Safety and Tolerability of Carboplatin and Paclitaxel in Cancer Patients with HIV (AMC-078), an AIDS Malignancy Consortium (AMC) Study

Missak Haigentz Jr.1, Page Moore2, Milan Bimali3, Timothy Cooley4, Joseph Sparano5, Michelle Rudek6, Lee Ratner7, David Henry8, Juan Ramos9, John Deeken10, Paul Rubinstein11, Elizabeth Chiao12∗,†

1Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA
2CorEvitas, Waltham, MA, USA
3University of Arkansas for Medical Sciences, Little Rock, AK, USA
4Boston Medical Center, Boston, MA, USA
5Mount Sinai School of Medicine, New York, NY, USA
6Johns Hopkins University School of Medicine, Baltimore, MD, USA
7Washington University School of Medicine, St. Louis, MO, USA
8Pennsylvania Hospital, Philadelphia, PA, USA
9University of Miami School of Medicine, Miami, FL, USA
10Inova Schar Cancer Institute, Fairfax, VA, USA
11John H. Stroger, Jr. Hospital of Cook County, Chicago, IL, USA
12MD Anderson Cancer Center, Baylor College of Medicine, Houston, TX, USA

∗Corresponding author; Elizabeth Chiao, MD, MPH, MD Anderson Cancer Center, Baylor College of Medicine, 1155 Pressler Street, Unit 1340, Houston, TX, USA. Tel: +1 713 792 1480; Email: eychiao@mdanderson.org

Abstract

Background: Persons living with human immunodeficiency virus are an underserved population for evidence-based cancer treatment. Paclitaxel and carboplatin (PCb) is an active regimen against a variety of solid tumors, including several seen in excess in patients with HIV infection. We performed a pilot trial to evaluate the safety of full-dose PCb in people living with human immunodeficiency virus and cancer.

Methods: Eligible patients, stratified by concurrent antiretroviral therapy (ART) that included CYP3A4 inhibitors or not, received paclitaxel (175 mg/m2) in combination with carboplatin (target AUC 6) intravenously every 3 weeks for up to 6 cycles.

Results: Sixteen evaluable patients received 64 cycles of PCb, including 6 patients treated with CYP3A4 inhibiting ART (ritonavir). The adverse event profile was consistent with the known toxicity profile of PCb, with no differences between the 2 strata. There were 4 partial responses (25%, 95% CI: 7%-52%), and overall, CD4+ lymphocyte count was similar after completion of therapy (median: 310/μL) compared with baseline values (median: 389/μL). Pharmacokinetic studies in 6 patients revealed no significant differences in Cmax or AUCinf for paclitaxel between the 2 cohorts.

Conclusion: Full doses of PCb chemotherapy are tolerable when given concurrently with ART in people living with human immunodeficiency virus with cancer, including patients receiving CYP3A4 inhibitors.

ClinicalTrials.gov Identifier: NCT01249443.

Key words: HIV; paclitaxel; carboplatin; ritonavir; antiretroviral

Lessons Learned

• The event profile and broad clinical activity of full-dose carboplatin and paclitaxel treatment in people living with HIV demonstrated an adverse effect profile consistent with the regimen in immunocompetent patients, no significant change in CD4+ cell counts after therapy, and no opportunistic infections.

• Pharmacokinetic studies in 6 patients stratified use of a potent CYP3A4 inhibitor (ritonavir) use revealed no significant differences in Cmax or AUCinf for paclitaxel, a CYP3A4 substrate.
Discussion

In this prospective study of full-dose paclitaxel and carboplatin (PCb) for advanced cancers in people living with HIV (Table 1), we found an adverse event profile consistent with the regimen in immunocompetent patients, no significant change in CD4+ cell counts after therapy, and no opportunistic infections. A total of 64 cycles of therapy were administered to 16 patients, for a median of 4 cycles per patient; all patients tolerated at least 2 full cycles of therapy. Three of 16 patients (19%) had durable partial responses ranging from 19 to 22 months (including patients with anal cancer, other squamous cell carcinoma, and follicular dendritic cell sarcoma), and 6 additional patients (38%) had disease stabilization. Ten percent of the patients experienced grade 3 or higher toxicities, the most common of which were granulocytopenia (40%), infection (15%), and anemia (15%); primary GCSF support was not permitted.

