Supplementary Materials

Patient Preferences for First-Line Treatment of Locally Advanced or Metastatic Urothelial Carcinoma: An Application of Multidimensional Thresholding

Andrea B. Apolo • Christine Michaels-Igbokwe • Nicholas I. Simon • David J. Benjamin • Mallory Farrar • Zsolt Hepp • Lisa Mucha • Sebastian Heidenreich • Katelyn Cutts • Nicolas Krucien • Natasha Ramachandran • John L. Gore

Corresponding author: Christine Michaels-Igbokwe, Evidera, Montreal, QC, Canada. Telephone: +1 (301) 654-9729, Email: christine.michaels-igbokwe@evidera.com

Supplementary Methods

The MDT exercise consisted of a list of 6 treatment attributes relevant to la/mUC. Each MDT exercise was implemented in a 2-step process: (1) Patients were first presented with all the treatment attributes and asked to select the one they would most prefer to improve (**Supplementary Figure 1**); (2) When an attribute was selected as the most important, it was removed from the list, and the question was repeated with the remaining attributes until all items were selected and ranked by order of selection. The difference between the base level and maximum level for each attribute in the initial ranking exercises was used as the range between each treatment attribute in the thresholding exercises.

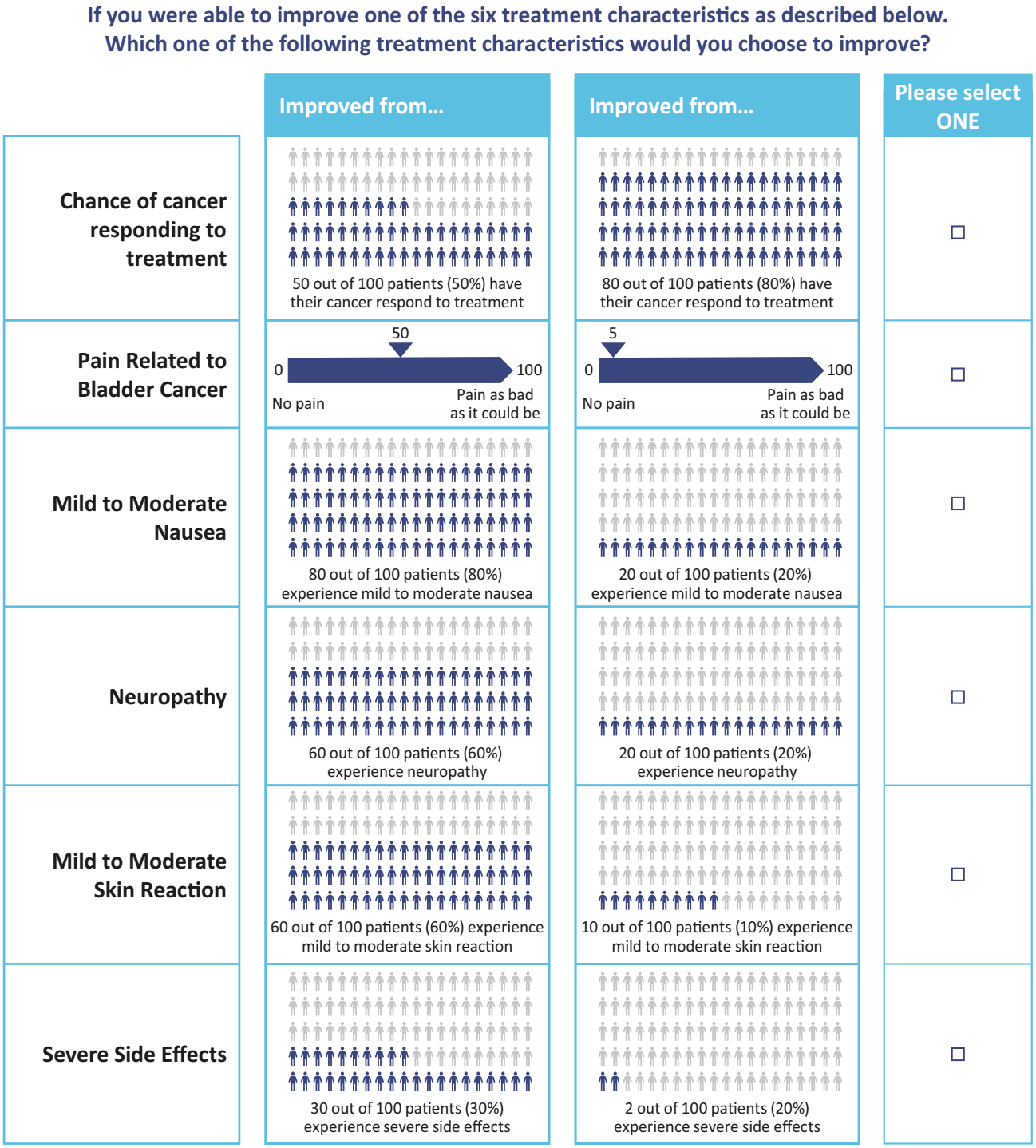
The results of the first step were used to generate 5 thresholding exercises, each eliciting a trade-off between 2 attributes:

