THE LANCET Oncology

# Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol* 2015; published online Jan 16. http://dx.doi.org/10.1016/S1470-2045(14)71207-0.

# Appendices

**Appendix 1: Normal tissue dose-volume guidelines within protocol document (section 6 of protocol)**

6.5 Critical Structures
Normal tissue constraints shall be prioritized in the following order for treatment planning: 1=spinal cord, 2=lungs, 3=esophagus, 4=brachial plexus, and 5=heart

6.5.1 Spinal Cord: The spinal cord dose limitation is the highest priority dose constraint and thus must be met irrespective of other constraints. Total "direct" plus "scatter" dose to the spinal cord must not exceed 50.5 Gy.

6.5.2 Lungs: The dose-volume constraint to the lungs is the second highest priority and must be met, except if it conflicts with the cord dose constraints. The volume of both lungs that receive more than 20 Gy (the V20) should not exceed 37% of the total. Alternatively, the mean lung dose should optimally be □ 20 Gy. (By total lung volume we mean the total lung minus the CTV).

If either of these constraints is exceeded, several solutions can be entertained.
First, one might increase the weighting of AP / PA treatments by one and reduce the obliques. This can be done as long as the cord dose (above), which takes precedence, is not exceeded.
Second, one can reduce the CTV to the minimum range suggested above.
Third, one can try to reduce the PTV by using respiratory gating techniques.
If after all attempts to decrease the V20 to below 37%, the V20 value still exceeds this limit, the patient should be treated to the dose on the arm to which they were randomized.

6.5.3 Esophagus: The mean dose to the esophagus is optimally kept below 34 Gy.[47] This is not an absolute requirement, but is strongly recommended unless other, more critical constraints force the situation. The V60 (% volume of esophagus exceeding 60 Gy) should be calculated for each patient.

6.5.4 Heart: The following limits are recommended: 60Gy to <1/3, 45 Gy to <2/3, and 40 Gy to <100% of the heart.

**Appendix 2: Protocol Compliance Definitions**

- **Credentialing process for enrolling institutions**
  - Completion of a facility questionnaire (http://atc.wustl.edu).
  - Completion of baseline physics questionnaire for 3DCRT, IMRT, or both (http://atc.wustl.edu).
  - Completion of Dry Run Submission to Image-guided Therapy Center
  - For IMRT, Completion of phantom irradiation (http://rpc.mdanderson.org/rpc/).
- **Radiation Therapy**
  - Contouring: Normal contours (consisting of ipsilateral lung, contralateral lung, spinal cord, heart, esophagus, brachial plexus and skin) were scored individually for each patient. Scores assigned to each were per protocol, minor corrections requested, or major corrections/unevaluable. Contours scored as per protocol or minor were termed 'acceptable variations'. Major deviations/unevaluable' normal tissue contours reflected judgment by the reviewer that the dose volume histograms for a specific normal tissue were unevaluable.
  - Dose
    - Per protocol: 95% of the PTV is covered by the prescription dose. Maximum dose is < 120% of prescription dose.
    - Acceptable Variation: 90% - < 95% of the PTV is covered by the prescription dose. The maximum dose is 120%-125% of the prescription dose.
    - Unacceptable Deviation: Exceeding any of the Acceptable Variation limits.

- **Systemic Therapy**
  - Evaluation is based on dose and treatment delays. The overall evaluation is the worst criteria met in either protocol dose or treatment delays. For example, a dose of 85-115% but treatment delays > 2 weeks would be considered an Unacceptable Deviation.

    **Per Protocol:**
    - Protocol Dose:
      - 85-115%
      - < 85%, due to protocol-specified dose modifications
    - Treatment Delays
      - No delays
      - ≤ 1 week, regardless of reason
      - > 1 week, due to protocol-specified reasons

    **Acceptable variation:**
    - Protocol Dose:
      - 70 - < 85%, due to non-protocol-specified reasons
    - Treatment Delays
      - >1 - ≤ 2 week delay, due to non-protocol-specified reasons

    **Unacceptable deviation:**
    - Protocol Dose:
      - < 70%, due to non-protocol-specified reasons
      - > 115%
      - Wrong drug/agent given
    - Treatment Delays:
      - > 2 weeks, due to non-protocol-specified reasons
      - No delay when delay required by protocol

**Appendix 3a**
**Radiation Therapy Review**
**By Radiation Dose**

| | Standard Dose: 60 Gy (n=217) | High Dose: 74 Gy (n=207) | Total (n=424) |
|---|---|---|---|
| Overall RT Review | (n=217) | (n=207) | (n=424) |
| Per Protocol | 180 (82.9%) | 153 (73.9%) | 333 (78.5%) |
| Acceptable Variation# | 4 (1.8%) | 11 (5.3%) | 15 (3.5%) |
| Unacceptable Deviation | 16 (7.4%) | 25 (12.1%) | 41 (9.7%) |
| Incomplete RT - Death during RT | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| Incomplete RT - Progression | 0 (0.0%) | 2 (1.0%) | 2 (0.5%) |
| Incomplete RT - Refusal | 3 (1.4%) | 8 (3.9%) | 11 (2.6%) |
| No RT Given | 6 (2.8%) | 4 (1.9%) | 10 (2.4%) |
| Not Evaluable | 7 (3.2%) | 3 (1.4%) | 10 (2.4%) |
| p-value* | 0.02 | | |
| RT Dose, Fractionation | (n=217) | (n=206) | (n=423) |
| Not applicable | 2 (0.9%) | 2 (1.0%) | 4 (0.9%) |
| Per protocol | 200 (92.2%) | 179 (86.9%) | 379 (89.6%) |
| Acceptable variation# | 1 (0.5%) | 7 (3.4%) | 8 (1.9%) |
| Unacceptable variation | 7 (3.2%) | 14 (6.8%) | 21 (5.0%) |
| Not evaluable | 7 (3.2%) | 4 (1.9%) | 11 (2.6%) |
| p-value* | 0.08 | | |
| Elapsed Days | (n=217) | (n=206) | (n=423) |
| Not applicable | 2 (0.9%) | 2 (1.0%) | 4 (0.9%) |
| Per protocol | 195 (89.9%) | 171 (83.0%) | 366 (86.5%) |
| Acceptable variation# | 5 (2.3%) | 13 (6.3%) | 18 (4.3%) |
| Unacceptable variation | 8 (3.7%) | 16 (7.8%) | 24 (5.7%) |
| Not evaluable | 7 (3.2%) | 4 (1.9%) | 11 (2.6%) |
| p-value* | 0.04 | | |
| TV/OAR Contouring Overall Score | (n=217) | (n=207) | (n=424) |
| Not applicable | 2 (0.9%) | 3 (1.4%) | 5 (1.2%) |
| Per protocol | 180 (82.9%) | 158 (76.3%) | 338 (79.7%) |
| Acceptable variation# | 13 (6.0%) | 20 (9.7%) | 33 (7.8%) |
| Unacceptable variation | 14 (6.5%) | 23 (11.1%) | 37 (8.7%) |
| Not evaluable | 8 (3.7%) | 3 (1.4%) | 11 (2.6%) |
| p-value* | 0.09 | | |
| GTV Contour | (n=208) | (n=200) | (n=408) |
| Per protocol | 192 (92.3%) | 179 (89.5%) | 371 (90.9%) |
| Acceptable variation# | 7 (3.4%) | 9 (4.5%) | 16 (3.9%) |
| Unacceptable variation | 9 (4.3%) | 12 (6.0%) | 21 (5.1%) |
| p-value* | 0.32 | | |
| PTV Contour | (n=208) | (n=200) | (n=408) |
| Per protocol | 193 (92.8%) | 172 (86.0%) | 365 (89.5%) |
| Acceptable variation# | 6 (2.9%) | 7 (3.5%) | 13 (3.2%) |
| Unacceptable variation | 8 (3.8%) | 20 (10.0%) | 28 (6.9%) |
| Not evaluable | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| p-value* | 0.03 | | |

**Appendix 3a**
**Radiation Therapy Review**
**By Radiation Dose**

| | Standard Dose: 60 Gy (n=217) | High Dose: 74 Gy (n=207) | Total (n=424) |
|---|---|---|---|
| Ipsilateral Lung Contour | (n=208) | (n=200) | (n=408) |
| Per protocol | 202 (97.1%) | 192 (96.0%) | 394 (96.6%) |
| Acceptable variation# | 5 (2.4%) | 7 (3.5%) | 12 (2.9%) |
| Unacceptable variation | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| p-value* | 0.54 | | |
| Contralateral Lung Contour | (n=208) | (n=200) | (n=408) |
| Per protocol | 202 (97.1%) | 189 (94.5%) | 391 (95.8%) |
| Acceptable variation# | 5 (2.4%) | 8 (4.0%) | 13 (3.2%) |
| Unacceptable variation | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| Not evaluable | 0 (0.0%) | 2 (1.0%) | 2 (0.5%) |
| p-value* | 0.19 | | |
| Spinal Cord Contour | (n=208) | (n=200) | (n=408) |
| Per protocol | 206 (99.0%) | 198 (99.0%) | 404 (99.0%) |
| Acceptable variation# | 0 (0.0%) | 1 (0.5%) | 1 (0.2%) |
| Not evaluable | 2 (1.0%) | 1 (0.5%) | 3 (0.7%) |
| p-value* | 0.97 | | |
| Heart Contour | (n=208) | (n=200) | (n=408) |
| Per protocol | 163 (78.4%) | 145 (72.5%) | 308 (75.5%) |
| Acceptable variation# | 43 (20.7%) | 52 (26.0%) | 95 (23.3%) |
| Unacceptable variation | 2 (1.0%) | 2 (1.0%) | 4 (1.0%) |
| Not evaluable | 0 (0.0%) | 1 (0.5%) | 1 (0.2%) |
| p-value* | 0.17 | | |
| Esophagus Contour | (n=208) | (n=200) | (n=408) |
| Per protocol | 207 (99.5%) | 197 (98.5%) | 404 (99.0%) |
| Acceptable variation# | 0 (0.0%) | 1 (0.5%) | 1 (0.2%) |
| Unacceptable variation | 0 (0.0%) | 1 (0.5%) | 1 (0.2%) |
| Not evaluable | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| p-value* | 0.30 | | |
| Brachial Plexus Contour | (n=208) | (n=200) | (n=408) |
| Per protocol | 192 (92.3%) | 171 (85.5%) | 363 (89.0%) |
| Acceptable variation# | 11 (5.3%) | 22 (11.0%) | 33 (8.1%) |
| Unacceptable variation | 4 (1.9%) | 6 (3.0%) | 10 (2.5%) |
| Not evaluable | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| p-value* | 0.03 | | |
| Skin Contour | (n=208) | (n=200) | (n=408) |
| Per protocol | 205 (98.6%) | 197 (98.5%) | 402 (98.5%) |
| Not evaluable | 3 (1.4%) | 3 (1.5%) | 6 (1.5%) |
| p-value* | 0.96 | | |
| TV DVA Score | (n=217) | (n=207) | (n=424) |
| Per protocol | 196 (90.3%) | 179 (86.5%) | 375 (88.4%) |
| Acceptable variation# | 5 (2.3%) | 7 (3.4%) | 12 (2.8%) |
| Unacceptable variation | 7 (3.2%) | 15 (7.2%) | 22 (5.2%) |
| Not evaluable | 9 (4.1%) | 6 (2.9%) | 15 (3.5%) |

**Appendix 3a**
**Radiation Therapy Review**
**By Radiation Dose**

| | Standard Dose: 60 Gy (n=217) | High Dose: 74 Gy (n=207) | Total (n=424) |
|---|---|---|---|
| p-value* | 0.22 | | |
| | | | |
| OAR DVA Score | (n=217) | (n=207) | (n=424) |
| Per protocol | 192 (88.5%) | 172 (83.1%) | 364 (85.8%) |
| Acceptable variation# | 1 (0.5%) | 0 (0.0%) | 1 (0.2%) |
| Unacceptable variation | 15 (6.9%) | 29 (14.0%) | 44 (10.4%) |
| Not evaluable | 9 (4.1%) | 6 (2.9%) | 15 (3.5%) |
| p-value* | 0.11 | | |

*p-value from chi-square test comparing Per Protocol vs. everything else
TV=tumor volume; OAR=organs at risk; GTV=gross tumor volume; PTV=planning target volume; DVA=dose volume analysis
#See Appendix 10 for definitions of variations.