We found no evidence for pharmacokinetic interaction when ritonavir (potent CYP3A4 inhibitor) given at a “boosting dose” for ART was used in combination with paclitaxel, a substrate for CYP3A4 (Table 3). Of note, the C\text{max} was similar regardless of ART regimen, and there was no correlation of exposure with efficacy or tolerability.

Table 1. Patient characteristics

| Characteristics                  | Overall (N = 16) | Ritonavir (N = 6) | Non-ritonavir (N = 10) |
|---------------------------------|-----------------|-------------------|------------------------|
| Age, years, median (range)      | 56 (42-70)      | 53.5 (47-63)      | 58 (42-70)             |
| Gender                          |                 |                   |                        |
| Male                            | 10              | 3                 | 7                      |
| Female                          | 6               | 3                 | 3                      |
| Race and Ethnicity              |                 |                   |                        |
| Hispanic                        | 2               | 0                 | 2                      |
| Non-Hispanic/White              | 2               | 1                 | 1                      |
| Non-Hispanic/Black              | 12              | 5                 | 7                      |
| Histology                       |                 |                   |                        |
| Non-small cell lung             | 7               | 2                 | 5                      |
| Anal carcinoma                  | 3               | 2                 | 1                      |
| Other cancers\(^a\)             | 6               | 2                 | 4                      |
| Baseline CD4+ count median (range) | 389 (109-642) | 357.5 (109-576) | 403 (152-642)          |
| Baseline HIV Viral Load         |                 |                   |                        |
| Undetectable                    | 13              | 5                 | 8                      |
| Detectable                      | 3               | 1                 | 2                      |
| Vorinostat                      |                 |                   |                        |
| None                            | 14              | 0                 | 0                      |
| 400 mg PO BID days 1-5          | 2               | 0                 | 2                      |

\(^a\)Other cancers: Ritonavir group (breast cancer, esophageal squamous cell carcinoma); non-ritonavir group (cervical cancer; follicular dendritic cell sarcoma; squamous cell carcinoma of unknown primary site; adenocarcinoma of an unknown primary site).

Author disclosures and references available online.
Additional Details of Endpoints or Study Design

Eligibility Criteria
Eligibility criteria included histologically confirmed metastatic or unresectable malignancy with at least one measurable lesion (by RECIST), known HIV infection (positive ELISA, positive Western blot, or any other federally approved licensed HIV test) and CD4 count >100/μL, age >18 years, ECOG performance status 0-2, normal organ function and electrolytes within 2 weeks of study entry (leukocytes, >3000/μL, neutrophils >1500/μL, platelets, >100 000/μL, total bilirubin within normal institutional limits (WNL), AST(SGOT)/ALT(SGPT) <2.5-fold above the institutional upper limit of normal, serum creatinine WNL or >30 mL/minute/1.73 m² for patients with creatinine levels above institutional normal or normal serum magnesium and phosphorus. Exclusion criteria included chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C), persistent grade 2 or higher toxicity from prior cytotoxic therapy, grade 2 or higher neuropathy from other causes, treatment with other investigational agents, known brain metastases, history of hypersensitivity to agents used in the study, uncontrolled intercurrent illness, or pregnant or lactating women.

Antiretroviral Therapy
Patients were evaluated as treated either with ritonavir containing ART or others. Treatment with zidovudine or stavudine was not permitted due to potential for hematological toxicity. Paclitaxel dosing was not modified based on ART due to results from a prior trial of paclitaxel alone in people living with HIV concluding that despite pharmacokinetic differences the therapeutic effects were similar in patients on a CYP3A4 inhibitor-containing ART.1 However, patients were stratified to ritonavir or non-ritonavir cohorts to adequately capture differences in safety, efficacy, and pharmacokinetics.

