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Phase IB study of induction chemotherapy with XELOX, followed by radiation therapy, Carboplatin and Everolimus in patients with locally advanced Esophageal Cancer.

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Abstract

Purpose: Preclinical studies have shown synergy between everolimus, an mTOR inhibitor, radiation and platinum agents. We conducted a phase IB trial to determine the recommended phase II dose of everolimus with carboplatin and radiation.

Methods: Patients with Stage II/III esophageal cancer were enrolled. Following two cycles of Capecitabine/Oxaliplatin (XELOX), patients with no disease progression, received 50.4 Gy in 28 fractions and concurrent weekly carboplatin (AUC=2), with escalating doses of everolimus. A standard 3+3 dose escalation design was used.

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Conceptualization (1,23,24), data curation (1–14, 23,24), formal analysis (1,8, 21,22,24) funding acquisition (1,24), investigation (1,13,15,16–24), methodology (8,22), project administration (1,24) resources (1,24), supervision (1), validation (1,24), writing - original draft (1), review and editing (all authors)

Conflicts of Interest: None

Results: Nineteen patients were enrolled. Two patients were screen failures and four were removed due to poor tolerance to XELOX (n = 2) or disease progression (n = 2). All treated patients had adenocarcinoma. Median age was 58 (44–71 yrs) and 85% were males. One patient at dose level 1 was replaced due to ongoing anxiety. One of 6 patients had a DLT of bowel ischemia that was fatal. At dose level 2, 2 out of 6 patients had a DLT (fever with neutropenia and nausea). The recommended phase II dose of everolimus was 2.5 mg QOD. Grade 3 toxicities included lymphopenia (11%); nausea (10%), low white blood cell (8.0%) vomiting (5.5%) decreased neutrophils (4.0%). All patients achieved an R0 resection with a pathologic response rate (RR) of 40% and a pathologic complete response (ypCR) rate of 23%. The 2-year PFS and OS were 50% and 49.6% respectively.

Conclusions: The recommended phase II dose of everolimus with concurrent weekly carboplatin and radiation is 2.5 mg QOD.

Introduction

Esophageal carcinoma is the eighth most common cancer in incidence, and accounts for the sixth most common cause of cancer-related mortality, with an estimated 400,000 deaths worldwide[1]. In the United States, there were 16,910 new cases and 15,690 deaths from esophageal cancer in 2016 [2]. Despite recent advances in the diagnosis, staging, and treatment of this disease, there has been very small improvements in survival[2]. Following complete surgical resection, the survival rate approaches 30–40% for stage II disease, and 10–15% for stage III disease [3, 4]. Whereas radiotherapy alone does not cure Stage II/III esophageal cancer, the combination of radiotherapy and concurrent platinum-based chemotherapy significantly improves long-term survival in patients with resectable disease[5].

Pre-clinical studies suggest that the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway plays a role in gastric and esophageal cancer [6]. A selective inhibitor of the mammalian target of rapamycin (mTOR), everolimus, appears to have anti-tumor activity in a variety of cell lines [7–13]. In a phase II trial of everolimus in patients with refractory metastatic adenocarcinoma of the esophagus, gastroesophageal junction and stomach, close to 40% of patients derived clinical benefit [14]. At the preclinical level there is synergy between everolimus and radiation. Tumor growth delay with everolimus and radiotherapy might rely on its anti-angiogenic effect [15].

Oxaliplatin and capecitabine in combination demonstrates activity in metastatic adenocarcinoma of the esophagus, gastroesophageal junction and gastric cardia. A phase I trial testing this combination found that capecitabine 1000 mg/m² given twice daily on days 1–14 plus oxaliplatin 130 mg/m² on day 1, both of which were given on a 21-day cycle, was well tolerated [16]. The lower dose (capecitabine 850 mg/m² orally twice a day, days 1–14, and oxaliplatin 130 mg/m² intravenously on day 1, yielded an acceptable toxicity profile and a response rate of 35% [17].

We hypothesized that the pre-selection of patients who had not progressed following induction chemotherapy as well as the use of a novel radiosensitizer, everolimus may lead to a higher rate of pathologic response that could translate into clinical benefit for patients with

resectable disease. We therefore proceeded with a phase IB clinical trial investigating this approach.