**Appendix 3b**
**Systemic Therapy Review**
**Paclitaxel and Carboplatin**

| | Standard Dose: 60 Gy (n=217) | High Dose: 74 Gy (n=207) | Cetuximab (n=237) | No Cetuximab (n=228) |
|---|---|---|---|---|
| **Concurrent** | | | | |
| Overall review | (n=217) | (n=207) | (n=237) | (n=228) |
| Per Protocol | 192 (88.5%) | 175 (84.5%) | 198 (83.5%) | 203 (89.0%) |
| Acceptable Variation | 14 (6.5%) | 12 (5.8%) | 19 (8.0%) | 10 (4.4%) |
| Unacceptable Deviation | 7 (3.2%) | 12 (5.8%) | 12 (5.1%) | 10 (4.4%) |
| Not Evaluable | 4 (1.8%) | 8 (3.9%) | 8 (3.4%) | 5 (2.2%) |
| | | | | |
| Dose | (n=213) | (n=199) | (n=229) | (n=223) |
| 85-115% | 148 (69.5%) | 146 (73.4%) | 159 (69.4%) | 166 (74.4%) |
| <85%, due to protocol-specified reasons | 45 (21.1%) | 38 (19.1%) | 46 (20.1%) | 40 (17.9%) |
| 70 - < 85%, due to non-protocol-specified reasons | 14 (6.6%) | 7 (3.5%) | 16 (7.0%) | 8 (3.6%) |
| < 70%, due to non-protocol-specified reasons | 5 (2.3%) | 5 (2.5%) | 5 (2.2%) | 7 (3.1%) |
| > 115% | 1 (0.5%) | 3 (1.5%) | 3 (1.3%) | 2 (0.9%) |
| | | | | |
| Treatment delays | (n=213) | (n=199) | (n=229) | (n=223) |
| No delays | 188 (88.3%) | 164 (82.4%) | 202 (88.2%) | 188 (84.3%) |
| <= 1 week | 17 (8.0%) | 21 (10.6%) | 15 (6.6%) | 22 (9.9%) |
| > 1 week, due to protocol-specified reasons | 8 (3.8%) | 12 (6.0%) | 12 (5.2%) | 10 (4.5%) |
| >= 2 weeks, due to non-protocol-specified reasons | 0 (0.0%) | 2 (1.0%) | 0 (0.0%) | 3 (1.3%) |
| | | | | |
| **Consolidation** | | | | |
| Overall review | (n=216) | (n=207) | (n=237) | (n=227) |
| Per Protocol | 151 (69.9%) | 133 (64.3%) | 159 (67.1%) | 153 (67.4%) |
| Acceptable Variation | 11 (5.1%) | 11 (5.3%) | 9 (3.8%) | 15 (6.6%) |
| Unacceptable Deviation | 23 (10.6%) | 18 (8.7%) | 25 (10.5%) | 17 (7.5%) |
| Not Evaluable | 31 (14.4%) | 45 (21.7%) | 44 (18.6%) | 42 (18.5%) |

**Appendix 3b**
**Systemic Therapy Review**
**Paclitaxel and Carboplatin**

| | Standard Dose: 60 Gy (n=217) | High Dose: 74 Gy (n=207) | Cetuximab (n=237) | No Cetuximab (n=228) |
|---|---|---|---|---|
| Dose | (n=184) | (n=161) | (n=193) | (n=183) |
| 85-115% | 131 (71.2%) | 112 (69.6%) | 126 (65.3%) | 137 (74.9%) |
| <85%, due to protocol-specified reasons | 28 (15.2%) | 28 (17.4%) | 42 (21.8%) | 23 (12.6%) |
| 70 - < 85%, due to non-protocol-specified reasons | 9 (4.9%) | 6 (3.7%) | 8 (4.1%) | 8 (4.4%) |
| < 70%, due to non-protocol-specified reasons | 14 (7.6%) | 12 (7.5%) | 15 (7.8%) | 12 (6.6%) |
| > 115% | 2 (1.1%) | 3 (1.9%) | 2 (1.0%) | 3 (1.6%) |
| Treatment delays | (n=183) | (n=161) | (n=192) | (n=183) |
| No delays | 135 (73.8%) | 118 (73.3%) | 143 (74.5%) | 136 (74.3%) |
| <= 1 week | 23 (12.6%) | 23 (14.3%) | 23 (12.0%) | 22 (12.0%) |
| > 1 week, due to protocol-specified reasons | 16 (8.7%) | 15 (9.3%) | 19 (9.9%) | 18 (9.8%) |
| > 1 - 2 week delay, due to non-protocol specified reasons | 4 (2.2%) | 2 (1.2%) | 2 (1.0%) | 3 (1.6%) |
| >= 2 weeks, due to non-protocol-specified reasons | 5 (2.7%) | 3 (1.9%) | 5 (2.6%) | 4 (2.2%) |

**Appendix 3c**
**Systemic Therapy Review**
**Cetuximab**

| | Arm C: 60 Gy + Cetuximab (n=137) | Arm D: 74 Gy + Cetuximab (n=100) | Total (n=237) |
|---|---|---|---|
| **Concurrent** | | | |
| Overall review | (n=137) | (n=100) | (n=237) |
| Per Protocol | 131 (95.6%) | 90 (90.0%) | 221 (93.2%) |
| Acceptable Variation | 2 (1.5%) | 3 (3.0%) | 5 (2.1%) |
| Unacceptable Deviation | 2 (1.5%) | 3 (3.0%) | 5 (2.1%) |
| Not Evaluable | 2 (1.5%) | 4 (4.0%) | 6 (2.5%) |
| Dose | (n=135) | (n=96) | (n=231) |
| 85-115% | 110 (81.5%) | 78 (81.3%) | 188 (81.4%) |
| <85%, due to protocol-specified reasons | 22 (16.3%) | 17 (17.7%) | 39 (16.9%) |
| 70 - < 85%, due to non-protocol-specified reasons | 1 (0.7%) | 1 (1.0%) | 2 (0.9%) |
| < 70%, due to non-protocol-specified reasons | 2 (1.5%) | 0 (0.0%) | 2 (0.9%) |
| Treatment delays | (n=135) | (n=96) | (n=231) |
| No delays | 118 (87.4%) | 86 (89.6%) | 204 (88.3%) |
| <= 1 week | 10 (7.4%) | 6 (6.3%) | 16 (6.9%) |
| > 1 week, due to protocol-specified reasons | 7 (5.2%) | 4 (4.2%) | 11 (4.8%) |
| **Consolidation** | | | |
| Overall review | (n=137) | (n=99) | (n=236) |
| Per Protocol | 107 (78.1%) | 73 (73.7%) | 180 (76.3%) |
| Acceptable Variation | 5 (3.6%) | 4 (4.0%) | 9 (3.8%) |
| Unacceptable Deviation | 6 (4.4%) | 3 (3.0%) | 9 (3.8%) |
| Not Evaluable | 19 (13.9%) | 19 (19.2%) | 38 (16.1%) |

**Appendix 3c**
**Systemic Therapy Review**
**Cetuximab**

| | Arm C: 60 Gy + Cetuximab (n=137) | Arm D: 74 Gy + Cetuximab (n=100) | Total (n=237) |
|---|---|---|---|
| Dose | (n=118) | (n=80) | (n=198) |
| 85-115% | 73 (61.9%) | 45 (56.3%) | 118 (59.6%) |
| <85%, due to protocol-specified reasons | 38 (32.2%) | 30 (37.5%) | 68 (34.3%) |
| 70 - < 85%, due to non-protocol-specified reasons | 2 (1.7%) | 2 (2.5%) | 4 (2.0%) |
| < 70%, due to non-protocol-specified reasons | 5 (4.2%) | 3 (3.8%) | 8 (4.0%) |
| Treatment delays | (n=118) | (n=80) | (n=198) |
| No delays | 79 (66.9%) | 56 (70.0%) | 135 (68.2%) |
| <= 1 week | 14 (11.9%) | 12 (15.0%) | 26 (13.1%) |
| > 1 week, due to protocol-specified reasons | 22 (18.6%) | 8 (10.0%) | 30 (15.2%) |
| > 1 - 2 week delay, due to non-protocol specified reasons | 1 (0.8%) | 1 (1.3%) | 2 (1.0%) |
| >= 2 weeks, due to non-protocol-specified reasons | 2 (1.7%) | 3 (3.8%) | 5 (2.5%) |

**Appendix 4: Additional Statistical Methods**

- Interim analyses
  - Three interim safety analyses were incorporated using Flemming's method[1] after 20, 40, and 80 evaluable patients per arm were accrued and followed for at least 90 days from the start of treatment. A rate of 40% or greater was considered too excessive with a maximum significance level of 0.05.
  - Three interim efficacy analyses of each endpoint were planned to be performed at 85, 170, and 255 deaths. At each planned interim analysis, the 1-sided p-value from the tests for assessing treatment efficacy and futility with respect to overall survival were compared to nominal significance levels. Haybittle-Peto boundaries were used for efficacy[2,3] and Freidlin-Korn methodologies[4] were used for the alternative hypothesis.
- Endpoints were defined as follows:
  - Overall survival
    - An event was death due to any cause.
    - Corresponding outcome time was the time from date of randomization until date of death or last date known alive.
  - Progression-free survival
    - An event was progression of disease or death due to any cause, whichever occurred first.
    - Corresponding outcome time was time from date of randomization until date of progression, date of death, or in the absence of progression and death, the last date known alive.
  - Local failure
    - An event was local failure.
    - Death without local failure was considered as a competing risk.
    - Corresponding outcome time was the time from date of randomization until date of local failure, or in the absence of local failure, the date of death or last date known alive.
  - Distant metastasis
    - An event was development of distant metastasis.
    - Death without development of distant metastasis was considered as a competing risk.
    - Corresponding outcome time was the time from date of randomization until date of distant failure, or in the absence of distant failure, the date of death or last date known alive.
- Endpoints of toxicity and outcome, including local failure and cause of death determinations, were based on institutional reporting, without central review monitoring.
- Follow-up evaluations were to be performed every 3 months for the first year, every 4 months for year 2, every 6 months for years 3-5, then annually. Routine follow-up evaluations included assessment of vital signs, Zubrod performance status, and any adverse events. CT scans were to be done every 6 months for the first two years, and then annually. Pulmonary functioning was evaluated at 6 months and then 1 year following completion of therapy.


1. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549-556.
2. Haybittle JL. Repeated assessments of results in clinical trials of cancer treatment. *Brit J Radiol* 1971;44(526):793-797.
3. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. *British Journal of Cancer* 1976;34:585-612.
4. Freidlin B., Korn EL. A comment on futility monitoring. *Controlled Clinical Trials* 2002;23:355-66.

