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Uwe Pelzer
Universitätsmedizin Berlin

Jean-Frédéric Blanc
Université de Bordeaux

Davide Melisi
University of Verona

Antonio Cubillo
Hospital Universitario Madrid Sanchinarro

Daniel D. Von Hoff
Virginia G. Piper Cancer Center

See next page for additional authors

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Authors

Uwe Pelzer, Jean-Frédéric Blanc, Davide Melisi, Antonio Cubillo, Daniel D. Von Hoff, Andrea Wang-Gillam, Li-Tzong Chen, Jens T. Siveke, Yin Wan, Caitlyn T. Solem, Marc F. Botteman, Yoojung Yang, Floris A. de Jong, and Richard A. Hubner

Keywords: Q-TWiST; metastatic pancreatic cancer; clinical trial; NAPOLI-1

Quality-adjusted survival with combination nal-IRI + 5-FU/LV vs 5-FU/LV alone in metastatic pancreatic cancer patients previously treated with gemcitabine-based therapy: a Q-TWiST analysis

Uwe Pelzer¹, Jean-Frédéric Blanc², Davide Melisi³, Antonio Cubillo⁴, Daniel D Von Hoff⁵, Andrea Wang-Gillam⁶, Li-Tzong Chen⁷, Jens T Siveke^{8,9}, Yin Wan¹⁰, Caitlyn T Solem¹⁰, Marc F Botteman¹⁰, Yoojung Yang¹¹, Floris A de Jong¹² and Richard A Hubner¹³

¹Department of Hematology/Oncology/Tumorimmunology, Charité – Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany; ²Service d'Hépatogastroentérologie et Oncologie Digestive, Hôpital Haut-Lévêque, CHU de Bordeaux, Inserm UMR 1053, Université de Bordeaux, Bordeaux, France; ³Digestive Molecular Clinical Oncology Unit, University of Verona, Piazzale L.A. Scuro, 10, 37134 Verona, Italy; ⁴Servicio de Oncología Médica, Centro Integral Oncológico Clara Campal (CIOCC), Hospital Universitario Madrid Sanchinarro, Calle Oña, 10, 28050 Madrid, Spain; ⁵Virginia G. Piper Cancer Center at HonorHealth/TGen, 10460 N 92nd St #206, Scottsdale, AZ 85258, USA; ⁶Division of Oncology, Washington University in St Louis, 660 South Euclid Avenue, St Louis, MO 63110, USA; ⁷National Institute of Cancer Research, National Health Research Institutes, 2F, No. 367, Sheng-Li Road, Tainan 70456, Taiwan; ⁸Division of Solid Tumor Translational Oncology, DKTK Partner Site Essen, West German Cancer Center, University Hospital Essen, Hufelandstrasse 55, 45147 Essen, Germany; ⁹German Cancer Consortium (DKTK) and German Cancer Research Center (DKFZ), Heidelberg, Germany; ¹⁰Pharmerit International, 4350 East-West Hwy #430, Bethesda, MD 20814, USA; ¹¹Shire, Plc, 650 East Kendal St, Cambridge, MA 02142, USA; ¹²Department of Global Medical Affairs Oncology, Shire GmbH, Zählerweg 10, 6300 Zug, Switzerland and ¹³Department of Medical Oncology, Christie Hospital NHS Foundation Trust, 550 Wilmslow Rd, Manchester M20 4BX, UK

Background: In the NAPOLI-1 Phase 3 trial, nal-IRI + 5-fluorouracil and leucovorin (5-FU/LV) significantly improved median overall survival (6.1 vs 4.2 months, $P=0.012$) and progression-free survival (3.1 vs 1.5 months, $P=0.0001$) vs 5-FU/LV alone in metastatic pancreatic adenocarcinoma patients previously treated with gemcitabine-based therapy. This analysis evaluated between treatment differences in quality-adjusted time without symptoms of disease progression or toxicity (Q-TWiST).

Methods: Overall survival was partitioned into time with grade ≥ 3 toxicity (TOX), disease progression (REL), and time without disease progression symptoms or grade ≥ 3 toxicity (TWiST). Mean Q-TWiST was calculated by weighting time spent by a utility of 1.0 for TWiST and 0.5 for TOX and REL. In threshold analyses, utility for TOX and REL were varied from 0.0 to 1.0.

Results: Patients in nal-IRI + 5-FU/LV ($n=117$) vs 5-FU/LV ($n=119$) had significantly more mean time in TWiST (3.4 vs 2.4 months) and TOX (1.0 vs 0.3 months) but similar REL (2.5 vs 2.7 months). In the base case, nal-IRI + 5-FU/LV patients had 1.3 months (95% CI, 0.4–2.1; 5.1 vs 3.9) greater Q-TWiST (threshold analyses range: 0.9–1.6 months).

Conclusions: Within NAPOLI-1, nal-IRI + 5-FU/LV resulted in statistically significant and clinically meaningful gains in quality-adjusted survival vs 5-FU/LV alone.

