**Manuscript Title:** Treatment of metastatic recurrence of urothelial carcinoma after previous cisplatin-based chemotherapy for localized disease: A retrospective comparison of different chemotherapy regimens.

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**Conflict of Interest Page**

**LCH:** Reports consulting fees from Genentech, Dendreon, Pfizer, Medivation/Astellas, Exelixis, Bayer, Kew Group, Corvus, Merck, Novartis, Bristol-Myers Squibb.  Michael J Hennessy Associates (Healthcare Communications Company and several brands such as OncLive and PER), Jounce, EMD Serrano,  ASIM CME, and Ology Medical Education; Research funding from Bayer, Sotio, Bristol-Myers Squib, Merck, Takeda, Dendreon/Valient, Jannsen, Medivation/Astellas, Genentech, Pfizer, Endocyte (Novartis), and Support for research travel from Bayer and Genentech. Currently employed by Surface Oncology.

**UDG:** Reports grant/funding from AstraZeneca, Roche, Sanofi. Board member of Astellas, Bayer, BMS, Ipsen, Janssen, Merck, Pfizer, Sanofi. Support for research travel for BMS, Ipsen, Janssen, Pfizer.

**SJC:** Reports personal fees from Roche, Janssen, MSD, Astellas, Bayer, AstraZeneca. Research grant from Clovis Oncology, AstraZeneca, Astex Pharmaceuticals, outside the submitted work.

**EYY:** Reports consulting fees from Abbvie, Advanced Accelerator Applications, Bayer, Clovis, Janssen, Merck, Sanofi. Research grant/funding to institution from Bayer, Blue Earth, Daiichi-Sankyo, Dendreon, Merck, Pharmacyclics, Seattle Genetics, Taiho, outside the submitted work.

**Highlights**

* Optimal chemotherapy for cisplatin-treated, recurrent metastatic urothelial carcinoma is unclear
* There is no significant difference in outcomes between platinum retreatment and non-platinum chemotherapy
* Treatment outcomes did not vary based on time from previous cisplatin-based chemotherapy
* These findings can provide patient and provider flexibility in selection of systemic chemotherapy
* This data is particularly relevant for those patients who are not ideal candidates for immune-oncology therapy

**Abstract**

**Background:**

Optimal choice of first-line chemotherapy for patients who received cisplatin for locally-advanced urothelial carcinoma (UC) and who recur with metastatic disease is unclear. We compared the efficacy of platinum (PBC) vs non-platinum (NPBC) based first-line chemotherapy for these patients.

**Patients and Methods**

Data were collected from the Retrospective International Study of Cancers of the Urothelial Tract (RISC), a database of 3,024 patients from 28 international academic centers from 2005 to 2012. Patient inclusion criteria included: 1) predominant UC, 2) any primary tumor site, 3) cT2-4, cN0-N2, and cM0), 4) administration of cisplatin-containing chemotherapy in the locally-advanced setting, and 5) administration of cytotoxic chemotherapy in the first-line metastatic setting. Multivariate Cox Proportional Hazards models were used to show progression-free survival (PFS) and overall survival (OS) from the last day of cisplatin-based treatment to date of censor.

**Results:**

Eligibility criteria for analysis was met by 149 patients (n=86 PBC, n=63 NPBC). Median OS was 8.7 (95% CI: 7.5 to 11.2) and 10.3 months (95% CI: 7.4 to 13.1) for PBC and NPBC, respectively. Neither OS nor PFS differed for PBC vs NPBC (OS HR: 1.0, 95% CI: 0.6 – 1.6, PFS HR: 0.8, 95% CI: 0.6 – 1.2). A greater number of previous cisplatin-based cycles (3-4 vs 1-2, HR: 0.4, 95% CI: 0.2 – 1.0) and whether surgery was performed (HR: 0.4, HR: 0.2 – 0.9) was associated with increased OS.

**Conclusion:**

There is no significant outcome difference between PBC vs NPBC in patients with metastatic-recurrent UC who previously received cisplatin-based chemotherapy for locally-advanced disease.