**Appendix 5**
**Dose Volume Data**
**By Arm**

| | Arm A: 60 Gy (n=151) | Arm B: 74 Gy (n=107) | Arm C: 60 Gy + Cetuximab (n=137) | Arm D: 74 Gy + Cetuximab (n=100) |
|---|---|---|---|---|
| GTV volume (cc) | (n=105) | (n=78) | (n=98) | (n=75) |
| Mean | 123.1 | 117.8 | 117.5 | 135.5 |
| Median | 92.8 | 110.0 | 92.9 | 75.3 |
| Min - Max | 5.9 - 552.8 | 13.2 - 492.9 | 4.6 - 485.9 | 8.6 - 735.8 |
| Q1 - Q3 | 41.7 - 170.8 | 55.3 - 151.3 | 51.4 - 151.8 | 39.1 - 177.6 |
| ITV volume (cc) | (n=53) | (n=36) | (n=53) | (n=34) |
| Mean | 153.3 | 136.4 | 153.9 | 141.3 |
| Median | 98.1 | 108.0 | 92.7 | 92.2 |
| Min - Max | 41.9 - 1192.4 | 23.8 - 634.2 | 4.9 - 960.6 | 12.9 - 537.7 |
| Q1 - Q3 | 69.6 - 166.2 | 82.3 - 166.9 | 51.7 - 207.5 | 60.0 - 185.0 |
| PTV volume (cc) | (n=143) | (n=105) | (n=130) | (n=96) |
| Mean | 535.4 | 510.1 | 491.5 | 509.6 |
| Median | 481.2 | 477.5 | 432.1 | 429.0 |
| Min - Max | 138.5 - 2232.3 | 100.6 - 1836.4 | 99.0 - 1851.2 | 164.2 - 1427.3 |
| Q1 - Q3 | 334.5 - 642.1 | 303.0 - 607.2 | 302.5 - 598.3 | 307.0 - 643.8 |
| Maximum dose to PTV (Gy) | (n=143) | (n=105) | (n=130) | (n=96) |
| Mean | 66.45 | 79.71 | 66.07 | 79.66 |
| Median | 66.50 | 81.70 | 66.65 | 81.30 |
| Min - Max | 6.60 - 81.30 | 42.10 - 88.80 | 9.70 - 78.90 | 27.80 - 92.30 |
| Q1 - Q3 | 48.20 - 55.60 | 54.80 - 65.60 | 47.40 - 55.30 | 49.95 - 65.95 |
| Lung V5 (%) | (n=143) | (n=105) | (n=130) | (n=96) |
| Mean | 58.3 | 58.9 | 57.1 | 57.1 |
| Median | 57.9 | 58.3 | 56.7 | 57.8 |
| Min - Max | 5.6 - 95.2 | 16.2 - 97.9 | 18.8 - 92.1 | 24.6 - 97.7 |
| Q1 - Q3 | 2668.2 - 3965.1 | 2899.2 - 4281.2 | 2653.7 - 4029.2 | 2795.0 - 3744.8 |
| Lung V20 (%) | (n=143) | (n=105) | (n=130) | (n=96) |
| Mean | 28.7 | 31.1 | 28.1 | 30.7 |
| Median | 29.0 | 32.4 | 28.4 | 30.9 |
| Min - Max | 0.0 - 47.6 | 8.4 - 50.3 | 0.0 - 71.6 | 10.9 - 55.5 |
| Q1 - Q3 | 24.7 - 34.8 | 26.9 - 35.7 | 23.0 - 33.8 | 25.3 - 35.1 |
| Mean lung dose (Gy) | (n=143) | (n=105) | (n=130) | (n=96) |
| Mean | 16.6 | 19.0 | 16.1 | 18.9 |
| Median | 16.5 | 19.9 | 16.5 | 19.3 |
| Min - Max | 1.9 - 26.5 | 4.8 - 29.9 | 3.2 - 43.1 | 6.8 - 32.2 |
| Q1 - Q3 | 14.2 - 19.5 | 16.7 - 21.3 | 13.1 - 19.1 | 16.3 - 22.1 |
| Heart V5 (%) | (n=143) | (n=105) | (n=130) | (n=94) |
| Mean | 50.4 | 45.3 | 45.3 | 46.4 |
| Median | 50.4 | 38.1 | 42.2 | 49.3 |
| Min - Max | 0.0 - 100.0 | 0.0 - 100.0 | 0.0 - 100.0 | 0.0 - 100.0 |

**Appendix 5**
**Dose Volume Data**
**By Arm**

| | Arm A: 60 Gy (n=151) | Arm B: 74 Gy (n=107) | Arm C: 60 Gy + Cetuximab (n=137) | Arm D: 74 Gy + Cetuximab (n=100) |
|---|---|---|---|---|
| Q1 - Q3 | 23.3 - 77.2 | 20.7 - 70.1 | 18.9 - 67.3 | 20.7 - 66.0 |
| Heart V30 (%) | (n=143) | (n=105) | (n=130) | (n=94) |
| Mean | 20.0 | 21.6 | 15.8 | 21.6 |
| Median | 14.3 | 12.7 | 11.5 | 15.8 |
| Min - Max | 0.0 - 94.6 | 0.0 - 90.7 | 0.0 - 94.6 | 0.0 - 85.4 |
| Q1 - Q3 | 2.4 - 29.3 | 4.6 - 35.5 | 1.9 - 22.8 | 5.9 - 34.9 |
| Esophagus V20 (%) | (n=142) | (n=105) | (n=129) | (n=95) |
| Mean | 44.3 | 48.9 | 47.8 | 48.9 |
| Median | 44.5 | 48.3 | 48.6 | 46.9 |
| Min - Max | 0.0 - 78.9 | 10.5 - 92.7 | 0.0 - 80.8 | 16.4 - 82.5 |
| Q1 - Q3 | 35.7 - 56.0 | 39.2 - 55.6 | 40.4 - 59.3 | 40.1 - 55.8 |
| Esophagus V60 (%) | (n=142) | (n=105) | (n=129) | (n=95) |
| Mean | 13.8 | 25.5 | 16.1 | 25.2 |
| Median | 11.7 | 25.4 | 15.5 | 24.7 |
| Min - Max | 0.0 - 65.6 | 0.0 - 62.7 | 0.0 - 56.8 | 0.0 - 55.1 |
| Q1 - Q3 | 1.6 - 22.6 | 12.2 - 38.4 | 3.0 - 25.7 | 17.4 - 35.3 |

Q1=Quartile 1, Q3=Quartile 3

**Appendix 6**
**RT Endpoint: Multivariate Cox Model of Overall Survival**
**(n=407)**

| **Covariate** | **Comparison** | **Dead/Total RL** | **Dead/Total Group 2** | **HR (95% CI)** | **p-value*** |
|---|---|---|---|---|---|
| Radiation Level | Standard Dose (RL) vs. High Dose | 121/208 | 136/199 | 1.34 (1.04, 1.73) | 0.0213 |
| Maximum related esophagitis/dysphagia grade | Maximum grade < 3 (RL) vs. Maximum grade ≥ 3 | 210/349 | 47/58 | 1.54 (1.11, 2.15) | 0.0102 |
| Volume of PTV | Continuous | 257/407 | | 1.000 (1.000, 1.001) | 0.0729 |
| Heart V5 | Continuous | 257/407 | | 1.007 (1.002, 1.011) | 0.0035 |
| Zubrod PS | 0 (RL) vs. 1 | 151/240 | 106/167 | 1.14 (0.89, 1.47) | 0.3045 |
| PET Staging | No (RL) vs. Yes | 30/39 | 227/368 | 0.77 (0.52, 1.13) | 0.1766 |
| Gender | Male (RL) vs. Female | 153/240 | 104/167 | 0.97 (0.74, 1.26) | 0.7975 |
| Histology | Non-squamous (RL) vs. Squamous | 146/228 | 111/179 | 1.01 (0.78, 1.31) | 0.9380 |
| Smoking History | Non-smoker/former light smoker (RL) vs. | 39/60 | | -- | -- |
| | Former heavy/current smoker vs. | 206/328 | | 1.14 (0.80, 1.63) | 0.4617 |
| | Unknown | 12/19 | | 1.44 (0.74, 2.80) | 0.2776 |

RL = reference level, HR = hazard ratio, CI = confidence interval
*Two-sided log-rank p-value
17 patients are missing dose-volume and/or smoking history information and are excluded from this model

**Appendix 7**
**Cetuximab Endpoint: Multivariate Cox Model of Overall Survival**
**(n=442)**

| Covariate | Comparison | Dead/Total RL | Dead/Total Group 2 | HR (95% CI) | p-value* |
|---|---|---|---|---|---|
| Radiation Level | Standard Dose (RL) vs. High Dose | 144/258 | 125/184 | 1.31 (1.02, 1.67) | 0.0325 |
| Cetuximab Assignment | Cetuximab (RL) vs. No Cetuximab | 134/224 | 135/218 | 1.05 (0.82, 1.34) | 0.7013 |
| Maximum related esophagitis/dysphagia grade | Maximum grade < 3 (RL) vs. Maximum grade ≥ 3 | 219/378 | 50/64 | 1.50 (1.09, 2.07) | 0.0128 |
| Volume of PTV | Continuous | 269/442 | | 1.000 (1.000, 1.001) | 0.1563 |
| Heart V5 | Continuous | 269/442 | | 1.006 (1.001, 1.010) | 0.0086 |
| Zubrod PS | 0 (RL) vs. 1 | 155/251 | 114/191 | 1.09 (0.86, 1.40) | 0.4699 |
| PET Staging | No (RL) vs. Yes | 29/40 | 240/402 | 0.76 (0.51, 1.12) | 0.1684 |
| Gender | Male (RL) vs. Female | 166/264 | 103/178 | 0.92 (0.71, 1.19) | 0.5067 |
| Histology | Non-squamous (RL) vs. Squamous | 148/247 | 121/195 | 1.07 (0.84, 1.38) | 0.5804 |
| Smoking History | Non-smoker/former light smoker (RL) vs. | 37/63 | | -- | -- |
| | Former heavy/current smoker vs. | 215/356 | | 1.20 (0.84, 1.72) | 0.3213 |
| | Unknown | 17/23 | | 2.28 (1.26, 4.12) | 0.0064 |

RL = reference level, HR = hazard ratio, CI = confidence interval
*Two-sided log-rank p-value
23 patients are missing dose-volume and/or smoking history information and are excluded from this model

**Appendix 8: Outcomes within Protocol Compliant Cohorts**

| | Physician RT Review: Per Protocol | | 90% of PTV Covered by ≥95% of RX Dose | |
|---|---|---|---|---|
| **Overall Survival** | **60 Gy (RL)** | **74 Gy** | **60 Gy (RL)** | **74 Gy** |
| Dead/Total | 103/180 | 102/153 | 117/201 | 121/181 |
| 1 Year (95% CI) | 81.0% (74.5, 86.1) | 73.6% (65.8, 79.9) | 80.9% (74.8, 85.8) | 72.2% (65.0, 78.1) |
| 2 Year (95% CI) | 58.4% (50.8, 65.2) | 45.5% (37.3, 53.2) | 58.6% (51.3, 65.1) | 44.9% (37.4, 52.0) |
| Median (months) (95% CI) | 28.8 (24.1, 40.4) | 20.4 (18.0, 25.9) | 28.7 (24.2, 39.5) | 20.6 (18.0, 25.9) |
| HR (95% CI) | 1.40 (1.06, 1.84) | | 1.40 (1.08, 1.81) | |
| p-value (log-rank, two-sided) | 0.0178 | | 0.0099 | |
| **Local Failure** | **60 Gy (RL)** | **74 Gy** | **60 Gy (RL)** | **74 Gy** |
| Fail/Total | 66/180 | 64/153 | 72/201 | 75/181 |
| 1 Year (95% CI) | 16.2% (11.2, 22.0) | 25.7% (19.1, 32.9) | 16.1% (11.3, 21.5) | 24.5% (18.5, 31.0) |
| 2 Year (95% CI) | 30.4% (23.7, 37.2) | 39.0% (31.2, 46.8) | 30.4% (24.1, 36.9) | 39.2% (32.0, 46.3) |
| HR (95% CI) | 1.25 (0.89, 1.76) | | 1.26 (0.92, 1.74) | |
| p-value (Gray, two-sided) | 0.1902 | | 0.1482 | |
| HR=hazard ratio, RL=referent level, CI=confidence interval | | | | |

**Appendix 9: Interaction of RT Dose and Cetuximab on Overall Survival**

| Covariate | Comparison | HR (95% CI) | p-value* |
|---|---|---|---|
| Radiation therapy (RT) dose | 60 Gy (RL) vs 74 Gy | 1.52 (1.10, 2.12) | 0.0122 |
| Cetuximab | No cetuximab (RL) vs. Cetuximab | 1.07 (0.76, 1.52) | 0.6971 |
| Interaction | RT dose/Cetuximab interaction | 0.81 (0.50, 1.32) | 0.3984 |
| HR=hazard ratio, RL=referent level, CI=confidence interval<br>*log-rank test, two-sided | | | |