*Correspondence: Dr U Pelzer; E-mail uwe.pelzer@charite.de

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Pancreatic cancer remains one of the most fatal and least understood human malignancies and continues to be a major unsolved health problem (Melisi *et al*, 2014). It has a five-year relative survival rate at 7.7% (SEER Stat Fact Sheets), and is projected to become the second leading cause of cancer-related death by the year 2030 in western countries (Rahib *et al*, 2014). More than 338 000 people per year are diagnosed with pancreatic cancer worldwide, and approximately the same number die of this disease (Ferlay *et al*, 2013). The poor prognosis associated with pancreatic cancer can be attributed to the disease's early metastatic behaviour during progression, its aggressive course, and, in particular, to the limited efficacy of currently approved classic chemotherapeutic treatments (Tamburrino *et al*, 2013). Current treatment guidelines – most notably those from the National Comprehensive Cancer Network (version 2, 2016) and the European Society for Medical Oncology (ESMO, 2015) – recommend the following first-line treatment options for advanced pancreatic cancer depending on patients' performance status (measured by Eastern Cooperative Oncology Group (ECOG) scale): gemcitabine and nab-paclitaxel combination therapy or fluorouracil–leucovorin–irinotecan–oxaliplatin (FOLFIRINOX) regimen (ECOG 0 or 1), and these two regimens are preferred chemotherapy as recommended in National Comprehensive Cancer Network and other acceptable regimens include gemcitabine + erlotinib, gemcitabine + capecitabine, and so on; gemcitabine monotherapy (ECOG 2); or best supportive care (ECOG 3–4 or comorbidities). However, the majority of patients progress while on first-line therapy and have limited proven options in the second-line setting. National Comprehensive Cancer Network guideline(s) have suggested that fluoropyrimidine-based chemotherapy, such as 5-fluorouracil and leucovorin (5-FU/LV), is an acceptable second-line option among patients previously treated with gemcitabine-based therapy (Tempero *et al*, 2014; Ducreux *et al*, 2015; Oettle *et al*, 2015).

Nanoliposomal irinotecan (nal-IRI; US trade name Onivyde) was recently approved by the US Food and Drug Administration and the European Medicines Agency review for the treatment of metastatic pancreatic adenocarcinoma (mPAC) in combination with 5-FU/LV in patients previously treated with gemcitabine-based therapy. The US Food and Drug Administration approved nal-IRI + 5-FU/LV based on results from the NAPOLI-1 (NAnoliPOsomaLIrinotecan) clinical trial (NLM identifier: NCT01494506). NAPOLI-1 was a global, multicenter, open-label, Phase 3 trial that included adult metastatic pancreatic cancer patients whose disease had progressed following previous gemcitabine-based therapy (Wang-Gillam *et al*, 2016). The NAPOLI-1 trial demonstrated that the nal-IRI + 5-FU/LV significantly improved patients' median overall survival (OS) (6.1 vs 4.2 months, HR = 0.67, $P = 0.012$) and median progression-free survival (3.1 vs 1.5 months, HR = 0.56, $P = 0.0001$) compared with 5-FU/LV therapy alone. In its 2015 updated guidelines, ESMO indicated nal-IRI + 5-FU + folinic acid as the best second-line treatment option based on the currently available evidence for this patient population (Ducreux *et al*, 2015).

The present analysis aimed to compare the quality-adjusted time without symptoms of disease progression or toxicity (Q-TWiST) of nal-IRI + 5-FU/LV treatment over 5-FU/LV treatment alone using the NAPOLI-1 clinical trial data. The Q-TWiST method (Chen *et al*, 2015) integrates the quality and quantity of survival by partitioning survival time into three clinically relevant periods, which are assigned different quality-of-life weights (i.e., 'utilities'), including the periods in which patients (1) experienced toxicity (TOX) due to treatment, (2) did not experience any TOX and had not yet progressed (i.e., pre-progression time without adverse events (AEs)), and (3) experienced progression after disease recurrence. This approach facilitates comparison between treatments by penalising treatments with increased toxicities or

shorter times to disease progression and rewarding those with lower TOX and longer progression-free and OS times (Cole and Gelber, 1995).

MATERIALS AND METHODS

Study cohorts. The study cohorts for this analysis were from the NAPOLI-1 clinical trial (Chen *et al*, 2015; Wang-Gillam *et al*, 2016). Patients were randomised into three treatment arms: nal-IRI, 5FU/LV, and nal-IRI + 5-FU/LV (1:1:1 ratio). The primary end point was OS; secondary end points included progression-free survival, time to treatment failure, and tumour reponse. The study's full inclusion and exclusion criteria and findings can be found in the NAPOLI-1 primary publication (Wang-Gillam *et al*, 2016).