Protocol Therapy
Patients received carboplatin (AUC 6 via 30-minute infusion) and paclitaxel (175 mg/m² via 1-hour infusion) intravenously every 3 weeks for a maximum of 6 cycles. Cycles were administered if neutrophil count was >1500/μL and platelets >100 000/μL, and once recovered from non-hematologic toxicity. Primary GCSF prophylaxis was not permitted, and toxicities were primarily managed with dose reduction. The original design of the study was a phase I trial evaluating the PCb combination with vorinostat (400 mg, 500 mg, or 600 mg orally on days 1-5 of each chemotherapy cycle); the study design was modified after the accrual of 2 patients who received the first vorinostat dose level (without prohibitive toxicity), due to a decision by the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) to suspend further development of vorinostat in solid tumors in NCT/CTEP-sponsored trials following a negative phase III trial of chemotherapy with vorinostat/placebo in non–small cell lung cancer.2

Patients were assessed with radiological studies every 2 cycles, and tumor response was assessed by RECIST. NCI Common Terminology Criteria for Adverse Events (CTCAE) were used for grading adverse events (version 4.0).

Pharmacokinetic Sampling and Evaluation
Plasma samples were obtained on cycle 1 day 1 after the first dose of paclitaxel. Paclitaxel concentrations were determined using liquid chromatography with tandem mass spectrometric detection with a lower limit of quantitation of 2 ng/mL.1 PK variables were calculated by standard noncompartmental methods using Phoenix WinNonlin (version 6.3; Pharsight A Certara Company, Cary, NC) as previously described.1

Statistical Analysis
Descriptive statistics were reported as median (range: min-max) for continuous variables and as a frequency for categorical variables. Descriptive statistics were computed for participant characteristics, response, adverse events, and paclitaxel pharmacokinetic variables. A 2-sided exact binomial 95% confidence intervals were calculated for the proportion of participants responding.
Carboplatin

| Generic/working name | carboplatin |
|----------------------|-------------|
| Drug type            | second-generation platinum compound |
| Schedule of administration | paclitaxel (175 mg/m²) in combination with carboplatin (target AUC 6) intravenously every 3 weeks for up to 6 cycles. |

**Patient Characteristics**

| Number of patients, male | 10 |
| Number of patients, female | 6 |
| Age, years | Median (range): 56 (42-70) |
| Performance status: ECOG | 0—0 |
| | 1—0 |
| | 2—0 |
| | 3—0 |
| | Unknown—0 |

**Adverse Events**

Table 2 shows data available for all grades, and grades 3 and 4.

**Pharmacokinetics/Pharmacodynamics**

**Pharmacokinetic (PK) Sampling and Evaluation**

Plasma samples were obtained on cycle 1 day 1 after the first dose of paclitaxel. Paclitaxel concentrations were determined using liquid chromatography with tandem mass spectrometric detection with a lower limit of quantitation of 2 ng/mL. PK variables were calculated by standard noncompartmental methods using Phoenix WinNonlin version 6.3 (Pharsight A Certara Company, Cary, NC) as previously described.

**Statistical Analysis**

Descriptive statistics were reported as median (range: min-max) for continuous variables and as a frequency for categorical variables. Descriptive statistics were computed for participant characteristics, response, adverse events, and paclitaxel pharmacokinetic variables. A 2-sided exact binomial 95% confidence interval were calculated for the proportion of participants responding.

**Assessment, Analysis, and Discussion**

Completion

| Investigator’s assessment | Study completed |
| | Active and should be pursued further |

Worldwide, approximately 37 million people are living with human immunodeficiency virus (HIV) infection, the virus that causes the acquired immunodeficiency syndrome (AIDS). HIV testing is recommended as a component of routine medical care, not just for individuals with known risk factors, including patients with cancer. Combination antiretroviral therapy (ART) has led to substantial declines in mortality in individuals living with HIV infection in the US and worldwide and the average life expectancy for people living with HIV infection is approaching that of the general population.

Although the risks of non-Hodgkin’s lymphoma and Kaposi’s Sarcoma, which are “AIDS-defining cancers,” are increased substantially in patients with HIV infection, the overall mortality and incidence of these cancers have declined with ART. In sharp contrast, other cancers have increased due to aging of the HIV population and increased (2-fold) rates of tobacco use than the general population. These common non-AIDS defining cancers, now accounting for more than one-half of all cancers in people living with HIV, may be broadly categorized as (1) tobacco-associated, such as non–small cell lung cancer and head and neck cancer, (2) age-associated cancers, such as cancers of the colon, breast, and prostate, and (3) viral-associated cancers, such as hepatocellular cancer and anal cancer.