**MicroAbstract**

The optimal chemotherapy regimen for recurrent metastatic urothelial carcinoma following previous cisplatin-based chemotherapy, administered for locally-advanced disease, remains unclear. We found no differences in clinical outcomes between patients who received platinum versus non-platinum based first-line chemotherapy for metastatic recurrence. Time from prior cisplatin did not identify ideal candidates for platinum re-treatment. These findings support flexibility in selection of chemotherapy regimen.

**Keywords** cisplatin, first-line, metastatic, platinum, urothelial carcinoma

**Introduction**

Neo-adjuvant or adjuvant chemotherapy has an integral role in the treatment of muscle invasive bladder cancer, contributing significant improvements in overall survival.1-3  Combination chemotherapy regimens that contain cisplatin are strongly recommended.4,5 Unfortunately, in patients that relapse with metastasis after chemotherapy for locally-advanced disease, the prognosis is generally poor and the treatment options are limited.6-7 Platinum-based chemotherapy (PBC) has been the standard of care in patients with metastatic disease, with an overall survival (OS) of 9 to 15 months.8

In recent years, immune checkpoint inhibitors have shifted the treatment paradigm. Anti-PD-L1 therapies, including atezolizumab, durvalumab and avelumab, and anti-PD-1 therapies, including nivolumab and pembrolizumab, have received United States Food and Drug Administration (FDA) approval in the treatment of metastatic urothelial carcinoma.9 Erdafitinib, has received accelerated FDA approval for patients with locally advanced inoperable or metastatic urothelial carcinoma with fibroblast growth factor receptor (FGFR2 or FGFR3) alterations who progressed on prior platinum-containing chemotherapy.10 Most recently, enfortumab vedotin, a Nectin-4-directed antibody and microtubule inhibitor conjugate, was FDA approved on an accelerated pathway for patients with advanced urothelial cancer who progressed on previous chemotherapy and immunotherapy.11

Clinical decision making for treatment selection of first-line therapy for metastatic urothelial carcinoma is becoming more complicated. National Comprehensive Cancer Network (NCCN) guidelines recommend gemcitabine and cisplatin (GC) or dose-dense methotrexate, vinblastine, Adriamycin and cisplatin (MVAC) as preferred combination chemotherapy regimens for patients who are cisplatin eligible.4 However, these guidelines may not take into account prior receipt of cisplatin-combination therapy in the locally-advanced disease setting. In cisplatin-ineligible patients, preferred chemotherapy regimens range from carboplatin combination regimens, taxane-based, or single-agent chemotherapy. NCCN guidelines suggest non-cisplatin-containing regimens for patients who have renal impairment and other comorbidities.4,5 More recently, patients who are cisplatin-ineligible may receive atezolizumab or pembrolizumab if PD-L1 immunostaining is at a high level.12 However, if a patient is completely platinum ineligible, either atezolizumab or pembrolizumab may be administered.

A clinical dilemma of whether to give more platinum therapy exists in patients who have received cisplatin chemotherapy in the locally-advanced disease setting and then relapse with metastatic disease. Physicians and patients must choose between more platinum chemotherapy, a chemotherapy regimen with a different mechanism of action, or immunotherapy. A multitude of factors are usually considered, such as type of past systemic therapy agents received and response, time from previous chemotherapy, cisplatin eligibility, and performance status. The current label for PD-(L)1 antibody therapy is if a patient received prior platinum chemotherapy for metastatic disease or if prior platinum was administered for localized disease within one year. Hence, if prior platinum was received over a year ago in the perioperative setting, there is no label that supports the use of immunotherapy. Choosing between retreatment with another platinum chemotherapy regimen or a different cytotoxic therapy is highly relevant.

In this study, we sought to ascertain whether return to a platinum regimen or switch to a non-platinum chemotherapy would have superior outcomes. Specifically, the aim of our retrospective analysis is to compare the efficacy of platinum (PBC) versus non-platinum (NPBC) based first-line chemotherapy regimens for patients with metastatic urothelial carcinoma after receiving prior cisplatin-based chemotherapy for locally-advanced disease, using the Retrospective International Study of Cancers of the Urothelial Tract (RISC) database.13

**Materials and Methods**

Retrospective International Study of Cancers of the Urothelial Tract (RISC) includes individual patient-level data from 3,024 patients with muscle-invasive, advanced or non-UC histology who received systemic therapy in any clinical setting. This database consists of patient data abstracted from 28 centers treated between 2005 and 2012.

