Harnessing Technology to Improve Clinical Trials: Study of Real-Time Informatics to Collect Data, Toxicities, Image Response Assessments, and Patient-Reported Outcomes in a Phase II Clinical Trial

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Supplemental Information: Symptom Tracking and Reporting (STAR)

Patients electronically self-reported 13 toxicity- and disease-related symptoms and Karnofsky performance status using STAR, a validated patient version of the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.[1-3] The adverse events were predefined at study onset based on known symptoms of patients with Stage IV NSCLC and on the side effect profile of the drugs used. The symptoms/toxicities that were asked on the STAR platform were as follows: performance status, anorexia, fatigue, alopecia, epiphora, epistaxis, hoarseness, mucositis/stomatitis, nausea, cough, dyspnea, pain, sensory peripheral neuropathy, and myalgias (Supplemental Table 1). Each screen contained one question. Prior to logging out of the system, patients were required to answer all questions.

STAR data were provided to clinicians during visits on the same tablet computer as a longitudinal report (Supplemental Figure 1). Clinicians then had the option to either accept or modify these symptoms and toxicities based on their own assessments. Importantly, the final CTCAE grade and attribution were assigned by the clinician, which are the results that we will eventually discuss when we publish our paper on the chemotherapeutic regimen. Supplemental Table 3 contains clinician CTCAE grades for each adverse event, alongside those documented by the patients.

Less common symptoms/toxicities that were noted by the patients and addressed by the clinicians were graded via the standard CTCAE reporting mechanism, attributed and documented in StudyTracker. These adverse events, whether symptomatic or non-symptomatic, are listed in Supplemental Table 2. Overall for the trial, there were 42 total CTCAE adverse events of any grade reported (i.e., symptomatic and non-symptomatic, related and not related to study treatment), as shown in Supplemental Table 3. The predetermined form contained 13 of the symptoms/toxicities documented, or 31%. Notably, through STAR, we captured the adverse events that occurred in over

60% of patients. With the exception of edema and rash, the additional symptoms and toxicities were reported in less than 20% of patients.

Supplemental Table 1. STAR Questionnaire

SENSORY NEUROPATHY

Over the past week, have you had numbness or tingling in hands or feet?

- GRADE 0: I have not had any numbness or tingling in my hands or feet.
- GRADE 1: I have had numbness or tingling in my hands or feet which has not affected my everyday activities such as buttoning buttons, feeling small objects with my hands, or walking.
- GRADE 2: I have had numbness or tingling in my hands or feet which makes it harder for me to do my everyday activities such as buttoning buttons, feeling small objects with my hands, or walking.
- GRADE 3: Because of numbness or tingling in my hands or feet, I am not able to do my everyday activities such as buttoning buttons, feeling small objects with my hands, or walking.
- GRADE 4: Because of numbness or tingling in my hands or feet, I rarely am able to get out of bed.

PAIN

Over the past week, have you had pain?

- GRADE 0: I have not had pain.
- GRADE 1: I have had pain or side effects from pain medications without any effects on my everyday activities, normal work (including housework and work outside the home), enjoyment of life, or sleep.
- GRADE 2: I have had pain or side effects from pain medications that make it harder for me to do my everyday activities or normal work (including housework and work outside the home), enjoy life, or sleep comfortably.
- GRADE 3: Because of pain or side effects from pain medications, I am not able to do everyday activities or normal work on my own (including housework and work outside the home), enjoy life, or sleep comfortably.
- GRADE 4: Because of pain or side effects from pain medications, I rarely am able to get out of bed.

MYALGIA

Over the past week, have you had muscle pain?

- GRADE 0: I have not had muscle pain.
- GRADE 1: I have had muscle pain that has not affected my being able to do my everyday activities, normal work (including housework and work outside the home), enjoy life or sleep well.
- GRADE 2: I have had muscle pain that makes it harder for me to do my everyday activities, normal work (including housework and work outside the home) enjoy life, or sleep well.
- GRADE 3: Because of muscle pain, I am not able to do my everyday activities, normal work (including housework and work outside the home), enjoy life, or sleep well.
- GRADE 4: Because of muscle pain, I rarely am able to get out of bed.

