetite (20; 26%), and dry skin (17; 22%), and with TVB-2640+paclitaxel were fatigue (29; 53%), alopecia (25; 46%), PPE syndrome (25; 46%), nausea (22; 40%), and peripheral neuropathy (20; 36%). One fatal case of drug-related pneumonitis occurred with TVB-2640+paclitaxel; no other treatment-related deaths occurred. Target engagement (FASN inhibition) and inhibition of lipogenesis were demonstrated with TVB-2640. The disease control rate (DCR) with TVB-2640 monotherapy was 42%; no patient treated with monotherapy had a complete or partial response (CR or PR). In

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combination with paclitaxel, the PR rate was 11% and the DCR was 70%. Responses were seen across multiple tumor types, including in patients with KRAS^{MUT} NSCLC, ovarian, and breast cancer.

Interpretation: TVB-2640 demonstrated potent FASN inhibition and a predictable and manageable safety profile, primarily characterized by non-serious, reversible adverse events affecting skin and eyes. Further investigation of TVB-2640 in patients with solid tumors, particularly in KRAS^{MUT} lung, ovarian, and breast cancer, is warranted.

Funding: This trial was funded by 3-V Biosciences, Inc. (now known as Sagimet Biosciences Inc.).

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Research in context

Evidence before this study

Fatty acid synthase (FASN) is a multifunctional, homodimeric protein overexpressed by many solid and hematopoietic tumors, including non-small cell lung, breast, ovarian, prostate, colon, pancreatic cancers, and lymphoma. Moreover, FASN tumor expression increases in a stage-dependent manner that is associated with diminished survival. TVB-2640 is a small molecule (molecular weight 439.55 g/mol) human FASN inhibitor. Despite the compelling support for FASN as an oncology therapeutic target, TVB-2640 is the first highly selective FASN inhibitor to enter clinical studies.

Added value of this study

TVB-2640 demonstrated a favorable tolerability profile, with no significant gastrointestinal or serum chemistry toxicities or evidence of QTc prolongation. The maximum tolerated dose with TVB-2640 monotherapy and in combination with paclitaxel was 100 mg/m². Target engagement (FASN inhibition) and inhibition of lipogenesis were demonstrated with TVB-2640. The disease control rate (DCR) with TVB-2640 monotherapy was 42%; no patient treated with monotherapy had a complete or partial response (CR or PR). In combination with paclitaxel, the PR rate was 11% and the DCR was 70%. Responses were seen across multiple tumor types, including in patients with KRAS-mutant (KRAS^{MUT}) non-small cell lung cancer (NSCLC), ovarian cancer, and breast cancer.

Implications of all the available evidence

Given TVB-2640's potent FASN inhibition in the clinical setting, emergent favorable safety profile and clinical activity, notably in patients with KRAS^{MUT} NSCLC (NCT03808558), breast cancer (NCT03179904), and ovarian cancer, further investigation of TVB-2640 at the RP2D of 100 mg/m² in these indications in larger clinical studies is warranted.

1. Introduction

Fatty acid synthase (FASN) is a multifunctional, homodimeric protein with 6 separate enzymatic activities and domains. Many solid and hematopoietic tumors overexpress FASN, including non-small cell lung, breast, ovarian, prostate, colon, pancreatic cancers, and lymphoma [1–9]. Moreover, FASN tumor expression increases in a stage-dependent manner that is associated with diminished survival [10,11].

Nonclinical data indicate that FASN inhibition can restore sensitivity to many chemotherapeutics, including gemcitabine and cisplatin [12–14]. The mechanism by which FASN inhibition re-sensitizes tumors may be through plasma membrane remodeling in response to decreased palmitate, inhibition of protein palmitoylation, and the

subsequent impaired interaction and activation among membrane-associated signaling molecules such as protein kinase B (AKT).

FASN inhibition using short-interfering RNAs (siRNAs) and small molecules with varied mechanisms of action and selectivity profiles has been shown to inhibit AKT phosphorylation, induce tumor cell apoptosis, sensitize chemotherapy-resistant tumor cells to drug activity, and inhibit mouse xenograft tumor growth.

TVB-2640 is a small molecule (molecular weight 439.55 g/mol) human FASN inhibitor. Despite the compelling support for FASN as an oncology therapeutic target [15,16], TVB-2640 is the first highly selective FASN inhibitor to enter clinical studies. We conducted a first-in-human clinical study with this novel agent with the primary objective to determine the dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) of TVB 2640 given orally (PO) and establish the TVB 2640 dose recommended for further investigation in phase 2 (i.e., recommended phase 2 dose [RP2D]), when given as monotherapy and in combination with a taxane (paclitaxel or docetaxel). Secondary objectives were to elucidate the safety profile, examine the pharmacokinetics (PK), and identify any early signs of anti-tumor activity of TVB-2640 alone and in combination. Examination of biomarkers and their relationship to PK was an exploratory objective.

2. Methods

2.1. Study design

This first-in-human study of TVB-2640 employed a multi-center, open-label, dose-escalation and cohort expansion design. This study was conducted in accordance with International Council for harmonization Good Clinical Practice guidelines and applicable regulatory guidelines. The ethics committee at all participating sites (7 in the United States and 4 in the United Kingdom) reviewed and approved the clinical study protocol, which was registered at ClinicalTrials.gov (NCT02223247), and all patients provided informed consent before performance of any study-related procedures.

The initial TVB-2640 dose, both as monotherapy and in combination, was 60 mg/m², equivalent to 0.1 of the non-severely toxic dose from preclinical toxicity assessment, consistent with International Council for harmonization (ICH) S9 Guidance. An accelerated titration design initially was employed. The dose was escalated in 100% increments until \geq Grade 2 toxicity (except alopecia), after which a classical “3 + 3” design was followed, with escalation in 25 – 50% increments until reaching the MTD.

A 3 + 3 design also was employed to determine the MTD of TVB-2640 in combination. In the combination cohorts, paclitaxel and docetaxel were administered intravenously (IV), with associated pre-medications, at the dose and schedules indicated in the prescribing information or by institutional guidelines.

DLT was defined as any of the following events within the first treatment cycle (C1) that were considered at least possibly TVB-2640-related: 1) a treatment interruption >3 days (or inability to begin C2 for >3 days) due to any TVB-2640-related toxicity; 2) \geq Grade 3 hematologic toxicity that initially improved after dose interruption for ≤ 3 days, but recurred upon treatment

resumption; 3) \geq Grade 3 hematologic toxicity with complications (e.g., thrombocytopenia with bleeding); 4) febrile neutropenia; 5) \geq Grade 3 non-hematologic toxicity, with the exception of nausea, vomiting, constipation, or rash resolving within 48 h of supportive treatment; and 6) any vision-threatening adverse event (AE).