Recent National Comprehensive Cancer Network (NCCN) guidelines recommend that ART should be continued in individuals with HIV infection and cancer; however, regimens may need to be modified to avoid drug-drug interactions with antineoplastic therapy. Despite increased awareness of cancer risk, evidence-based treatment approaches are generally lacking for this population due to historical exclusion from cancer clinical trials, and concern for tolerability of cancer therapies due to general immunosuppression and other biases have resulted in known treatment disparities. Ritonavir and cobicistat are antiretroviral agents commonly used in the treatment of advanced HIV infection that are strong CYP3A4 inhibitors that may interfere with the metabolism of paclitaxel, a CYP3A4 substrate. Although single-agent paclitaxel is a standard treatment option for advanced Kaposi sarcoma, rare reports of severe paclitaxel toxicity have been described that have been attributed to a potential pharmacokinetic interaction between paclitaxel, a known CYP3A4 substrate, with PIs such as ritonavir. A previous study evaluated the pharmacokinetics, adverse events, and efficacy of paclitaxel at a dose of 100 mg/m² with ART including protease inhibitors in 27 patients with Kaposi Sarcoma and HIV infection. Paclitaxel exposure as measured by AUC was higher among patients receiving PIs (nelfinavir, indinavir, and other multiple protease inhibitors; 5.5 ± 2.2
HIV viral load. were no complete and 4 (25%) partial responses as a best
Of the 16 patients who were evaluable for response, there
Antitumor Response and Survival
treatment delays were required in 5/24 cycles (21%) in the
Reasons for discontinuation of protocol therapy included
disease progression in 5 (31%), adverse events in 4 (25%),
Adverse Events
The worst grade adverse events (of any attribution) observed in any cycle of therapy are summarized in Table 2. The most common adverse events (all grades) were neutropenia (n = 17 events in 8 participants), anemia (n = 13 events in 8 participants), nausea (n = 12 events in 8 participants), peripheral sensory neuropathy (n = 12 events in 7 participants) and fatigue (n = 11 events in 10 participants). No opportunistic infections were observed, although one participant (treated with vorinostat prior to study modification) had a recurrence of herpes zoster.
Effect of Chemotherapy on CD4+ Lymphocyte Count and Viral Load
CD4+ lymphocyte counts were similar after completion of therapy in 12 patients (310 and 353/μL, median and mean) compared with baseline value in 16 patients (389 and 389/μL, median and mean).
Antitumor Response and Survival
Of the 16 patients who were evaluable for response, there
Response rate in cancers of the aerodigestive tract, and to determine whether there was any pharmacokinetic interaction between paclitaxel and ritonavir-containing ART.
Discussion
We performed a prospective study of carboplatin and paclitaxel, a commonly used chemotherapy regimen for the treatment of advanced cancer, in patients with HIV infection. We found an adverse event profile consistent with the cytotoxic regimen in immunocompetent patients, no significant change in CD4+ cell counts after therapy, and no opportunistic infections during chemotherapy. A total of 64 cycles of therapy were administered to 16 patients, for a median of 4 cycles per patient; all patients tolerated at least 2 full cycles of therapy. Three of 16 patients (19%) had durable partial responses ranging from 19-22 months (including patients with anal cancer, other squamous cell carcinoma, and follicular dendritic cell sarcoma), and 6 additional patients (38%) had disease stabilization.
Pharmacokinetic Analysis
Pharmacokinetic studies were performed in 6 patients: 2 in the ritonavir cohort, 3 in the non-ritonavir cohort (backbones of raltegravir or rilpivirine), and one not on ART. Due to the small number, the patient not on ART was combined with the non-ritonavir cohort. The other patients had incomplete collection of pharmacokinetic samples and therefore are not reported. Pharmacokinetic variables are listed in Table 3. There was a trend for paclitaxel maximal plasma concentration (Cmax) and area under the curve (AUCinf) to be elevated in the patients on the ritonavir cohort compared to the patients on the non-ritonavir cohort (Cmax 6.8 and 17.7 vs 4.7 ± 0.6 μM; AUCinf 50.2 vs. 22.8 ± 8.1 μM·hr). The duration spent at a paclitaxel concentration >0.05 μM (22.7 vs. 23.8 hr) was similar. Patients who experienced more significant adverse events had exposures that were in the range of the patients who did not experience the adverse events.