For this analysis, data was extracted to select patients who fulfilled the following requirements: 1) predominant urothelial carcinoma, 2) any primary tumor site, 3) no initial presence of metastatic disease (cT2-4, cN0-N2, and cM0), 4) administration of cisplatin-containing chemotherapy in the locally-advanced (e.g. neo-adjuvant or adjuvant) setting, and 5) administration of cytotoxic chemotherapy in the first-line metastatic setting. Patients with incomplete data relevant to either their treatment dates or survival status were excluded.

Type of first-line chemotherapy for metastatic disease was the primary predictor variable. It was classified according to receipt of platinum-based (PBC) or other regimens (NPBC). Overall survival (OS) was the primary endpoint. Survival status ascertainment entailed patients designated as alive or dead, with or without disease. Secondary endpoints included progression-free survival (PFS) and investigator-designated response to chemotherapy. Progression was defined as investigator-designated radiographic progression, symptomatic progression, or disease specific death. Response criteria was investigator-designated without central review, designated time intervals for imaging or utilization of formal Response Evaluation Criteria In Solid Tumors (RECIST) criteria.

**Statistical Analyses**

Descriptive statistics were used to summarize demographics, clinical and treatment characteristics by type of first-line chemotherapy for metastatic disease (NPBC vs PBC). Cox Proportional Hazards models were used to estimate OS and PFS. Kaplan Meier curves were generated to graphically represent outcome events over time. Multivariate models were adjusted for age, gender, Eastern Cooperative Oncology Group (ECOG-PS), Charlson comorbidity index (CCI), surgery, T and N stage, albumin, number of initial cisplatin cycles, liver and brain metastases, and time from last chemotherapy. Time to event analysis for both OS and PFS began on the last date of first-line chemotherapy used for localized disease. Subjects were censored on date of death or last follow up. In order to conserve degrees of freedom with limited sample size, parsimonious models were limited to primary independent and secondary independent variables that appreciable modified model fit and risk estimates. Analysis were performed using SAS (version 9.4, Cary NC). A two-sided p value of <0.05 was considered statistically significant.

**Results**

From 2005 to 2012, a total of 3,024 patients were included in the RISC database. Overall, 2259 patients had urothelial carcinoma. Of those with urothelial carcinoma, 2086 patients were clinically T2-4, N0-2, and M0. Cisplatin combination chemotherapy was administered to 891 of these patients for locally-advanced disease, and 399 of these patients later relapsed with metastatic disease. Of these relapsed patients, 207 patients were treated with first-line chemotherapy for metastatic disease. Finally, 54 patients were excluded due to incomplete treatment data and 4 were excluded due to missing survival data, leaving a total of 149 patients eligible for analysis.

Of the 149 patients included in this analysis, 86 patients were treated with first-line PBC and 63 patients received a NPBC regimen for metastatic disease. Patient characteristics are included in Table 1. The majority of patients (82.6%) were male, and 71% of patients were current or former smokers. There were essentially no significant differences in these baseline demographics between the PBC and NPBC groups, with the exception of smoking history. This significant difference (p = 0.01) between the PBC and NPBC groups may be attributed to the fact there were more never smokers in the NPBC group (27% vs 19%). Seventy-one/86 (82.5%) PBC patients and 53/63 (84.1%) NPBC patients underwent surgery. Twelve/149 (8.1%) patients received local definitive radiation, some from the PBC (n=7/12, 58.3%) and some from the NPBC (n=5/12, 41.7%) groups. Seven of these 12 patients who received radiation also underwent cystectomy. Of these patients, 4/7 (57.1%) received PBC and 3 (42.9%) received NPBC.

