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Women With Synchronous or Metachronous Lung and Ovarian Cancer: A Multi-Institutional Report

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Abstract. *Background/Aim: Double diagnosis of lung cancer (LC) and ovarian cancer (OC) is rare. Here, we describe patients with synchronous/metachronous LC and OC to identify common clinical and pathological patterns. Patients and Methods: Clinical, pathological and molecular data of patients diagnosed and treated at 30 European Institutions from 2008 to 2018 were retrieved and analysed. Whenever tissue was available, centralized pathology revision was performed. Results: A total of 19 cases were found; one was excluded at pathology revision. Most LCs were adenocarcinomas (15/18) and most OCs were high-grade serous (15/18) carcinomas. Of the 9 patients analysed, 7 carried oncogene-addicted LC (4 EGFR, 1 B-RAF and 2 ALK) and five out of 7 carried BRCA mutations. One patient with a germline-BRCA1 mutation received olaparib, resulting in a durable response of both malignancies. Median overall survival was 33 months. Conclusion: In our series, most synchronous/metachronous LCs and OCs showed genetic alterations. Further analyses with wide NGS panel could shed light on the biological mechanisms driving their occurrence.*

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Over the past few decades, lung cancer (LC) diagnoses and mortality have progressively increased in the female population. Non-small cell LC (NSCLC) accounts for about 85% of all LC cases and represents the first cause of cancer death and the third most common cancer in women living in developed countries (1). In the same context, ovarian cancer (OC) is the eighth malignancy for incidence and the fifth for mortality (2).

In advanced stages, despite multidisciplinary management and treatment combining surgery, chemotherapy and targeted therapy, prognosis remains poor for both malignancies (2).

Epidemiological studies and – more recently – molecular testing have revealed that in the female population NSCLC could be a biologically distinct entity, due to shared clinical and molecular features associated with better prognosis (3). Women affected by NSCLC show a higher incidence of mutations in the epidermal growth factor receptor (*EGFR*) gene, irrespective from being more often never-smokers. Moreover, whenever these mutations are present, patients receiving targeted therapy with the highly effective tyrosine-kinase inhibitors (TKIs) can achieve a longer life expectancy than the one traditionally obtained with chemotherapy (4).

In the OC scenario, the availability of DNA sequencing technologies had similar implications: the detection of impairments in genes involved in homologous recombination repair of DNA breaks (Homologous Recombination Deficiency, HRD) has identified a subset of patients with high-grade serous OCs who most likely benefit from treatment with poly(ADP-ribose) polymerase inhibitors (PARPi). Germline or somatic loss-of-function mutations in the BReast CAncer (*BRCA*) genes are the most common aberrations in HRD. However, other genomic or post-transcriptional events can be responsible for HRD (5). As reported by the Cancer Genome Atlas, almost half of the high-grade serous OC exhibits HRD (6). On the other hand, even though rare, cases of HRD have been described also in LC (7).

Despite the increasing incidence of LC, association with OC is rare and, so far, no literature data are available on this topic. The aim of this report was to describe a series of patients with synchronous or metachronous LC and OC and to identify common clinical and pathological patterns.

Patients and Methods

In this descriptive case series, we retrospectively retrieved the medical charts of patients referred to 30 Oncological Institutes in Europe (Italy, France, Slovenia), from 2008 to 2018.

When patients with history of LC and OC were found, detailed medical history was recorded including the following pathological features and clinical outcomes: i) age at first cancer diagnosis; ii) family history of cancer, smoking habits and hormonal status; iii) morphological features of LC and OC including tumor histotype, grade and stage (according to 8th TNM Edition for LC and to the International Federation of Gynecology and Obstetrics (FIGO) for OC); iv) timing and types of either local and systemic treatments received as well as of data regarding treatment initiation and progression; v) survival information. Median overall survival was calculated from the date of diagnosis of the first malignancy to the date of death or date of last follow-up. Whenever tested, genetic alterations, including germline *BRCA* (*gBRCA*) mutations in OC, were also reported.

LC and OC were considered synchronous, when the time interval between disease onsets was shorter than 3 months, whereas for metachronous we included all the cases of LC and OC that occurred within a time frame longer than 3 months.

Concerning pathology examination, centralized pathology revision on cytological or histological formalin fixed paraffin embedded tumor tissue (FFPE) was performed at the San Luigi Gonzaga Hospital, where an immunohistochemistry (IHC) marker panel including TTF-1 and PAX-8 was carried out when necessary. In ambiguous cases, a broader panel including p40, CK-7, WT1, CA125, Calretinin, EMA, CEA, CgA, Vimentin, Napsin-A was performed.