FATIGUE

Over the past week, have you had fatigue, tiredness, or lack of energy?

- GRADE 0: I have not had fatigue.
- GRADE 1: I have had fatigue, tiredness, or lack of energy without any effects on my everyday activities or normal work (including housework and work outside the home).
- GRADE 2: I have had fatigue, tiredness, or lack of energy that make it harder for me to do my everyday activities or normal work (including housework and work outside the home).
- GRADE 3: Because of fatigue, tiredness, or lack of energy, I am not able to do my everyday activities or normal work on my own (including housework and work outside the home).
- GRADE 4: Because of fatigue, tiredness, or lack of energy, I rarely am able to get out of bed.

DYSPNEA

Over the past week, have you had shortness of breath?

- GRADE 0: I have not had any shortness of breath.
- GRADE 1: I have been short of breath with exercise, but I can walk up a flight of stairs without stopping.
- GRADE 2: I have been short of breath with exercise but I am not able to walk up a flight of stairs or a city block without stopping.
- GRADE 3: I have been short of breath during my normal daily activities (dressing, showering, cleaning, cooking, etc).
- GRADE 4: I have been short of breath even when I am resting in bed.

COUGH

Over the past week, have you had coughing?

- GRADE 0: I have not had coughing symptoms which require medications.
- GRADE 1: I have had coughing symptoms which require mild medications (like Robitussin or cough drops), but not requiring narcotics (like codeine or morphine).
- GRADE 2: I have had coughing symptoms which require narcotic medications (like codeine or morphine).
- GRADE 3: I have had coughing symptoms that are interfering with my sleep or daily activities.

ANOREXIA

Over the past week, have you had problems with your appetite or eating?

- GRADE 0: I have not had problems with my appetite or eating.
- GRADE 1: I have lost my appetite but have not changed my eating habits.
- GRADE 2: I have been eating less but have not lost a lot of weight or become malnourished.
- GRADE 3: I am losing a lot of weight or I am malnourished, and I am taking in very little food or fluids (or I have needed to get IV fluids).

NAUSEA

Over the past week, have you had nausea?

- GRADE 0: I have not had nausea.
- GRADE 1: I have lost my appetite due to nausea, but I am able to eat.
- GRADE 2: The amount I eat or drink has decreased due to nausea, but I have not lost weight or become dehydrated or malnourished. I have not needed IV fluids for greater than 24 hours.
- GRADE 3: I have not been eating or drinking adequately and I have required IV fluids for 24 hours or longer.

VOICE CHANGES/HOARSENESS

Over the past week, have you had voice changes or hoarseness?

- GRADE 0: I have not had voice changes or hoarseness.
- GRADE 1: I have had mild or occasional voice changes or hoarseness, but my voice is still easy to understand.
- GRADE 2: I have voice changes that have been constant or make it necessary for me to repeat myself sometimes.
- GRADE 3: I have voice changes that make it necessary for me to whisper all the time, and it is difficult for people to understand me.
- GRADE 4: People cannot understand anything I say.

ALOPECIA

Over the past week, have you had hair loss on your head or body?

- GRADE 0: I have not had any hair loss.
- GRADE 1: I have had some thinning of my hair or patchy hair loss.
- GRADE 2: I have lost all of my hair.

MUCOSITIS/STOMATITIS

Over the past week, have you had mouth sores?

- GRADE 0: I have not had any mouth sores.
- GRADE 1: I have had redness or mild irritation in my mouth.
- GRADE 2: I have had mouth sores or ulcers in my mouth.
- GRADE 3: I have had severe mouth sores or bleeding from sores in my mouth.
- GRADE 4: Most of the skin in my mouth has come off and bleeding in my mouth won't stop.

EPISTAXIS

Over the past week, have you had nose bleeding?

- GRADE 0: I have not had any nose bleeding.
- GRADE 1: I have had mild nose bleeding, but no medical treatment has been necessary.
- GRADE 2: I have moderate nose bleeding which has required packing or medical treatment to stop it.
- GRADE 3: I have had severe nose bleeding which has required surgery to stop it.