Of the total 149 patients in the analysis, neoadjuvant therapy was administered in 76/149 (51%), adjuvant therapy in 69/149 (46.3%), and both in 4/149 (2.7%). Of the 76 patients who received neoadjuvant cisplatin-based therapy for localized disease, 45 (59.2%) eventually received PBC and 31 (40.8%) eventually received NPBC for first-line metastatic recurrence treatment. Thirty-eight/69 (55.1%) of the adjuvant cisplatin-based therapy patients later received PBC, and 31 (44.93%) received NPBC treatment for metastatic recurrence. Three/4 (75.0%) patients who received both adjuvant and neoadjuvant treatment received PBC and 1/4 (25%) received NPBC for metastatic recurrence.

Of the 86 patients that received first-line PBC for metastatic disease, 45/86 (52.3%) patients received carboplatin and 41/86 (47.7%) patients received cisplatin. The most common NPBC regimens included taxanes, gemcitabine, pemetrexed, and fluorouracil. Thirty-six/63 (57.1%) patients received paclitaxel and 12/63 patients (19.0%) received docetaxel. Eleven/63 patients (17.5%) received gemcitabine, 3/63 (4.8%) patients received pemetrexed, and 1/63 (1.6%) received fluorouracil. Of the 63 patients that received NPBC regimens, 40/63 (63.5%) received single agent therapy and 23/63 (36.5%) received combination regimens.

Overall survival was not statistically different between the PBC and NPBC groups. Median OS was 8.7 (95% CI: 7.5 to 11.2) and 10.3 months (95% CI: 7.4 to 13.1) for PBC and NPBC respectively (Figure 1). In the univariate analyses, current smoking status (HR: 1.8, 95% CI: 1.0 to 3.3, p = 0.03) and number of previous cisplatin cycles received (3-4 vs. 1-2) (HR: 0.4, 95% CI: 0.2 to 0.8, p = 0.02) were significantly associated with OS.

In the final multivariable model for the entire study population, the HR for OS for PBC versus NPBC was 1.0, 95% CI 0.6-1.6. The association with number of previous cisplatin-based chemotherapy cycles (3-4 vs. 1-2, HR: 0.4, 95% CI 0.3 – 0.9, p = 0.03) and whether surgery was performed (HR: 0.44, 95% CI 0.3 – 0.8, p = 0.003) was retained. Time from chemotherapy for locally-advanced disease until chemotherapy for metastatic recurrence (HR: 0.9, 95% CI: 0.9 – 1.0, p = 0.2) and retreatment with platinum (HR: 1.0, 95% CI: 0.7 – 1.6, p = 0.9) were not associated with OS for the total population.

Stratified modeling for PBC and NPBC groups for variables relationship to OS is shown in Table 2. This demonstrated an association between age at diagnosis (HR: 1.1, 95% CI: 1.0 – 1.1, p = 0.02), number of previous chemotherapy cycles (3-4 vs. 1-2) (HR: 0.4, 95% CI: 0.1 – 1.0, p = 0.05) and whether surgery was performed (HR: 0.4, HR: 0.2 – 0.9, p = 0.03) with OS for the PBC treatment group. In the NPBC group, whether surgery was performed (HR: 0.2, 95% CI: 0.05 – 0.6, p = 0.01) and a CCI of three or greater (HR: 0.3, 95% CI: 0.1 – 1.0, p = 0.05) had association with OS. Neither treatment group had an association with OS in regards to length of time from chemotherapy for locally-advanced disease to initiation of first-line chemotherapy for metastatic disease (PBC HR: 1.0, 95% CI: 0.9 – 1.0, p = 0.5 and NPBC HR: 1.0, 95% CI: 0.9 – 1.0, p = 0.3).

Investigator-designated PFS is shown in Figure 2. Median PFS was 6.3 months (95% CI: 4.1 to 7.2) and 4.2 months (95% CI: 2.8 to 6.4) for PBC and NPBC chemotherapy (HR: 0.8, 95% CI: 0.6 – 1.2, p = 0.4) groups, respectively. There was no significant difference in PFS for patients that were retreated with PBC for metastatic disease compared to patients treated with NPBC (HR: 0.8, 95% CI: 0.6 to 1.2, p = 0.5).