This multi-institutional phase I study was conducted to determine the maximum tolerated dose (MTD) of everolimus following two cycles of induction Capecitabine/Oxaliplatin (XELOX). Patients would be restaged and those without evidence of disease progression would go on to receive radiation to a total dose of 50.4 Gy in 28 fractions and concurrent weekly carboplatin (AUC=2), with escalating doses of everolimus. Secondary objectives were to determine the toxicities, pathologic complete response rate, progression free survival and overall survival of this combination.

When investigating novel drug combinations, it is useful to be able to develop biomarkers that can predict either response or resistance to therapy. Data from tumor xenograft mouse models have suggested that Aurora Kinase A plays an important role in the development of everolimus resistance and that this is mediated through upregulation of c-MYC [18]. We postulated that patients with persistent disease following treatment with this combination will therefore have pretreatment levels that are higher for both Aurora kinase A as well as c-MYC expression.

Methods and Materials

From 2012 to 2016, eligible patients were accrued to this multi-institutional prospective phase I study. The study was reviewed and approved by institutional review boards at each site and was monitored by the institutional data safety and monitoring boards at each site.

Patient Eligibility

Patients with histologically confirmed and newly diagnosed esophageal carcinoma who were deemed resectable were enrolled on study. Resectability was determined by a surgical oncologist. Patients with concomitant other malignancy or significant comorbidities precluding participation in the trial were excluded. Inclusion criteria included 18 years old, ability to provide written informed consent, ECOG performance status 0–1, adequate bone marrow, hepatic and renal function. Exclusion criteria included prior radiation to any area within the planned radiation field; brain metastases; a known history of viral hepatitis B or C; steroid therapy within one month prior to enrollment; or the use of a medication known to be a CYP3A4 inhibitor as well as inability to swallow pills. All patients were staged with total-body positron emission tomography/computed tomography (PET/CT).

Treatment administration

A complete history and physical examination was performed at screening, which included: a complete blood count with platelets and differential, biochemistry and lipid profile, liver function test and 12-lead ECG. LFTs were also obtained following each cycle of XELOX.

Figure 1 outlines the treatment schema. Following two cycles of induction Capecitabine/Oxaliplatin (XELOX), patients without evidence of disease progression by restaging CT or PET/CT, received concurrent chemoradiation (total dose: 50.4 Gy in 28 fractions), with weekly carboplatin (AUC=2), and escalating doses of everolimus. Concurrent therapy was

started within 4 weeks of the second cycle of XELOX with radiotherapy initiated on day 1 of the concomitant therapy. Carboplatin was administered once weekly for a maximum of 6 weeks, starting on day 1. Everolimus was administered orally, once daily throughout the course of radiotherapy. Adverse events were graded and recorded according to the National Cancer Institute Common Toxicity Criteria version 4.0 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).

Dose escalation

This study used a standard 3+3 dose escalation design[19]. We planned to evaluate four dose levels of everolimus as follows: (1) 2.5 mg every other day (2) 2.5 mg daily (3) 5.0 mg daily and (4) 7.5 mg daily. Each cohort was evaluated for dose-limiting toxicities (DLT). The following events during or within three weeks of completion of concurrent therapy were considered dose limiting toxicities: grade 3 or 4 neutropenia with fever, grade 4 thrombocytopenia; grade 3 or 4 non-hematological toxicity with the exception of grade 3 esophagitis, more than 2 weeks interruption of radiation or inability to deliver at least 35 days of everolimus. Each cohort consisted of three initial patients. If a DLT was observed in 1 of 3 patients, the cohort was expanded to include 3 additional patients. MTD was defined as the highest dose at which DLT was observed in 2 of 6 patients or the final dose cohort was reached.

Radiation Therapy:

External beam radiation with megavoltage linear accelerators (6 MV) were used to deliver multiple field techniques. Patients were treated 5 days/week at 1.8 Gy/day to a total dose of 45Gy. This was followed by a boost to 50.4 Gy. The Gross Tumor Volume (GTV) was defined as the primary tumor and any involved lymph nodes. If the primary tumor extended at least 2 cm above the carina (proximal esophagus), the supraclavicular nodes were included. If the primary tumor was in the distal third of the esophagus, or celiac nodes were clinically positive, the target volume was enlarged to include the celiac nodal volume. The Clinical Target Volume (CTV) was defined as the GTV with a 5 cm margin superiorly and inferiorly beyond the primary tumor and with lateral borders 1.5 –2 cm beyond the primary tumor. All involved lymph nodes had at least a 1.5 –2 cm margin. Planning Target Volume (PTV) was defined as a margin for set up error or patient movement is to be added to the Clinical Target Volume. Exact margins were left to the discretion of the treating radiation oncologist and did not have to be uniform in all dimensions. The prescription point was at the isocenter. The dose variation was +7% and –5% of the prescription point dose.