Toxicities were graded by the Investigator using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03.

After identifying the MTD as monotherapy and in combination, cohorts were expanded at the MTD to further explore activity and safety. Six dose-escalation monotherapy cohorts and 6 expansion monotherapy cohorts were evaluated, with the latter 6 enrolling patients with specific tumor types, including non-small cell lung cancer (NSCLC), prostate cancer, rectal cancer, gastric cancer, and an experimental cohort including patients with endometrial or

hepatocellular carcinoma or liposarcoma. Additionally, 6 combination cohorts, 5 with paclitaxel and 1 with docetaxel, were evaluated, with 3 involving specific tumor types, including NSCLC, ovarian/cervical, and breast cancer (Fig. 1).

2.2. Eligibility

Adult men and women with histologically- or cytologically- confirmed metastatic or advanced solid malignant tumors refractory to standard therapy were eligible. Patients may have received up to 4 prior cytotoxic chemotherapy regimens for metastatic disease as well as prior endocrine therapy and/or non-myelosuppressive therapy. Patients were required to have adequate renal, hepatic, and bone marrow function and performance status (Eastern Cooperative Oncology Group [ECOG] performance status [PS] of 0 or 1).

	Dose Escalation Cohorts	Expansion Cohorts
	Dose, N	Dose, Indication, N
Monotherapy	60 mg/m ² N=7	100 mg/m ² ; NSCLC N=16
	120 mg/m ² N=6	100 mg/m ² ; Colorectal N=7
	240 mg/m ² N=4	100 mg/m ² ; Mixed N=9
	80 mg/m ² N=3	100 mg/m ² ; Prostate N=4
	200 mg N=6	100 mg/m ² ; Rectal N=6
	250 mg N=5	100 mg/m ² ; Gastric N=5
Combination Therapy with Paclitaxel	60 mg/m ² N=6	100 mg/m ² ; NSCLC N=12
	200 mg N=7	100 mg/m ² ; Ovarian/Cervical N=20
Combination Therapy with Docetaxel	60 mg/m ² N=5	100 mg/m ² ; Breast N=13

Fig. 1. Dose cohorts.

2.3. Treatment

All patients received TVB-2640 orally (PO) once-daily (QD) continuously, with each dose separated by ~24 h, excepting the first 2 doses. To allow for collection of single-agent PK samples, the first and second doses were administered at least 3 days and up to 7 days apart.

The dose (in mg) of TVB-2640 initially was based on body surface area (BSA). As TVB-2640 was supplied as 50 mg and 200 mg strength capsules and 300 mg strength tablets, the actual dose administered was to be within -20 to +15% of the calculated mg/m² dose. After sufficient data were collected with BSA-based dosing, in subsequent cohorts TVB-2640 was administered as a range of flat doses (mg) to the nearest 50 mg in order to accommodate tablet sizes.

Paclitaxel and docetaxel were administered at the dose and schedule indicated in the prescribing information or per institutional standard of care. On days when both TVB-2640 and the combination agent were administered, TVB-2640 was taken ~2 h prior to starting the infusion of the combination agent.

Assessments:

Safety: Safety assessments included documentation of AEs, ophthalmologic examinations, clinical laboratory tests (hematology, clinical chemistry, and urinalysis), physical examinations, vital signs, ECOG PS, and 12-lead electrocardiograms (ECGs). Additionally, 24-hour digital Holter monitoring was performed around the first dose to examine potential QTc changes.

Pharmacokinetics: Serial blood samples (K₂ EDTA) were collected in all cohorts on Cycle 1, Day 1 (predose, 2, 4, 6, 24 hr post dose), and Cycle 1, Day 8 (predose, 2, 4, 6 hr post dose), for determination of the single- and multiple-dose PK of TVB-2640, respectively. TVB-2640 concentrations in human plasma were measured using a Good Laboratory Practice (GLP)-validated liquid chromatography/tandem mass spectrometry bio-analytical method performed in accordance with GLP regulations (Alturas Inc, Moscow, Idaho, US).

Pharmacodynamics: Fresh tumor biopsies were collected from patients both pre-treatment and after the first treatment cycle. Serial sections were stained with hematoxylin and eosin (H&E) to assess tumor cell content followed by a series of immunohistochemistry analyses, which, depending on sample quantity, included FASN engagement markers (FASN, pAKT, pS6, Ki67).

Serum FASN levels were measured in human serum samples using a commercially available enzyme-linked immunosorbent assay (ELISA) (ImmTech, Inc). Mucin5AC (MUC5AC) levels were measured in human K² EDTA plasma samples using a commercially available ELISA (R&D Systems), with samples analyzed at 1:10 dilution in duplicate following the manufacturer's instructions. Data analysis for ELISAs was performed using SoftMax Pro-software, version 5.4, and GraphPad Prism.

Sebaceous secretions (sebum) were collected from the forehead of patients (via Sebutape[®] patches) and analyzed for composition and mass (Metabolon, Inc., Morrisville, North Carolina, US), using a proprietary quantitative protocol. Five classes of lipids were separated by thin layer chromatography; squalene was quantitated separately and the remaining classes (wax esters, fatty acids, diglycerides, and triglycerides) were trans-methylated and further analyzed quantitatively by gas chromatography with flame ionization (GC-FID) with internal standards.

2.4. Efficacy

For patients with measurable disease, disease response was assessed by the Investigator using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [17].

2.5. Statistical analysis

Statistical analyses of safety, PK, and anti-tumor activity were primarily descriptive in nature. Continuous variables were summarized

using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Categorical variables were summarized showing the number and percentage (n,%) of patients within each classification.

2.6. Role of the funding source

This study, including design, conduct, data collection, data analysis, data interpretation, and writing of the report, was funded by Sagimet Biosciences Inc. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

2.7. Results

Overall, 142 patients with heavily pretreated solid tumors were enrolled between 19 November 2013 and 26 October 2016 at 11 study centers in the United States (N = 91) and United Kingdom (N = 51). Of these, 136 received TVB-2640. The CONSORT diagram is presented in Fig. 2.

Overall, 76 patients received monotherapy at BSA-based doses of 60 to 240 mg/m² and flat doses of 200 or 250 mg. The starting TVB-2640 monotherapy dose was 60 mg/m², with subsequent escalation to 120 mg/m² and then 240 mg/m². Two patients at 240 mg/m² experienced DLTs (corneal edema; Grade 3); accordingly, the TVB-2640 dose was reduced to 120 mg/m², with 5 additional patients treated at this dose level. Two additional patients experienced DLTs (palmar-plantar erythrodysesthesia [PPE] syndrome), and the TVB-2640 dose was further reduced back to the starting dose of 60 mg/m², with 6 additional patients treated at this dose, with no DLTs. The dose was then escalated to 80 mg/m² (N = 3), with no DLTs.