In the univariate analyses, number of previous cisplatin-based cycles received (3-4 vs. 1-2) (HR: 0.6, 95% CI: 0.3 to 0.9, p = 0.04) were significantly associated with PFS. In the final multivariable model for the entire study population, patients with a CCI of three or greater (HR: 0.5, 95% CI: 0.3 to 0.8, p = 0.009) and number of previous cisplatin-based cycles received (3-4 vs. 1-2) (HR: 0.5, 95% CI: 0.3 to 0.9, p = 0.03) were significantly associated with PFS.

Stratified modeling between PBC and NPBC groups in the multivariable analysis demonstrated no variables to be associated with PFS in the PBC group (Table 3).

There were no significant differences for investigator-designated response to chemotherapy between the PBC and NPBC groups (p = 0.6; Table 4).

**Discussion**

Currently, the optimal selection for chemotherapy for recurrent metastatic urothelial carcinoma following previous cisplatin-based chemotherapy, administered for locally-advanced disease, remains an area of uncertainty. Necchi et al. found longer time from previous chemotherapy to be prognostic for better survival with cisplatin rechallenge14, whereas Locke et al. demonstrated reinstituting cisplatin-based chemotherapy for metastatic disease after previous cisplatin chemotherapy may have a worse impact on overall survival.15 Our study retrospectively investigated outcomes of PBC and NPBC in the first-line setting for metastatic urothelial carcinoma after previous cisplatin-based chemotherapy received for locally-advanced disease, and from this cohort of patients, we could not confirm either of those previous findings.

Our analyses account for the impact of known prognostic factors for metastatic urothelial carcinoma, notably the time from prior previous chemotherapy, ECOG-PS, and smoking history based on their prognostic impact in previous reports.16-18 Those who previously underwent radical surgery or who received 3-4 cycles of cisplatin had better OS with PBC. This is not surprising as patients who received very few cycles of cisplatin likely either had highly chemotherapy resistant disease and progressed through it or had significant comorbidities precluding more cisplatin exposure. In contrast, time from last chemotherapy and ECOG-PS were not significant on multivariable analysis. The former is surprising, given that there are manuscripts that provide hints that longer duration of time between platinum chemotherapy retreatment portends better outcomes, presumably through a resensitization effect.14,17,18

This study has several limitations that derive mainly from its retrospective nature. A variety of factors are taken into account when considering selection of first-line chemotherapy regimen and cannot be fully captured in a retrospective chart review. Another major limitation in this study are the designations of disease response and progression. These were investigator-defined without any formal, mandated criteria, such as RECIST 1.1. Moreover, no standardized imaging time points were mandated, which likely had effect on PFS results.

Our results suggest that the chemotherapy regimen utilized for metastatic urothelial carcinoma in patients who received prior cisplatin-based chemotherapy for locally-advanced disease has no significant difference in clinical outcomes. We believe this adds valuable information for physician and patient decision making when selecting systemic therapy at recurrence. Although, the field is moving towards PD-1/PD-L1 antibody therapy in this clinical situation, there are still situations where a strong clinical rationale or preference may lead towards return to cytotoxic chemotherapy for first-line treatment of metastatic recurrence. This includes patients who may be progressing rapidly, who may have autoimmune disorders or other contraindications to immunotherapy, who may have liver metastases that may not respond as well to PD-1/PD-L1 antibody therapy19, 20, and simply those patients who received cisplatin for locally-advanced disease more than a year prior, since regulatory approvals do not support the use of PD-1/PD-L1 antibody therapy in this patient population. Therefore, we recognize that this manuscript provides both a weakness and a strength that the patients were all treated in an era prior to the widespread use of PD-1/PD-L1 antibody therapy. It does not allow us to compare different chemotherapy regimens with PD-1/PD-L1 antibody therapy, yet it does allow a clean cohort where chemotherapy effect was not confounded by such therapies.