Dose constraints were specified as follows: (1) spinal cord dose 43 Gy (2) lung more than 2 cm outside the target volume 40 Gy (3) The entire heart 30 Gy with less than 50% of the organ 40 Gy.

Biomarkers

Paraffin-embedded tissue blocks were obtained for immunohistochemical analysis for Aurora Kinase A and c-MYC. Immunohistochemical results were evaluated for intensity of nuclear and cytoplasmic components. The intensity of staining was graded 0 (negative), 1

(weak), 2 (moderate), and 3 (strong). Evaluation of immunohistochemical data was carried out by a single GI pathologist without knowledge of clinical outcomes.

Statistics

The primary endpoint of this study was to determine the MTD of everolimus when combined with weekly carboplatin and radiation following two cycles of induction Capecitabine/Oxaliplatin (XELOX).

Secondary endpoints included the pathologic complete response rate of patients taking everolimus. Using Simon's two stage design, we designed this study with a power of 80% and alpha level of 5% to distinguish a promising ypCR rate of 35% if everolimus is active or ypCR rate less than 20% if the regimen is inactive. The Kaplan-Meier method was used to determine actuarial progression-free survival and overall survival.

Exploratory endpoints included correlating Aurora kinase A and c-MYC expression with pathologic response.

Results:

A total of nineteen patients were enrolled (table 1). There were two screen failures (thrombocytopenia, metastases) and four patients were removed due to poor tolerance of XELOX (2 patients) or disease progression documented during or after XELOX chemotherapy (2 patients). A total of 13 patients with stage II/III (6/7) esophageal carcinoma completed concurrent therapy. The median age was 58 (44–71yrs) and 85% of patients were males and all patients had adenocarcinoma. One patient at dose level 1 (2.5 mg/QOD), was replaced due to ongoing anxiety. One of 6 patients at dose level 1 had a DLT (bowel ischemia). At dose level 2 (2.5mg/QD), 2 out of 6 patients had a DLT (fever with neutropenia and nausea). Therefore, the recommended phase II dose of everolimus was 2.5 mg QOD.

Safety:

Clinically relevant grade 3 toxicities included lymphopenia (11%); nausea (10%), low white blood cell (8.0%) vomiting (5.5%) decreased neutrophils (4.0%). Additional grade 3 or higher toxicities occurred in less than 3% and are listed in Table 2.

Efficacy:

R0 resection was achieved in 100%. Pathologic response rate (RR) (partial response and complete response) of 40% and a pathologic complete response (ypCR) rate of 23% were observed. The 2-year PFS and OS based on intent to treat analysis were 50% and 49.6% respectively (Figures 2 and 3)

Results of biomarker Analysis:

Only 8 of the 13 patients that completed treatment had pretreatment tissue available for biomarker analysis. None of these patients showed a pathologic complete response but all

patients had a pathologic response (stable disease + partial response). Since the dominant cellular localization of Aurora Kinase A is the centrosome, we would count all of these patients with distinct nuclear staining as Aurora Kinase A positive. As there was only one patient who had mild staining and none with no staining, we were unable to correlate overexpression of Aurora Kinase A with pathologic response rates. It is of interest however to note that all cases of high Aurora Kinase A also had moderate to high expression of c-MYC. The one patient with mild Aurora Kinase A also had mild expression of c-MYC (Table 3).

Discussion:

Therapeutic targets of interest in the esophageal carcinoma have included anti-angiogenesis agents. Ramcicirumab an antibody director to the vascular endothelial growth factor-2(VEGF-2) has resulted in improvement in survival when combined with paclitaxel for patients with GE junction adenocarcinoma [20]. Although EGFR inhibition has not provided encouraging results[21], the addition of the HER-2 inhibitor, trastuzumab to platinum based therapy for patients with metastatic esophageal carcinoma has become the standard of care metastatic esophageal cancers expressing the HER-2 receptor[22].

The phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin-pathway (PI3K/AKT/mTOR-pathway) exerts a role in cell survival and proliferation as well as angiogenesis and resistance to antitumor agents. Based on preclinical data that mTOR inhibitors can overcome resistance to cytotoxic agents [23] as well are their potential role as radiosensitizers, mTOR inhibitors seem to be well-suited for combinations with other antitumor drugs and radiation [24]. More specifically in squamous cell carcinoma of the esophagus this pathway seems to be activated. However, while preclinical evidence suggests that esophageal carcinoma would be an appropriate tumor type to benefit from mTOR inhibition there is very limited clinical data to support this and particularly in combination with radiation therapy.

Our study is the first to combine everolimus with radiation therapy in patients with esophageal carcinoma. In a previously reported trial combining everolimus with radiation therapy in treating patients with non-small cell lung carcinoma, the recommended phase II dose of everolimus in combination with thoracic radiotherapy was 50 mg per week. Of note, pulmonary toxicity was of concern in this study, as one patient developed interstitial pneumonitis at the weekly dose level of 20 mg and another patient receiving the daily regimen of 2.5 mg a day developed a dose limiting toxicity of interstitial pneumonitis with a fatal outcome [25]. In our study, one patient at the first dose level of 2.5 mg developed a dose-limiting toxicity of bowel ischemia that was fatal. As the perforation was outside the radiation field it is unlikely to be related to radiosensitization but raises a concern regarding the safety of this combination. In our study we were not able to increase the dose of everolimus beyond the lowest possible dose of 2.5 mg every other day. The commonly observed acute side effects were those that would be expected from everolimus monotherapy. The addition of everolimus did not increase expected radiation related side effects. None of the patients required interruption of the planned radiation as a result of drug related side effects. It is arguable however that the required tolerability to XELOX as well as

the exclusion of patients with significant dysphagia may have introduced a selection bias. Although the small number of patients does not allow us to draw definitive conclusions regarding the synergistic efficacy of this combination, the overall pathologic response rate (RR) of 40% and a pathologic complete response (ypCR) rate of 23% are not significantly better than historical controls. The 2-year PFS of 50% and overall survival of 49.6% is also not significantly improved over historical controls. As far as future development of mTOR inhibitors in the definitive management of locally advanced esophageal cancer, our results precluded the use of high enough doses of everolimus that would be deemed appropriate to test against current standards such as the CROSS regimen; in addition, even if we account for bad luck, the observed DLTs are enough in our view to be very hesitant in adding everolimus to a regimen of paclitaxel, carboplatin and radiation.

We were able to perform biomarker analysis on only 8 of the 13 patients who completed treatment. In this small group of samples we found that 7 of the 8 (88%) had overexpression of Aurora Kinase A and also had increased c-MYC expression. All of the patients had a pathologic response but none of these patients achieved a pathologic complete response. Although the small number of cases do not allow us to prove an association, the consistency of this finding raises the question of whether Aurora Kinase A results in resistance to everolimus via c-MYC. Preclinical studies suggest that targeting Aurora Kinase A with an inhibitor such as alisertib may result in overcoming the resistance to mTOR inhibition and this resistance may be activated by c-MYC[18, 26]

In conclusion, the recommended phase II dose of everolimus with concurrent weekly carboplatin and radiation is 2.5 mg QOD. Despite the 100% R0 resection rate, the pathologic complete remission (ypCR) and overall survival (OS) rates of patients treated with this regimen were not significantly improved over historical controls.

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References:

1. Alsop BR and Alsop SP, Esophageal Cancer. *Gastroenterol Clin North Am*, 2016 9;45(3):399–412. [PubMed: 27546839]
2. Siegel RL, Miller KD, and Miller JA, Cancer statistics, 2016. *CA Cancer J Clin*, 2016 Jan-Feb; 66(1):7–30. [PubMed: 26742998]
3. Pera M, Trastek VF, and Trastek e.a. Carpenter HA, Barrett's esophagus with high-grade dysplasia: an indication for esophagectomy? *Ann Thorac Surg*, 1992 73: p. 1697–702.
4. Headrick JR, Nichols FC, III, and Nichols e.a. Miller DL, High-grade esophageal dysplasia: long-term survival and quality of life after esophagectomy. *Ann Thorac Surg*, 2002 73: p. 1697–702. [PubMed: 12078755]
5. van Hagen P, et al., Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*, 2012 5 31;366(22):2074–84. [PubMed: 22646630]
6. Matsuoka T and Matsuoka YM, The Role of PI3K/Akt/mTOR Signaling in Gastric Carcinoma. *Cancers (Basel)*, 2014 7 7;6(3):1441–63. [PubMed: 25003395]
7. Zeng Z, et al., Rapamycin derivatives reduce mTORC2 signaling and inhibit AKT activation in AML. *Blood*, 2007 109(8): p. 3509–12. [PubMed: 17179228]