The dose was converted from BSA-calculated dosing to a flat dose of 200 mg (N = 6), with no DLTs observed. The dose was escalated to 250 mg, and 2 of 6 patients treated at that dose experienced DLTs (bilateral eye keratitis and PPE syndrome). The TVB-2640 dose was reduced to 150 mg for both patients (equivalent to 100 mg/m², based on BSA).

Thus, in summary, 6 DLTs were associated with TVB-2640 monotherapy, including Grade 3 corneal edema (n = 1), keratitis (n = 1), iritis (n = 1), and PPE syndrome (n = 3). The MTD/RP2D with TVB-2640 monotherapy was concluded to be 100 mg/m², which is typically equivalent to a flat dose of 150 to 200 mg depending on body surface area of the patient.

Sixty patients received TVB-2640 in combination with a taxane, either paclitaxel (N = 55) at doses of 60 or 100 mg/m² or 200 mg or with docetaxel at 100 mg/m² (N = 5) (Fig. 1). In combination with paclitaxel, six patients were treated at the initial 60 mg/m² dose, with no DLTs observed. The dose was increased to a 200 mg flat dose, with 2 DLTs observed (PPE syndrome and uveitis). The TVB-2640 dose was reduced to 150 mg (equivalent to 100 mg/m² based on BSA), and the MTD/RP2D of TVB-2640 in that combination was concluded to be 100 mg/m². All 5 patients treated with the combination of TVB-2640 and docetaxel developed ≥ Grade 3 hematological toxicity; therefore, this combination was not further explored in this study.

2.8. Patient characteristics

Most patients were female (57%) and Caucasian (95%), with age ranging from 33 to 81 years. All patients had a baseline ECOG PS of 0 or 1. Most (90%) had Stage IV disease at baseline, and nearly all (97%) had known metastatic disease.

The median time since diagnosis was 32 months (range 8 to 119 months); 21 months (range of 6 to 262 months); and 71 months (30 to 131 months) for monotherapy, paclitaxel combination, and docetaxel combination patients, respectively.

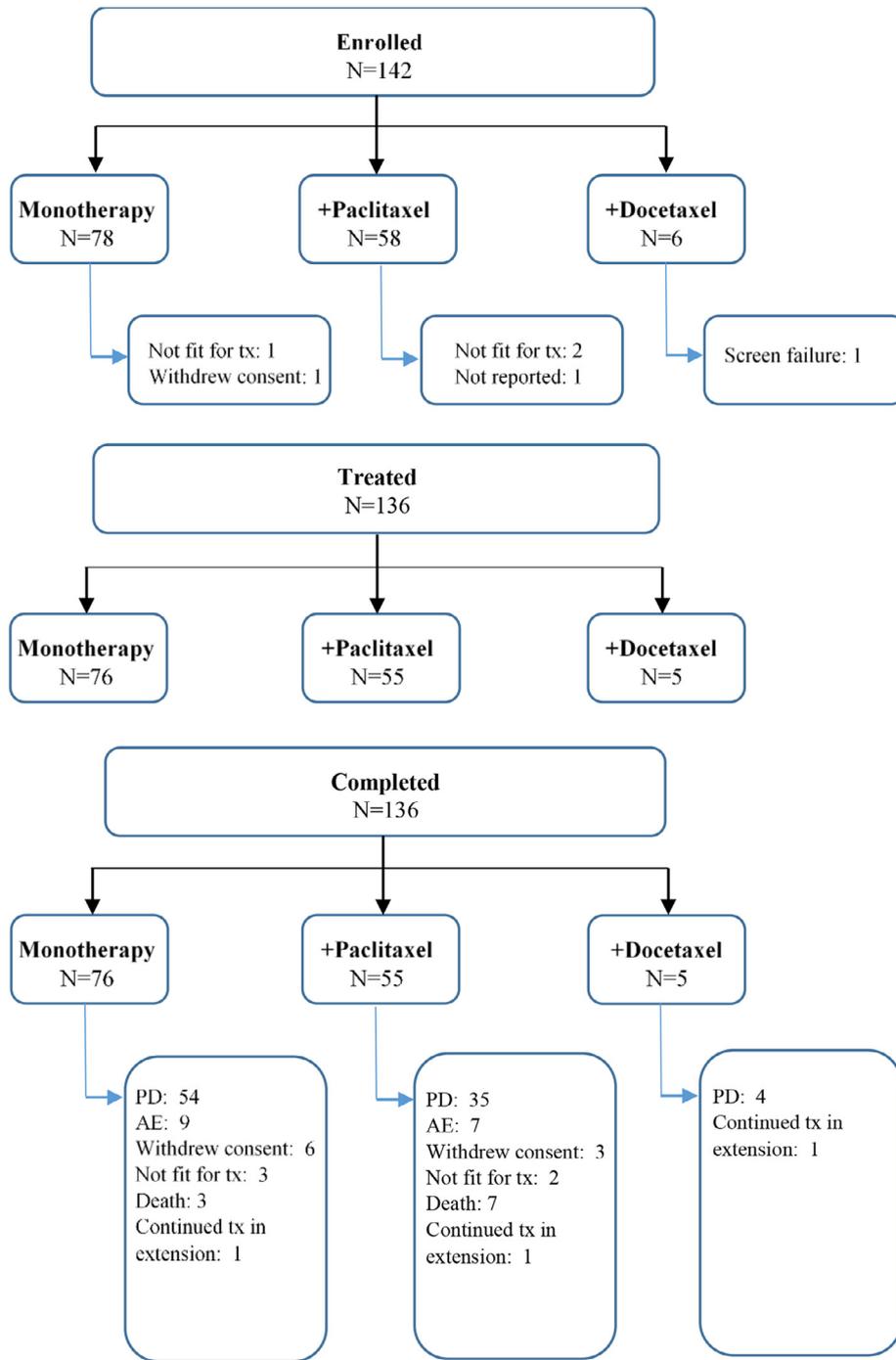


Fig. 2. CONSORT diagram.

The patient population was generally heavily pretreated (mean number of prior treatment regimens 4•0, 4•6, and 5•5 among monotherapy, paclitaxel combination, and docetaxel combination patients, respectively; range 1, 16).

2.9. Exposure

Mean and median days on treatment were 62.4 days and 42.0 days (range 6, 324 days), respectively, for monotherapy; 128•6 days and 105•0 days (range 1, 589 days) for the paclitaxel combination; and 89•0 and 77•0 days (range 21, 214 days) for the docetaxel combination. Two combination patients discontinued

paclitaxel and received TVB-2640 as monotherapy thereafter (for ~5•5 and 11 months).