The primary Q-TWiST analysis was performed using the intent to treat population, and was supplemented with analyses in the per-protocol population (i.e., patients who received $\geq 80\%$ of the protocol-defined treatment during the first 6 weeks of treatment) (Chen *et al*, 2015) and analyses in nine pre-specified subgroups: race (Asian), baseline Karnofsky performance status scores (< 90 , 90–100), time since treatment (< 1.3 months, > 1.3 months), cancer stage at diagnosis (stage IV, other), and tumour location (head, other). The Q-TWiST analysis was performed specifically on the combination treatment arm (nal-IRI + 5-FU/LV) vs 5-FU/LV. The current study focused on the treatment arms amended after safety data on the combination became available, which is consistent with the primary analysis (Chen *et al*, 2015).

Statistical analysis. The Q-TWiST method combines treatment benefits and risks into a single measure by partitioning survival time into three health states and subsequently assigning quality-of-life weights to the survival time in each state (Gelber *et al*, 1993). These three health states include time with grade ≥ 3 TOX (i.e., all-cause AEs), disease progression (REL), and time without disease progression symptoms or grade ≥ 3 toxicity (TWiST). The restricted mean duration of each health state was calculated as the area under its Kaplan–Meier curve through 12 months of follow-up (Kaplan and Meier, 1958; Fairclough, 2010).

TOX time was defined as the period during which a patient experienced AEs between randomisation and progression. It was calculated as the total number of days between randomisation and progression in which each patient experienced grade ≥ 3 all-cause adverse events (AEs; defined using the National Cancer Institute Common Terminology Criteria for Adverse Events). Any day with multiple AEs was only counted once, and the total number of TOX days were grouped together during a patient's treatment, regardless of when TOX days occurred (but only counting AEs prior to relapse). REL time was defined as the time after disease progression (i.e., the period when patients experience disease relapse).

The Q-TWiST value is the linear combination of the health state durations adjusted by the respective utilities (U):

$$Q\text{-TWiST} = U(\text{TOX}) \times \text{TOX} + U(\text{TWiST}) \times \text{TWiST} + U(\text{REL}) \times \text{REL}$$

Within this analysis, two assumptions about TOX time were made: (1) the utility associated with TOX was the same regardless of AE type or grade; (2) AE duration was truncated on the date the patient progressed if the AE continued past that date.

In the base case, the utility of TOX and REL were both assigned as 0.5 and TWiST was assigned as 1.0 consistent with prior Q-TWiST analyses in various oncology disease areas (Solem *et al*, 2014). In a threshold analysis, the difference in Q-TWiST between treatments was calculated over all possible combinations of U(TOX) and U(REL), ranging from 0.0 to 1.0. To understand how the utility weight of TWiST affects the results, alternative utility weights were used in a sensitivity analysis:

$U(\text{TWiST}) = 0.80$, $U(\text{TOX}) = 0.65$, and $U(\text{REL}) = 0.75$. These alternative utility weights of TWiST and REL were obtained from a clinical trial, which prospectively collected utility data of patients with mPAC (Romanus *et al*, 2012) who received gemcitabine monotherapy or gemcitabine-based combination therapy. The utility weight of TOX was calculated based on a series of study results reporting the utility decrement of AEs (Lloyd *et al*, 2006; Nafees *et al*, 2008; Swinburn *et al*, 2010; Tolley *et al*, 2013; Goldstein *et al*, 2014). Additionally, since afebrile neutropenia may not be clinically symptomatic, a sensitivity analysis was performed to assess the Q-TWiST difference when removing the AE of neutropenia from TOX time. Given that certain grade 2 toxicities also impact patients' quality of life, such as fatigue, a sensitivity analysis was performed by including grade 2 toxicities in the TOX time calculation.

Consistent with Revicki *et al* (2006), the relative gain in Q-TWiST in nal-IRI + 5-FU/LV over 5-FU/LV was calculated as the difference in Q-TWiST divided by the OS time of 5-FU/LV group (i.e., control group). It was reported for the base case Q-TWiST analysis and threshold analysis. The relative gain in Q-TWiST was used to define clinical important difference (10%) and clearly clinically important difference (15%) of Q-TWiST in Revicki *et al*.

Statistical testing was limited to a comparison of the overlap of 95% confidence intervals (CIs), which were calculated using 1000 sample nonparametric bootstraps of the data (Fairclough, 2010). Mean durations of each health state and quality-adjusted survival time were compared and differences calculated between treatment groups. If the 95% CI did not overlap between treatment groups (or the 95% CI around the difference did not overlap 0), the difference was considered statistically significant. SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA) was used to perform the statistical analyses.

RESULTS

Patient sample. A total of 236 patients were randomised to nal-IRI + 5-FU/LV treatment ($n = 117$) or 5-FU/LV treatment ($n = 119$). Patients randomised to nal-IRI + 5-FU/LV had a mean (s.d.) age of 63.2 (9.06) years and were 59% male and 29.1% Asian, while 5-FU/LV patients were aged 61.0 (9.46) years, 56.3% male, and 30.3% Asian (Table 1). There were no significant differences in baseline characteristics between treatment groups.

Duration of time spent in each health state. The mean duration of time spent in TWiST, TOX, and REL was significantly longer among patients receiving nal-IRI + 5-FU/LV vs 5FU/LV alone (Table 2). In both cohorts, the mean TWiST duration was significantly higher than the mean TOX duration, indicating a greater amount of time without significant symptoms prior to progression compared to time with AEs.