EPIPHORA

Over the past week, have you had increased tearing or watery eyes?

- GRADE 0: I have not had increased tearing or watery eyes.
- GRADE 1: I have had mildly increased tearing or watery eyes that does not interfere with my vision.
- GRADE 2: I have had moderately increased tearing or watery eyes that interferes with my vision, but I am still able to carry out my daily activities.
- GRADE 3: I have had severely increased tearing or watery eyes that interferes with my daily activities.

KPS

GENERAL WELLBEING

- ○ 100% I feel completely normal without any complaints or problems related to my disease.
- ○ 90% I am able to carry on my normal activities, but I have minor symptoms.
- ○ 80% I am able to carry on my normal activities with effort, and I have some symptoms.
- ○ 70% I am able to care for myself, although I cannot carry on my normal activities.
- ○ 60% I require occasional assistance although I can care for most of my own needs.
- ○ 50% I require a lot of assistance and frequent care.
- ○ 40% I am disabled and require special care and assistance.

Supplemental Table 2. Additional Adverse Events Described

System	Toxicity
General	Anxiety
	Insomnia
Cardiovascular	Edema
	Hypertension
Pulmonary	Pleural effusion
	Hemorrhage, pulmonary
Neurologic	Ataxia
	Headache
	Dizziness
	Cranial neuropathy
Ocular	Ocular surface dysfunction
	Dry eyes
	Blurred vision
Otolaryngology	Rhinorrhea
Gastrointestinal	Dysgeusia
	Gastroesophageal reflux
	Odynophagia
	Vomiting
	Constipation
	Diarrhea
	Hemorrhage, rectal
Dermatologic	Rash*
	Xerosis
	Hyperpigmentation
	Nail bed changes
Vascular	Vessel injury, arterial
	Thrombophlebitis, superficial
Syndrome	Hypersensitivity reaction to paclitaxel
Musculoskeletal	Osteonecrosis of the jaw