2.10. Safety

TVB-2640 demonstrated a favorable tolerability profile both as monotherapy and in combination with a taxane, with no significant clinical chemistry or gastrointestinal toxicities. Most TEAEs were Grade 1 or 2 in intensity, non-serious, and manageable (Table 1).

As anticipated, based on nonclinical toxicology study findings, the principal toxicities associated with TVB-2640 monotherapy were

Table 1
Safety summary.

Parameter	TVB-2640 Monotherapy (N = 76) n (%)		TVB-2640 + Paclitaxel (N = 55) n (%)	
	Any Grade	≥Grade 3	Any Grade	≥Grade 3
Any TEAE	75 (98.7)	–	55 (100)	–
Any ≥Grade 3 TEAE	–	44 (57.9)	–	39 (70.9)
<i>Most Common Type of TEAE:</i>				
Skin and subcutaneous tissue disorders	63 (82.9)	8 (10.5)	47 (85.5)	10 (18.2)
Gastrointestinal disorders	52 (68.4)	3 (3.9)	45 (81.8)	12 (21.8)
General disorders and administration site conditions	48 (63.2)	13 (17.1)	40 (72.7)	7 (12.7)
Eye disorders	38 (50.0)	3 (3.9)	26 (47.3)	0
Infections and infestations	36 (47.4)	5 (6.6)	29 (52.7)	7 (12.7)
Respiratory, thoracic, and mediastinal disorders	34 (44.7)	2 (2.6)	32 (58.2)	5 (9.1)
Metabolism and nutrition system disorders	31 (40.8)	5 (6.6)	24 (43.6)	3 (5.5)
Nervous system disorders	27 (35.5)	1 (1.3)	31 (56.4)	5 (9.1)
Investigations	22 (28.9)	6 (7.9)	17 (30.9)	3 (5.5)
Musculoskeletal and connective tissue disorders	20 (26.3)	3 (3.9)	22 (40.0)	2 (3.6)
Blood and lymphatic system disorders	11 (14.5)	3 (3.9)	20 (36.4)	9 (16.4)

skin and ocular effects with most being Grade 1 or 2 in intensity and all non-serious. Common (i.e., incidence >10%) skin effects included PPE syndrome (46%), dry skin (22%), skin exfoliation (12%), and rash (11%). Ocular effects included dry eye (17%) and lacrimation increased (13%).

As monotherapy, the most common individual TEAEs were alopecia (61%), PPE syndrome (46%), fatigue (37%), decreased appetite (26%), and dry skin (22%). Across all dose levels, adverse events resulted in dose reduction for 28% of patients and treatment discontinuation in 22% of patients. At the MTD, no >Grade 2 skin or eye toxicities were observed.

With TVB-2640 administered in combination with paclitaxel, skin and ocular effects also were common. Most skin events were Grade 1 or 2 in intensity, and all but one skin event were non-serious. As with monotherapy, the MTD of TVB-2640 with paclitaxel was 100 mg/m²; Two DLTs were observed with this combination, including Grade 3 PPE syndrome (n = 1) and Grade 2 uveitis (n = 1). The most common TEAEs were fatigue (53%), alopecia (46%), PPE syndrome (46%), nausea (40%), and peripheral neuropathy (36%). Across all dose levels, AEs resulted in dose reduction for 42% of patients and treatment discontinuation in 23% of patients. At the MTD, no >Grade 2 skin or eye toxicities were observed.

Six episodes of serious pneumonitis were experienced by 5 patients receiving TVB-2640+paclitaxel, one of which was fatal, all assessed by the Investigator as at least possibly related to both TVB-2640 and paclitaxel. Pneumonitis was not observed in patients treated with TVB-2640 monotherapy.

ECG and Holter monitoring data revealed no clinically relevant QTc prolonging effect with TVB-2640.

2.11. Pharmacokinetics

Overall, 136 subjects had sufficient PK samples for calculation of PK parameters, with the analysis focused on the dose groups with the majority of patients.

The TVB-2640 maximum concentration (C_{max}) and area under the plasma concentration curve from time 0 to 24 h (AUC_{0–24}) increased linearly with increasing dose (Fig. 3). The time to maximum concentration (T_{max}) was ~4 h. The terminal elimination half-life was approximately 10–13 h. There was moderate accumulation at steady-state, with the ratio of the geometric mean C_{max} at steady-state to that on Day 1 ranging from 1.43 (i.e., 43% accumulation) for the 150-mg dose group to 1.65 (65% accumulation) for the 200-mg dose group.

3. Pharmacodynamics

3.1. FASN engagement and inhibition

Malonyl carnitine (MC), a metabolite of the FASN substrate malonyl CoA, and tripalmitin, a surrogate for the FASN product palmitate, were measured in serum to assess FASN pathway engagement. These specific analytes were selected because Malonyl CoA has a short half-life in serum and palmitate can be confounded by diet. TVB-2640 treatment had a significant effect on malonyl carnitine a derivative of a FASN substrate malonyl-CoA, and tripalmitin (Fig. 4, $p < 0.0001$ [2-sided *t*-test], for comparison of pre-treatment C1D1 to C1D8 or C1D15), indicative of inhibition of FASN enzymatic activity by TVB-2640. This was observed in both monotherapy and paclitaxel combination therapy patients. Overall, mean serum MC levels increased by 3.8-fold from C1D1 (mean 0.59) to C1D8/15. On an individual patient basis, increases were observed in >90% of patients, with mean increases of 4.5-fold and 3.2-fold among monotherapy and paclitaxel combination therapy patients, respectively.

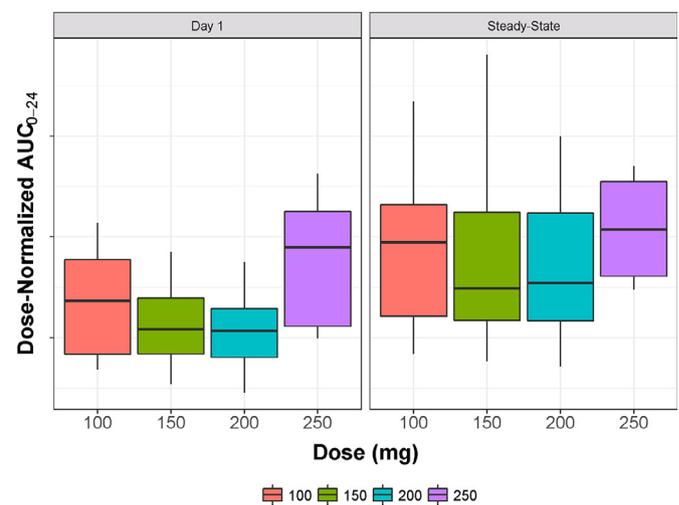


Fig. 3. Dose-normalized AUC_{0–24} by Dose, Stratified by PK Day. TVB-2640 levels were measured in patient sera on C1D1 (left panel) and on C1D8 (steady state) (right panel). The AUC_{0–24} was calculated for each patient and is shown normalized to a dose of 150 mg once daily. The horizontal line is the median, box shows the 25th–75th percentiles and whiskers extend to the 5th and 95th percentiles. On Day 1, n of 14, 74, 36 and 8 at 100, 150, 200 and 250 mg respectively. At steady state, n of 14, 65, 35 and 7 at 100, 150, 200 and 250 mg respectively.