**Conclusion**

This retrospective analysis found no outcome difference between platinum-based vs non-platinum based chemotherapy regimens in patients with metastatic recurrent urothelial carcinoma who previously received cisplatin-based chemotherapy in the locally-advanced setting. This supports provider and patient flexibility in chemotherapy regimen selection for those who cannot or choose not to receive anti-PD-1/PD-L1 therapy.

**Clinical Practice Points**

1. Clinical decision making after a patient receives cisplatin chemotherapy in a locally-advanced disease setting and relapses with metastatic disease is complex. Although the field is moving toward PD-1/PD-L1 antibody therapy in this clinical situation, there are situations where a strong clinical rationale or preference leads towards return to cytotoxic chemotherapy for first-line treatment of metastatic recurrence.
2. Leveraging a multicenter retrospective study, we found that the chemotherapy regimen utilized for metastatic urothelial carcinoma recurrence in patients who received prior cisplatin-based chemotherapy for locally-advanced disease has no significant difference in clinical outcomes.
3. Time from receipt of prior cisplatin chemotherapy did not associate with outcomes with platinum chemotherapy retreatment for metastatic recurrence.
4. Our results support patient and provider flexibility for those who cannot or choose not to receive immunotherapy.

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**Table 1 – Patient Characteristics**

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| **Table 1. Patient Characteristics** |
|   | **Platinum (n = 86)** | **Non-Platinum (n = 63)** | **P-value** |
| **Variable** | Median (Range)/Frequency (%) | Median (Range)/Frequency (%) |   |
| **Age** | 62 (56 - 67) | 61 (56-67) | 0.6 |
|   |  |  |   |
| **Gender** |  |  |   |
| Male | 73 (84.9%) | 50 (79.4%) | 0.4 |
| Female | 13 (15.1%) | 13 (20.6%) |   |
|   |  |  |   |
| **Smoking History** |  |  |   |
| Never | 16 (18.6%) | 17 (27.0%) | 0.01 |
| Former | 30 (34.9%) | 32 (50.8%) |   |
| Current | 31 (36.0%) | 13 (20.6%) |   |
| Missing | 9 (10.5%) | 1 (1.6%) |   |
|   |  |  |   |
| **Charlson Comorbidity Index** |  |  |   |
| 0 | 34 (39.5%) | 26 (41.3%) | 0.8 |
| 1-2 | 34 (39.5%) | 22 (34.9%) |   |
| 3+ | 18 (21.0%) | 15 (23.8%) |   |
|   |  |  |   |
| **ECOG-PS** |  |  |   |
| 0 | 46 (53.5%) | 40 (63.5%) | 0.2 |
| 1-2 | 25 (29.1%) | 18 (28.6%) |   |
| Missing | 15 (17.4%) | 5 (7.9%) |   |
|   |  |  |   |
| **cT stage** |  |  |   |
| Tis, T1, T2 | 46 (53.5%) | 30 (47.6%) | 0.3 |
| 3 | 25 (29.1%) | 26 (41.3%) |   |
| 4 | 13 (15.1%) | 5 (7.8%) |   |
| Missing | 2 (2.3%) | 2 (3.1%) |   |
|   |  |  |   |
| **cN stage** |  |  |   |
| 0 | 62 (72.1%) | 45 (71.4%) | 0.6 |
| 1 | 7 (8.1%) | 7 (11.1%) |   |
| 2 | 12 (14.0%) | 10 (15.9%) |   |
| Missing | 5 (5.8%) | 1 (1.6%) |   |
|   |  |  |   |
| **Surgery**  |  |  |   |
| No | 15 (17.4%) | 10 (15.9%) | 0.7 |
| Yes | 71 (82.6%) | 53 (84.1%) |   |
|   |  |  |   |
| **Liver/Brain Metastasis** |   |  |   |
| No | 73 (84.9%) | 52 (82.5%) | 0.7 |
| Yes | 13 (15.1%) | 11 (17.5%) |   |
|   |  |  |   |
| **Number of Previous Cisplatin Cycles Received** |  |  |   |
| 1-2 | 10 (11.6%) | 6 (9.5%) | 0.7 |
| 3-4 | 60 (69.8%) | 40 (63.5%) |   |
| 5-9 | 12 (14.0%) | 15 (23.8%) |   |
| Missing | 4 (4.6%) | 2 (3.2%) |   |