µM·h) compared to patients not receiving protease inhibitors (2.9 ± 0.7 µM·h). Based on these considerations, we performed a pilot study to evaluate the safety of carboplatin and paclitaxel (175 mg/m²), a commonly used chemotherapy regimen for a variety of cancers, in patients with cancer and HIV infection. Secondary objectives included determining the response rate in cancers of the aerodigestive tract, and to determine whether there was any pharmacokinetic interaction between paclitaxel and ritonavir-containing ART.

Results
Patient Population
Sixteen evaluable patients were accrued from 7 AMC sites between August 2011 and January 2016. The characteristics of the 16 evaluable patients are shown in Table 1, including 6 patients receiving ronavir-containing ART and 10 patients receiving non-ritonavir containing ART. Histology included non–small cell lung cancer in 7 patients, anal carcinoma in 3 patients, and other cancers in 6 patients. The median CD4 count was 389/μL, and 13 had an undetectable HIV viral load.

Treatment Administered
Sixteen patients received 65 cycles of PCb, including 6 patients in the ritonavir cohort who received 24 cycles of therapy (median 4, range 2-6), and 10 patients in the non-ritonavir cohort who received 41 cycles of therapy (median 4, range 2-6 cycles). All patients received at least 2 full cycles of therapy. No dose modification or concomitant GCSF was required for paclitaxel or carboplatin in any patient, although treatment delays were required in 5/24 cycles (21%) in the ritonavir cohort, and 8/41 cycles (20%) in the non-ritonavir cohort. Reasons for discontinuation of protocol therapy included completion of therapy in 5 (31%), adverse events in 4 (25%), and change to alternative therapy in 2 (13%) patients, with similar distribution in ritonavir and non-ritonavir cohorts.
We found a trend for paclitaxel maximal plasma concentration (Cmax) and area under the curve (AUCinf) to be elevated in the patients on the ritonavir cohort compared to the patients on the non-ritonavir cohort (Cmax 6.8 and 17.7 vs 4.7 ± 0.6 μM; AUCinf 50.2 vs. 22.8 ± 8.1 μM·hr). The duration spent at a paclitaxel concentration >0.05 μM (22.7 vs. 23.8 hr) was similar. Patients who experienced more significant adverse events had exposures that were in the range of the patients who did not experience the adverse events.
used in this study (175 mg/m²)—the dose commonly used in treating a wide variety of non-AIDS defining cancers, with the addition of carboplatin does not appear to alter the pharmacokinetics of paclitaxel, particularly in patients receiving non-ritonavir containing regimens. These findings are important since ritonavir-containing regimens are no longer first-line therapy for HIV disease.28

The strengths of the study include its prospective conduct which allowed for systematic and careful documentation of the adverse events and collection of multiple pharmacokinetic endpoints. The study’s weaknesses include the small sample size. However, because the patients were followed over time, we were able to capture the adverse events over a larger number of chemotherapy cycles. Related to the small sample size, each pharmacokinetic cohort for the ART regimens (the ritonavir and the non-ritonavir cohorts) had a small number of observations, limiting formal comparisons.

We conclude that full-dose PCb may be administered to people living with HIV and cancer in clinical practice, regardless of ART, with expected broad clinical activity. Routine use of GCSF or empiric dose reductions for presumed risk associated with PCb does not seem to be necessary based on our findings. PCb, albeit administered in a different schedule from this report, has been recently established as a standard of care for the management of advanced anal cancer25; our results provide additional confidence in treating patients with HIV infection. PCb is also an important cytotoxic chemotherapy backbone for the addition of targeted therapies (eg, bevacizumab),30 cancer immunotherapies (eg, pembrolizumab)31 and their combination (eg, bevacizumab plus atezolizumab).32 Although not all cytotoxic chemotherapy regimens can be evaluated as ritonavir containing regimens. These findings are important since ritonavir-containing regimens are no longer first-line therapy for HIV disease.28

Acknowledgments

Coordinated by the AIDS Malignancy Consortium (Joseph Sparano, MD, Chair) and supported in part by Public Health Service Grant No. UM1CA121947 and the National Cancer Institute, National Institutes of Health, and the Department of Health and Human Services. This research was also supported by the Analytical Pharmacology Core of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (NIH grants P30 CA06973 and UL1TR001079) and the Shared Instrument Grant (S10RR026824). The project described was supported by Grant Number UL1TR001079 from the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health (NIH) and NIH Roadmap for Medical Research, and its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCATS or NIH.