Q-TWiST (NAL-IRI + 5-FU/LV vs 5-FU/LV). In the base case, when the utility weights for the TOX and REL health states were set to 0.5 in the intent to treat population, there was a statistically significant 1.3-month gain (95% CI, 0.4–2.1 months) in Q-TWiST favouring nal-IRI + 5-FU/LV (5.1 months (95% CI, 4.5–5.8 months)) over 5-FU/LV alone (3.9 months (95% CI, 3.3–4.5 months)). This translated to a relative improvement of 23.8% at 12-month follow-up. In the per-protocol population, the results remained in favour of nal-IRI + 5-FU/LV over 5-FU/LV alone (difference in Q-TWiST: 1.8 months (95% CI, 0.7–3.0 months)) (Table 3).

In the threshold analysis, the absolute gain in Q-TWiST at 12-month follow-up showed that the gain in Q-TWiST increased from 0.9 to 1.7 months as $U(\text{TOX})$ and $U(\text{REL})$ increased from 0.0 to 1.0 (Figure 1A). The Q-TWiST gains were all statistically significant

across all combinations of utilities in TOX and REL while TWiST was set at 1.0, except when utility of REL was close to 1.0 and utility of AE was close to 0.0. Similarly, the relative improvement ranged from 16.9 to 30.8% (Figure 1B).

In a sensitivity analysis applying literature-based mPAC utilities to each health state ($U(\text{TOX}) = 0.65$, $U(\text{REL}) = 0.75$, and $U(\text{TWiST}) = 0.80$), the Q-TWiST gain in nal-IRI + 5-FU/LV over 5-FU/LV remained statistically significant at 1.1 months (95% CI, 0.3–1.9 months), with a relative gain of 20%. Another sensitivity analysis was performed by removing neutropenia from the TOX time calculation, and the result remained similar to the main analysis (difference in Q-TWiST: 1.3 months (95% CI, 0.4–2.2 months)). The Q-TWiST at various time points during follow-up consistently showed significant improvement in the nal-IRI + 5-FU/LV group over the 5-FU/LV group, except at the first 3 months (Figure 2).

In another sensitivity analysis including grade ≥ 2 toxicities, it was found that patients treated with nal-IRI + 5-FU/LV experienced longer quality-adjusted survival time compared to 5-FU/LV (difference in Q-TWiST: 0.9 month (95% CI: 0.1, 1.7)), which corresponds to a 17.5% improvement. This sensitivity analysis result remained consistent with the main analysis, which included grade ≥ 3 toxicities.

In subgroup analyses, the results across all pre-specified subgroups were in favour of nal-IRI + 5-FU/LV over 5-FU/LV alone (Figure 3). These positive differences were significant for patients of Asian ethnicity, patients with Karnofsky performance status scores < 90 , < 1.3 months since prior treatment, stage IV cancer at diagnosis, and tumour location other than the head of pancreas.

DISCUSSION

This analysis is the first to use the Q-TWiST approach to assess the efficacy of nal-IRI + 5-FU/LV combination treatment vs 5-FU/LV treatment alone in patients with metastatic pancreatic cancer. Within the NAPOLI-1 Q-TWiST analyses, nal-IRI in combination with 5-FU/LV provided significantly greater quality-adjusted survival time compared to 5-FU/LV alone in patients previously treated with gemcitabine-based therapy. This result reflects both the significantly greater median survival time (6.1 vs 4.2 months; HR = 0.67 (95% CI 0.49–0.92), $P = 0.012$) and progression-free survival time (3.1 vs 1.5 months HR = 0.56 (95% CI 0.41–0.75), $P = 0.0001$) observed for nal-IRI + 5-FU/LV treatment over 5-FU/LV alone within the NAPOLI-1 trial (Wang-Gillam *et al*, 2016). This also supports the original trial's finding that despite patients receiving more medicine in the combination arm, quality of life (measured using the European Organization for Research and Treatment of Cancer Quality-of-Life Core Questionnaire (EORTC-QLQ-C30)) was not appreciably different between these two treatment groups (Wang-Gillam *et al*, 2016).

The Q-TWiST findings were consistent across the threshold analysis and various sensitivity and subgroup analyses. Most clinical trials do not collect utility data by health states, such as toxicities, as described in this study. The threshold analysis in Q-TWiST method allows TOX and post-progression utilities to vary across their possible ranges (0–1), addressing some of the uncertainty associated with the assigned utility values. Additionally, these Q-TWiST data may help inform physicians in discussing quality-of-life issues with pancreatic cancer when considering second-line chemotherapy in patients previously treated with gemcitabine-based therapy. In this study, the absolute gain and relative gain in Q-TWiST ranged from 0.9 to 1.7 months and from 17 to 31% in the threshold analysis, respectively. The results confirmed the robustness of the results given varying utilities