**Appendix 10**
**Number of Patients with an Adverse Event by Category, Term, and Grade**
**Definitely, Probably, or Possibly Related to Protocol Treatment**
**All Eligible Patients - By Arm**

| Category | Arm A: 60 Gy (n=151) Grade | | | | | Arm B: 74 Gy (n=107) Grade | | | | | Arm C: 60 Gy + Cetuximab (n=137) Grade | | | | | Arm D: 74 Gy + Cetuximab (n=100) Grade | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Term | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| ALLERGY/IMMUNOLOGY | 0 | 3 | 4 | 0 | 0 | 3 | 4 | 3 | 1 | 0 | 7 | 6 | 3 | 2 | 0 | 5 | 3 | 5 | 1 | 0 |
| Allergic rhinitis | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Hypersensitivity | 0 | 3 | 4 | 0 | 0 | 2 | 3 | 3 | 1 | 0 | 6 | 6 | 3 | 2 | 0 | 5 | 3 | 5 | 1 | 0 |
| AUDITORY/EAR | 0 | 3 | 1 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ear disorder | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hearing loss | 0 | 2 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Tinnitus | 0 | 2 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| BLOOD/BONE MARROW | 12 | 23 | 50 | 28 | 0 | 14 | 23 | 23 | 24 | 0 | 5 | 20 | 36 | 37 | 0 | 4 | 11 | 35 | 27 | 0 |
| Blood disorder | 3 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| CD4 lymphocytes decreased | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Haptoglobin decreased | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Hemoglobin decreased | 46 | 31 | 10 | 2 | 0 | 23 | 32 | 6 | 2 | 0 | 30 | 28 | 13 | 0 | 0 | 22 | 23 | 6 | 1 | 0 |
| Hemolysis | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Leukopenia | 17 | 22 | 37 | 5 | 0 | 9 | 19 | 28 | 5 | 0 | 10 | 19 | 27 | 15 | 0 | 3 | 14 | 29 | 8 | 0 |
| Lymphopenia | 1 | 9 | 20 | 12 | 0 | 1 | 4 | 16 | 6 | 0 | 0 | 4 | 18 | 11 | 0 | 2 | 2 | 12 | 2 | 0 |
| Neutrophil count decreased | 7 | 18 | 20 | 16 | 0 | 8 | 14 | 14 | 14 | 0 | 6 | 13 | 26 | 30 | 0 | 2 | 11 | 24 | 22 | 0 |
| Platelet count decreased | 37 | 10 | 8 | 2 | 0 | 24 | 12 | 4 | 4 | 0 | 27 | 11 | 8 | 3 | 0 | 20 | 8 | 10 | 6 | 0 |
| CARDIAC ARRHYTHMIA | 3 | 2 | 0 | 0 | 0 | 1 | 7 | 4 | 1 | 0 | 3 | 3 | 4 | 0 | 0 | 1 | 6 | 2 | 1 | 0 |
| Arrhythmia | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Arrhythmia supraventricular | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Atrial fibrillation | 0 | 1 | 0 | 0 | 0 | 0 | 3 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| Atrial flutter | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Atrial tachycardia | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Palpitations | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Premature ventricular contractions | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Sinus arrhythmia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Appendix 10**
**Number of Patients with an Adverse Event by Category, Term, and Grade**
**Definitely, Probably, or Possibly Related to Protocol Treatment**
**All Eligible Patients - By Arm**

| Category | Arm A: 60 Gy (n=151) Grade | | | | | Arm B: 74 Gy (n=107) Grade | | | | | Arm C: 60 Gy + Cetuximab (n=137) Grade | | | | | Arm D: 74 Gy + Cetuximab (n=100) Grade | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Term | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Sinus tachycardia | 1 | 1 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 1 | 3 | 1 | 0 | 0 |
| Supraventricular tachycardia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 |
| Syncope vasovagal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ventricular tachycardia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| CARDIAC GENERAL | 5 | 5 | 6 | 3 | 0 | 2 | 2 | 3 | 0 | 0 | 4 | 11 | 6 | 0 | 0 | 3 | 8 | 3 | 0 | 0 |
| Cardiac disorder | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Cardiopulmonary arrest | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hypertension | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Hypotension | 5 | 2 | 3 | 1 | 0 | 0 | 2 | 1 | 0 | 0 | 5 | 8 | 5 | 0 | 0 | 2 | 6 | 3 | 0 | 0 |
| Myocardial ischemia | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pericardial effusion | 2 | 0 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| Pericarditis | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| COAGULATION | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Coagulopathy | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| INR increased | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Thrombotic microangiopathy | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| CONSTITUTIONAL SYMPTOMS | 54 | 55 | 15 | 2 | 0 | 32 | 41 | 13 | 2 | 0 | 27 | 57 | 25 | 1 | 0 | 22 | 41 | 27 | 0 | 0 |
| Chills | 7 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 9 | 2 | 0 | 0 | 0 | 5 | 2 | 0 | 0 | 0 |
| Fatigue | 49 | 47 | 13 | 1 | 0 | 30 | 38 | 8 | 1 | 0 | 26 | 50 | 18 | 1 | 0 | 26 | 35 | 21 | 0 | 0 |
| Fever | 6 | 3 | 2 | 1 | 0 | 12 | 1 | 1 | 1 | 0 | 20 | 3 | 4 | 0 | 0 | 17 | 4 | 2 | 0 | 0 |
| General symptom | 3 | 3 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 4 | 0 | 0 | 1 | 0 | 3 | 0 | 0 | 0 | 0 |
| Insomnia | 10 | 5 | 0 | 0 | 0 | 4 | 4 | 0 | 0 | 0 | 5 | 0 | 3 | 0 | 0 | 8 | 4 | 0 | 0 | 0 |
| Sweating | 3 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Weight loss | 34 | 16 | 0 | 0 | 0 | 22 | 18 | 5 | 0 | 0 | 35 | 22 | 3 | 0 | 0 | 22 | 23 | 8 | 0 | 0 |
| DEATH | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Disease progression | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Appendix 10**
**Number of Patients with an Adverse Event by Category, Term, and Grade**
**Definitely, Probably, or Possibly Related to Protocol Treatment**
**All Eligible Patients - By Arm**

| Category | Arm A: 60 Gy (n=151) Grade | | | | | Arm B: 74 Gy (n=107) Grade | | | | | Arm C: 60 Gy + Cetuximab (n=137) Grade | | | | | Arm D: 74 Gy + Cetuximab (n=100) Grade | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Term | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Sudden death | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| DERMATOLOGY/SKIN | 54 | 37 | 2 | 0 | 0 | 32 | 27 | 4 | 0 | 0 | 35 | 68 | 22 | 0 | 0 | 21 | 52 | 17 | 0 | 0 |
| Acne | 7 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 47 | 49 | 12 | 0 | 0 | 20 | 39 | 9 | 0 | 0 |
| Alopecia | 26 | 19 | 0 | 0 | 0 | 16 | 16 | 0 | 0 | 0 | 19 | 9 | 0 | 0 | 0 | 21 | 10 | 0 | 0 | 0 |
| Bruising | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| Decubitus ulcer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dermatitis radiation | 32 | 9 | 1 | 0 | 0 | 21 | 13 | 2 | 0 | 0 | 25 | 16 | 2 | 0 | 0 | 26 | 10 | 3 | 0 | 0 |
| Dry skin | 13 | 4 | 0 | 0 | 0 | 8 | 2 | 0 | 0 | 0 | 34 | 16 | 2 | 0 | 0 | 27 | 11 | 0 | 0 | 0 |
| Erythema multiforme | 0 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 |
| Fat atrophy | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Flushing | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hand-and-foot syndrome | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 2 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Injection site reaction | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nail disorder | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 11 | 3 | 0 | 0 | 0 | 6 | 2 | 0 | 0 | 0 |
| Photosensitivity | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pruritus | 18 | 2 | 0 | 0 | 0 | 11 | 0 | 0 | 0 | 0 | 35 | 11 | 2 | 0 | 0 | 17 | 6 | 0 | 0 | 0 |
| Radiation recall reaction (dermatologic) | 12 | 4 | 0 | 0 | 0 | 9 | 6 | 4 | 0 | 0 | 14 | 18 | 1 | 0 | 0 | 8 | 7 | 4 | 0 | 0 |
| Rash desquamating | 6 | 3 | 1 | 0 | 0 | 8 | 3 | 0 | 0 | 0 | 20 | 16 | 5 | 0 | 0 | 15 | 13 | 4 | 0 | 0 |
| Skin disorder | 2 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 6 | 1 | 0 | 0 | 0 | 2 | 2 | 0 | 0 | 0 |
| Skin hyperpigmentation | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 6 | 1 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| Skin hypopigmentation | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Skin ulceration | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Telangiectasia | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Thermal burn | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| Urticaria | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| ENDOCRINE | 1 | 0 | 0 | 0 | 0 | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Glucose intolerance | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hot flashes | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

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**Definitely, Probably, or Possibly Related to Protocol Treatment**
**All Eligible Patients - By Arm**

| Category | Arm A: 60 Gy (n=151) Grade | | | | | Arm B: 74 Gy (n=107) Grade | | | | | Arm C: 60 Gy + Cetuximab (n=137) Grade | | | | | Arm D: 74 Gy + Cetuximab (n=100) Grade | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Term | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Hypothyroidism | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| GASTROINTESTINAL | 44 | 54 | 29 | 1 | 0 | 19 | 42 | 27 | 0 | 1 | 24 | 63 | 28 | 3 | 0 | 19 | 35 | 37 | 4 | 1 |
| Abdominal distension | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| Acquired tracheo-esophageal fistula | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Anorexia | 16 | 16 | 7 | 0 | 0 | 13 | 12 | 6 | 0 | 0 | 23 | 19 | 7 | 1 | 0 | 17 | 20 | 10 | 0 | 1 |
| Appendicitis perforated | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Colitis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Colonic fistula | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Constipation | 29 | 7 | 0 | 0 | 0 | 14 | 5 | 1 | 0 | 0 | 30 | 8 | 2 | 0 | 0 | 19 | 11 | 2 | 0 | 0 |
| Dehydration | 6 | 5 | 12 | 0 | 0 | 0 | 5 | 7 | 0 | 0 | 2 | 19 | 16 | 2 | 0 | 0 | 9 | 15 | 1 | 0 |
| Diarrhea | 19 | 2 | 4 | 0 | 0 | 11 | 1 | 1 | 0 | 0 | 26 | 6 | 3 | 0 | 0 | 12 | 8 | 8 | 0 | 0 |
| Dry mouth | 5 | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 |
| Duodenal ulcer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Dyspepsia | 13 | 6 | 0 | 0 | 0 | 8 | 4 | 1 | 0 | 0 | 19 | 9 | 1 | 0 | 0 | 13 | 7 | 1 | 0 | 0 |
| Dysphagia | 31 | 35 | 4 | 0 | 0 | 14 | 25 | 11 | 0 | 0 | 35 | 29 | 5 | 0 | 0 | 24 | 20 | 13 | 1 | 0 |
| Ear, nose and throat examination abnormal | 4 | 1 | 0 | 0 | 0 | 4 | 1 | 0 | 0 | 0 | 3 | 3 | 0 | 0 | 0 | 1 | 3 | 0 | 0 | 0 |
| Endoscopy small intestine abnormal | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Esophageal mucositis | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| Esophageal perforation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Esophageal stenosis | 0 | 2 | 1 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 6 | 1 | 0 |
| Esophageal ulcer | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 3 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 |
| Esophagitis | 23 | 36 | 11 | 0 | 0 | 12 | 31 | 16 | 0 | 0 | 10 | 41 | 8 | 1 | 0 | 10 | 25 | 19 | 0 | 1 |
| Esophagoscopy abnormal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Flatulence | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Gastic fistula | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Gastric mucositis | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Gastric ulcer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |

**Appendix 10**
**Number of Patients with an Adverse Event by Category, Term, and Grade**
**Definitely, Probably, or Possibly Related to Protocol Treatment**
**All Eligible Patients - By Arm**

| Category | Arm A: 60 Gy (n=151) Grade | | | | | Arm B: 74 Gy (n=107) Grade | | | | | Arm C: 60 Gy + Cetuximab (n=137) Grade | | | | | Arm D: 74 Gy + Cetuximab (n=100) Grade | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Term | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Gastritis | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Gastro-intestinal fistula | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Gastrointestinal disorder | 2 | 1 | 1 | 0 | 0 | 2 | 1 | 1 | 0 | 0 | 3 | 3 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 |
| Laryngoscopy abnormal | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Mucositis oral | 11 | 2 | 0 | 0 | 0 | 7 | 1 | 1 | 0 | 0 | 16 | 10 | 1 | 0 | 0 | 11 | 6 | 0 | 0 | 0 |
| Nausea | 48 | 12 | 8 | 0 | 0 | 34 | 8 | 3 | 0 | 0 | 33 | 21 | 6 | 0 | 0 | 26 | 13 | 9 | 0 | 0 |
| Periodontal disease | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Pharyngeal examination abnormal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| Pharyngeal mucositis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Salivary gland disorder | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Taste alteration | 8 | 2 | 0 | 0 | 0 | 8 | 2 | 0 | 0 | 0 | 15 | 2 | 0 | 0 | 0 | 8 | 5 | 0 | 0 | 0 |
| Tooth disorder | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Vomiting | 17 | 7 | 4 | 0 | 0 | 8 | 8 | 0 | 0 | 0 | 15 | 15 | 3 | 0 | 0 | 7 | 10 | 7 | 0 | 0 |
| HEMORRHAGE/BLEEDING | 15 | 1 | 1 | 0 | 0 | 8 | 0 | 2 | 1 | 0 | 15 | 0 | 1 | 1 | 1 | 14 | 0 | 0 | 0 | 1 |
| Bronchial hemorrhage | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| Bronchopulmonary hemorrhage | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Gastric hemorrhage | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hemorrhage | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Hemorrhage nasal | 8 | 1 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 11 | 0 | 0 | 1 | 0 | 7 | 0 | 0 | 0 | 0 |
| Lower gastrointestinal hemorrhage | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Petechiae | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pharyngeal hemorrhage | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pulmonary hemorrhage | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 6 | 0 | 0 | 0 | 1 |
| Respiratory tract hemorrhage | 4 | 0 | 0 | 0 | 0 | 3 | 0 | 1 | 0 | 0 | 4 | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 0 | 0 |
| HEPATOBILIARY/PANCREAS | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Hepatic failure | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |

**Appendix 10**
**Number of Patients with an Adverse Event by Category, Term, and Grade**
**Definitely, Probably, or Possibly Related to Protocol Treatment**
**All Eligible Patients - By Arm**

| Category | Arm A: 60 Gy (n=151) Grade | | | | | Arm B: 74 Gy (n=107) Grade | | | | | Arm C: 60 Gy + Cetuximab (n=137) Grade | | | | | Arm D: 74 Gy + Cetuximab (n=100) Grade | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Term | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| INFECTION | 1 | 13 | 15 | 1 | 0 | 1 | 9 | 10 | 1 | 0 | 1 | 8 | 16 | 3 | 1 | 0 | 7 | 9 | 2 | 1 |
| Bronchitis [with normal or Grade 1-2 ANC] | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Bronchitis [with unknown ANC] | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Catheter related infection [with Grade 3-4 ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Catheter related infection [with normal or Grade 1-2 ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Device related infection [with unknown ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Endocarditis infective [with normal or Grade 1-2 ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Endocarditis infective [with unknown ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Esophageal infection [with normal or Grade 1-2 ANC] | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Febrile neutropenia | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 4 | 1 | 0 | 0 | 0 | 5 | 3 | 1 | 0 | 0 | 2 | 1 | 0 |
| Gingival infection [with Grade 3-4 ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Gingival infection [with normal or Grade 1-2 ANC] | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Infection [other] | 1 | 1 | 0 | 0 | 0 | 1 | 6 | 2 | 0 | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Infectious colitis [with unknown ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Laryngitis [with normal or Grade 1-2 ANC] | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Mucosal infection [with normal or Grade 1-2 ANC] | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Mucosal infection [with unknown ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |

**Appendix 10**
**Number of Patients with an Adverse Event by Category, Term, and Grade**
**Definitely, Probably, or Possibly Related to Protocol Treatment**
**All Eligible Patients - By Arm**

| Category | Arm A: 60 Gy (n=151) Grade | | | | | Arm B: 74 Gy (n=107) Grade | | | | | Arm C: 60 Gy + Cetuximab (n=137) Grade | | | | | Arm D: 74 Gy + Cetuximab (n=100) Grade | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Term | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Nail infection [with normal or Grade 1-2 ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Opportunistic infection | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Penile infection [with Grade 3-4 ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Peritoneal infection [with Grade 3-4 ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pharyngitis [with normal or Grade 1-2 ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Phlebitis infective [with normal or Grade 1-2 ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pleural infection [with normal or Grade 1-2 ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pneumonia [with Grade 3-4 ANC] | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pneumonia [with normal or Grade 1-2 ANC] | 0 | 4 | 8 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 0 | 2 | 3 | 0 | 0 | 0 | 2 | 0 | 1 | 0 |
| Pneumonia [with unknown ANC] | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 1 | 5 | 0 | 0 | 0 | 1 | 2 | 0 | 1 |
| Sepsis [with Grade 3-4 ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Sepsis [with normal or Grade 1-2 ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Sepsis [with unknown ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Sinusitis [with Grade 3-4 ANC] | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Sinusitis [with normal or Grade 1-2 ANC] | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Skin infection [with normal or Grade 1-2 ANC] | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 |
| Soft tissue infection [with normal or Grade 1-2 ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Appendix 10**
**Number of Patients with an Adverse Event by Category, Term, and Grade**
**Definitely, Probably, or Possibly Related to Protocol Treatment**
**All Eligible Patients - By Arm**

| Category | Arm A: 60 Gy (n=151) Grade | | | | | Arm B: 74 Gy (n=107) Grade | | | | | Arm C: 60 Gy + Cetuximab (n=137) Grade | | | | | Arm D: 74 Gy + Cetuximab (n=100) Grade | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Term | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Upper aerodigestive tract infection [with normal or Grade 1-2 ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Upper respiratory infection [with Grade 3-4 ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Upper respiratory infection [with unknown ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| Urinary tract infection [with Grade 3-4 ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Urinary tract infection [with normal or Grade 1-2 ANC] | 0 | 2 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Urinary tract infection [with unknown ANC] | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Wound infection [with Grade 3-4 ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Wound infection [with normal or Grade 1-2 ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Wound infection [with unknown ANC] | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| LYMPHATICS | 7 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 |
| Edema limbs | 6 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 |
| Localized edema [head and neck] | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lymphatic disorder | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| METABOLIC/LABORATORY | 37 | 16 | 14 | 3 | 0 | 22 | 7 | 15 | 4 | 0 | 34 | 23 | 28 | 4 | 0 | 28 | 18 | 19 | 1 | 0 |
| Alanine aminotransferase increased | 13 | 0 | 1 | 0 | 0 | 7 | 2 | 1 | 1 | 0 | 10 | 0 | 1 | 0 | 0 | 12 | 3 | 0 | 0 | 0 |
| Alkaline phosphatase increased | 5 | 1 | 0 | 0 | 0 | 7 | 2 | 0 | 0 | 0 | 10 | 0 | 1 | 0 | 0 | 10 | 0 | 0 | 0 | 0 |
| Amylase increased | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Appendix 10**
**Number of Patients with an Adverse Event by Category, Term, and Grade**
**Definitely, Probably, or Possibly Related to Protocol Treatment**
**All Eligible Patients - By Arm**

| Category | Arm A: 60 Gy (n=151) Grade | | | | | Arm B: 74 Gy (n=107) Grade | | | | | Arm C: 60 Gy + Cetuximab (n=137) Grade | | | | | Arm D: 74 Gy + Cetuximab (n=100) Grade | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Term | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Aspartate aminotransferase increased | 6 | 3 | 0 | 0 | 0 | 6 | 2 | 0 | 0 | 0 | 11 | 0 | 0 | 0 | 0 | 12 | 3 | 0 | 0 | 0 |
| Blood bicarbonate decreased | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Creatinine increased | 6 | 1 | 0 | 0 | 0 | 6 | 1 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 0 |
| Gamma-glutamyltransferase increased | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hemoglobinuria | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Hyperbilirubinemia | 2 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 |
| Hypercalcemia | 2 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Hyperglycemia | 11 | 10 | 7 | 0 | 0 | 6 | 5 | 3 | 1 | 0 | 11 | 7 | 5 | 0 | 0 | 7 | 7 | 1 | 0 | 0 |
| Hyperkalemia | 7 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 |
| Hypermagnesemia | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hypernatremia | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 4 | 0 | 3 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| Hypertriglyceridemia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hyperuricemia | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hypoalbuminemia | 11 | 11 | 0 | 0 | 0 | 6 | 9 | 1 | 0 | 0 | 15 | 14 | 0 | 0 | 0 | 12 | 12 | 3 | 0 | 0 |
| Hypocalcemia | 16 | 6 | 0 | 0 | 0 | 8 | 6 | 0 | 1 | 0 | 21 | 7 | 0 | 1 | 0 | 10 | 4 | 0 | 0 | 0 |
| Hypoglycemia | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Hypokalemia | 12 | 0 | 4 | 1 | 0 | 8 | 0 | 6 | 0 | 0 | 28 | 0 | 8 | 1 | 0 | 14 | 0 | 9 | 1 | 0 |
| Hypomagnesemia | 15 | 1 | 0 | 0 | 0 | 11 | 1 | 0 | 1 | 0 | 39 | 20 | 7 | 2 | 0 | 33 | 12 | 5 | 0 | 0 |
| Hyponatremia | 20 | 0 | 5 | 1 | 0 | 14 | 0 | 8 | 0 | 0 | 22 | 0 | 8 | 0 | 0 | 19 | 1 | 5 | 0 | 0 |
| Hypophosphatemia | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 2 | 0 | 0 | 0 | 3 | 0 | 0 | 0 |
| Laboratory test abnormal | 4 | 0 | 1 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 6 | 3 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 |
| Proteinuria | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| MUSCULOSKELETAL/SOFT TISSUE | 9 | 6 | 2 | 0 | 0 | 4 | 3 | 2 | 0 | 0 | 5 | 4 | 3 | 0 | 0 | 4 | 7 | 3 | 0 | 0 |
| Arthritis | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Fibrosis deep connective tissue | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Fracture | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| Joint disorder | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |

**Appendix 10**
**Number of Patients with an Adverse Event by Category, Term, and Grade**
**Definitely, Probably, or Possibly Related to Protocol Treatment**
**All Eligible Patients - By Arm**

| Category | Arm A: 60 Gy (n=151) Grade | | | | | Arm B: 74 Gy (n=107) Grade | | | | | Arm C: 60 Gy + Cetuximab (n=137) Grade | | | | | Arm D: 74 Gy + Cetuximab (n=100) Grade | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Term | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Muscle weakness | 4 | 3 | 2 | 0 | 0 | 1 | 3 | 2 | 0 | 0 | 2 | 0 | 3 | 0 | 0 | 2 | 5 | 3 | 0 | 0 |
| Muscle weakness lower limb | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| Muscle weakness right-sided | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Muscle weakness trunk | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Muscle weakness upper limb | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Musculoskeletal disorder | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Osteoporosis | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Superficial soft tissue fibrosis | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| NEUROLOGY | 41 | 25 | 5 | 0 | 0 | 30 | 12 | 4 | 0 | 0 | 22 | 22 | 11 | 1 | 0 | 24 | 16 | 5 | 1 | 0 |
| Agitation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Anxiety | 2 | 3 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 |
| Ataxia | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cognitive disturbance | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Confusion | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Depressed level of consciousness | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Depression | 4 | 1 | 0 | 0 | 0 | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| Dizziness | 11 | 4 | 2 | 0 | 0 | 6 | 3 | 0 | 0 | 0 | 13 | 3 | 0 | 0 | 0 | 4 | 2 | 0 | 1 | 0 |
| Leukoencephalopathy | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Memory impairment | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Neurological disorder NOS | 3 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| Peripheral motor neuropathy | 4 | 5 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 2 | 2 | 2 | 0 | 0 | 3 | 1 | 0 | 0 | 0 |
| Peripheral sensory neuropathy | 37 | 15 | 2 | 0 | 0 | 27 | 9 | 3 | 0 | 0 | 23 | 19 | 5 | 0 | 0 | 23 | 11 | 5 | 0 | 0 |
| Speech disorder | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Syncope | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Tremor | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| OCULAR/VISUAL | 4 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 0 | 6 | 2 | 0 | 0 | 0 |
| Conjunctival disorder | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Diplopia | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dry eye syndrome | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Appendix 10**
**Number of Patients with an Adverse Event by Category, Term, and Grade**
**Definitely, Probably, or Possibly Related to Protocol Treatment**
**All Eligible Patients - By Arm**