Conflict of Interest

Missak Haigentz, Jr.: Jazz Pharmaceuticals, Blueprint Medicines, AstraZeneca, Takeda (SAB); Paige Moore: CorEvitas (E [after work on this study]); Michelle A. Rudek: Celgene Corporation, Cullinan Apollo, RenovoRx, Taiho Pharmaceutical (RF [institutional]); Geminus Therapeutics, LLC (E, OI), GlaxoSmithKline (E [spouse]). The other authors indicated no financial relationships.

References

1. Cianfrocca M, Lee S, Von Roenn J, et al. Pilot study evaluating the interaction between paclitaxel and protease inhibitors in patients with human immunodeficiency virus-associated Kaposi’s sarcoma: an Eastern Cooperative Oncology Group (ECOG) and AIDS Malignancy Consortium (AMC) trial. Cancer Chemother Pharmacol. 2011;68(4):827-833.
2. Ramalingam SS, Maitland ML, Frankel P, et al. Carboplatin and paclitaxel in combination with either vorinostat or placebo for first-line therapy of advanced non-small-cell lung cancer. J Clin Oncol. 2010;28(1):56-62.
3. Gardner ER, Liu CT, Chu ZE, Figg WD, Sparreboom A. Determination of paclitaxel in human plasma following the administration of Genexol or Genetaxyl by liquid chromatography/tandem mass spectrometry. Rapid Commun Mass Spectrom. 2006;20(14):2170-2174.
4. Qaseem A, Snow V, Shekelle P, Hopkins R Jr, Owens DK; Clinical Efficacy Assessment Subcommittee, American College of Physicians. Screening for HIV in health care settings: a guidance statement from the American College of Physicians and HIV Medicine Association. Ann Intern Med. 2009;150(2):125-131.
5. Chiao EY, Dezube BJ, Krown SE, et al. Time for oncologists to opt in for routine opt-out HIV testing? JAMA. 2010;304(3):334-339.
6. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV outpatient study investigators. N Engl J Med. 1998;338(13):833-860.
7. Organization WH. Global Health Observatory (GHO) data: number of deaths due to HIV/AIDS. http://www.who.int/gho/hiv/epidemic_status/deaths_text/en/. 2015.
8. Siddiqi AE, Hall HI, Hu X, Song R. Population-based estimates of life expectancy after HIV diagnosis: United States 2008-2011. J Acquir Immune Defic Syndr. 2016;72(2):230-236.
9. Patel P, Hanson DL, Sullivan PS, et al; Adult and Adolescent Spectrum of Disease Project and HIV Outpatient Study Investigators. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. Ann Intern Med. 2008;148(10):728-736.
10. Shieh MS, Pfeiffer RM, Gail MH, et al. Cancer burden in the HIV-infected population in the United States. J Natl Cancer Inst. 2011;103(9):753-762.
11. Vandenbende MA, Roussillon C, Henard S, et al; ANRS EN20 Mortalité 2010 study group. Cancer-related causes of death among HIV-infected patients in France in 2010: evolution since 2000. PLoS One. 2015;10(6):e0129550.
12. Boldo R, Frazier EL, Dube SR, et al. Cigarette smoking prevalence among adults with HIV compared with the general adult population in the United States: cross-sectional surveys. Ann Intern Med. 2015;162(5):335-344.
13. Winstead TA, Man SFP, Hull M, Montaner JS, Sin DD. Epidemiology of lung cancer in patients with HIV infection. Chest. 2013;143(2):305-314.
14. Mani D, Haigentz M Jr, Aboulafia DM. Lung cancer in HIV infection. Clin Lung Cancer. 2012;13(1):6-13.
15. McLemore MS, Haigentz M Jr, Smith RV, et al. Head and neck squamous cell carcinomas in HIV-positive patients: a preliminary investigation of viral associations. Head Neck Pathol. 2010;4(2):97-105.
16. Berretta M, Cappellani A, Di Benedetto F, et al. Clinical presentation and outcome of colorectal cancer in HIV-positive patients: a clinical case-control study. *Onkologie.* 2009;32(6):319-324.
17. Oliver NT, Chiao EY. Malignancies in women with HIV infection. *Curr Opin HIV AIDS.* 2017;12(1):69-76.
18. Shieh MS, Goedert JJ, Moore RD, Platz EA, Engels EA. Reduced risk of prostate cancer in U.S. men with AIDS. *Cancer Epidemiol Biomarkers Prev.* 2010;19(11):2910-2915.
19. Marcus JL, Chao CR, Leyden WA, et al. Prostate cancer incidence and prostate-specific antigen testing among HIV-positive and HIV-negative men. *J Acquir Immune Defic Syndr.* 2014;66(5):495-502.
20. Wosnitzer MS, Lowe FC. Management of prostate cancer in HIV-positive patients. *Nat Rev Urol.* 2010;7(6):348-357.
21. Rudek MA, Flexner C, Ambinder RF. Use of antineoplastic agents in patients with cancer who have HIV/AIDS. *Lancet Oncol.* 2011;12(9):905-912.
22. Reid E, Suneja G, Ambinder RF, et al. Cancer in people living with HIV, version 1.2018, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw.* 2018;16(8):986-1017.
23. Rositch AF, Jiang S, Coghill AE, Suneja G, Engels EA. Disparities and determinants of cancer treatment in elderly Americans living with human immunodeficiency virus/AIDS. *Clin Infect Dis.* 2018;67(12):1904-1911.
24. Hossain MA, Tran T, Chen T, Mikus G, Greenblatt DJ. Inhibition of human cytochromes P450 in *vitro* by ritonavir and cobicistat. *J Pharm Pharmacol.* 2017;69(12):1786-1793.
25. Cianfrocca M, Lee S, Von Roenn J, et al. Randomized trial of paclitaxel versus pegylated liposomal doxorubicin for advanced human immunodeficiency virus-associated Kaposi sarcoma: evidence of symptom palliation from chemotherapy. *Cancer.* 2010;116(16):3969-3977.
26. Bundow D, Abouala N. Potential drug interaction with paclitaxel and highly active antiretroviral therapy in two patients with AIDS-associated Kaposi sarcoma. *Am J Clin Oncol.* 2004;27(1):81-84.
27. Schwartz JD, Howard W, Scadden DT. Potential interaction of antiretroviral therapy with paclitaxel in patients with AIDS-related Kaposi's sarcoma. *AIDS.* 1999;13(2):283-284.
28. Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV.* Department of Health and Human Services. Accessed June 24, 2021, [https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/guidelines-adult-adolescent-arv.pdf](https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/guidelines-adult-adolescent-arv.pdf)
29. Rao S, Sclafani F, Eng C, et al. International rare cancers initiative multicenter randomized phase II trial of cisplatin and fluorouracil versus carboplatin and paclitaxel in advanced anal cancer: InterAAct. *J Clin Oncol.* 2020;38(22):2510-2518.
30. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med.* 2006;355(24):2542-2550.
31. Paz-Ares L, Luft A, Vicente D, et al; KEYNOTE-407 Investigators. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med.* 2018;379(21):2040-2051.
32. Socinski MA, Jotte RM, Cappuzzo F, et al; IMpower150 Study Group. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med.* 2018;378(24):2288-2301.
### Table 2. Adverse events, worst grade in any cycle of therapy, by participants