**Table 2 – Adjusted Hazard Ratio Risk Estimates for Overall Survival by Treatment for Metastatic Disease**

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| **Table 2. Adjusted Hazard Ratio Risk Estimates for Overall Survival by Treatment for Metastatic Disease** |
|  | **Platinum (n = 86)** | **Non-Platinum (n = 63)** |
| **Parameters** | **Hazard Ratio (95% CI)** | **P-value** | **Hazard Ratio (95% CI)** | **P-value** |
| **Age at Diagnosis, Years** | 1.1 (1.0 - 1.1) | 0.02 | 1.0 (0.9 - 1.0) | 0.9 |
| **Gender, Male vs Female** | 1.4 (0.6 - 3.0) | 0.4 | 0.8 (0.3 - 2.2) | 0.7 |
| **Smoking History** |  |  |  |   |
| Current vs Never | 2.6 (1.0 - 6.5) | 0.04 | 1.6 (0.5 - 4.6) | 0.4 |
| Former vs Never | 1.8 (0.7 - 4.7) | 0.2 | 2.5 (0.9 - 7.1) | 0.1 |
| Unknown vs Never | 3.8 (0.9 - 15.3) | 0.05 | 1.3 (0.1 - 15.3) | 0.8 |
| **CCI** |  |  |  |   |
| 1-2 vs 0 | 1.2 (0.6 - 2.5) | 0.7 | 1.0 (0.4 - 2.8) | 1.0 |
| 3+ vs 0 | 1.4 (0.5 - 3.6) | 0.5 | 0.3 (0.1 - 1.0) | 0.05 |
| **T Stage** |  |  |  |   |
| 3 vs <2 | 1.5 (0.7 - 3.4) | 0.3 | 0.7 (0.3 - 1.6) | 0.5 |
| 4 vs <2 | 0.6 (0.2 - 1.8) | 0.4 | 3.3 (0.5 - 21.4) | 0.2 |
| Unknown vs <2 | 11.8 (0.8 – 174.0) | 0.07 | 0 (0 - 0) | 1.0 |
| **N Stage** |  |  |  |   |
| 1 vs 0 | 0.6 (0.2 - 1.9) | 0.3 | 1.7 (0.5 - 5.3) | 0.4 |
| 2 vs 0  | 0.9 (0.4 - 2.4) | 0.8 | 0.4 (0.07 - 2.2) | 0.3 |
| Unknown vs 0 | 0.2 (0.4 - 2.4) | 0.9 | 0.5 (0 - 0) | 1.0 |
| **ECOG** |  |  |  |   |
| 1,2 vs 0 | 1.5 (0.7 - 3.2) | 0.3 | 0.9 (0.3 - 2.5) | 0.8 |
| Unknown vs 0 | 0.9 (0.4 - 2.4) | 0.9 | 1.5 (0.3 - 7.3) | 0.7 |
| **Number of Previous Cisplatin Cycles** |  |  |  |   |
| 3-4 vs 1-2 | 0.4 (0.1 – 1.0) | 0.05 | 1.0 (0.2 - 4.4) | 1.0 |
| 5-9 vs 1-2 | 0.8 (0.2 - 2.6) | 0.7 | 1.0 (0.2 - 4.4) | 1.0 |
| Unknown vs 1-2 | 0.9 (0.1 - 7.0) | 1.0 | 0 (0 - 0) | 1.0 |
| **Surgery, Yes vs No** | 0.4 (0.2 - 0.9) | 0.03 | 0.2 (0.05 - 0.6) | 0.01 |
| **Time from Previous Chemotherapy, Months** | 1.0 (0.9 - 1.0) | 0.5 | 1.0 (0.9 - 1.0) | 0.3 |