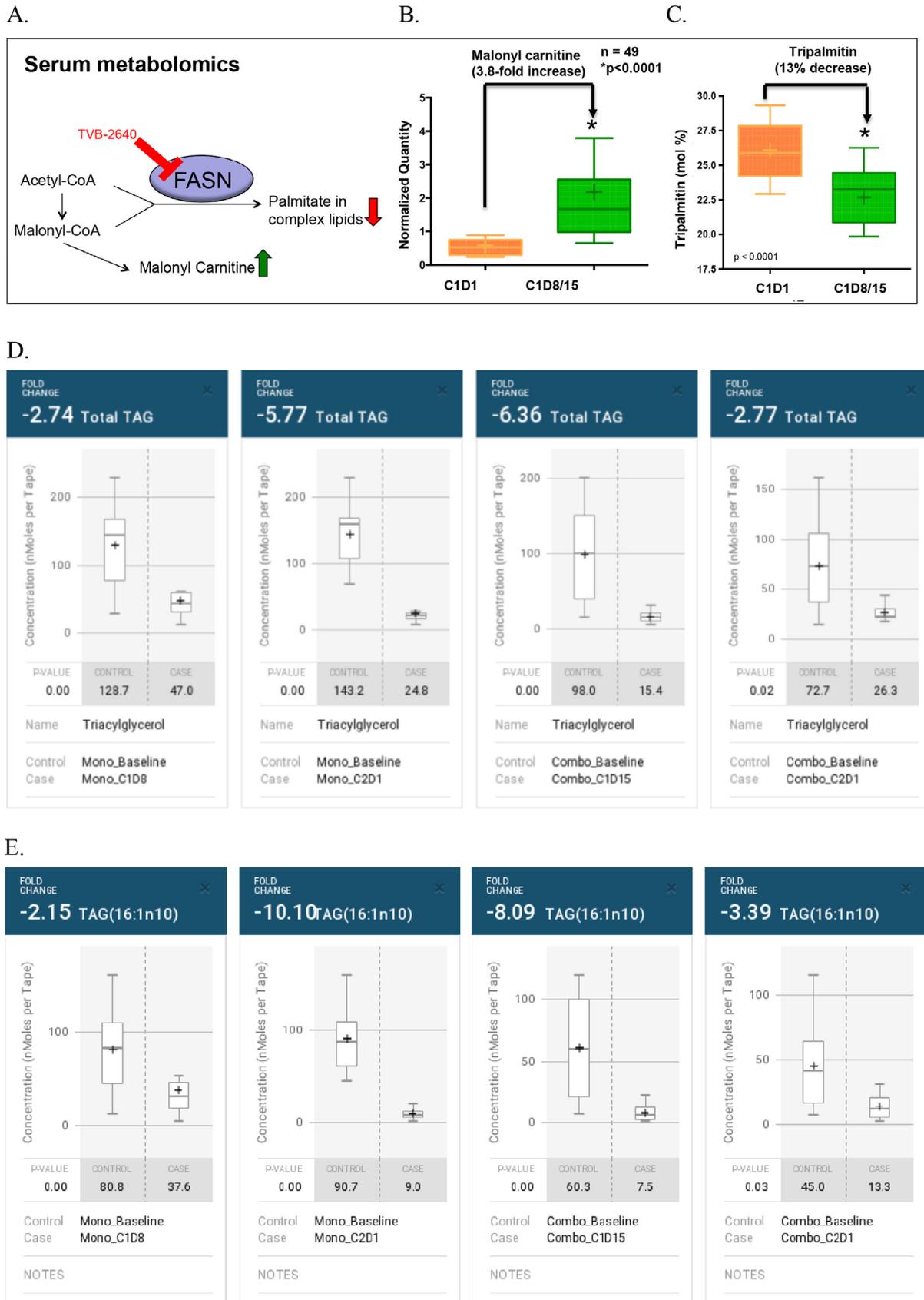


Fig. 4. TVB-2640 Significantly increases Malonyl Carnitine and Decreases Tripalmitin and Sebum Triglycerides and Sapienic Acid, Indicating Inhibition of FASN Enzymatic Activity. A) Model of FASN pathway activity and proposed impact of TVB-2640. B) MC levels in patient sera. Relative levels of MC are shown from Metabolon data; considered to be a semi-quantitative assay where levels for each samples were normalized to the median of that run ($n = 49$ pts in 3 runs, with all samples from a given patient assayed on the same run). Whiskers represent 10th and 90th percentile, with median and mean indicated by a line and + respectively. Mean/median normalized levels on C1D1 and C1D8 were $0.59/0.52$ and $2.26/1.67$ respectively. C) Tripalmitin levels in patient sera. Mol% of total triglyceride data are included for all patients analyzed ($n = 49$). Whiskers represent 10th and 90th