Results

As of May 2018, across the 30 Institutes inquired, we retrieved 19 cases of synchronous/metachronous LC and OC in the last 10 years. One patient was excluded, since centralized pathology revision revealed that the lung lesions were actually metastases from OC. Thus, 18 patients were considered eligible for final data analysis. Details of patients' characteristics are reported in Table I.

In the majority of cases (12/18), LC and OC were metachronous, with a median time interval between diagnoses of 6.5 years (range=7 months - 9 years). In the 70.6% of cases, OC preceded LC onset.

As for medical history, median age at diagnosis of the first malignancy was 62 years (range=37-79 years); the majority of patients (61.1%) were never-smokers and 38% had a family history of cancer. Interestingly, five patients (27.7%) were diagnosed with a third or fourth malignancy during their lifetime (1 case of breast cancer, 1 case of lymphoma and colon cancer, 1 case of small bowel cancer, 1 case of breast and kidney cancer and 1 case of medullary thyroid carcinoma).

In most cases, LC was diagnosed at an early or locally advanced stage (33.3% for stage I-IIb and 33.3% stage IIIA), 22.2% cases were metastatic. For two patients, LC staging data were missing. Conversely, at the time of diagnosis, OC cases were predominantly at advanced stage (50% III-IV).

Regarding pathology data, all of the LC diagnoses were performed on the primary tumor lesion. In three cases biopsy tissue consisted of a cytological specimen from bronco-alveolar lavage, in four cases of a cyto-histological specimen from fine (18 Gauge) needle aspiration, in one case of a histological sample from pleural biopsy and one case is unknown. In the remaining nine cases, irrespective of the initial biopsy modality, LC diagnosis was confirmed on surgical specimens. In all of the OC cases, diagnosis was confirmed on surgical specimens. Paired specimens of both primary tumors were available in seven cases.

Regarding histology, 83.3% of LC were adenocarcinoma and 83.3% of OC were high-grade serous carcinoma.

Twelve patients underwent molecular screening for LC oncogene drivers. Of them, 58.3% showed oncogene-addicted lung disease: four cases were *EGFR* mutant, one *B-RAF-V600* mutant and two had *EMLA4-ALK* rearrangement. Testing for gBRCA status was performed in seven cases: three had mutations (2 *BRCA2* and 1 *BRCA1*), two were wild-type and two carried variants of unknown significance (VUS). Remarkably, one synchronous case of lung and ovarian carcinoma presented both a *BRCA*-VUS and a *B-RAF-V600* mutation at the lung site.

As for treatment, consistent with disease stage at diagnosis, most cases of OC underwent primary de-bulking surgery as frontline therapy (14/18, 77.7%), whereas for LC, lobectomy was performed in eight cases (44.4%). Of the remaining LC cases, four were treated with platinum-based chemotherapy, four received a TKI and two chemo-radiotherapy. Regarding OC, all patients received platinum-based chemotherapy, either in adjuvant or first-line setting.

Remarkably, one patient with synchronous advanced

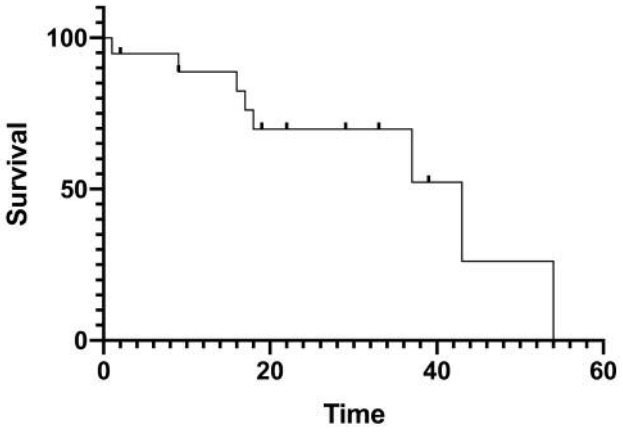

Figure 1. *Overall survival in our case-series: median overall survival was 33 months (95%CI=1.98-55.5).*

Table I. *Characteristics of the study population.*

Patients number	18
Median age at first diagnosis (years, range)	62 (37-79)
Smoking habit	
Never-smoker	11 (61.1%)
Former-smoker	4 (22.2%)
Current-smoker	2 (11.1%)
Unknown	1 (5.5%)
Cancer familial history	
Yes	7 (38.8%)
No/unknown	11 (61.1%)
Synchronous LC and OC	6 (33.3%)
Metachronous LC and OC	12 (66.7%)
Median time interval between LC and OC diagnoses (years, range)	4.5 (0.7-9)
LC histology	
Adenocarcinoma	15 (83.3%)
Squamous	2 (11.1%)
Small cell lung cancer	1 (5.5%)
OC histology	
High-grade serous	15 (83.4%)
Endometrioid	1 (5.5%)
Mucinous	2 (11.1%)
LC stage (TNM 8th edition)	
I-IIa	6 (33.3%)
IIIa	6 (33.3%)
IIIb-IV	4 (22.2%)
Unknown	2 (11.2%)
OC stage (FIGO)	
IC	7 (38.9%)
III	7 (38.9%)
IV	2 (11.1%)
Unknown	2 (11.1%)
Median follow-up (years, range)	6.8 (1-15)
Median overall survival (months, 95%CI)	33 (1.98-55.5)

