Thank you for taking your time to review my article. We have reviewed your thoughtful comments and made some corrections and clarifications accordingly. We have attached point-by-point reply to each of your comments with revised manuscript. Also we received a professional English proofreading service one more time for the revised manuscript to meet the publication requirement (Language quality Grade A). (Editage, YNURS_3031_2).

Reviewer #1

The author reported a case of ATC after receiving a successful BRAF inhibitor targeting therapy along with an accepted side effects. It is encouraging and valuable. However, some information needed to be illustrated as well.

1. I wondered the thyroglobulin levels before and after the targeting therapy.

Thank you for your comment.
According to your comment, we have added the thyroglobulin level in outcome and follow-up section. (Page 9, Line 175~179)

After 3 and 6 months of surgery, the thyroglobulin (TG) levels were 0.14 and 0.21 ng/mL, respectively. (reference range for TG: 2–70 ng/mL). Medication was administered from 7 months after the first surgery. After 5 and 16 months of the target therapy, it measured 0.07 and 0.28 ng/mL, respectively. Throughout the follow-up period, the TG levels indicated a serologically complete response state.

2. Also, I'm curious about the mutation status of TERT promoter.

Thank you for the comment.

According to your comment, we have added the mutation status of TERT promoter in further diagnostic work-up section. (Page 8, Line 147 ~ 149)

However, no mutations were observed in the telomerase reverse transcriptase (TERT) promoter through next-generation sequencing analysis.

3. Also, considering the side effects frequently occured in the targeting therapy, it may be better to discuss the given doses and methods of derafenib and trametinib between their group and other groups.

Thank you for your good advice. We reviewed the current literatures regarding the dose adjustments in dabrafenib and trametinib medication. In the process of rewriting, we discussed the recent studies you recommended and supplemented the additional information about dose adjustment in discussion section. (Page 9, Line 187 ~ Page 10, Line 198)

Among the 34 participants in that clinical trial, medication was discontinued for six (17%) due to adverse events. [2,3] While there are some reports regarding the safety of dabrafenib and trametinib for BRAF V600E-mutant melanoma, there have been no studies on their safety and dose adjustment for treating ATC. [7] The drug manufacturer indicates that for dabrafenib, the dosage can be reduced to 150, 100, 75, or 50 mg BID; and for trametinib, dosages of 2, 1.5, or 1 mg QD can be adjusted while monitoring for side effects. A case has been reported where dosage adjustments (dabrafenib 150 mg QD+trametinib 1 mg QD) were made to prevent rhabdomyolysis and achieve therapeutic effects in BRAF V600E-mutant non-small cell lung cancer. [8] However, a study conducted on BRAF V600E-mutant melanoma reported higher side effects with full dose usage, but superior progression-free survival. [9] Due to the limited number of ATC cases that have been reported, studies involving dosage adjustments are lacking at this time.

According to some modifications, new references were supplemented in the process of rewriting introduction section. Newly added references are follows; (Page 13, Line 276 ~ 292)

7 **González-Barrallo I**, Castellón Rubio VE, Medina J, España S, Mujika K, Majem M, Aguado C, Cabrera Suárez M, Palacio I, Osterloh L, Martínez-Fernández A, García-Castaño A. Safety of combining dabrafenib plus trametinib in elderly BRAF V600 mutation-positive advanced melanoma patients: real-world data analysis of Spanish patients (ELDERLYMEL). *Melanoma Res* 2022; **32**: 343-352 [PMID: 35762583 doi: 10.1097/cmr.0000000000000837]

8 **Adachi Y**, Yanagimura N, Suzuki C, Ootani S, Tanimoto A, Nishiyama A, Yamashita K, Ohtsubo K, Takeuchi S, Yano S. Reduced doses of dabrafenib and trametinib combination therapy for BRAF V600E-mutant non-small cell lung cancer prevent rhabdomyolysis and maintain tumor shrinkage: a case report. *BMC Cancer* 2020; **20**: 156doi: 10.1186/s12885-020-6626-9]

9 **Flaherty KT**, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, Hamid O, Schuchter L, Cebon J, Ibrahim N, Kudchadkar R, Burris HA, 3rd, Falchook G, Algazi A, Lewis K, Long GV, Puzanov I, Lebowitz P, Singh A, Little S, Sun P, Allred A, Ouellet D, Kim KB, Patel K, Weber J. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med* 2012; **367**: 1694-1703 [PMID: 23020132 doi: 10.1056/NEJMoa1210093]

Reviewer #2

This is a good topic for treatment of advanced ATC。 However, I think authors should illusate the differenc of the clinical trail for fdabrafenib plus trametinib and this case.Otherwise, I could not clearly get the innovation of this case

Thank you for your good advice.
We discussed the difference between our report and clinical trial in discussion section. (Page 10, Line 203 ~ 215)

This case exhibits several differences from the existing clinical trials. [2,3] First, the pre-operative diagnosis through core needle biopsy was PTC; however, post-operative pathological examination confirmed mixed anaplastic (70%) and papillary (30%) carcinomas. This case provided insights into appropriate treatments for patients with PTC

and anaplastic dedifferentiation. Second, we were able to secure time and achieve definitive local control through multiple neck dissections in the context of recurrent neck relapses. Additionally, adjuvant chemotherapy was administered to treat the metastatic lung nodule. The ATA guidelines recommend dabrafenib plus trametinib as the optimal initial treatment for unresectable BRAF V600E-mutant ATC. [4] This case is unique because we performed complete resection through surgery and the patient received new targeted chemotherapy rather than conventional concurrent chemoradiotherapy based on a cytotoxic agent. However, the therapeutic effects of dabrafenib plus trametinib for other treatment types, such as adjuvant, neoadjuvant, and palliative treatments, have not yet been fully elucidated.

We appreciate your good advice with regard to our manuscript. Thank you.