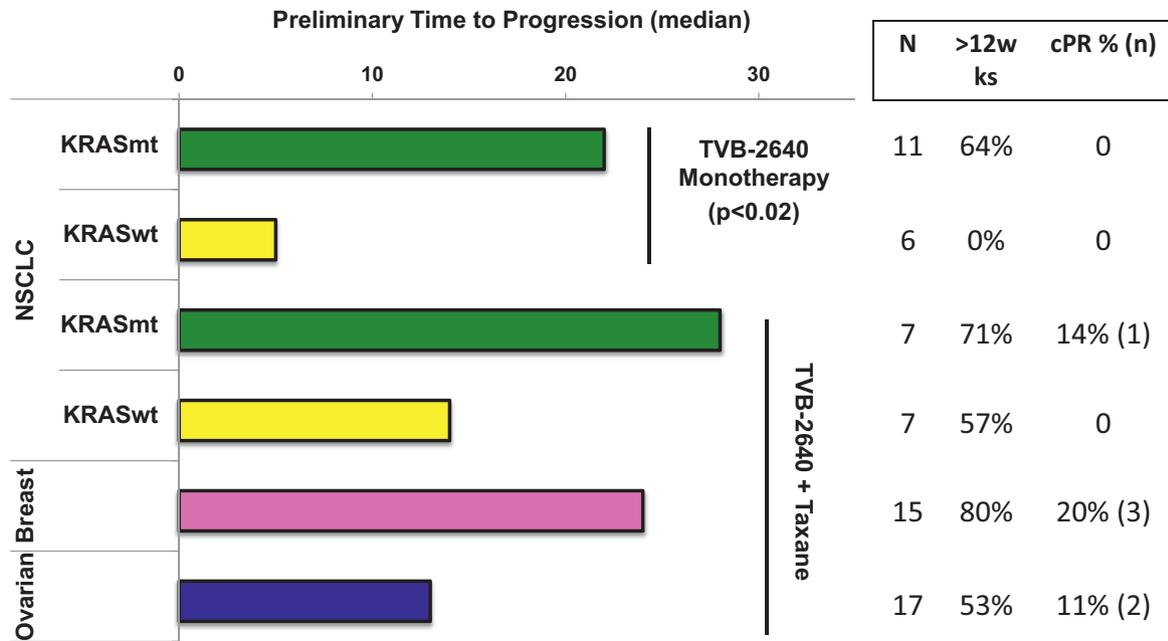


Fig. 5. Median Time to Progression among Monotherapy and Combination Therapy Patients with KRAS^{MUT} versus KRAS^{WT} Non-small Cell Lung, Breast, and Ovarian Cancer. Median time to progression is presented in weeks by tumor type for both KRAS^{WT} (yellow bars) and KRAS^{MUT} (green bars) NSCLC as well as breast (pink bar) and ovarian (blue bar) cancer. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Sebum lipid analysis: Highly significant inhibition of sebum triglyceride production was seen after initiation of TVB-2640 as monotherapy and in combination. The triglyceride sapienic acid (16:1 n10), a sebum-specific lipid, was also found to be reduced, with this reduction persisting over the treatment period (Fig. 4). Of note, dietary lipids were unrestricted during study participation and did not appear to be able to substitute for *de novo* synthesized lipids in maintaining normal sebum production under the condition of FASN inhibition. These data provide evidence of inhibition of the *de novo* lipogenesis pathway by TVB-2640.

KRAS mutational analysis: Mutant KRAS alters cell metabolism. Nonclinical studies performed with TVB-3166, a close analog of TVB-2640, indicated that NSCLC cell lines harboring KRAS mutations (KRAS^{MUT}) were more sensitive to killing with FASN inhibition than KRAS wild-type (KRAS^{WT}) lines [15]. Therefore, we assessed the KRAS mutational status of NSCLC patients in this clinical study. Mutational analyses suggested a correlation between KRAS^{MUT} NSCLC and increased time on study in both monotherapy and combination therapy groups, although the effect was less marked in the latter (Fig. 5).

Mucin 5AC in NSCLC patients: FASN enzymatic activity produces palmitate which can be used for cellular protein palmitoylation. Mucin 1 and 2 are upregulated in some tumor types known to require palmitoylation for optimal activity, and both Mucin 5AC and Mucin 2 have a homologous palmitoylation consensus site [18,19]. RNA sequence analysis from patient tumors showed high Mucin 5AC RNA levels in the tumor of a TVB-2640 monotherapy patient with long-duration stable disease (SD) compared to other patients (not shown). Consequently, Mucin 5AC levels were measured in patient plasma samples.

Pre-treatment Mucin 5AC was higher in patients with SD compared to those with progressive disease (PD) (median 34•8 versus 17•3 ng/mL, $p = 0•02$ [2-sided *t*-test]). Mucin 5AC decreased significantly with TVB-2640 treatment in patients with SD (from median 37•5 to 25•5 ng/mL at Day 8; $p = 0•038$). The group with SD had a higher proportion of KRAS^{MUT} patients (6/10) than the group with PD (1/7); the difference in proportions was not compared statistically. These data suggest high Mucin 5AC to be a potential enrichment and/or response marker.

3.2. Efficacy

No patient had a best response of complete response (CR) or partial response (PR) with TVB-2640 monotherapy; however, 42% (29/69 evaluable patients) experienced SD, making the disease control rate (DCR) 42%. Although not a study objective, no clear dose relationship was seen.

With TVB-2640+paclitaxel, the confirmed PR rate was 11% (6/53 evaluable patients), and the DCR was 70% (37/53 evaluable patients). A higher DCR was seen at the higher TVB-2640 doses of 100 mg/m² and 200 mg (36 of 49 patients; 73%) than at the lower dose of 60 mg/m² (1 of 4 patients; 25%); given the disparity in numbers of patients at each dose level, the difference in DCR was not compared statistically by dose. Disease control was seen across multiple tumor types, including breast (100%), NSCLC (82%), and gynecological (ovarian and cervical) (53%).

In patients treated with TVB-2640 monotherapy, evaluation of time to progression (TTP) among patients with NSCLC revealed significantly longer TTP for KRAS^{MUT} disease ($N = 11$) compared to KRAS^{WT} disease ($N = 6$) (22 weeks versus 5 weeks; $p < 0•02$) (Fig. 5). With the combination, median TTP also was longer among NSCLC patients

percentile, with median and mean indicated by a line and + respectively. Mean/median normalized levels on C1D1 and C1D8/15 were 26•09/25•89 and 22•68/23•27 respectively. D) Effect of TVB-2640 on sebum triglyceride levels and E) Effect of TVB-2640 on sebum sapienic acid levels. Relative levels of MC are shown from Metabolon data. Fold change is the relative change in analyte of interest at the on-treatment timepoint indicated, compared to baseline (C1D1), for monotherapy or combination treatment. The graphs show the measured results and the fold change is a calculation based on the median values. This has been added to the figure legend. E) Effect of TVB-2640 on sebum sapienic acid levels. For D) and E), fold change is the relative change in analyte of interest at the on-treatment timepoint indicated, compared to baseline (C1D1), for monotherapy or combination treatment. The graphs show the measured results and the fold change is a calculation based on the median values.