ovarian and lung adenocarcinoma (both in stage IIIA at diagnosis and radically resected) carrying a germline *BRCA1* mutation had a durable partial response of both cancers following olaparib treatment for relapse. Ovarian cancer relapse was diagnosed with computed tomography (CT) and positron emission tomography (PET) where increased metabolic activity was detected in interaortocaval and lombo-aortic lymph nodes, along with an increase in CA-125 levels; lung cancer relapse was diagnosed as increased metabolic activity in mediastinal and supraclavicular lymph nodes, with an increase in the levels of CEA and CA 19.9 markers.

At the time of data analysis, after a median follow-up of 6.8 years, median overall survival was 33 months (95% confidence interval (IC)=1.98-55.5)) and 11 patients are still alive (Figure 1).

Two examples of the pathological revisions performed in this study are provided in Figures 2 and 3.

Discussion

In this report, we showed that patients who develop double LC and OC primaries share common clinical and pathological features. Notably, in most cases either LC or OC had an underlying molecular alteration. Across the patients who underwent molecular testing for LC, 58.3% showed oncogene-addicted disease. Similarly, of the seven cases tested for *BRCA*, five showed abnormalities. Moreover, even in cases carrying an unknown variant or were negative for a *BRCA* mutation, individual history of other associated malignancies or a family history of cancer were observed (2/4 cases and 3/5 cases, respectively).

HRD has been described also in LC, but the overall incidence of germline *BRCA* mutations in NSCLC is unknown. Among the little available evidence, an interesting perspective is provided by a small report on two *EGFR* mutant NSCLC male patients, whose family history for breast and OC led to the detection of a *gBRCA2* mutation in both cases. The authors, to investigate if genetic susceptibility to DNA repair defects could predispose to the development of *EGFR* mutant tumors, screened 110 Jewish patients with lung cancer and found that three harbored g*BRCA* mutations (2.7%). They further screened 13 Ashkenazi Jewish patients with *EGFR* mutant NSCLC and found that none had gBRCA1/2 mutations (8).

However, in contrast to defects caused due to a single genomic mutation, as in the case of *BRCA* mutations, DNA repair in LC seems to be more often affected at the epigenetic level. It has been reported that epigenetic alterations combined with reduced mRNA and protein expression levels of BRCA1 occur in up to 44% of NSCLC, through various mechanisms, such as promoter hypermethylation (7). For example, low expression of *ERCC1* was shown in 56% of cases of a large cohort of NSCLC patients, whereas *PTEN* mutations have