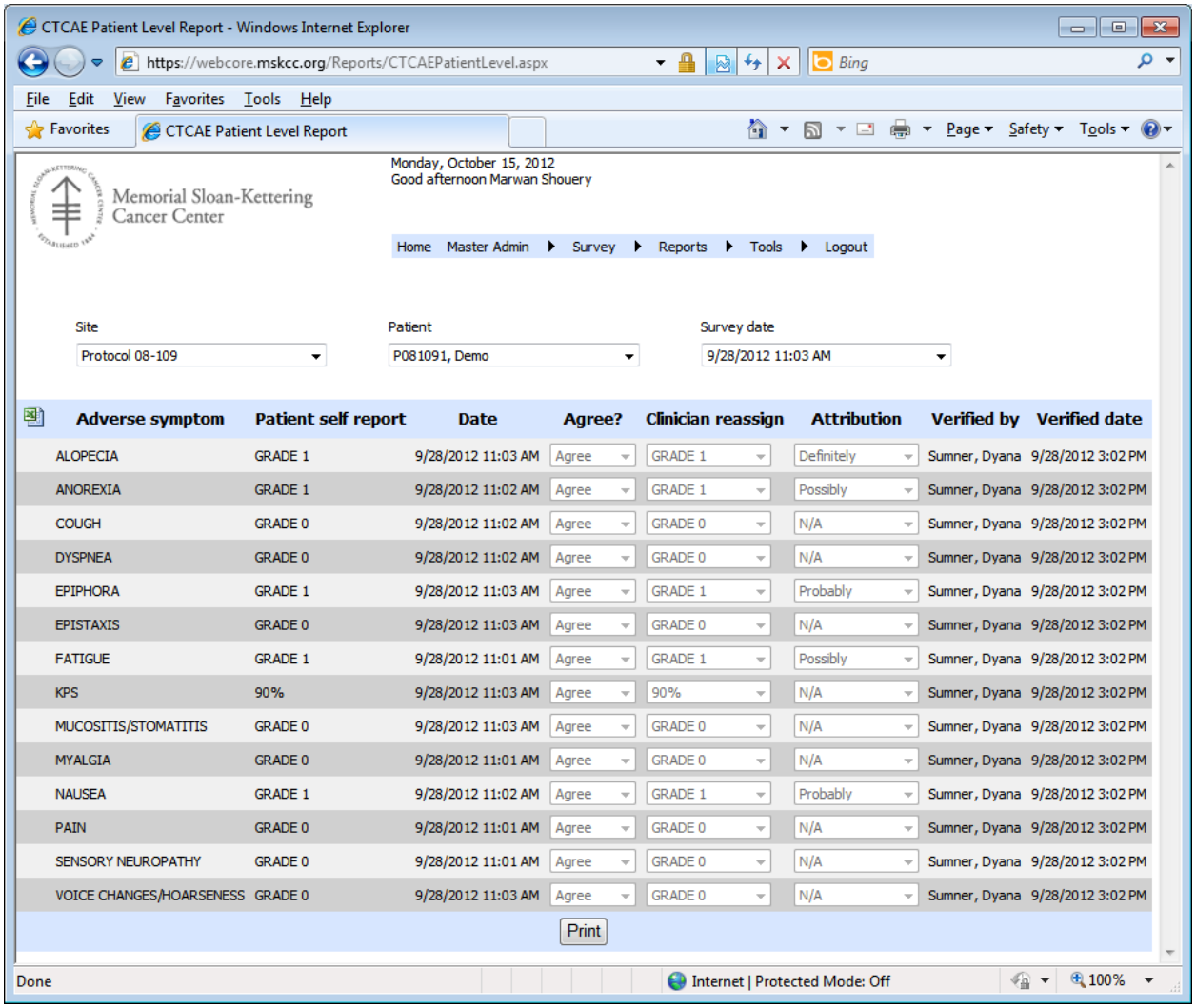
*Includes fungal rash

Supplemental Table 3. Adverse Events

	Patient Report		Investigator Report	
Adverse Event	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
STAR				
Anorexia	33 (75%)	4 (9%)	33 (75%)	1 (2%)
Fatigue	43 (98%)	15 (34%)	43 (98%)	7 (16%)
Alopecia	41 (93%)	--	41 (93%)	--
Epiphora	33 (75%)	3 (7%)	33 (75%)	1 (2%)
Epistaxis	38 (86%)	1 (2%)	38 (86%)	--
Hoarseness	36 (82%)	3 (7%)	35 (80%)	1 (2%)
Mucositis/Stomatitis	30 (68%)	1 (2%)	30 (68%)	1 (2%)
Nausea	28 (64%)	3 (7%)	30 (68%)	1 (2%)
Cough	31 (71%)	9 (21%)	33 (75%)	4 (9%)
Dyspnea	37 (84%)	10 (23%)	37 (84%)	4 (9%)
Pain	40 (91%)	17 (39%)	42 (96%)	8 (18%)
Sensory peripheral neuropathy	33 (75%)	1 (2%)	33 (75%)	--
Myalgias	37 (84%)	10 (23%)	31 (71%)	4 (9%)
Additional Events not captured by STAR				
Anxiety	N/A	N/A	2 (5%)	--
Insomnia	N/A	N/A	1 (2%)	--
Edema	N/A	N/A	13 (30%)	1 (2%)
Hypertension	N/A	N/A	8 (18%)	1 (2%)
Pleural effusion	N/A	N/A	3 (7%)	--
Hemorrhage, pulmonary	N/A	N/A	3 (7%)	1 (2%)
Ataxia	N/A	N/A	3 (7%)	--
Headache	N/A	N/A	4 (9%)	--
Dizziness	N/A	N/A	3 (7%)	--
Cranial neuropathy	N/A	N/A	1 (2%)	1 (2%)
Ocular surface dysfunction	N/A	N/A	1 (2%)	1 (2%)
Dry Eyes	N/A	N/A	3 (7%)	--
Blurred Vision	N/A	N/A	3 (7%)	--
Rhinorrhea	N/A	N/A	7 (16%)	--
Dysgeusia	N/A	N/A	1 (2%)	--
Gastroesophageal reflux	N/A	N/A	2 (5%)	--
Odynophagia	N/A	N/A	1 (2%)	--
Vomiting	N/A	N/A	6 (14%)	1 (2%)
Constipation	N/A	N/A	2 (5%)	--
Diarrhea	N/A	N/A	5 (11%)	1 (2%)
Hemorrhage, rectal	N/A	N/A	2 (5%)	--
Rash*	N/A	N/A	9 (21%)	--
Xerosis	N/A	N/A	2 (5%)	--
Hyperpigmentation	N/A	N/A	3 (7%)	--
Nail bed changes	N/A	N/A	1 (2%)	--
Vessel injury, arterial	N/A	N/A	1 (2%)	1 (2%)
Thrombophlebitis, superficial	N/A	N/A	1 (2%)	--
Hypersensitivity reaction to paclitaxel	N/A	N/A	4 (9%)	--
Osteonecrosis of the jaw	N/A	N/A	1 (2%)	--

