

Cough, dyspnea, chest pain or a composite?

Analysis of key symptoms in metastatic non-small cell lung cancer (mNSCLC) clinical trials

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BACKGROUND

- Lung cancer remains the leading cause of cancer deaths worldwide [1]. Given its highly symptomatic nature, clinical trials often focus on “composite” patient-reported endpoints of mNSCLC symptoms including chest pain, cough, dyspnea, arm and shoulder pain, and general pain.
- The analysis of these composites/combinations of symptoms has been inconsistently operationalized, both in terms of the items included and method of analysis. It is often unclear whether these composites reflect combined symptoms scores (e.g. the mean score based on the included number of symptoms), or rather, a “first-past-the-post” method where the first symptom meeting the definition of deterioration is recorded.
- To clarify this endpoint, we used a dataset of completed trials in mNSCLC that each included the patient-reported outcome (PRO) measures the European Organisation for Research and Treatment of Cancer Core Questionnaire (EORTC QLQ-C30) [2] and the EORTC Lung Cancer module (LC13) [3].

OBJECTIVE

- To establish empirical support for the use of individual or composite symptom groupings in mNSCLC, regardless of treatment.

METHODS

- EORTC QLQ-C30 and LC13 data from 3 Phase 2 trials (FIR, POPLAR, BIRCH) and 6 Phase 3 trials (OAK, IMpower110, IMpower130, IMpower131, IMpower132, IMpower150) in mNSCLC were pooled and analyzed.
- Key patient-reported lung cancer symptoms were included for analysis:
 - From EORTC QLQ-C30: dyspnea (single-item, dyspnea in general: “short of breath”) and general pain
 - From EORTC LC13: cough, chest pain, arm/shoulder pain, and multi-item dyspnea (3 items: “short of breath when you rested”, “short of breath when you walked”, “short of breath when you climbed stairs”).
- Four different symptom composites based on frequently used groupings in the literature were created:
 - 3-Dyspnea Single-Item (DS): cough, chest pain, single-item dyspnea (3 items total)
 - 3-Dyspnea Multi-item (DM): cough, chest pain, multi-item dyspnea (5 items total)
 - 4-DS: cough, chest pain, single-item dyspnea, arm/shoulder pain (4 items total)
 - 4-DM: cough, chest pain, multi-item dyspnea, arm/shoulder pain (6 items total)
- Spearman correlations were calculated to assess associations between items, and Kaplan-Meier (KM) curves of time to confirmed deterioration (TTCD) for symptom groups to compare the patterns of confirmed deterioration (CD).
- TTCD is defined as the first time point with a symptom (single-item or multi-item) that has deteriorated by at least 10 points from baseline, and is followed at the next time point (at least three weeks later) by either a deterioration of at least 10 points from baseline or death.
- For composites, two analysis methods were used:
 - The “**first-past-the-post**” method calculates TTCD for the first symptom to reach CD regardless of the occurrence of CD for the other symptoms.
 - The “**true composite**” method calculates TTCD based the mean of all symptoms at each time point.

RESULTS

Pooled patient population

Table 1. Baseline demographics and clinical characteristics

	Pooled patient population (N=5,510)
Age, mean (SD)	63.2 (9.4) years
Male, n (%)	3,556 (64.5%)
Race, n (%)	
White	4,218 (76.6%)
Asian	948 (17.2%)
Black or African American	111 (2.0%)
Unknown	158 (2.9%)
Other or multiracial	75 (1.4%)
Baseline ECOG status, n (%)	
0	1,969 (35.8%)
1	3,508 (63.7%)

ECOG = Eastern Cooperative Oncology Group

- 5,510 patients with confirmed mNSCLC and a baseline PRO measurement were included in the analyses (Table 1)
- The median time to PFS was almost 6 months (174 days or approximately eight 3-week treatment cycles)
- The frequency of response at baseline for each patient-reported symptom is presented in Table 2. Cough was the symptom most frequently reported by patients at baseline (78.9%), in contrast less than half of patients reported Arm/Shoulder Pain (40.1%) at baseline.