1. **Thresholding 1 (A vs B)**: first-ranked attribute vs second-ranked attribute
2. **Thresholding 2 (B vs C)**: second-ranked attribute vs third-ranked attribute
3. **Thresholding 3 (C vs D)**: third-ranked attribute vs fourth-ranked attribute
4. **Thresholding 4 (D vs E)**: fourth-ranked attribute vs fifth-ranked attribute
5. **Thresholding 5 (E vs F)**: fifth-ranked attribute vs sixth-ranked attribute

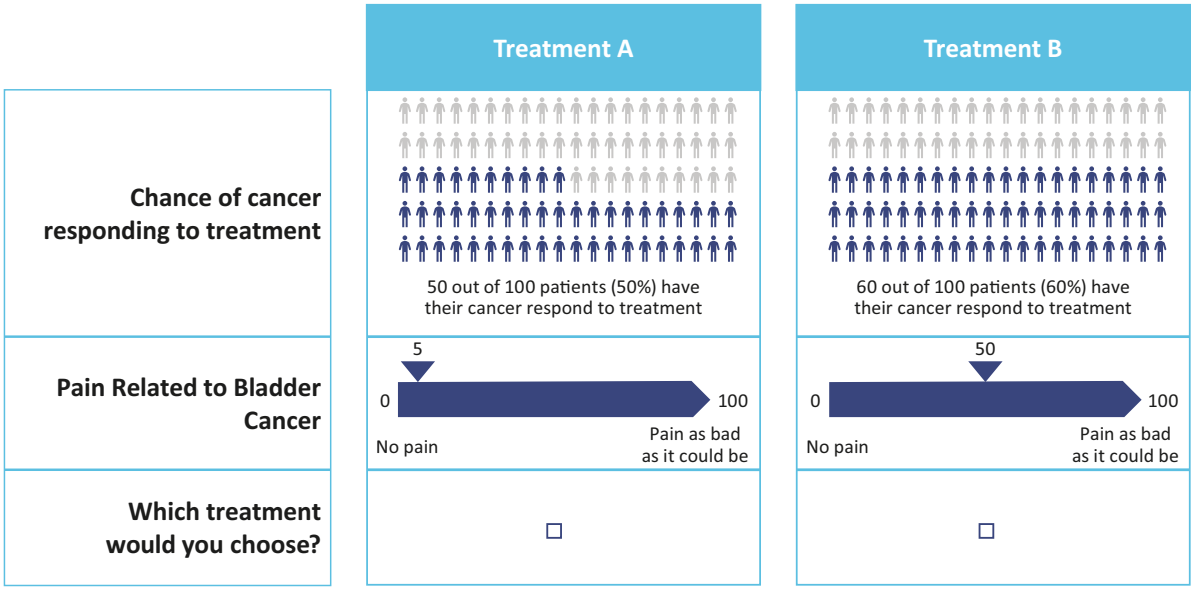
Each thresholding exercise consisted of 2 alternatives (**Supplementary Figure 2**). Alternative A was composed of the least desirable level of the preferred attribute and the most desirable level of the lower-ranked attribute. Alternative B consisted of the least desirable level of the lower-ranked attribute, and levels of the higher-ranked attribute were varied adaptively based on patient choices. The levels of the higher-ranked attribute in

Alternative B was varied according to a structured design which used a thresholding value tree (**Supplementary Figure 3**) to find the change in the higher-ranked attribute valued equivalent to the full attribute range of the lower-ranked attribute. The answers to the 3 iterative choice tasks were used to identify the interval in which this indifference point was likely to lie. Selected treatment attributes for the MDT used in the pre-testing interviews are reported in **Supplementary Table 1**.