Table 1. Study populations and demographics

Characteristic	nal-IRI + 5-FU/LV combo (n = 117)	5-FU/LV combo control (n = 119)
Age (y)		
Mean (s.d.)	63.2 (9.06)	61.0 (9.46)
Median	63.0	62.0
Min, max	41, 81	34, 80
Gender, n (%)		
Female	48 (41.0)	52 (43.7)
Male	69 (59.0)	67 (56.3)
Race, n (%)		
American Indian or Alaska Native	0	0
Asian	34 (29.1)	36 (30.3)
Black or African American	4 (3.4)	3 (2.4)
White	72 (61.5)	76 (63.9)
Other	7 (6.0)	4 (3.4)
Baseline KPS level, n (%)		
50	1 (0.9)	0
60	2 (1.7)	0
70	7 (6.0)	10 (8.4)
80	38 (32.5)	51 (42.9)
90	51 (43.6)	40 (33.6)
100	18 (15.4)	17 (14.3)
Baseline albumin, g dl ⁻¹		
Mean (s.d.)	3.97 (0.459)	3.98 (0.506)
Min, max	2.6, 5.1	2.4, 5.0
Measurable lesions at baseline, n (%)	113 (96.6)	114 (95.8)
No measurable lesions at baseline, n (%)	4 (3.4)	5 (4.2)
Measurable metastatic lesions at baseline, n (%)	97 (82.9)	103 (86.6)
No measurable metastatic lesions at baseline, n (%)	20 (17.1)	16 (13.4)
Subjects at baseline with: n (%)		
One measurable metastatic lesion	19 (16.2)	22 (18.5)
Two measurable metastatic lesions	49 (41.9)	58 (48.7)
Three measurable metastatic lesions	22 (18.8)	15 (12.6)
> Three measurable metastatic lesions	7 (6.0)	8 (6.7)
Anatomical location of lesions at baseline, n (%)		
Distant lymph node	32 (27.4)	31 (26.1)
Liver	75 (64.1)	83 (69.7)
Lung	36 (30.8)	36 (30.3)
Pancreas	75 (64.1)	72 (60.5)
Peritoneal	28 (23.9)	32 (26.9)
Regional lymph node	13 (11.1)	14 (11.8)
Other	27 (23.1)	39 (32.8)
Prior lines of treatment		
First-line advanced/metastatic	15 (12.8)	15 (12.8)
Second-line advanced/metastatic	62 (53.0)	67 (56.3)
Third-line advanced/metastatic	40 (34.2)	37 (31.1)
Time since last prior anticancer therapy (months)		
Mean (s.d.)	2.1 (2.4)	2.6 (5.4)
Median	1.4	1.1
Min, max	0.2, 16.8	0.0, 43.2
Location of pancreatic tumour of diagnosis, n (%)		
Head	76 (64.9)	69 (58.0)
Other	41 (35.1)	50 (42.0)
Disease stage, n (%)		
Stage I	2 (1.8)	5 (4.2)
Stage II	32 (27.3)	31 (26.1)
Stage III	21 (17.9)	19 (16.0)
Stage IV	61 (52.1)	62 (52.1)
Missing	1 (0.9)	2 (1.7)

Abbreviation: KPS = Karnofsky Performance Status.

assigned to TOX and disease symptoms or progression. Additional sensitivity analysis was performed using alternative literature utilities (i.e., prospectively collected utilities in pancreatic cancer patients): Utility for TWiST was 0.8, REL was 0.75, and TOX was 0.65. The results showed a statistically significant and 20% relative Q-TWiST gain for nal-IRI + 5-FU/LV vs 5-FU/LV, which further

supports the study conclusion. Five out of the nine subgroups had significant Q-TWiST gains by nal-IRI + 5-FU/LV vs 5-FU/LV, including baseline Karnofsky performance status <90, time since treatment at baseline <1.3 months, stage IV cancer, Asian ethnicity, and tumour location other than head. It showed that patients with poor performance status or more advanced disease at

Table 2. Mean duration of TOX, TWiST, and REL between treatment groups at 12 months for nal-IRI + 5-FU/LV vs 5-FU/LV in the ITT cohort

Survival duration (mo) by health states	5-FU/LV, mean (95% CI)	nal-IRI + 5-FU/LV, mean (95% CI)	Difference, mean (95% CI)
TOX	0.3 (0.2, 0.5)	1.0 (0.7, 1.3)	0.5 (0.3, 1.0) ^a
TWiST	2.4 (1.8, 2.9)	3.4 (2.6, 4.1)	1.1 (0.1, 1.9) ^a
REL	2.7 (2.1, 3.3)	2.5 (2.0, 3.1)	-0.1 (-0.9, 0.7)

Abbreviations: TOX = time with adverse event grade ≥ 3 ; TWiST = time without symptoms or adverse event grade ≥ 3 toxicity; REL = time in relapse after disease progression; ITT = intent to treat.
^aStatistically significant difference between treatments.

