EXPERT PANEL CONSENSUS STATEMENTS ON THE MEDICAL TREATMENT OF UNRESECTABLE PANCREATIC NEUROENDOCRINE TUMORS

Fisher G,[1] Strosberg JR,[2*] Benson AB,[3*] Malin JL,[4] Anthony L,[5*] Arslan B,[6] Gibbs JF,[7] Greeno E,[8] Iyer R,[9*] Kim MK,[10] Maples W,[11] Philip PA,[12*] Wolin E,[13*] Cherepanov D,[14*] Broder MS[14*]

[1] Stanford University Medical Center, [2] H. Lee Moffitt Cancer Center and Research Institute, [3] Robert H. Lurie Comprehensive Cancer Center of Northwestern University, [4] University of California, Los Angeles, [5] University of Kentucky, [6] Rush University Medical Center, [7] State University of New York at Buffalo, [8] University of Minnesota, [9] Roswell Park Cancer Institute, [10] Mount Sinai Medical Center, [11] Mission Health System, [12] Karmanos Cancer Institute, [13] Cedars-Sinai Medical Center, [14] Partnership for Health Analytic Research, LLC

* Potential conflict of interest may exist. Refer to the abstract.

BACKGROUND

- Neuroendocrine tumors (NETs) of the pancreas (PNETs) are a major subtype of gastrointestinal NETs. Treatment guidelines for these rare neoplasms lack some specificity.[1]
- The RAND/UCLA modified Delphi process, a systematic method for group decision-making, has demonstrated validity and reliability as a way to establish the appropriateness of a wide variety of medical procedures.[2]
- Fundamental features of the method are[2,3]: diversity of the panel, anonymity of ratings, iteration, controlled feedback, statistical analysis of responses.

OBJECTIVE

- To use the RAND/UCLA modified Delphi panel process to develop a consensus on medical treatment of well-differentiated (grade 1-2 tumors) unresectable PNETs.

METHODS

The modified RAND/UCLA Delphi process involved recruitment of physician experts, development of patient scenarios, collection of ratings, statistical summary of panel agreement, and development of consensus statements.[2,3]

Physician Experts

- Thirteen physician experts in treatment of NETs, representing various specialties, were appointed to serve on the study steering committee, on the panel, or both; one physician was assigned the moderator role.
- Experts and the moderator were blinded to the funding source.

Development of Clinical Patient Scenarios

- Following the review of published evidence on treatment of NETs, the experts collaborated to develop a list of key variables and used these variables to construct patient scenarios.

Variables Used to Construct Clinical Patient Scenarios in PNETS

Variable	Range of Values
Line of treatment	Observation; first-line treatment; second-line treatment; third-line treatment
Patient's primary problem	Uncontrolled secretory symptoms; uncontrolled tumor-related symptoms, (rapid) radiographic progression; nonrapid radiographic progression; no symptoms and no radiographic progression; no symptoms
Postmarker and postscan testing status	No progression from prior marker and scan; progression after prior marker and scan
Frequency of testing a patient with markers and scans	Every 3 months; every 6 months; every 9 months; every 12 months
Cytoreductive surgery	Appropriateness of initial therapy following: optimal cytoreductive surgery; suboptimal cytoreductive surgery; not a candidate for surgery
Systemic therapy	Somatostatin analog; everolimus; sunitinib; cytotoxic chemotherapy; interferon-α; temozolomide-containing regimen; streptozotocin-containing regimen
Response to lower octreotide LAR dose	Who previously responded to a lower dose or frequency; who previously did not respond to a lower dose or frequency
Octreotide LAR frequency	Every 2 weeks; every 3 weeks; every 4 weeks
Octreotide LAR dosing	30 mg; 40 mg; 60 mg; 90 mg; 120 mg

Rating of Patient Scenarios

- Experts rated the appropriateness of systematic therapies for each scenario on a scale of 1 to 9. [a]

[a] A rating of 1 implied that expected harms greatly outweighed expected benefits; 9 indicated that expected benefits greatly outweighed expected harms.

- Two rounds of ratings were collected: 1st round before and the 2nd round after a face-to-face panel meeting.

Statistical Summary of Panel Agreement

- For every rated scenario, we calculated two statistics: median of the panelists' ratings and absolute deviation (i.e., distance) from every panelist's rating to the median.
- Using previously established standards for defining disagreement[2,3] each scenario was scored for appropriateness:
  - *Appropriate*: median rating of 7-9 with no disagreement.
  - *Inappropriate*: median rating of 1-3 with no disagreement.
  - *Uncertain*: median rating of 4-6 with no disagreement.
- Scenarios considered to have *disagreement* were not assigned a rating.

Development of Consensus Statements

- Treatment of consensus statements were drafted based on statistical summary of panel agreement in the 2nd round.

RESULTS

Panelist Characteristics

- The 10 panelists were from northeast, midwest, south, and west regions, all were in academic practice.
- Specialties included medical and surgical oncology, interventional radiology, and gastroenterology.
- Panelists had practiced a mean of 15 (range: 6-33) years and reported 49% (range 15-60%) of their time was spent seeing patients.
- Five panelists had been involved with the development of other NET treatment guidelines.