| Adverse events                  | Ritonavir-based (N = 6) | Non-ritonavir based (N = 10) |
|--------------------------------|-------------------------|-----------------------------|
|                                | All grades | Grade 3 | Grade 4 | All grades | Grade 3 | Grade 4 |
| Hematologic                    |            |         |         |            |         |         |
| Anemia                         | 2          | 1       | 0       | 6          | 2       | 0       |
| Neutropenia                    | 3          | 0       | 1       | 4          | 2       | 2       |
| Lymphopenia                    | 0          | 0       | 0       | 2          | 0       | 0       |
| Thrombocytopenia               | 1          | 0       | 0       | 4          | 1       | 0       |
| Febrile Neutropenia            | 1          | 1       | 0       | 0          | 0       | 0       |
| Non-hematologic
| Gastrointestinal
| Nausea                         | 4          | 1       | 0       | 4          | 1       | 0       |
| Vomiting                       | 3          | 1       | 0       | 1          | 1       | 0       |
| Diarrhea                       | 2          | 0       | 0       | 3          | 0       | 0       |
| Colitis                        | 1          | 1       | 0       | 0          | 0       | 0       |
| Abdominal pain                 | 4          | 1       | 0       | 0          | 0       | 0       |
| Anorexia                       | 1          | 1       | 0       | 0          | 0       | 0       |
| Neurologic                     |            |         |         |            |         |         |
| Sensory neuropathy             | 4          | 1       | 0       | 3          | 0       | 0       |
| Pain in extremity              | 1          | 0       | 0       | 0          | 0       | 0       |
| Mucocutaneous                  |            |         |         |            |         |         |
| Mucositis                      | 2          | 0       | 0       | 0          | 0       | 0       |
| Metabolic and Laboratory       |            |         |         |            |         |         |
| Hyperglycemia                  | 1          | 0       | 0       | 2          | 0       | 0       |
| Hypoglycemia                   | 1          | 1       | 0       | 0          | 0       | 0       |
| Hyperkalemia                   | 1          | 0       | 0       | 1          | 0       | 0       |
| Hypokalemia                    | 0          | 0       | 0       | 1          | 0       | 0       |
| Hypocalcemia                   | 1          | 0       | 0       | 2          | 0       | 0       |
| Hypomagnesemia                 | 1          | 0       | 0       | 2          | 0       | 0       |
| Hyponatremia                   | 0          | 0       | 0       | 2          | 1       | 0       |
| Hypercalcemia                  | 1          | 0       | 1       | 0          | 0       | 0       |
| Abnormal liver function        | 1          | 0       | 0       | 3          | 0       | 0       |
| Abnormal renal function        | 0          | 0       | 0       | 1          | 0       | 0       |
| Cardiopulmonary                |            |         |         |            |         |         |
| Dyspnea                        | 3          | 0       | 0       | 4          | 1       | 0       |
| Cough                          | 3          | 0       | 0       | 2          | 0       | 0       |
| Aspiration                     | 1          | 1       | 0       | 0          | 0       | 0       |
| Thromboembolism                | 1          | 1       | 0       | 2          | 1       | 0       |
| Visceral arterial ischemia     | 1          | 1       | 0       | 0          | 0       | 0       |
| Constitutional and Other       |            |         |         |            |         |         |
| Fatigue                        | 6          | 0       | 0       | 4          | 0       | 0       |
| Dehydration                    | 1          | 1       | 0       | 1          | 1       | 0       |
| Weight loss                    | 2          | 0       | 0       | 1          | 0       | 0       |
| Limb edema                     | 1          | 0       | 0       | 1          | 0       | 0       |
| Infection\*                    | 1          | 0       | 0       | 2          | 1       | 0       |
| Non-cardiac chest pain         | 1          | 1       | 0       | 0          | 0       | 0       |