| Category | Arm A: 60 Gy (n=151) Grade | | | | | Arm B: 74 Gy (n=107) Grade | | | | | Arm C: 60 Gy + Cetuximab (n=137) Grade | | | | | Arm D: 74 Gy + Cetuximab (n=100) Grade | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Term | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Eye disorder | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| Flashing vision | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Vision blurred | 2 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 |
| Watering eyes | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| PAIN | 26 | 33 | 10 | 0 | 0 | 22 | 23 | 8 | 0 | 0 | 27 | 30 | 10 | 0 | 0 | 22 | 22 | 5 | 0 | 0 |
| Abdominal pain | 1 | 1 | 1 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 1 | 2 | 3 | 0 | 0 | 1 | 2 | 1 | 0 | 0 |
| Back pain | 1 | 4 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 0 |
| Bone pain | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| Breast pain | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Buttock pain | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cardiac pain | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Chest pain | 4 | 9 | 4 | 0 | 0 | 4 | 4 | 3 | 0 | 0 | 4 | 4 | 2 | 0 | 0 | 5 | 3 | 0 | 0 | 0 |
| Chest wall pain | 4 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 2 | 1 | 0 | 0 | 1 | 4 | 0 | 0 | 0 |
| Esophageal pain | 3 | 4 | 2 | 0 | 0 | 4 | 10 | 4 | 0 | 0 | 4 | 6 | 1 | 0 | 0 | 5 | 4 | 2 | 0 | 0 |
| Gastrointestinal pain | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Headache | 10 | 2 | 1 | 0 | 0 | 5 | 2 | 1 | 0 | 0 | 12 | 6 | 1 | 0 | 0 | 9 | 6 | 1 | 0 | 0 |
| Joint pain | 12 | 5 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 5 | 3 | 0 | 0 | 0 | 4 | 3 | 0 | 0 | 0 |
| Laryngeal pain | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lip pain | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Myalgia | 8 | 5 | 2 | 0 | 0 | 7 | 4 | 1 | 0 | 0 | 4 | 4 | 1 | 0 | 0 | 5 | 1 | 0 | 0 | 0 |
| Neck pain | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Neuralgia | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Oral pain | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pain [NOS] | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 2 | 2 | 0 | 0 | 0 |
| Pain [other] | 4 | 2 | 1 | 0 | 0 | 3 | 4 | 1 | 0 | 0 | 5 | 1 | 2 | 0 | 0 | 6 | 1 | 1 | 0 | 0 |
| Pain in extremity | 5 | 5 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| Pain of skin | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| Pericardial pain | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Pharyngolaryngeal pain | 5 | 5 | 1 | 0 | 0 | 3 | 3 | 0 | 0 | 0 | 3 | 2 | 3 | 0 | 0 | 4 | 1 | 1 | 0 | 0 |
| Sinus pain | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Appendix 10**
**Number of Patients with an Adverse Event by Category, Term, and Grade**
**Definitely, Probably, or Possibly Related to Protocol Treatment**
**All Eligible Patients - By Arm**

| Category | Arm A: 60 Gy (n=151) Grade | | | | | Arm B: 74 Gy (n=107) Grade | | | | | Arm C: 60 Gy + Cetuximab (n=137) Grade | | | | | Arm D: 74 Gy + Cetuximab (n=100) Grade | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Term | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| PULMONARY/UPPER RESPIRATORY | 33 | 32 | 24 | 4 | 1 | 33 | 21 | 16 | 1 | 2 | 33 | 23 | 25 | 3 | 2 | 17 | 23 | 16 | 4 | 0 |
| Adult respiratory distress syndrome | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Atelectasis | 2 | 3 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 1 | 2 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 |
| Bronchial fistula | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Bronchial obstruction | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Bronchospasm | 0 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 1 | 0 | 0 | 2 | 1 | 0 | 0 | 0 |
| Carbon monoxide diffusing capacity decreased | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Cough | 35 | 19 | 6 | 0 | 0 | 30 | 8 | 5 | 0 | 0 | 36 | 10 | 2 | 0 | 0 | 19 | 13 | 6 | 0 | 0 |
| Dyspnea | 29 | 15 | 17 | 3 | 0 | 25 | 11 | 8 | 0 | 0 | 22 | 17 | 9 | 2 | 1 | 17 | 14 | 10 | 0 | 0 |
| Forced expiratory volume decreased | 0 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Hiccough | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 0 |
| Hypoxia | 0 | 3 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 1 | 0 | 0 | 1 | 2 | 0 | 0 |
| Laryngeal edema | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pleural effusion | 6 | 0 | 2 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 1 | 0 | 2 | 0 | 0 | 3 | 1 | 1 | 0 | 0 |
| Pneumonitis | 7 | 16 | 6 | 1 | 1 | 4 | 10 | 2 | 1 | 0 | 2 | 8 | 10 | 0 | 1 | 1 | 11 | 5 | 1 | 0 |
| Pneumothorax | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pulmonary fibrosis | 11 | 3 | 0 | 0 | 0 | 4 | 3 | 0 | 0 | 0 | 7 | 2 | 1 | 0 | 0 | 3 | 2 | 0 | 0 | 0 |
| Respiratory disorder | 1 | 0 | 3 | 0 | 0 | 2 | 1 | 1 | 0 | 2 | 0 | 2 | 3 | 1 | 1 | 1 | 0 | 0 | 3 | 0 |
| Tracheal fistula | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Voice alteration | 7 | 4 | 1 | 0 | 0 | 6 | 1 | 0 | 0 | 0 | 9 | 1 | 0 | 0 | 0 | 8 | 2 | 0 | 0 | 0 |
| RENAL/GENITOURINARY | 1 | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 5 | 1 | 0 | 0 | 0 | 2 | 2 | 2 | 0 | 0 |
| Cystitis | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Renal failure | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Urinary frequency | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| Urinary retention | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |

**Appendix 10**
**Number of Patients with an Adverse Event by Category, Term, and Grade**
**Definitely, Probably, or Possibly Related to Protocol Treatment**
**All Eligible Patients - By Arm**

| Category | Arm A: 60 Gy (n=151) Grade | | | | | Arm B: 74 Gy (n=107) Grade | | | | | Arm C: 60 Gy + Cetuximab (n=137) Grade | | | | | Arm D: 74 Gy + Cetuximab (n=100) Grade | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Term | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Urogenital disorder | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| SEXUAL/REPRODUCTIVE FUNCTION | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Erectile dysfunction | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Irregular menstruation | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Libido decreased | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| SYNDROMES | 1 | 1 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 0 | 1 | 3 | 1 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| Cytokine release syndrome | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Flu-like symptoms | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ill-defined disorder | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| VASCULAR | 0 | 1 | 0 | 2 | 0 | 0 | 1 | 0 | 2 | 0 | 0 | 1 | 2 | 1 | 1 | 0 | 2 | 1 | 4 | 1 |
| Phlebitis superficial | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Thrombosis | 0 | 0 | 0 | 2 | 0 | 0 | 1 | 0 | 2 | 0 | 0 | 1 | 2 | 1 | 1 | 0 | 1 | 0 | 4 | 1 |
| Vascular access complication | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Vascular disorder | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| PENDING CLARIFICATION OF TERM | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 |

Includes adverse events where relationship to protocol treatment is missing.
Adverse events were graded with CTCAE version 3.0.

**Appendix 11:**
**Grade 5 Adverse Events**

| Assigned Treatment | Category | Term | Relationship to Treatment | Days from Start of Treatment | Days from End of Treatment |
|---|---|---|---|---|---|
| Arm A: 60 Gy | [2]Pulmonary/upper respiratory | Dyspnea | Unlikely | 130 | 46 |
| | [1]Death | Death | Unlikely | 172 | 89 |
| | [3]Pulmonary/upper respiratory | Pneumonitis | Possibly | 176 | 91 |
| | [3]Hemorrhage/bleeding | Pulmonary hemorrhage | Unrelated | 114 | 28 |
| Arm B: 74 Gy | [2]Vascular | Thrombosis | Unlikely | 103 | 33 |
| | [2]Infection | Pneumonia [with unknown ANC] | Unrelated | 627 | 508 |
| | [1]Pulmonary/upper respiratory | Respiratory disorder | Probably | 775 | 677 |
| | [1]Death | Disease progression | Unlikely | 62 | 7 |
| | [1]Vascular | Thrombosis | Unrelated | 88 | 33 |
| | [1]Gastrointestinal | Acquired tracheo-esophageal fistula | Definitely | 710 | 612 |
| | [1]Infection | Pneumonia [with normal or Grade 1-2 ANC] | Unlikely | 83 | 40 |
| | [1]Death | Sudden death | Unlikely | 105 | 7 |
| | [1]Pulmonary/upper respiratory | Respiratory disorder | Possibly | 115 | 10 |
| | [1]Death | Disease progression | Possibly | 216 | 158 |
| Arm C: 60 Gy + Cetuximab | [1]Death | Sudden death | Possibly | 109 | 11 |
| | [1]Hemorrhage/bleeding | Pulmonary hemorrhage | Unlikely | 30 | 1 |
| | [1]Pulmonary/upper respiratory | Pneumonitis | Probably | 159 | 54 |
| | [1]Vascular | Thrombosis | Probably | 120 | 15 |
| | [1]Cardiac general | Myocardial ischemia | Unlikely | 98 | 0 |
| | [1]Death | Sudden death | Unrelated | 54 | 4 |
| | [1]Death | Death | Unrelated | 65 | 12 |
| | [3]Hemorrhage/bleeding | Respiratory tract hemorrhage | Probably | 67 | 4 |
| | [3]Infection | Febrile neutropenia | Definitely | 85 | 7 |
| | [3]Pulmonary/upper respiratory | Respiratory disorder | Probably | 65 | 15 |
| Arm D: 74 Gy + Cetuximab | [1]Vascular | Thrombosis | Probably | 95 | 43 |
| | [1]Cardiac arrhythmia | Supraventricular tachycardia | Unlikely | 204 | 85 |
| | [1]Hemorrhage/bleeding | Esophageal hemorrhage | Unrelated | 680 | 568 |
| | [1]Infection | Sepsis [with normal or Grade 1-2 ANC] | Unlikely | 438 | 326 |
| | [1]Infection | Pneumonia [with unknown ANC] | Probably | 131 | 19 |
| | [1]Cardiac general | Cardiac disorder | Unrelated | 415 | 303 |
| | [1]Vascular | Thrombosis | Unlikely | 14 | 1 |
| | [1]Hemorrhage/bleeding | Pulmonary hemorrhage | Possibly | 56 | 1 |
| | [1]Gastrointestinal | Esophagitis | Probably | 193 | 116 |
| | [1]Death* | Death | Unrelated | . | . |

[1]Included in both RT and cetuximab endpoint analyses
[2]Included in only RT endpoint analysis
[3]Included in only cetuximab endpoint analysis
*Patient received no protocol treatment