**Table 3 – Adjusted Hazard Ratio Risk Estimates for Progression Free Survival by Treatment for Metastatic Disease**

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| **Table 3. Adjusted Hazard Ratio Risk Estimates for Progression Free Survival by Treatment for Metastatic Disease** |
|  | **Platinum (n = 86)** | **Non-Platinum (n = 64)** |
| **Parameters** | **Hazard Ratio (95% CI)** | **P-value** | **Hazard Ratio (95% CI)** | **P-value** |
| **Age at Diagnosis, Years** | 1.0 (0.9 - 1.0) | 0.9 | 1.0 (0.9 - 1.1) | 0.3 |
| **Gender, Male vs Female** | 2.0 (0.9 - 4.3) | 0.06 | 1.0 (0.4 - 2.5) | 0.9 |
| **Smoking History** |  |  |  |   |
| Current vs Never | 1.2 (0.5 – 2.8) | 0.6 | 0.7 (0.3 - 1.8) | 0.5 |
| Former vs Never | 1.2 (0.5 - 2.7) | 0.09 | 0.7 (0.3 - 1.7) | 0.5 |
| Unknown vs Never | 0.9 (0.2 - 3.2) | 0.8 | 0.5 (0.05 – 5.5) | 0.6 |
| **CCI** |  |  |  |   |
| 1-2 vs 0 | 1.4 (0.8 - 2.8) | 0.3 | 1.0 (0.4 - 2.5) | 0.9 |
| 3+ vs 0 | 1.2 (0.5 – 3.0) | 0.6 | 0.4 (0.1 – 0.9) | 0.6 |
| **T Stage** |  |  |  |   |
| 3 vs <2 | 1.3 (0.7 - 2.7) | 0.4 | 1.2 (0.5 - 2.7) | 0.7 |
| 4 vs <2 | 0.9 (0.4 – 2.4) | 0.9 | 3.0 (0.6 – 14.5) | 0.2 |
| Unknown vs <2 | 0 (0 – 0) | 1.0 | 0 (0 – 0) | 1.0 |
| **N Stage** |  |  |  |   |
| 1 vs 0 | 2.3 (0.9 - 6.2) | 0.09 | 0.8 (0.3 – 2.3) | 0.6 |
| 2-3 vs 0  | 1.3 (0.5 - 3.1) | 0.3 | 0.5 (0.1 – 1.8) | 0.3 |
| Unknown vs 0 | 0.2 (0.04 – 1.14) | 0.07 | 0 (0 - 0) | 1.0 |
| **ECOG** |  |  |  |   |
| 1,2 vs 0 | 0.9 (0.5 - 1.9) | 0.9 | 1.3 (0.6 – 2.9) | 0.6 |
| Unknown vs 0 | 0.5 (0.2 - 1.2) | 0.1 | 1.9 (0.6 – 6.2) | 0.3 |
| **Number of Previous Cisplatin Cycles** |  |  |  |   |
| 3-4 vs 1-2 | 0.7 (0.2 - 1.9) | 0.5 | 0.4 (0.1 - 1.4) | 0.2 |
| 5-9 vs 1-2 | 0.9 (0.3 - 2.6) | 0.8 | 0.7 (0.2 - 2.5) | 0.5 |
| Unknown vs 1-2 | 1.6 (0.29 – 8.9)  | 0.6 | 0.2 (0.02 – 1.9) | 0.2 |
| **Surgery, Yes vs No** | 0.6 (0.3 - 1.3) | 0.2 | 0.9 (0.2 - 3.0) | 0.8 |
| **Time from Previous Chemotherapy, Months** | 1.0 (0.9 - 1.0) | 0.6 | 1.0 (0.9 – 1.0) | 1.0 |

**Table 4 – Response to Chemotherapy**

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| **Table 6. Response to Chemotherapy Based on Treatment** |
| **Response** | **Platinum** | **Non-Platinum**  | **P-value** |
| Complete Response | 6 (7.0%) | 3 (4.8%) | 0.6 |
| Partial Response | 19 (22.1%) | 9 (14.3%) |   |
| Stable Disease | 16 (18.6%) | 14 (22.2%) |   |
| Progressive Disease | 28 (32.6%) | 21 (33.3%) |   |
| Not Evaluated | 10 (11.6%) | 11 (17.5%) |   |
| Missing | 7 (8.1%) | 5 (7.9%) |   |