\*Includes adverse events observed in at least 1 participant.
\*Infection associated with normal absolute neutrophil count.
Table 3: Paclitaxel pharmacokinetic variables during cycle 1 (n = 6)

| Antiretroviral regimen       | n  | Pharmacokinetic parameters\(^a\) | Time > C\(_{\text{0.5 \mu M}}\) (hr) |
|------------------------------|----|----------------------------------|-------------------------------------|
|                              |    | C\(_{\text{max}}\) (µM)       | AUC\(_{\text{inf}}\) (µM·hr)  | Cl (L/hr/m\(^2\)) |                              |
| Ritonavir cohort             | 2  | 6.8, 17.7                       | 50.2                                | 4.1                | 22.7                         |
| Non-ritonavir cohort         | 4  | 4.7 ± 0.6                       | 22.8 ± 8.1                         | 9.8 ± 3.0          | 23.8 (22.2-24.8)             |

\(^a\)Values are reported as the average ± standard deviation (n) except for Time > C\(_{0.5 \mu M}\), which is reported as a median (range). The individual data are presented for 2 or fewer patients.

Abbreviations: AUC, area under the concentration–time curve; C\(_{\text{max}}\), maximal plasma concentration; Cl, systemic clearance; Time > C\(_{0.5 \mu M}\), time above a concentration of 0.5 µM; NR, not reportable.