*Includes fungal rash

Supplemental Figure 1. STAR longitudinal report presented to and modified by clinicians.



Adverse symptom	Patient self report	Date	Agree?	Clinician reassign	Attribution	Verified by	Verified date
ALOPECIA	GRADE 1	9/28/2012 11:03 AM	Agree	GRADE 1	Definitely	Sumner, Dyana	9/28/2012 3:02 PM
ANOREXIA	GRADE 1	9/28/2012 11:02 AM	Agree	GRADE 1	Possibly	Sumner, Dyana	9/28/2012 3:02 PM
COUGH	GRADE 0	9/28/2012 11:02 AM	Agree	GRADE 0	N/A	Sumner, Dyana	9/28/2012 3:02 PM
DYSPNEA	GRADE 0	9/28/2012 11:02 AM	Agree	GRADE 0	N/A	Sumner, Dyana	9/28/2012 3:02 PM
EPIPHORA	GRADE 1	9/28/2012 11:03 AM	Agree	GRADE 1	Probably	Sumner, Dyana	9/28/2012 3:02 PM
EPISTAXIS	GRADE 0	9/28/2012 11:03 AM	Agree	GRADE 0	N/A	Sumner, Dyana	9/28/2012 3:02 PM
FATIGUE	GRADE 1	9/28/2012 11:01 AM	Agree	GRADE 1	Possibly	Sumner, Dyana	9/28/2012 3:02 PM
KPS	90%	9/28/2012 11:03 AM	Agree	90%	N/A	Sumner, Dyana	9/28/2012 3:02 PM
MUCOSITIS/STOMATITIS	GRADE 0	9/28/2012 11:03 AM	Agree	GRADE 0	N/A	Sumner, Dyana	9/28/2012 3:02 PM
MYALGIA	GRADE 0	9/28/2012 11:01 AM	Agree	GRADE 0	N/A	Sumner, Dyana	9/28/2012 3:02 PM
NAUSEA	GRADE 1	9/28/2012 11:02 AM	Agree	GRADE 1	Probably	Sumner, Dyana	9/28/2012 3:02 PM
PAIN	GRADE 0	9/28/2012 11:01 AM	Agree	GRADE 0	N/A	Sumner, Dyana	9/28/2012 3:02 PM
SENSORY NEUROPATHY	GRADE 0	9/28/2012 11:01 AM	Agree	GRADE 0	N/A	Sumner, Dyana	9/28/2012 3:02 PM
VOICE CHANGES/HOARSENESS	GRADE 0	9/28/2012 11:03 AM	Agree	GRADE 0	N/A	Sumner, Dyana	9/28/2012 3:02 PM

References

1. Basch E, Artz D, Dulko D, et al: Patient online self-reporting of toxicity symptoms during chemotherapy. J Clin Oncol 23:3552-3561, 2005
2. Basch E, Artz D, Iasonos A, et al: Evaluation of an online platform for cancer patient self-reporting of chemotherapy toxicities. J Am Med Inform Assoc 14:264-8, 2007
3. Basch E, Iasonos A, Barz A, et al: Long-term toxicity monitoring via electronic patient-reported outcomes in patients receiving chemotherapy. J Clin Oncol 25:5374-80, 2007