Supplementary Figure 1. Multidimensional thresholding: Initial ranking exercise

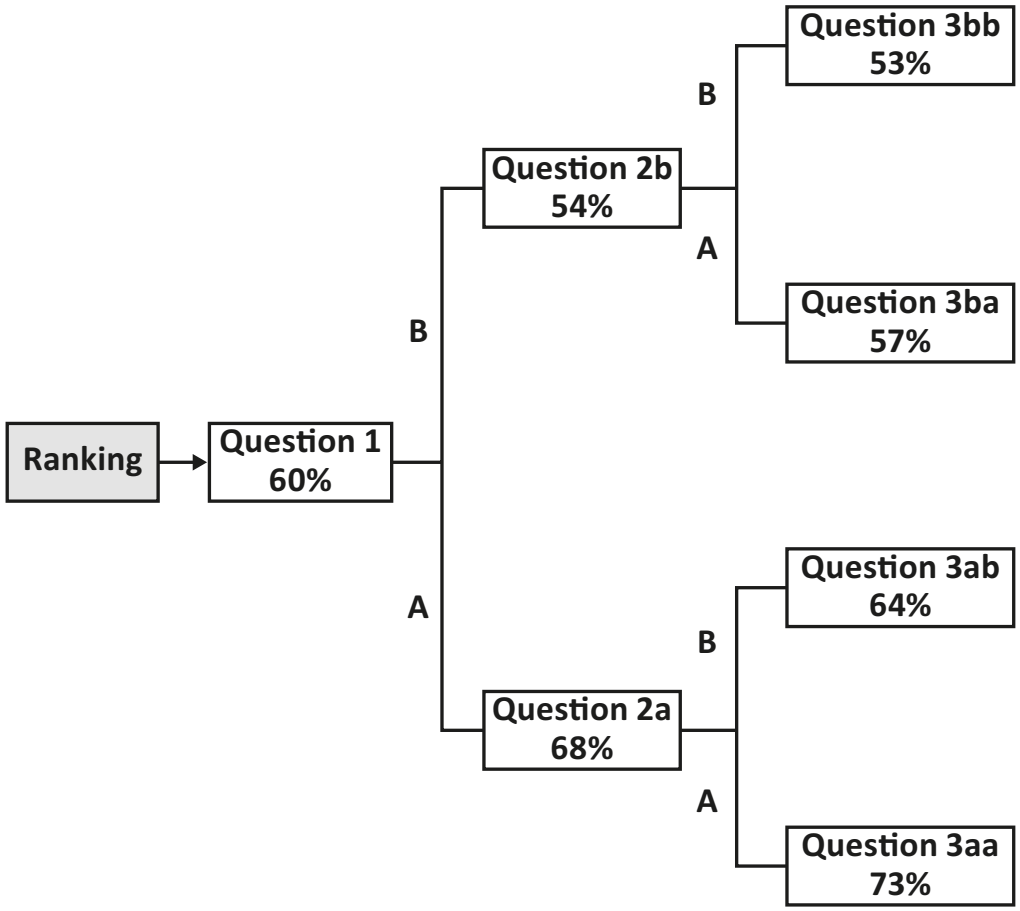


Supplementary Figure 2. Example thresholding task



Treatment A includes the least desirable level of the higher-ranked attribute (chance of cancer responding to treatment [overall response rate]) and the most desirable level of the lower-ranked attribute (pain); Treatment B includes most desirable level of lower-ranked attribute. The value for the higher-ranked attribute in Treatment B varies according to the thresholding value tree.

Supplementary Figure 3. Example thresholding value tree for overall response rate



Supplementary Table 1. Initial treatment attributes and level ranges used in pre-testing interviews

Attribute	Description	Level Range
Chance cancer responds to treatment (ORR)	The chance your cancer responds to the treatment, also known as ORR, is defined as the proportion of people who respond to the treatment. If someone responds to treatment this means that the size of the tumor or the amount of cancer in the body decreases, or the cancer could fully disappear.	50%-80%
Pain related to bladder cancer	The level of pain experienced on a typical day on a scale from 0 to 100, where 0 represents no pain and 100 represents pain as bad as it could be. Bladder cancer can cause patients to experience pain. Lower back pain and bone pain are common in patients whose cancer has spread to other parts of the body, or whose tumor has increased in size.	5-50
Mild to moderate nausea related to treatment	The chance you experience mild to moderate nausea with treatment. Some treatments for bladder cancer can cause mild to moderate nausea where you may have a loss of appetite or less desire to eat food but may be managed by medication.	20%-80%
Mild to moderate skin reaction related to treatment	The chance you experience mild to moderate skin reaction with treatment. You may experience a mild to moderate skin reaction while taking treatment. The skin reaction could be a rash, itching or dry skin, intermittently and possibly need treatment but would not be considered life-threatening.	10%-60%
Peripheral neuropathy related to treatment	The chance you experience peripheral neuropathy with treatment. Peripheral neuropathy is when you feel tingling, pain, numbness or weakness in the hands, feet, legs, and/or arms. Depending on where you experience the neuropathy, it can impact your ability to walk or perform fine motor skills like buttoning a shirt.	20%-60%
Severe side effects related to treatment	Cancer treatments may cause severe side effects such as kidney or an increased risk of infection. These side effects require medical treatment and cancer treatment to be paused or stopped.	2%-30%

ORR, overall response rate.