**Appendix 12**
**Participating Institutions**

| Institution | Principal Investigator | Accrual to RTOG 0617 |
|---|---|---|
| University of Texas Southwestern Medical School | Nedzi, Lucien Alexander | 18 |
| The Regional Cancer Center | Figura, Andrew T. | 16 |
| Christiana Care Health Services, Inc. CCOP | Raben, Adam | 15 |
| St. Joseph Mercy Hospital | Narayan, Samir | 14 |
| The Ottawa Hospital Regional Cancer Centre | Morgan, Scott Carlyle | 12 |
| Washington University | Michalski, Jeff M. | 12 |
| Kansas City CCOP | Gaur, Rakesh | 11 |
| Northeast Radiation Oncology Center | Peters, Christopher Albert | 9 |
| Princess Margaret Hospital | Sun, Alexander Y. | 9 |
| Emory University | Beitler, Jonathan J. | 8 |
| SUNY Upstate Medical University | Bogart, Jeffrey Alan | 8 |
| Cleveland Clinic Foundation | Suh, John H. | 7 |
| Penrose Cancer Center, Penrose-St. Francis Health Services | Peddada, Anuj V. | 7 |
| UCSD – University of California, San Diego | Mell, Loren K. | 7 |
| Cancer Care Manitoba Foundation | Leylek, Ahmet | 6 |
| Geisinger Medical Center CCOP | Gergel, Thomas James | 6 |
| Greenville Health System Cancer Institute-Eastside | Giguere, Jeffrey | 6 |
| Northern Indiana Cancer Research Consortium CCOP | Tran, Binh Nguyen | 6 |
| Radiological Associates of Sacramento | Jones, Christopher U. | 6 |
| Stanford University Medical Center | Le, Quynh-Thu Xuan | 6 |
| University of California San Francisco | Roach, Mack | 6 |
| University of Texas-MD Anderson Cancer Center | Komaki, Ritsuko R. | 6 |
| ICON – Cancer Center of Putnam | Johnson, Douglas W. | 5 |
| Mayo Clinic in Arizona | Wong, William Wailing | 5 |
| McGill University | Souhami, Luis | 5 |
| Memorial Sloan Kettering of Rockville Center | Gewanter, Richard M | 5 |
| Mount Sinai Comprehensive Cancer Center CCOP | Berk, Lawrence B. | 5 |
| St. Lukes Hospital | Deb, Nimisha | 5 |
| St. Mary Mercy Hospital | Narayan, Samir | 5 |
| The Rector and Visitors of the University of Virginia | Showalter, Timothy Norman | 5 |
| Thomas Jefferson University Hospital | Werner-Wasik, Maria | 5 |
| University of California Davis Medical Center | Valicenti, Richard K. | 5 |
| Wake Forest University Baptist Medical Center | Urbanic, James John | 5 |
| Abington Memorial Hospital | Pinover, Wayne H. | 4 |
| Albert Einstein Medical Center | Zeitzer, Kenneth Lee | 4 |
| Altru Cancer Center | Seeger, Grant | 4 |
| Billings Clinic Cancer Center | Schallenkamp, John M. | 4 |
| Flower Hospital | Mowat, Rex | 4 |
| Lankenau Hospital | DeNittis, Albert S. | 4 |
| Mayo Clinic Scottsdale | Schild, Steven | 4 |
| Northern Rockies Radiation Oncology Center | Schallenkamp, John | 4 |
| Ochsner Clinic CCOP | Scroggins, Troy Gene | 4 |
| Presbyterian Hospital | Roof, Kevin | 4 |
| Reading Hospital | Yuen, Albert | 4 |
| St. Vincent Regional Cancer Center CCOP | Leenstra, James L. | 4 |
| Tom Baker Cancer Centre | Balogh, Alexander G. | 4 |
| USON-Raleigh Hematology Oncology Associates | Reilly, John Francis | 4 |

**Appendix 12**
**Participating Institutions**

| Institution | Principal Investigator | Accrual to RTOG 0617 |
|---|---|---|
| University Hospitals of Cleveland | Lyons, Janice A. | 4 |
| University of Alabama at Birmingham Medical Center | De Los Santos, Jennifer F. | 4 |
| University of North Carolina | Stinchcombe, Thomas | 4 |
| University of North Carolina - Chapel Hill | Chera, Bhishamjit S. | 4 |
| University of Rochester | Chen, Yuhchyau | 4 |
| University of Utah Health Science Center | Gaffney, David K. | 4 |
| Alamance County Hospital | Choksi, Janak K. | 3 |
| Barnes Jewish West County Hospital | Zoberi, Imran | 3 |
| Baystate Health-D'Amour | Kaufman, Seth A. | 3 |
| Central Baptist Hospital | Beckman, Alan | 3 |
| ICON – Orange Park Cancer Center | Johnson, Douglas W. | 3 |
| Lehigh Valley Hospital | Friedman, Eliott | 3 |
| MD Anderson Cancer Center Orlando | Rineer, Justin | 3 |
| Mayo Clinic | Haddock, Michael G. | 3 |
| Medical College of Wisconsin | Gore, Elizabeth M. | 3 |
| Memorial Sloan-Kettering Cancer Center at Commack | Gelblum, Daphna Yael | 3 |
| Methodist Cancer Center | Huang, Tien-Shew William | 3 |
| OSF Saint Francis Medical Center Radiation Oncology | Le-Lindqwister, Nguyet Anh | 3 |
| Sanford Cancer Center | Jeffreys, Sana | 3 |
| Saskatoon Cancer Centre | El-Gayed, Ali Abdel | 3 |
| Spartanburg Regional Medical Center | Bearden, James Dewitt | 3 |
| St. Joseph Hospital | Ash, Robert B. | 3 |
| The Regional Cancer Center at Singing River Hospital System | Dennis, Wiley Sam | 3 |
| Thompson Cancer Survival Center | Scaperoth, Daniel D. | 3 |
| USON- New York Oncology Hematology, P.C. | Doyle, Todd H. | 3 |
| USON- Texas Oncology-Tyler | Saunders, Mark W. | 3 |
| USON-Arizona Radiation Oncology | Mack, Curtis F. | 3 |
| USON-Cancer Care Northwest - Spokane | Lee, Christopher M. | 3 |
| Zablocki VA Medical Center-Wood | Gore, Elizabeth | 3 |
| Akron City Hospital | Kunos, Charles A. | 2 |
| Aria Health | Rudoler, Shari B. | 2 |
| Baptist Cancer Institute | Augspurger, Mark Emerson | 2 |
| Carolinas Medical Center/Levine Cancer Institute | Burri, Stuart H. | 2 |
| Centre Hospitalier de l`Université de Montréal-Notre Dame | Bahary, Jean-Paul | 2 |
| Cooper Health System-Voorhees | LaCouture, Tamara Anne | 2 |
| Emory University Hospital Midtown | Godette, Karen Debra | 2 |
| Good Samaritan Health Systems | Liberman, Fishel Zev | 2 |
| Kaiser Permanente Northern California | Seaward, Samantha Andrews | 2 |
| LSU Health Science Center-New Orleans MB-CCOP | Veith, Robert W. | 2 |
| Lehigh Valley Hospital | Friedman, Eliot L. | 2 |
| London Regional Cancer Program | D'Souza, David Paul | 2 |
| Margaret & Howard Hall Rad Ctr | Wiesenfeld, Martin | 2 |
| Martin Memorial Medical Center | Castillo-Perez, Jorge G. | 2 |
| Mayo Clinic in Florida | Vallow, Laura A | 2 |
| Mercy Hospital Medical - Des Moines | Behrens, Robert | 2 |
| Mercy San Juan Radiation Oncology Center | Jones, Christopher | 2 |

**Appendix 12**
**Participating Institutions**

| Institution | Principal Investigator | Accrual to RTOG 0617 |
|---|---|---|
| Missouri Baptist Medical Center | Lyss, Alan | 2 |
| Piedmont Hospital | Nowlan, Adam Wayne | 2 |
| Renown Regional Medical Center | Hardacre, Michael Chandler | 2 |
| Saint Elizabeth Regional Medical Center | Yiee, Kevin | 2 |
| Saint Francis Medical Center | Le-Lindqwister, Nguyet Anh | 2 |
| Siteman Cancer Center/Barnes Jewish St. Peters Hospital | Hall-Daniels, Lannis Elese | 2 |
| St. Agnes Healthcare | Hudes, Richard S. | 2 |
| USON-Fort Worth | Sorgen, Stephen D. | 2 |
| University of Chicago | Chmura, Steven J. | 2 |
| University of Colorado Denver | Rabinovitch, Rachel Abrams | 2 |
| University of Kansas Cancer Center-North | Kumar, Parvesh | 2 |
| University of Maryland Medical Systems | Suntharalingam, Mohan | 2 |
| Warren Cancer Research Foundation-Oklahoma CCOP | Stewart, Charles E. | 2 |
| Wellmont Holston Valley Medical Center | Shipstone, Asheesh | 2 |
| Adena Regional Medical Center | Becker, Mark J. | 1 |
| Allegheny General Hospital | Parda, David S. | 1 |
| Atlanta VA Medical Center | Edelman, Scott | 1 |
| Aultman Hospital | Olson, Laird E. | 1 |
| Bay Medical Center | Murshed, Hasan | 1 |
| Broward General Medical Center | Lieberfarb, Marshal Evan | 1 |
| Center for Cancer Care @ Goshen Health System | Wheeler, James A. | 1 |
| Champlain Valley Physicians Hospital Medical Center | Vaccaro, Anthony | 1 |
| Community Cancer Center | Le-Lindqwister, Nguyet A. | 1 |
| Concord Hospital Payson Center for Cancer Care | Metcalfe, Su K. | 1 |
| D.N. Greenwald | Clapper, Wingate F. | 1 |
| Door County Cancer Center | Leenstra, James | 1 |
| Evanston Hospital Corp | Hensing, Thomas A. | 1 |
| Fairview Ridges Hospital | Sperduto, Paul W. | 1 |
| Fox Chase Cancer Center | Galloway, Thomas J. | 1 |
| Geisinger Wyoming Valley Medical Center | Gergel, Thomas James | 1 |
| Genesys Regional Medical Center | Kim, Haesook Song | 1 |
| Harold Alfond Center for Cancer Care | Hertler, Andrew | 1 |
| Hillcrest Hospital Cancer Center | Suh, John H. | 1 |
| ICON – Baptist Medical Center South | Johnson, Douglas | 1 |
| ICON – Flagler Cancer Center | Johnson, Douglas W. | 1 |
| ICON – Southside Cancer Center | Johnson, Douglas W. | 1 |
| Indiana University Health Methodist Hospital | Johnstone, Peter A.S. | 1 |
| Iowa Methodist Medical Center | Behrens, Robert J. | 1 |
| James Graham Brown Cancer Ctr at University of Louisville | Woo, Shiao Y. | 1 |
| Joe Arrington Cancer Research & Treatment Center | Anderson, Paul J. | 1 |
| John H. Stroger, Jr. Hospital of Cook County MBCCOP | Thakrar, Harish V. | 1 |
| Kaiser Permanente Northern California-Oakland | Lampenfeld, Myles E. | 1 |
| Kaiser Permanente Northern California-Rohnert Park | Parthasarathy, Anand | 1 |
| Kaiser Permanente Northern California-Roseville | Peng, Bihai | 1 |
| Kalamazoo CCOP-West Michigan Cancer Center | Lord, Raymond Sterling | 1 |