Table 3. Quality-adjusted time without symptoms or toxicities threshold analysis for nal-IRI + 5-FU/LV vs 5-FU/LV in the ITT cohort

Utility weights	5-FU/LV, mean Q-TWiST months (95% CI)	nal-IRI + 5-FU/LV, mean Q-TWiST months (95% CI)	Difference, mean Q-TWiST months (95% CI)
U(TOX) = 0, U(REL) = 0	2.4 (1.8, 2.9)	3.4 (2.6, 4.1)	1.0 (0.1, 1.9)
U(TOX) = 0, U(REL) = 0.5	3.7 (3.1, 4.3)	4.7 (4, 5.3)	1.0 (0.1, 1.8)
U(TOX) = 0, U(REL) = 1	5 (4.3, 5.8)	5.9 (5.2, 6.6)	0.9 (-0.2, 2.0)
U(TOX) = 0.5, U(REL) = 0	2.5 (2, 3.1)	3.9 (3.1, 4.5)	1.3 (0.4, 2.2)
U(TOX) = 0.5, U(REL) = 0.5	3.9 (3.3, 4.5)	5.1 (4.5, 5.8)	1.3 (0.4, 2.1)
U(TOX) = 0.5, U(REL) = 1	5.2 (4.4, 6)	6.4 (5.7, 7.1)	1.2 (0.2, 2.2)
U(TOX) = 1, U(REL) = 0	2.7 (2.1, 3.3)	4.4 (3.6, 4.9)	1.7 (0.7, 2.5)
U(TOX) = 1, U(REL) = 0.5	4 (3.4, 4.6)	5.6 (4.9, 6.2)	1.6 (0.7, 2.5)
U(TOX) = 1, U(REL) = 1	5.4 (4.6, 6.2)	6.9 (6.1, 7.6)	1.5 (0.4, 2.5)

Abbreviations: U(TOX) = utility of time with adverse event grade ≥ 3 ; U(REL) = utility of time in relapse after disease progression; Q-TWiST = quality-adjusted time without symptoms of disease progression or toxicity; ITT = intent to treat.

baseline were more likely to benefit in Q-TWiST from the treatment of nal-IRI + 5-FU/LV (vs 5-FU/LV).

The statistically significant Q-TWiST gains are relatively large in magnitude and may be considered clearly clinically important using the thresholds established by Revicki *et al* (2006), which state a clinically important improvement for Q-TWiST as 10% of OS in the control group, while 15% indicates a clearly clinically important improvement. In contrast, Solem *et al* (2014) found in a recent review of Q-TWiST literature in oncology that only 18% of Q-TWiST studies reported a clearly clinically important gain (i.e., $\geq 15\%$) in treatment over control groups in base case analyses.

A recent analysis assessing nab-paclitaxel plus gemcitabine combination treatment vs gemcitabine-only in first-line mPAC (Reni *et al*, 2014) found a 21% relative improvement in Q-TWiST in favour of the combination treatment over gemcitabine-only treatment. The Q-TWiST improvement observed in the current analysis for nal-IRI + 5-FU/LV (vs 5-FU/LV) was 24%. The difference in outcomes may be partially attributable to the study design and treatments; while Reni *et al* (2014) analysed first-line treatment on treatment-naive patients, the current analyses only included patients previously treated with gemcitabine-based regimen.

The present analysis has several limitations. First, patient-derived data regarding the utility weights were not collected prospectively. To account for this, the base case utilities for TOX