Table 3. Frequency of patient-reported lung cancer symptoms at baseline

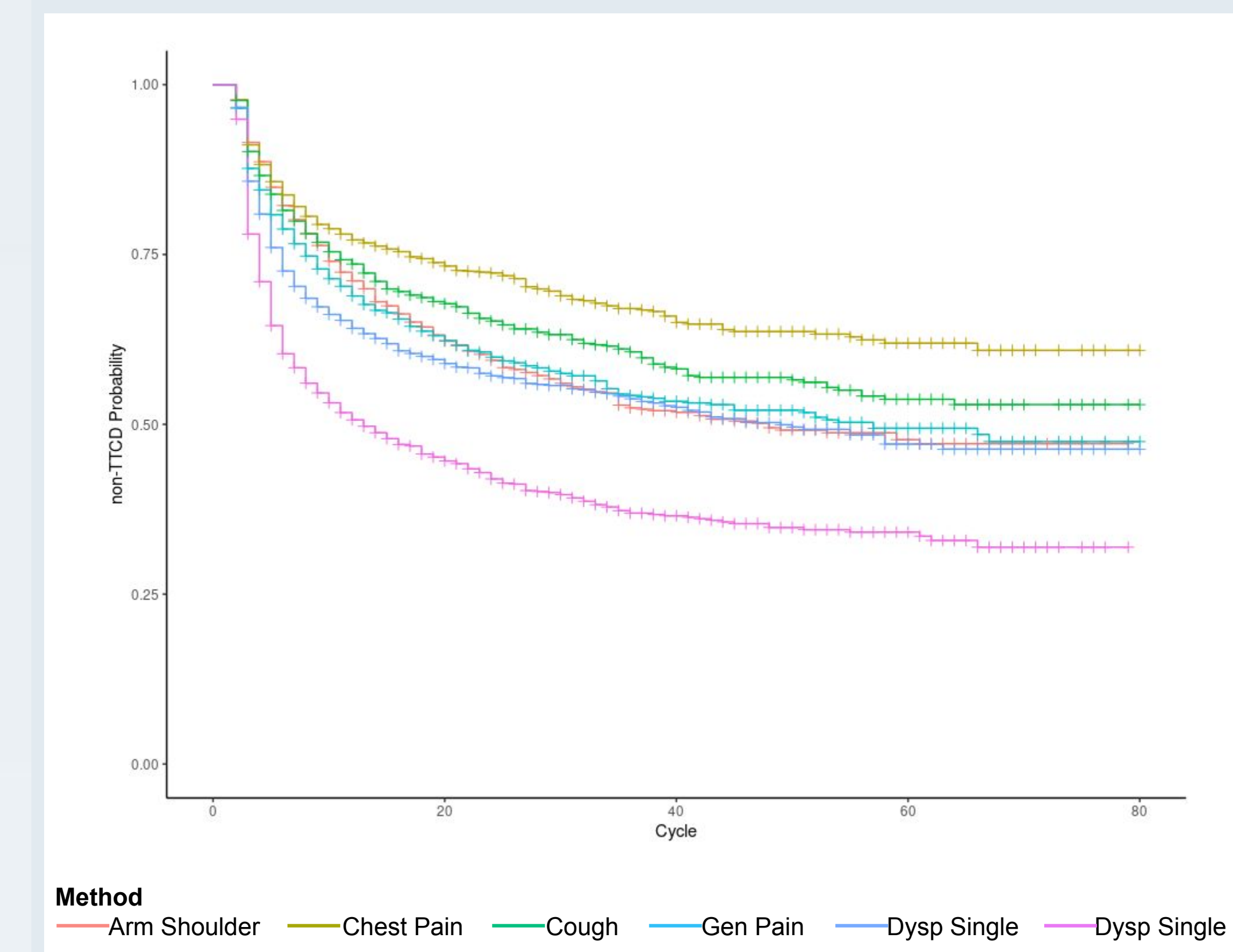
Symptom (number of responses)	Symptom absent at baseline	Symptom present at baseline		
		Not at all, n (%)	A little, n (%)	Quite a bit, n (%)
Cough (n=5,394)	1,136 (21.1%)	2,683 (49.7%)	1,134 (21.0%)	441 (8.2%)
Chest Pain (n=5,390)	3,127 (58.0%)	1,659 (30.8%)	454 (8.4%)	150 (2.8%)
Arm/Shoulder Pain (n=5,392)	3,230 (59.9%)	1,388 (25.7%)	569 (10.6%)	205 (3.8)
General Pain (n=5,494)	1,953 (35.5%)	2,006 (36.5%)	1,059 (19.3%)	476 (8.7%)
Single-item Dyspnea (n=5,497)	1,819 (33.1%)	2,312 (42.1%)	918 (16.7%)	448 (8.1%)
Multi-item Dyspnea (n=5,403)	1,049 (19.4%)	3,014 (55.8%)	1,068 (19.8%)	272 (5.0%)