Patient Scenarios Scored: 'Inappropriate', 'Uncertain', 'Appropriate', or 'Disagreement'

	1ST Round Results				2ND Round Results			
Agreement	**Freq.**	**Percent**	**Cum. Freq.**	**Cum. Percent**	**Freq.**	**Percent**	**Cum. Freq.**	**Cum. Percent**
Inappropriate	73	37.1	73	37.1	94	46.5	94	46.5
Uncertain	39	19.8	112	56.9	44	21.8	138	68.3
Appropriate	59	30.0	171	86.8	62	30.7	200	99.0
Disagreement	26	13.2	197	100	2	1.0	202	100

- Panelists rated 197 scenarios in the 1st round and 202 in the 2nd round.
- Among 202 scenarios, 46.5% (94 scenarios) were rated inappropriate, 21.8% (44) were uncertain, and 30.7% (62) were appropriate.
- In the 2nd round, disagreement decreased from 13.2% (26 scenarios) before the meeting to 1% (2) after.

Median Ratings and Average Absolute Deviation from Median

	1ST Round Results					2ND Round Results				
Variable	**N**	**Mean**	**SD**	**Min**	**Max**	**N**	**Mean**	**SD**	**Min**	**Max**
Median	197	4.3	2.6	1.0	9.0	202	4.1	2.9	1.0	9.0
Absolute Deviation	197	1.6	0.5	0.1	2.7	202	0.8	0.6	0.0	2.2

- In the 2nd round:
  - average median rating: was 4.1 (range: 1-9), and
  - average distance from median was 0.8 (range: 0-2.2).

Consensus Statements on the Appropriateness of Medical Therapies in PNETs

Observation without treatment

- Observation may be appropriate for patients with no symptoms and low-volume radiographically-stable disease.
- For patients with no progression from prior tests, markers and scans may be obtained every 3 to 12 months; for patients with progression after prior tests, an appropriate interval is 3 to 6 months.

First-line medical treatment

- Somatostatin analogs (SAs) are appropriate in hormonally functional tumors (particularly VIPomas and glucagonomas).[b]

  (SA may be appropriate in patients with nonfunctional tumors; however there are limited data to support their use as antiproliferative agents in PNETs.)
- Everolimus is an appropriate agent in patients with symptomatic or progressive tumors.
- Sunitinib is an appropriate agent in patients with symptomatic or progressive tumors.
- Cytotoxic chemotherapy (i.e., streptozocin or temozolomide-based regimens are recommended by NCCN) is appropriate, particularly in patients with rapidly progressive tumors, or in cases where tumor burden is high.

Beyond first-line therapy

- Everolimus, sunitinib, and cytotoxic chemotherapy (temozolomide or streptozocin-based regimens) are appropriate in the refractory setting. However, there are no studies guiding the appropriate sequence of treatments.
- In patients with uncontrolled secretory symptoms, increasing the dose/frequency of SA is appropriate, particularly among patients who had previously responded to lower dose.
  - The panel considered dose escalations of octreotide long-acting release (LAR) up to 60 mg every 3 or 4 weeks regardless of previous response to SA or up to 40 mg every 2 weeks in those who previously responded to a lower dose to be reasonable adjustments.
  - The hormonal syndromes most likely to respond to SA therapy are associated with secretion of glucagon and vasoactive intestinal peptide.

[b] Caution should be used in administration of SA in patients with insulinoma, which may result in worsening of hypoglycemia.

- For example, a patient with uncontrolled secretory symptoms who previously responded to a lower dose of SA, may be administered a dose escalation of octreotide-LAR up to 40 mg every 2 weeks.

LIMITATIONS

- The panelists relied on information from a variety of data sources, not just from randomized controlled trials.
- Although the Delphi panel method has been shown to be reproducible, all panelists were from academic settings, and a different panel composition may have developed different consensus statements.
- The Delphi panel process does not develop new information; observational and/or prospective studies may also be useful in further evaluating appropriateness of various treatment options.

CONCLUSIONS

- **We systematically obtained appropriateness ratings for a variety of medical therapies in PNETs from a group of physician experts.**
- **The Delphi process allowed the experts to quantify complex qualitative data to arrive at consensus on the appropriateness of medical therapies for the treatment of PNETs.**
- **This process produced statements that are concordant with, but increase the detail of, previously published PNET guidelines.[4-6]**
- **Compared to other studies that used the Delphi panel process, we were able to obtain consensus statements with relatively low levels of disagreement.[7-10]**
- **The detailed consensus statements provided using this expert Delphi panel may inform the development of treatment guidelines and also guide clinicians in their decision-making.**

References

1. Strosberg *Pancreas* 2011.
2. Fitch K RAND 2001.
3. ATGSRSG *Ophthalmology* 2009.
4. Kulke *Pancreas* 2010.
5. Vinik *Pancreas* 2010.
6. NCCN Guidelines™: Neuroendocrine Tumors Version 1.2011.
7. Broder *Obstet Gynecol* 2000.
8. Broder *RAND, MR-1258* 2001.
9. Hanley *Stroke Cerebrovascular Dis* 2004.
10. Fraser *Fertil Steril* 2007.

URL: http://novartis.medicalcongressposters.com/Default.aspx?doc=fcf05
Text Code: **Qfcf05** To: 8NOVA (86682) *US Only;* +18324604729 *North, Central and South Americas; Caribbean; China;* +447860024038 *UK, Europe & Russia;* +46737494608 *Sweden, Europe.* Standard data or message rates may apply.

This study was sponsored by Novartis Pharmaceuticals Corporation