8. Ikezoe T, et al., Longitudinal inhibition of PI3K/Akt/mTOR signaling by LY294002 and rapamycin induces growth arrest of adult T-cell leukemia cells. *Leuk Res*, 2007 31(5): p. 673–82. [PubMed: 17007924]
9. Wanner K, et al., Mammalian target of rapamycin inhibition induces cell cycle arrest in diffuse large B cell lymphoma (DLBCL) cells and sensitises DLBCL cells to rituximab. *Br J Haematol*, 2006 134(5): p. 475–84. [PubMed: 16856892]
10. Tuncyurek P, et al., Everolimus and mycophenolate mofetil sensitize human pancreatic cancer cells to gemcitabine in vitro: a novel adjunct to standard chemotherapy? *Eur Surg Res*, 2007 39(6): p. 380–7. [PubMed: 17700025]
11. Treeck O, et al., Effects of a combined treatment with mTOR inhibitor RAD001 and tamoxifen in vitro on growth and apoptosis of human cancer cells. *Gynecol Oncol*, 2006 102(2): p. 292–9. [PubMed: 16443261]
12. Mabuchi S, et al., RAD001 inhibits human ovarian cancer cell proliferation, enhances cisplatin-induced apoptosis, and prolongs survival in an ovarian cancer model. *Clin Cancer Res*, 2007 13(14): p. 4261–70. [PubMed: 17634556]
13. Sieghart W, et al., Mammalian target of rapamycin pathway activity in hepatocellular carcinomas of patients undergoing liver transplantation. *Transplantation*, 2007 83(4): p. 425–32. [PubMed: 17318075]
14. Wainberg ZA, et al., Phase II trial of everolimus in patients with refractory metastatic adenocarcinoma of the esophagus, gastroesophageal junction and stomach: possible role for predictive biomarkers. *Cancer Chemother Pharmacol*, 2015 7;76(1):61–7. [PubMed: 25969130]
15. Manegold PC, et al., Antiangiogenic therapy with mammalian target of rapamycin inhibitor RAD001 (Everolimus) increases radiosensitivity in solid cancer. *Clin Cancer Res*, 2008 14(3): p. 892–900. [PubMed: 18245553]
16. Diaz-Rubio E, et al., Capecitabine (Xeloda) in combination with oxaliplatin: a phase I, dose-escalation study in patients with advanced or metastatic solid tumors. *Ann Oncol*, 2002 13(4): p. 558–65. [PubMed: 12056706]
17. Jatoi A, et al., Oxaliplatin and capecitabine in patients with metastatic adenocarcinoma of the esophagus, gastroesophageal junction and gastric cardia: a phase II study from the North Central Cancer Treatment Group. *Ann Oncol*, 2006 17(1): p. 29–34. [PubMed: 16303863]
18. Katsha A, et al., Activation of EIF4E by Aurora Kinase A Depicts a Novel Druggable Axis in Everolimus-Resistant Cancer Cells. *Clin Cancer Res*, 2017 7 15;23(14):3756–3768. [PubMed: 28073841]
19. Crowley J and Crowley HA, *Handbook of Statistics in Clinical Oncology*, third edition.
20. Wilke H, et al., Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol*, 2014 10;15(11):1224–35. [PubMed: 25240821]
21. Suntharalingam M, et al., Effect of the Addition of Cetuximab to Paclitaxel, Cisplatin, and Radiation Therapy for Patients With Esophageal Cancer: The NRG Oncology RTOG 0436 Phase 3 Randomized Clinical Trial. *JAMA Oncology* 2017 11 1;3(11):1520–1528. [PubMed: 28687830]
22. Bang YJ, et al., Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010 8 28;376(9742):687–97. [PubMed: 20728210]
23. Konings IR, et al., The applicability of mTOR inhibition in solid tumors. *Curr Cancer Drug Targets*, 2009 5;9(3):439–50. [PubMed: 19442061]
24. Nassim R, et al., Combining mTOR inhibition with radiation improves antitumor activity in bladder cancer cells in vitro and in vivo: a novel strategy for treatment. *PLoS One*, 2013 6 17;8(6):e65257. [PubMed: 23799002]
25. Deutsch E, et al., Phase I trial of everolimus in combination with thoracic radiotherapy in non-small-cell lung cancer. *Annals Oncol*, 2015 6;26(6):1223–9.
26. Wang L, et al., Cisplatin-resistant cancer cells are sensitive to Aurora kinase A inhibition by alisertib. *Mol Oncol*, 2017 8;11(8):981–995. [PubMed: 28417568]