Multi-item Dyspnea is calculated based on QLQ-LC13 items 3, 4 and 5, and is scored using the scoring procedure outlined in the EORTC-QLQ Manual [4].

Analysis and Discussion

- Spearman correlations at baseline were predominantly low-moderate, ranging from 0.09 (Cough with Arm/Shoulder Pain) to 0.44 (Chest Pain with General Pain), indicating little overlap between items.
- As would be expected, the exception was with dyspnea: single-item dyspnea had a strong correlation (0.73) with multi-item dyspnea, indicating that only one need be included in a composite measure, due to the overlap in content.

Figure 1. KM plot of TTCD for individual symptoms and multi-item dyspnea



- Similar patterns of CD were observed for the patient-reported symptoms (Figure 1). For Cough and Chest Pain, two of the cardinal symptoms of lung cancer, the median TTCD was not reached.
- A closer examination of CD (Table 3) revealed that less than half of patients experienced CD for any individual symptom, ranging from 18.9% (Chest Pain) to 29.8% (Single-item Dyspnea).
- Patients who reported the maximum severity for a symptom at baseline (corresponding to the “Very much” response option in Table 2) could not experience CD, since by definition that requires a worsening from baseline (Table 3).

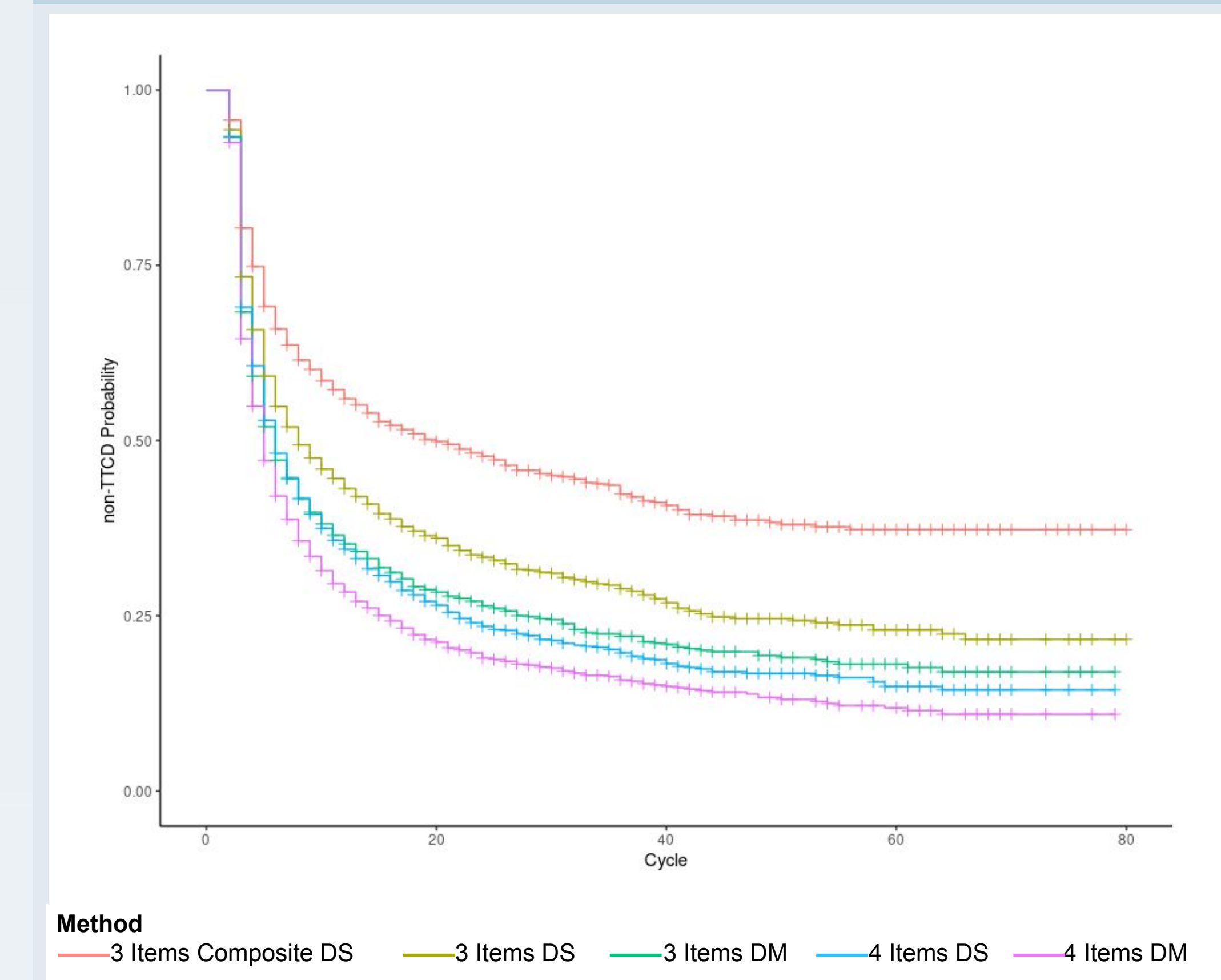
Table 3. Frequency of Confirmed Deterioration (CD), by symptom