Supplementary Table 2. Individual characteristics for subgroup analysis

Characteristic	Categories
Age	<65 years old ≥65 years old
Time since diagnosis	<1 year ≥1 year
Cancer type	Locally advanced Metastatic
Current cancer stage	T3a or T3b (unresectable) T4a T4b: any N, M0 or any T, any N, M1a/b
Treatment experience	Cisplatin experienced Cisplatin naïve Carboplatin experienced Carboplatin naïve
Severity of bladder cancer symptoms at their worst	Mild Moderate Severe
Cisplatin eligibility	Cisplatin eligible Cisplatin ineligible
Current cancer treatment	Chemotherapy Immunotherapy Targeted therapy Currently not receiving any treatment/medication Currently receiving treatment/medication as a part of a clinical trial Currently receiving treatment/medication but do not know/remember what kind
Goal of cancer treatment	Extend or maximize remaining survival Maximize QOL for the remaining time alive Other
Other health conditions	Neuropathy vs those without Eczema/psoriasis vs none Diabetes (type 1 or type 2) vs those without

QOL, quality of life.

Changes to Quantitative Survey Following Pre-testing Interviews

The final quantitative survey and MDT exercise were revised based on patient feedback during the cognitive pre-testing interviews and interviewer notes. The main changes are detailed below:

1. Descriptions for 3 attributes were updated based on patient feedback to improve clarity and emphasize elements most relevant to la/mUC patients—chance cancer responds to treatment, mild to moderate skin reaction, and severe side effects related to treatment.
2. A new page was added to provide a thorough explanation of the ranking exercise. The explanation asked patients to review all 6 treatment aspects by reading the descriptions and comparing the values in the "Improved from" column to those in the "Improved to" column for all treatment aspects before selecting the item that they wanted to improve the most. Following this, patients were informed that the treatment aspect that they selected as the most important would be removed from the list and that they had to continue to select the treatment aspect that they found most important to improve from the remaining treatment aspects on the list. This was added to ensure patients understood how the ranking exercise worked.
3. A new page was added following the ranking exercise to display the ranking selection that the patients had just made. This gave patients an opportunity to review the full ranking and confirm that the order of importance aligned with their valuation or to complete the ranking exercise again in order to adjust the order of importance.

Supplementary Results

Supplementary Table 3. Additional patient sociodemographic characteristics

Characteristic	*N* = 100
Insurance status, *n* (%)	
Employer-provided commercial insurance	12 (12)
Veterans Affairs/military healthcare	7 (7)
Medicare	51 (51)
Medicaid	1 (1)
Self-provided insurance (out of pocket)	36 (36)
None (uninsured) or unsure	1 (1)

SD standard deviation.

Supplementary Table 4. Patient-reported clinical characteristics

Characteristic	N=100
Time since diagnosis with BC, n (%)	
<6 months ago	26 (26%)
6 months to <1 year ago	36 (36%)
1 year to <3 years ago	25 (25%)
3 years to <5 years ago	10 (10%)
≥5 years ago	3 (3%)
Symptoms experienced due to BC, n (%)	
Blood in urine	39 (39)
Bladder spasm	10 (10)
Having to urinate more frequently	31 (31)
Pain or burning during urination	25 (25)
Feeling the need to go right away, even when bladder is not full	20 (20)
Having trouble urinating or having a weak stream	21 (21)
Increased frequency of urinating during the night	21 (21)
Lower back pain on one side	32 (32)
Loss of appetite	14 (14)
Weight loss	8 (8)
Feeling tired or weak	42 (42)
Swelling in the feet	7 (7)
Pain	8 (8)
Other	4 (4)
None	0
Symptoms experienced in the last 2 weeks due to BC, n (%)	
Blood in urine	3 (3)
Bladder spasm	1 (1)
Having to urinate more frequently	17 (17)
Pain or burning during urination	3 (3)
Feeling the need to go right away, even when bladder is not full	3 (30)
Having trouble urinating or having a weak stream	8 (8)
Increased frequency of urinating during the night	7 (7)
Lower back pain on one side	33 (33)
Loss of appetite	29 (29)
Weight loss	18 (18)
Feeling tired or weak	82 (82)
Swelling in the feet	8 (8)
Pain	12 (12)
Other	2 (2)
None	4 (4)
Experienced pain related to cancer, n (%)	
Yes	56 (56)