**Appendix 12**
**Participating Institutions**

| Institution | Principal Investigator | Accrual to RTOG 0617 |
|---|---|---|
| Lancaster General Hospital | Singapuri, Kishor | 1 |
| Mary Bird Perkins Cancer Center | Lo, Kenneth K. | 1 |
| Mayo Clinic Health System Eau Claire Hospital, Inc. | Past, Larry Robert | 1 |
| Medical University of South Carolina | Jenrette, Joseph M. | 1 |
| Memorial Sloan-Kettering Cancer Center | Lee, Nancy Y. | 1 |
| Mercy Cancer Center at St. Ann | Mowat, Rex B. | 1 |
| Meritcare Hospital | Steen, Preston | 1 |
| Nevada Cancer Research Foundation CCOP | Meoz, Raul T. | 1 |
| Northwestern Ontario Regional Cancer Centre | Gulavita, Sunil Premial Pushpakumar | 1 |
| Penn State University and The Milton S. Hershey Medical Ctr | Wagner, Henry | 1 |
| Pocono Cancer Center | Greenberg, Michael J. | 1 |
| Poudre Valley Hospital Radiation Oncology | Petit, Joshua Henry | 1 |
| Regions Radiation Therapy | Sperduto, Paul W. | 1 |
| Riverside Methodist Hospital | Becker, Mark J. | 1 |
| Rochester Methodist Hospital | Oliver, Kenneth | 1 |
| Roseville Radiation Oncology Center | Jones, Christopher | 1 |
| Sacred Heart Hospital | Krentel, Rod G. | 1 |
| Sanford Cancer Center | Tschetter, Loren K. | 1 |
| St Luke's-Roosevelt Hospital Center | Chadha, Manjeet | 1 |
| St. Charles Mercy Hospital | Mowat, Rex B. | 1 |
| St. Francis Hospital/Stormont-Vail Hospital | Petrik, Edwin Leo | 1 |
| St. Johns Hospital & Medical Center | Narayan, Samir | 1 |
| St. Luke's Mountain States Tumor Institute (MSTI) Twin Falls | Smith, Charles E. | 1 |
| St. Mary's Hospital Medical Center | Leenstra, James | 1 |
| St. Mary's Regional Medical Center | Tay, Jonathan S. | 1 |
| Swedish Medical Center | Tenny, Claire | 1 |
| Thedacare Cancer Institute | Ray, Michael Edward | 1 |
| UMDNJ-New Jersey Medical School | Motwani, Sabin B. | 1 |
| USON- Texas Oncology Longview Cancer Center | Taylor, Bernard W. | 1 |
| USON- Texas Oncology Odessa | Kaczor, Joseph | 1 |
| USON- Texas Oncology-Denton | Morton, Jeffery Douglas | 1 |
| USON- Texas Oncology-Sugar Land | Kavadi, Vivek S. | 1 |
| USON-Williamette Valley Cancer Center | Wendland, Merideth Michele Murphy | 1 |
| University of Cincinnati | Redmond, Kevin Patrick | 1 |
| University of Florida Health Science Center | Nichols, Romaine Charles | 1 |
| University of Kansas Cancer Center - Southwest | Kumar, Parvesh | 1 |
| University of Kansas Cancer Center-South | Kumar, Parvesh | 1 |
| University of Oklahoma Health Sciences Center | Herman, Terence S. | 1 |
| University of Pennsylvania Medical Center | Freedman, Gary Mitchel | 1 |
| University of Texas at San Antonio | Eng, Tony Yuen Lung | 1 |
| University of Vermont | Wallace, Harold James | 1 |
| Utah Valley Regional Medical Center | Blair, Tarlton Jay | 1 |
| Washington Cancer Institute | Randolph-Jackson, Pamela D. | 1 |
| Waukesha Memorial Hospital | Clapper, Wingate F. | 1 |
| Wayne State University-Karmanos Cancer Institute | Kim, Harold E. | 1 |

**Appendix 12**
**Participating Institutions**

| Institution | Principal Investigator | Accrual to RTOG 0617 |
|---|---|---|
| Wentworth-Douglass Hospital | Becht, James D | 1 |
| Wheaton Franciscan Cancer Care-All Saints | Taylor, James H. | 1 |

**Appendix 13 – Permitted Dose Modifications**

- **Radiation Therapy**
  - Interruptions in treatment were permitted for
    - Grade 4 dysphagia, odynophagia, or esophagitis
    - Grade 4 hematologic toxicities resulting in chemotherapy delays/modifications
    - Decline in Zubrod performance status to 2, 3, or 4

- **Systemic Therapy**

**Dose Levels of Paclitaxel, Carboplatin, and Cetuximab**

| | Starting Dose | Dose Level -1 | Dose Level -2 |
|---|---|---|---|
| **Concurrent Therapy**[a] | | | |
| Paclitaxel | 45 mg/m$^2$ | NA | NA |
| Carboplatin | AUC=2 | NA | NA |
| **Consolidation Therapy**[b] | | | |
| Paclitaxel | 200 mg/m$^2$ | 150 mg/m$^2$ | NA |
| Carboplatin | AUC=6 | AUC=4.5 | NA |
| **Cetuximab Dose Levels (post loading dose)** | | | |
| Cetuximab | 250 mg/m$^2$ | 200 mg/m$^2$ | 150 mg/m$^2$ |

[a] For concurrent therapy, paclitaxel and carboplatin doses were not to be adjusted.

[b] For consolidation therapy, dose reductions of paclitaxel and carboplatin below the -1 dose level were not allowed. Dose reductions for cetuximab were not allowed below the –2 dose level.

  - **Cetuximab**
    - If cetuximab was omitted for more than 4 consecutive infusions, then cetuximab was to be discontinued.
    - Dose modifications
      - Infusion reactions
        - Grade 1 to 2: Permanent reduction by 50% in the infusion rate.
        - Grade 3 or 4: Permanently discontinue cetuximab
      - Isolated drug fever
        - Initially reduce infusion rate by 50%
        - If persistent, permanently reduce infusion rate by 50%
      - Dermatologic Toxicity

| **Cetuximab Dose Modification Guidelines for Dermatologic Toxicity** | | | |
|---|---|---|---|
| **Grade 3 Acneform Rash** | **Cetuximab** | **Outcome** | **Cetuximab Dose Mod** |
| | | | |
| 1$^{st}$ occurrence | Delay infusion 1-2 wks | Improvement | Continue at 250 mg/m$^2$ |
| | | No improvement | Discontinue cetuximab |
| | | | |
| 2$^{nd}$ occurrence | Delay infusion 1-2 wks | Improvement | Reduce *Dose Level -1 |
| | | No improvement | Discontinue cetuximab |
| | | | |

| | | | |
|---|---|---|---|
| 3rd occurrence | Delay infusion 1-2 wks | Improvement | Reduce *Dose Level -2 |
| | | No improvement | Discontinue cetuximab |
| | | | |
| 4th occurrence | Discontinue cetuximab | | |

- **Paclitaxel/Carboplatin**
  - **Concurrent Therapy**
    - If paclitaxel or carboplatin was held for more than 2 weeks, then the applicable drug would be held permanently for the duration of concurrent therapy
    - Renal toxicity
      - Carboplatin doses were to be recalculated when serum creatinine increased by 10%.
    - Hematologic Toxicity

| **Toxicity NCI CTCAE Grade (CTCAE v3.0)** | **Paclitaxel Dose At Start of Subsequent Cycles of Therapy** [a] | **Carboplatin Dose at Start of Subsequent Cycles of Therapy** [a] |
|---|---|---|
| **Neutropenia** | | |
| 1 (1500-1999/$mm^3$) | Maintain dose level | Maintain dose level |
| 2 (1000-1499/$mm^3$) | Maintain dose level | Maintain dose level |
| 3 (500-999/$mm^3$) | Hold therapy | Hold therapy |
| 4 (< 500/$mm^3$) | Hold therapy | Hold therapy |
| **Neutropenic fever** | Hold therapy | Hold therapy |
| **Thrombocytopenia** | | |
| 1 (< LLN-75,000/$mm^3$) | Maintain dose level | Maintain dose level |
| 2 (50,000- 74,999/$mm^3$) | Hold therapy | Hold therapy |
| 3 (25,000- 49,999/$mm^3$) | Hold therapy | Hold therapy |
| 4 (< 25,000/$mm^3$) | Hold therapy | Hold therapy |
| **Other Hematologic toxicities** | There will be no dose modifications for changes in leukopenia or lymphopenia. | |

[a]Dose levels were relative to the starting dose in the previous cycle. For concurrent therapy, paclitaxel and carboplatin doses were not to be adjusted.

    - Non-Hematologic Toxicity

| **Worst Toxicity NCI CTCAE Grade (CTCAE v3.0)**[a] | **Paclitaxel Dose At Start of Subsequent Cycles of Therapy**[a] | **Carboplatin Dose At Start of Subsequent Cycles of Therapy**[b] |
|---|---|---|
| **Nail changes (paronychia)** Grade 2 | Maintain dose level | Maintain dose level |
| **Neuropathy** ≤ Grade 1 | Maintain dose level | Maintain dose level |
| Grade 2 | Hold therapy until Grade ≤ 1; restart at full dose[e] | Maintain dose level |
| Grade 3 | Discontinue therapy | Maintain dose level |
| **Other non-hematologic toxicities**[c] ≥ Grade 3 | Hold treatment until ≤ Grade 2 | Hold treatment until ≤ Grade 2 |

a. For ≤ CTCAE Grade 2 non-hematologic toxicity not described above, excluding neuropathy, maintain dose level of all study. For neuropathy, sites were to follow the guidelines listed above.
b. Dose levels were relative to the starting dose in the previous cycle. For concurrent therapy, paclitaxel and carboplatin doses were not to be adjusted.
c. With the exception of allergic/hypersensitivity or cytokine release reaction, acne-like rash (rash/desquamation), anorexia, and viral infections.

- **Consolidation Therapy**
  - If paclitaxel or carboplatin was held for more than 2 weeks, then the applicable drug would be held permanently for the duration of consolidation therapy
  - Renal toxicity
    - Carboplatin doses were to be recalculated when serum creatinine increased by 10%.
  - Hematologic toxicity

| **Toxicity NCI CTCAE Grade (CTCAE v3.0)** | **Paclitaxel Dose At Start of Subsequent Cycles of Therapy** [a] | **Carboplatin Dose at Start of Subsequent Cycles of Therapy** [a] |
|---|---|---|
| **Neutropenia** | | |
| 1 (1500-1999/$mm^3$) | Maintain dose level | Maintain dose level |
| 2 (1000-1499/$mm^3$) | Hold therapy. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,500 $mm^3$ | Hold therapy. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,500 $mm^3$ |
| 3 (500-999/$mm^3$) | Hold therapy. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,500 $mm^3$ | Hold therapy. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,500 $mm^3$ |
| 4 (< 500/$mm^3$) | Hold therapy and decrease by 1 dose level when ≥ 1,500 $mm^3$ | Hold therapy and decrease by 1 dose level when ≥ 1,500 $mm^3$ |
| **Neutropenic fever** | Hold therapy and decrease by 1 dose level when ≥ 1,500 $mm^3$ | Hold therapy and decrease by 1 dose level when ≥ 1,500 $mm^3$ |
| **Thrombocytopenia** | | |
| 1 (≥ 75,000/$mm^3$) | Maintain dose level | Maintain dose level |
| 2 (50,000 - 74,999/ $mm^3$) | Hold therapy. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 $mm^3$ | Hold therapy. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 $mm^3$ |
| 3 (25,000- 49,999/ $mm^3$) | Hold therapy. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 $mm^3$ | Hold therapy. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 $mm^3$ |
| 4 (< 25,000/$mm^3$) | Hold therapy and decrease by 1 dose level when ≥ 75,000 $mm^3$ | Hold therapy and decrease by 1 dose level when ≥ 75,000 $mm^3$ |
| **Other Hematologic toxicities** | There will be no dose modifications for changes in leukopenia or lymphopenia. | |

[a]Dose levels were relative to the worst toxicities in the previous cycle. For consolidation therapy, dose reductions of paclitaxel and carboplatin below the –1 dose level were not allowed.

- Non-hematologic toxicity

| **Worst Toxicity NCI CTCAE Grade (CTCAE v3.0)** [a, c] | **Paclitaxel Dose At Start of Subsequent Cycles of Therapy** [b] | **Carboplatin Dose At Start of Subsequent Cycles of Therapy** [b] |
|---|---|---|
| **Nail changes (paronychia)** | | |
| Grade 2 | Maintain dose level | Maintain dose level |
| **Neuropathy** | | |
| ≤ Grade 1 | Maintain dose level | Maintain dose level |
| Grade 2 | Hold therapy until Grade ≤ 1; restart at full dose | Maintain dose level |
| Grade 3 | Discontinue therapy | Maintain dose level |
| **Other non-hematologic toxicities** | | |
| Grade 3 | Hold treatment until ≤ Grade 2 | Hold treatment until ≤ Grade 2 |

a. For ≤ CTCAE Grade 2 non-hematologic toxicity not described above, excluding neuropathy, maintain dose level of all study drugs. For neuropathy, sites were to follow the guidelines above.
b. Dose levels were relative to the worst toxicities in the previous cycle.
c. With the exception of allergic/hypersensitivity reaction, acne-like rash (rash/desquamation), anorexia, and viral infections. When a chemotherapy dose reduction was required during consolidation, re-escalation of the chemotherapy dose was not allowed for subsequent doses during that specific course.