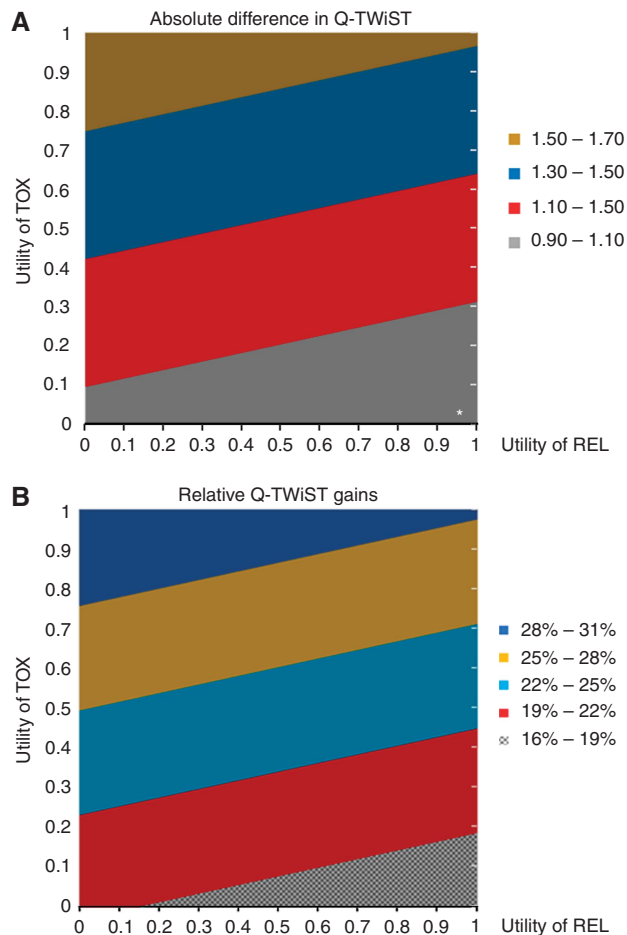


Figure 1. Utility threshold plot for Q-TWiST (nal-IRI + 5-FU/LV vs 5-FU/LV) at 12 months in intent to treat cohort. (A) The x-axis represents the utility for time after disease progression (REL) and y-axis represents the utility for TOX time. Both U(TOX) and U(REL) vary from 0 to 1, with U(TWiST) held at 1. The diagonal bands of different colours represent varying Q-TWiST gains by level of utility for TOX and REL. To understand the Q-TWiST gain associated with a given combination of U(REL) and U(TOX), one must select the corresponding values of U(REL) and U(TOX) on the x-axis and y-axis, respectively. The intersection of these two values inside the plot indicates which band of Q-TWiST gain the result from this combination belong. **(B)** The x-axis represents the utility for time after disease progression (REL) and y-axis represents the utility for TOX time. Both U(TOX) and U(REL) vary from 0 to 1, with U(TWiST) held at 1. The diagonal bands of different colour represent varying relative Q-TWiST gains by level of utility for TOX and REL, calculated by dividing the absolute Q-TWiST gain by the mean survival in the 5-FU/LV group. To understand relative Q-TWiST gain associated with a given combination of U(REL) and U(TOX), one must select the corresponding values of U(REL) and U(TOX) on the x-axis and y-axis, respectively. The intersection of these two values inside the plot indicates which band of relative Q-TWiST gain the result from this combination belong. *Not significant when utility of relapse is close to 1 and utility of AE is close to 0. REL = relapse; TOX = toxicity.

and REL were both set to 0.5, consistent with numerous previous studies. A utility threshold analysis was also applied with additional sensitivity analyses to assess how the Q-TWiST value would change under alternate assumption scenarios of individual patient preference. Second, the same utility was assumed regardless of the severity and type of AE (provided grade was ≥ 3). Neutropenia is one of the most common AEs observed in the clinical trial and it is often asymptomatic in nature. Therefore, additional sensitivity

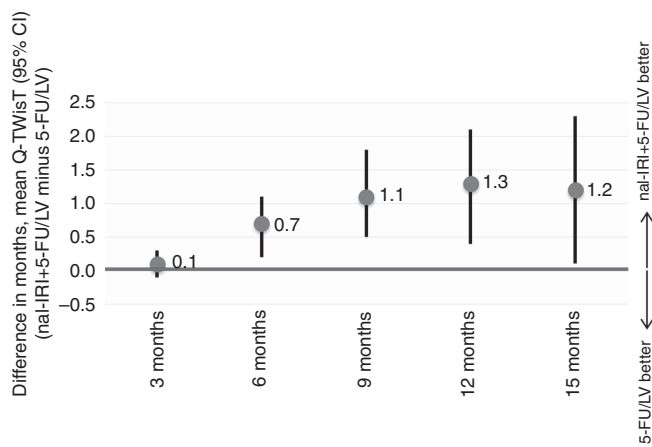


Figure 2. Differences in Q-TWiST between nal-IRI+5-FU/LV vs 5-FU/LV at 3, 6, 9, 12 and 15 Months of Follow-Up.

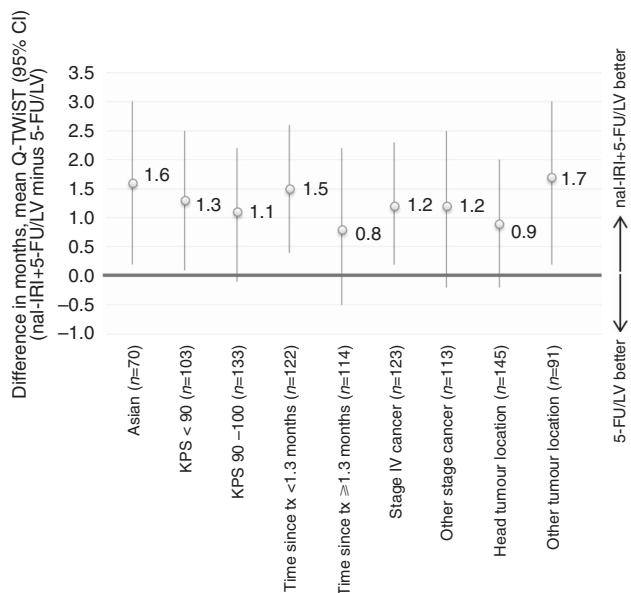


Figure 3. Quality-adjusted time without symptoms of disease progression or toxicity differences in months (5-FU/LV vs nal-IRI + 5-FU/LV) among subgroups. KPS = Karnofsky performance status; tx = treatment.

analysis with and without neutropenia was calculated, which revealed negligible differences in results.