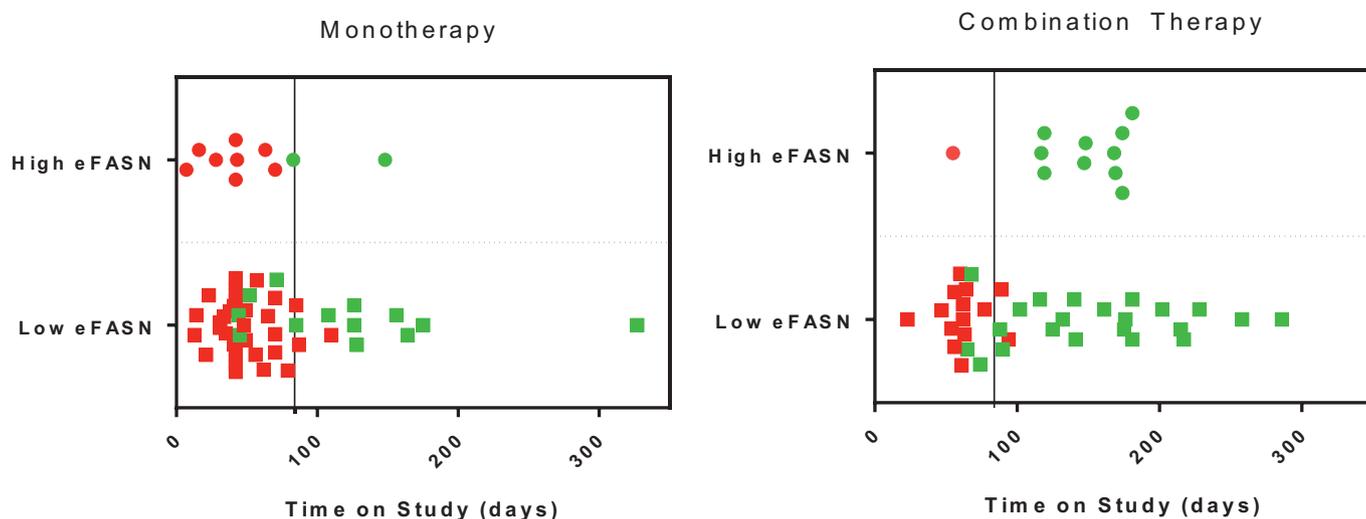


Fig. 6. Serum FASN Levels Among Monotherapy and Combination Therapy Patients, by Best Response. Serum FASN levels were measured by ELISA pre-dose (C1D1) in monotherapy (left panel) or combination (right panel) patients. FASN levels are defined as high (> 10 ng/ml) or low (< 10 ng/ml), and plotted against time on study for each patient. PD patients are represented by the red color, and stable disease or PR patients are represented by the green color. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

with KRAS^{MUT} disease compared to KRAS^{WT} disease (28 weeks versus 14 weeks, respectively), although the difference was not significant (Fig. 5).

Elevated pre-treatment serum FASN levels (≥ 10 ng/mL) correlated with response to treatment, with the majority of combination patients with elevated pre-treatment FASN having a best response of SD or better ($N = 10$) (Fig. 6).

Among the 15 patients with breast cancer treated with the paclitaxel combination, all of whom had received prior taxanes, 3 patients each had confirmed PR or long-term SD (> 6 months), with a median time to progression of 24 weeks (Fig. 5).

Among the 17 patients with ovarian cancer treated with a taxane combination, all of whom had received prior taxanes, 2 patients each experienced confirmed PR or long-term SD (> 6 months) (Fig. 5).

4. Discussion

Despite the compelling support for FASN as an oncology therapeutic target, to date, no compounds that selectively inhibit FASN other than TVB-2640 have progressed into clinical studies. Compounds described in the literature typically have been covalent inhibitors of the enzyme with significant off-target effects [20].

TVB-2640 exhibits a half-life in human of 10–13 h, which is attractive for once daily dosing, and oral exposure increased proportionately with dose. This first clinical investigation of TVB-2640 confirmed nonclinical study results, with TVB-2640 demonstrating potent target engagement (FASN inhibition evidenced by increased malonyl carnitine and decreased tripalmitin) both as monotherapy and in combination with taxanes. Furthermore, use of a novel non-invasive biomarker of forehead sebum showed decreased levels of sapienic acid, a lipogenesis-dependent sebocyte lipid, providing clear evidence of inhibition of lipogenesis by TVB-2640.

Elevated pre-treatment serum FASN levels (≥ 10 ng/mL) correlated with response to TVB-2640+paclitaxel, supporting FASN as a potential biomarker to enrich for patients best responding to such therapy.

Promising signs of clinical activity were seen in this population of heavily pre-treated patients with advanced solid tumors, particularly in KRAS^{MUT} NSCLC. Mutational analysis of patient tumors for a subset of NSCLC patients treated with TVB-2640 suggested a correlation between KRAS activating mutations, established as oncologic driver

mutations in NSCLC [21,22], and increased time on study in both monotherapy and combination therapy groups, although the effect was less marked in the latter. The KRAS^{MUT} splice variant 4A requires palmitoylation for activity and metabolic function, and it will be of interest to specifically assess the effect of FASN inhibition on this isoform in further studies [23,24].

TVB-2640 demonstrates a favorable tolerability profile, with no significant gastrointestinal or serum chemistry toxicities and no evidence of QTc prolongation in monotherapy administration. This study successfully identified the MTD in cancer patients as 100 mg/m² in both monotherapy and combination with paclitaxel.

As anticipated based on nonclinical study findings, the principal toxicities associated with TVB-2640 as monotherapy and in combination with a taxane were reversible skin and ocular effects, likely due to decreased lipid production, with such events representing the DLTs seen during the dose-escalation phase as well as the most common types of TEAEs overall. Skin effects appeared to be ameliorated by the concomitant use of emollients.

Six cases of symptomatic pneumonitis occurred in 5 patients treated with TVB-2640+paclitaxel. Pneumonitis was not observed with TVB-2640 as monotherapy, even when administered for prolonged periods. These 5 patients represented a heterogeneous group with different pathologies, prior treatments, baseline clinical status, and time courses before the occurrence of clinical events labeled as pneumonitis. Therefore, it is difficult to discern any pattern that would suggest pre-disposition to pneumonitis, with the exception of underlying lung disease.

Pneumonitis is typically a diagnosis of exclusion, as radiological findings are somewhat non-specific. In each case, no infective cause for the pulmonary findings was detected, although, in one patient, PD was clearly occurring in the lungs. Pneumonitis has been reported with taxanes, although not commonly, with a reported incidence of 1 to 4% [25–33]. A recent paper has suggested that low FASN expression in alveolar cells might pre-dispose to chemotherapy-induced lung injury although the connection with pneumonitis is not clear [34]. In view of these findings and the small number of patients affected, it is difficult to draw any definitive conclusion as to the contribution of TVB-2640 to these events.

Given TVB-2640's potent FASN inhibition in the clinical setting, emergent favorable safety profile and clinical activity, notably in patients with KRAS^{MUT} NSCLC (NCT03808558), breast cancer (NCT03179904), and ovarian cancer, further investigation of TVB-

2640 at the RP2D of 100 mg/m² in these indications in larger clinical studies is warranted.

Data sharing

The data reported in this manuscript were generated in Sagimet-sponsored Study 3V2640-CLIN-002 and are subject to access restriction to protect patient confidentiality.

Declaration of Interests

Arkenau: Dr. Arkenau has nothing to disclose.