	Patients with CD, n (%)	Patients without CD, n (%)	Patients where CD was not possible*, n (%)
Cough	1,114 (22.1%)	3,481 (69.1%)	441 (8.8%)
Chest Pain	951 (18.9%)	3,935 (78.1%)	150 (3.0%)
Arm/Shoulder Pain	1,181 (23.5%)	3,650 (72.5%)	205 (4.1%)
General Pain	1,300 (25.8%)	3,260 (64.7%)	476 (9.5%)
Single-item Dyspnea	1,500 (29.8%)	3,088 (61.3%)	448 (8.9%)
Multi-item Dyspnea	2,122 (42.1%)	2,848 (56.6%)	66 (1.3%)

N = 5,036
*CD not possible because patients had the maximum score at Baseline and therefore could not experience a further deterioration. Note that this corresponds to the “Very much” responses shown in Table 2

- Little differentiation in TTCD was observed in the KM curves for the 4 different symptom combinations 3-DS, 3-DM, 4-DS, and 4-DM when analyzed using the “first-past-the-post” method (Figure 2), with the 3-item Composite DS (the “true composite” method) yielding a longer TTCD.
- Median TTCD appeared to be driven by the total number of items within each combination, with median TTCD decreasing as the total number of items increased.

Figure 2. KM plot of TTCD for the symptom group



CONCLUSIONS

- Limitations were apparent with TTCD: few patients experienced CD, and others, by definition, were unable to deteriorate further. Future research will examine whether other deterioration metrics, change from baseline scores or landmark analyses at pre-specified timepoints are more informative approaches for symptomatic progression in this setting.
- This research has added to the body of knowledge by exploring the key symptoms which can help with future trial design and with clinical management. Our analyses demonstrated that there was no benefit for use of any specific symptom groupings, instead symptoms should be analyzed individually for greater clarity.

REFERENCES

- Bray F et al. *CA Cancer J Clin* 2024; doi:10.3322/caac.21834.
- Aaronson NK et al. *J National Cancer Institute* 1993;85:365-76.
- Bergman B et al. *EJC* 1994;30A:635-42.
- Fayers PM et al. *The EORTC QLQ-C30 Scoring Manual (3rd Edition)*. Published by: European Organisation for the Research and Treatment of Cancer, Brussels, 2001.

DISCLOSURES

AYCS is an employee of F. Hoffmann-La Roche Ltd; PCL was an employee of Genentech Inc at the time of research; CM is an employee of Genentech Inc; and TH is an employee of PAREXEL International, on assignment to Genentech Inc.

AYCS, PCL, and CM own stocks/shares in F. Hoffmann-La Roche Ltd.

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