CONCLUSION

Applying the Q-TWiST methods to the NAPOLI-1 trial data, the combination of nal-IRI with 5-FU/LV resulted in a statistically significant and clinically meaningful gain in quality-adjusted survival vs 5-FU/LV alone. The results remained robust regardless of all possible combinations of utility weights assigned to the TOX time and disease symptom/progression time, which confirmed the favourable clinical risk benefit of nal-IRI + 5-FU/LV in mPAC patients previously treated with a gemcitabine-based therapy. In addition, the magnitude of Q-TWiST gains (i.e., relative gains) is relatively large when compared to published Q-TWiST analyses in

other cancers, and is considered clearly clinically important based on the published thresholds.

CONFLICT OF INTEREST

UP has no disclosures. J-FB has received honoraria for lectures and consultancy and travel grants from Amgen, Bayer, Celgene, Merck, Roche and Sanofi-Aventis. J-FB has had a consultant or advisory role at Merck, Amgen, and Lilly. DM is a consultant for Lilly, and has received travel, accommodations, or expenses from Lilly and Celgene. AC has no disclosures. DDVH is employed by McKesson, and has had a consultant or advisory role at Arsia Therapeutics, Bionomics, Bristol-Myers Squibb, Cavion, Cerulean Pharma, CytRX Corporation, Dalian Wanchun Biotechnology, DNAtrix, Esperance Pharmaceuticals, Five Prime Therapeutics, Formula Pharmaceuticals, HealthCare Pharmaceuticals, Ignyta, Imaging Endpoints, Immodulon Therapeutics, Inform Genomics, Insys Therapeutics, Lilly, Medelis, Medical Prognosis Institute, Merus, miRNA Therapeutics, NuCana BioMed, Oncolytics Biotech, Pain Therapeutics, Pharmacyclics, Samumed, Senhwa Biosciences, Superlab Far East, Theravance, Tolero Pharmaceuticals, Toray Industries, Trovogene, Alethia Biotherapeutics, Alpha Cancer Technologies, Arvinas, Bellicum Pharmaceuticals, Biological Dynamics, CanBas, Horizon Discovery, Innate Pharma, Kinex, Lixte Biotechnology, MBC Pharma, Oncolyze, RenovoRx, Samsung, TD2, AADi, Aptose Biosciences, BiolineRx, CV6 Therapeutics, CytomX Therapeutics, Deciphera, EMD Serono, Evelo Therapeutics, Fujifilm, Gilead Sciences, Histogen, Horizon Pharma, Idera, Intezyne Technologies, Kalos Therapeutics, Kura, Lantern Pharma, Pain Therapeutics, Pfizer, Pharmamab, Phosphatin Therapeutics, Progen, SOTIO, Strategia Therapeutics, Sun Biopharma, Systems Imagination, Ventana Medical Systems. DDVH has received travel, accommodations, or expenses from FORMA Therapeutics and Merrimack. DDVH's patents, royalties, and other intellectual property include: intramedullary catheter, methods of human prostate cancer, use of 5,6-dihydro-5-azacytidine in the treatment of prostate cancer, targeting site-2 protease (S2P) for the treatment of pancreatic cancer (pending), targeting ecto-5-nucleotidase (CD73) for the treatment of pancreatic cancer, targeting a protein tyrosine phosphatase-PRL-1 for the treatment of pancreatic cancer (pending), targeting a protein PRC1 for the treatment of pancreatic cancer (pending), protein kinase inhibitors (pending), methods, compounds and compositions with genotype selective anticancer activity (pending), methods and kits to predict therapeutic outcome of BTK inhibitors (pending), muscle fatigue substance cytokines and methods of inhibiting tumour growth therewith (pending), 2-arylpyridylazoles for the treatment of solid tumours such as pancreatic cancer (pending). DDVH has stock or ownership interests in cell therapeutics, McKesson, Medtronic, CerRx, EmergingMed, and SynDevRx. DDVH has received honoraria from Celgene, Cerulean Pharma, and Genentech. DDVH's institution has received research funding from Lilly, Genentech, Celgene, Agios, Incyte, Merrimack, Plexikon, Minneamrita Therapeutics, 3-V Biosciences, Abbvie, Aduro Biotech, ArQule, Baxalta, Biomarin, Cleave Biosciences, CytRx Corporation, Daiichi Sankyo, Deciphera, Endocyte, Exelixis, ESSA, Five Prime Therapeutics, Gilead Sciences, Merck, miRNA Therapeutics, Pfizer, Pharmacyclics, Phoenix Biotech, Proderm IQ, Samumed, Strategia, Trovogene, and Verastem. AW-G has had a consultant or advisory role at Merrimack and Pfizer. AW-G has received travel, accommodations, or expenses from Axis Pharma. AW-G received honoraria from Pfizer and Merrimack. AW-G's institution has received research funding from Newlink Genetics, Precision Therapeutics, AstraZeneca, Merrimack, Aduro Biotech, Prometheus, EMD Serono, Pfizer, Halozyme, OncoMed, and CTI.

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