Borazanci: Dr. Borazanci reports personal fees from Fujifilm, personal fees from Corcept, personal fees from Imaging Endpoints, personal fees from Ipsen, grants from BMS, grants from 3 V, grants from Minneamrita, grants from Fujifilm, grants from Merck, grants from Stand Up To Cancer, grants from Seena Magowitz Foundation, grants from Pharmacyclics, grants from Samumed, grants from Northern Biologics, grants from Bioline, grants from Pfizer, outside the submitted work.

Brenner: Dr. Brenner has nothing to disclose.

Burris: Dr. Burris holds stock/other ownership interested in HCA Healthcare/Sarah Cannon. Dr. Burris serves in an advisory role to Mersana, AstraZeneca, FORMA Therapeutics, Janssen, Novartis, Roche/Genentech, MedImmune, Celgene/Bristol-Myers Squibb, Incyte, Boehringer Ingelheim, Eisai, and Tolero Pharmaceuticals. Dr. Burris's institution receives research funding from Roche/Genentech, Celgene/Bristol-Myers Squibb, Incyte, AstraZeneca, MedImmune, MacroGenics, Novartis, Boehringer Ingelheim, Lilly, Seattle Genetics Merck, Agios, Jounce Therapeutics, Moderna Therapeutics, CytomX Therapeutics, GlaxoSmithKline, Verastem, Tesaro, Immunocore, Takeda, Millennium, BioMed Valley Discoveries, TG Therapeutics, Loxo, Vertex, eFFECTOR Therapeutics, Janssen, Gilead Sciences, Bio-Atla, CicloMed, Harpoon Therapeutics, Jingsu Hengrui Medicine, Arch, Kyocera, Arvinas, and Revolution Medicine. Dr. Burris has provided expert testimony to Novartis.

Cook: Dr. Cook reports grants from Research at the Christie NHS Foundation Trust was supported by the NIHR Manchester Clinical Research Facility and Manchester Experimental Cancer Medicine Centre award.

Dean: The Christie NHS Foundation Trust received commercial income from the trial sponsor and has core funding from an ECMC grant. Dr. Emma Dean took up full-time employment with AstraZeneca and is a stockholder, subsequent to her contribution to this study.

Falchook: Dr Falchook reports:

Royalties (self): Wolters Kluwer (2014-present)

Advisory role (to institution): Fujifilm (2018)

Advisory role (self): EMD Serono (2010, 2011)

Travel (self): Bristol-Myers Squibb, EMD Serono (2011, 2012, 2013), Fujifilm (2018), Millennium (2013), Sarah Cannon Research Institute

Speakers bureau: Total Health Conferencing (2019)

Research funding [to institution, for any trial for which Dr. Falchook has been the PI (ever) or subinvestigator (minimum last 4 years)]: Sagimet (FKA 3-V Biosciences), Abbvie, ADC Therapeutics, Aileron, American Society of Clinical Oncology, Amgen, ARMO, AstraZeneca, BeiGene, Bioatla, Biothera, Celldex, Celgene, CicloMed, Curegenix, Curis, Cyteir, DelMar, eFFECTOR, Eli Lilly, EMD Serono, Exelixis, Fujifilm, Genmab, GlaxoSmithKline, Hutchison MediPharma, Ignyta, Incyte, Jacobio, Jounce, Koltan, Loxo, MedImmune, Millennium, Merck, miRNA Therapeutics, National Institutes of Health, Novartis, OncoMed, Oncothyreon, Precision Oncology, Regeneron, Rgenix, Ribon, Strategia, Syndax, Taiho, Takeda, Tarveda, Tesaro, Tocagen, Turning Point Therapeutics, U.T. MD Anderson Cancer Center, Vegenics, Xencor.

Frankel: Dr. Frankel has nothing to disclose.

Grimmer: Ms. Grimmer, an employee of Sagimet Biosciences Inc., reports personal fees and other from Sagimet Biosciences Inc. (fka 3-V Biosciences, Inc.), during the conduct of the study; personal fees and other from Sagimet Biosciences Inc. (fka 3-V Biosciences, Inc.), outside the submitted work.

Infante: Dr. Infante is an employee of Janssen Oncology and a consultant to Biomed Valley Discoveries and Argo Biosciences.

Kemle: Dr. Kemle, an employee of Sagimet Biosciences Inc., reports personal fees and other from Sagimet Biosciences, during the conduct of the study.

Lopez: Dr. Lopez reports grants from Roche-Genentech, grants from Genmab, grants and non-financial support from Basilea, personal fees from Eisai, personal fees from Novartis, outside the submitted work.

McCulloch: Dr. McCulloch, an employee of Sagimet Biosciences Inc., reports personal fees and other from Sagimet Biosciences Inc. (fka 3-V Biosciences, Inc), during the conduct of the study; personal fees and other from Sagimet Biosciences Inc. (fka 3-V Biosciences, Inc), outside the submitted work.

Moore: Dr. Moore reports personal fees and other from AstraZeneca, grants, personal fees and other from Genentech/Roche, grants, personal fees and other from Immunogen, grants, personal fees and other from Clovis, grants, personal fees and other from Tesaro, personal fees and other from Pfizer, personal fees from Janssen, personal fees from Aravive, personal fees from VBL Therapeutics, personal fees and other from Onco Med, personal fees from Samumed, grants and other from Lilly, personal fees from Eisai, outside the submitted work.

O'Farrell: Dr. O'Farrell, an employee of Sagimet Biosciences Inc., reports personal fees and other from Sagimet Biosciences Inc., during the conduct of the study; personal fees and other from Sagimet Biosciences Inc., outside the submitted work.

Pant: Dr. Pant has nothing to disclose.

Patel: Dr. Patel has nothing to disclose.

Schmid: Dr. Schmid reports other from Pfizer, other from AstraZeneca, other from Novartis, other from Roche, other from Merck, other from Boehringer Ingelheim, other from Bayer, other from Eisai, from Celgene, from Puma, grants from AstraZeneca, grants from Roche, grants from Genentech, grants from Oncogenex, grants from Novartis, grants from Roche, other from Genentech, other from Roche, outside the submitted work.

Authors Contribution: H-T A, EB, HB, NC, ED, GF, KG, JI, GK, JL, WM, KM, MP, and PS contributed to data analysis and interpretation; H-T A, EB, NC, GF, JI, and JL contributed to patient recruitment; H-T A, HB, GF, KG, JI, GK, WM, MP, and PS contributed to trial design; H-T A, EB, HB, NC, GF, JI, JL, and PS contributed to manuscript writing; EB, KG, JI, JL contributed to study supervision; HB, NC, ED, GF, KM, SP, MP, and PS contributed to data collection; ED presented interim data at scientific meetings. All authors contributed to critical revision of the manuscript. All authors approved the manuscript.

Funding: The study was funded by 3-V Biosciences, Inc. (now known as Sagimet Biosciences, Inc.).

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