Fig.1.
Study Schema

No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	24 Mo Survival	36 Month Survival
17	3 (18%)	14 (82%)	NA (13.6, NA)	100.0% (NA, NA)	50.0% (7.9%, 82.8%)	50.0% (7.9%, 82.8%)

Fig.2.
Progression Free Survival for patients on Everolimus

No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	24 Mo Survival	36 Mo Survival
19	11 (58%)	8 (42%)	21.9 (5.9, NA)	57.9% (33.2%, 76.3%)	49.6% (24.5%, 70.5%)	24.8% (4.7%, 53.0%)

Fig.3.
Overall Survival for patients on Everolimus

Table 1:

Patient Characteristics

Age	Gender	Histology	T	N	Stage
60	M	adeno, signet ring	3	0	IIB
45	M	squamous	3	2	IIIB
65	F	adeno	3	1	IIIA
73	M	adeno	1b	1	IIB
59	M	adeno	2	0	IIA
52	M	adeno, poorly differentiated	X	2	IIIA-C
64	M	adeno	3	2	IIIB
44	M	adeno, poorly differentiated	3	2	IIIB
67	M	adeno	3	1	IIIA
44	M	adeno	3	1	IIIA
61	M	squamous	2	2	IIIA
54	M	adeno	3	0	IIB
35	M	adeno	2	2	IIIA
57	F	adeno	3	0	IIB
66	M	adeno, poorly differentiated	3	0	IIB
70	M	adeno	3	1	IIIA
70	M	adeno, poorly differentiated	3	1	IIIA
52	M	adeno, poorly differentiated	3	0	IIB
57	M	adeno, poorly differentiated	1	1	IIB

Table 2:

Grade 3 or higher treatment related adverse events

Toxicity (Grade 3)	n (%)
↓ Absolute neutrophil count (ANC)	1 (1.5)
↑ Alanine aminotransferase (ALT)	2 (3.0)
↑ Alkaline phosphatase (ALP)	1 (1.5)
Allergic rhinitis	1 (1.5)
Anemia	1 (1.5)
Anorexia	1 (1.5)
↑ Aspartate aminotransferase (AST)	1 (1.5)
Changes—taste	1 (1.5)
Dehydration	3 (4.0)
Diarrhea	3 (4.0)
Diverticulitis	1 (1.5)
Dysphagia	2 (3.0)
Esophagitis	2 (3.0)
Eye infection	1 (1.5)
Fatigue	2 (3.0)
Headache	1 (1.5)
Hyperglycemia	3 (4.0)
Hypertension	1 (1.5)
Hypertriglyceridemia	1 (1.5)
Hypocalcemia	1 (1.5)
Hypokalemia	1 (1.5)
Hypophosphatemia	1 (1.5)
Insomnia	1 (1.5)
Lack of appetite	1 (1.5)
Leukopenia	1 (1.5)
Lymphocyte count—decreased	8 (11.0)
Nasal congestion	1 (1.5)
Nausea	7 (10.0)
Neutrophil count—decreased	3 (4.0)
Noncardiac chest pain	1 (1.5)
Right otitis media	1 (1.5)
Right-sided otitis media	1 (1.5)
Sinusitis	1 (1.5)
Thrombocytopenia	2 (3.0)
Vomiting	4 (5.5)
↓ White blood cell count (WBC)	6 (8.0)
Total	70 (100)

↑ indicates increased; ↓, indicates decreased.

Table 3:**Biomarker Analysis**

Case #	C-MYC		AURORA KINASE A		Path Response	ypCR
	Cytoplasm	Nuclear	Cytoplasm	Nuclear		
1	0	3	0	3	Yes	No
2	0	3	0	3	Yes	No
3	0	3	0	3	Yes	No
4	0	1	0	1	Yes	No
5	0	2	0	3	Yes	No
6	0	2	0	3	Yes	No
7	0	2	0	3	Yes	No
8	0	3	0	3	Yes	No

STAINING INTENSITY

0= NEGATIVE

1= MILD

2= MODERATE

3= MARKED