Characteristic	N=100
No	44 (44)
Overall health today (scale 0-10)[a]	
Mean (SD)	3.8 (1.7)
Min to max	0-7
Median (IQR)	4 (2-5)
Severity of BC symptoms at their worst, n (%)	
Mild	10 (10)
Moderate	31 (31)
Severe	59 (59)
Severity of BC symptoms in the last 2 weeks, n (%)	
Mild	33 (33)
Medium	33 (33)
Severe	34 (34)
Overall goal or hope of treatment, n (%)	
Good QOL for remaining time alive	43 (43)
Extend remining survival time	57 (57)
Other	0
Current BC treatment, n (%)	
Chemotherapy	29 (29)
Immunotherapy	20 (20)
Targeted therapy	9 (9)
Currently receiving treatment/medication as a part of a clinical trial	0
Currently receiving treatment/medication, but do not know/remember what kind	19 (19)
Other	4 (4)
Currently not receiving any treatment/medication	22 (22)
Previous BC treatment, n (%)	
Surgery (resection of tumor, radical or partial cystectomy)	18 (18)
Intravesical therapy (Bacillus Calmette-Guérin, mitomycin, gemcitabine)	23 (23)
Chemotherapy	56 (56)
Radiation therapy	16 (16)
Immunotherapy	28 (28)
Targeted therapy	10 (10)
Do not know/remember	12 (12)
Other	13 (13)
Currently participating in a clinical trial, n (%)	
Yes, I am	0
No, but I have participated in a clinical trial in the past	0
No, I have not participated in a clinical trial before	100 (100)
Health conditions, n (%)	

Characteristic	N=100
Allergies	34 (34)
Cardiovascular disease	29 (29)
Depression	19 (19)
Eczema	15 (15)
Hearing problems	1 (1)
Kidney disease	12 (12)
Neuropathy	5 (5)
Type 1 diabetes	5 (5)
Type 2 diabetes	18 (18)
Psoriasis	6 (6)
Other	19 (19)
None of the above	18 (18)

BC, bladder cancer; Min, minimum; Max, maximum; IQR, inter-quartile range; QOL, quality of life.

Supplementary Table 5. Dirichlet interacted model. Additional data

Model Characteristic	Levels	LL	Parameters	Deviance	*P* Value
Age	2	686.75	12	9.72	0.137
Time since diagnosis	2	683.91	12	4.04	0.671
Cancer type	2	688.43	12	13.08	0.042
Cancer stage	3	689.87	18	15.96	0.193
Previously received cisplatin	2	682.31	12	0.84	0.991
Cisplatin suitability	2	682.49	12	1.2	0.977
Previously received carboplatin	2	684.59	12	5.4	0.494
Severity of bladder cancer symptoms at their worst	3	693.49	18	23.2	0.026
Hope of treatment	2	684.08	12	4.38	0.625
History of neuropathy	2	686	12	8.22	0.222
History of eczema	2	683.95	12	4.12	0.660
History of diabetes	2	683.47	12	3.16	0.789
Current cancer treatment	5	689.46	30	15.14	0.917

LL, log-likelihood.

Supplementary Table 6. Dirichlet regression with interaction term for patient-reported severity of cancer symptoms (N=100)

Attributes	Marginal Utilities (SE)			Pairwise Comparison		
	Mild	Moderate	Severe	Mild vs Moderate	Mild vs Severe	Moderate vs Severe
Chance cancer responds to treatment	0.63 (0.16)***	0.87 (0.10)***	0.58 (0.06)***	-0.23 (0.19)	0.06 (0.18)	0.29 (0.12)*
Pain related to bladder cancer	0.41 (0.11)***	0.55 (0.6)***	0.58 (0.05)***	-0.14 (0.13)	-0.17 (0.12)	-0.03 (0.08)
Mild to moderate nausea related to treatment	0.28 (0.08)***	0.20 (0.03)***	0.25 (0.03)***	0.08 (0.08)	0.04 (0.08)	-0.04 (0.04)
Peripheral neuropathy related to treatment	0.61 (0.14)***	0.45 (0.06)***	0.51 (0.05)***	0.16 (0.16)	0.10 (0.15)	-0.06 (0.08)
Mild to moderate skin reaction related to treatment	0.23 (0.07)***	0.19 (0.03)***	0.23 (0.03)***	0.03 (0.07)	0.00 (0.07)	-0.04 (0.04)
Severe side effects related to treatment	0.35 (0.11)**	0.35 (0.6)***	0.36 (0.04)***	0.01 (0.12)	0.00 (0.12)	-0.01 (0.07)

*P<0.05; **P<0.01; ***P<0.001.