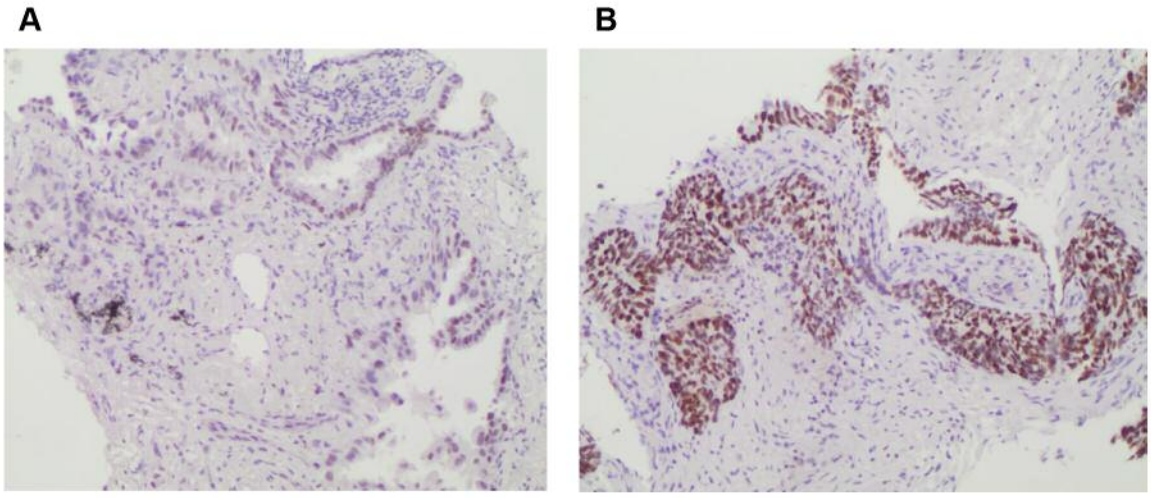

Figure 2. *Immunohistochemistry images from specimens obtained from Patient 1 representing (A) lung primary TTF-1 and (B) lung metastasis PAX-8. MF, Never smoker, 78 years old at the time of diagnosis of lung adenocarcinoma, EGFR mutated on exon 21, IV stage. She received afatinib as 1st line treatment. Twenty-nine months later, disease progression with new brain and lung lesions, for which she underwent a re-biopsy on a lung metastasis, showing an undifferentiated malignancy with loss of EGFR mutation, TTF-1 (-). One month later, onset of a pelvic mass, at the ago-biopsy poor differentiated ovarian carcinoma, PAX-8 (+), ER 10%. Patient died two months later. At the pathology revision, the lung metastasis was revealed to be a secondary lesion from the ovarian carcinoma (see Figure 1B).*

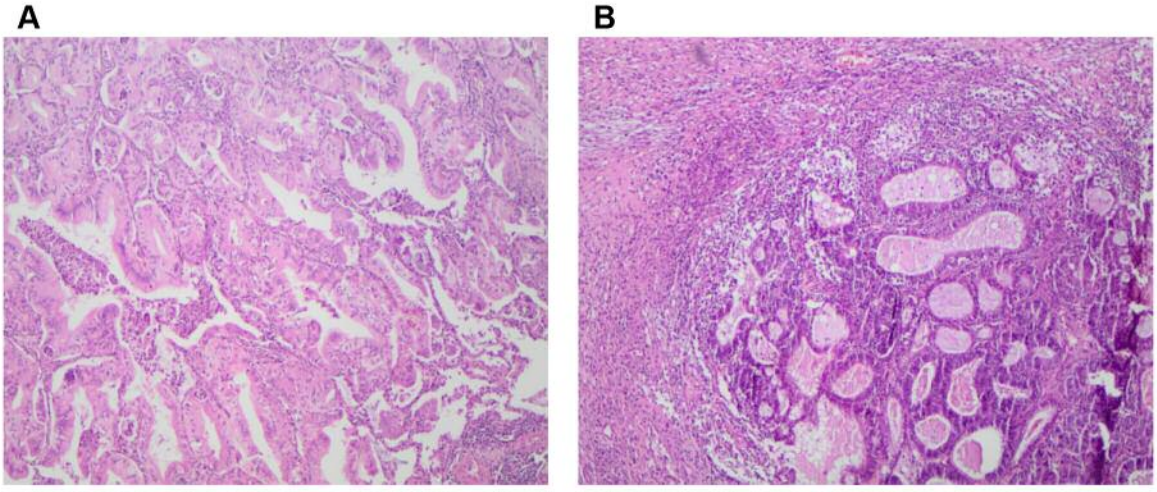

Figure 3. *Immunohistochemistry images from specimens obtained from Patient 2 representing (A) lung primary H/E and (B) ovarian primary H/E. GU, Never smoker, 51 years old at the time of diagnosis of lung adenocarcinoma, EGFR and KRAS wild type. Lung disease at stage I, thus an upper left lobectomy was performed. Three months later, onset of a pelvic mass, involving both uterus and left ovary. At the pathological examination, synchronous endometrioid carcinoma of the uterus and the ovary was diagnosed. Following hystero-annessiectomy, patient underwent adjuvant chemotherapy. Three years later, the patient developed breast cancer and BRCA examination was performed, revealing a BRCA2 mutation of unknown significance. Patient died one year later.*

been reported in 9% of NSCLC patients where they confer higher sensitivity to PARPi (7-9).

As for the implications on treatment outcome of patients with *EGFR*-mutant NSCLC, at least two studies showed that high *BRCA1* mRNA expression was associated with shorter progression-free survival when patients received erlotinib (10-11). This evidence provided the rationale for a combination trial of the anti-*EGFR* TKI, gefitinib, plus the PARPi olaparib (12). This subgroup of NSCLC patients with an HR dysfunction constitutes a rare population which may

also be sensitive to treatment with PARPi. So far, it is unknown if this phenotype occurs only at the somatic level in cancer cells or, in a few cases, may also reflect a germline pattern. In our case series, whole exome sequencing was not carried out, so we can only speculate that at least in some of the cases described, the association of LC and OC was driven by an underlying common germline alteration in the DNA repair machinery.

This study has certain limitations. It is a retrospective study, with missing clinical data and limited availability of paired histological specimens. In many instances, molecular testing for LC oncogene drivers and for *BRCA* status in OC was not performed, in part due to the extended time frame of the study – as the recommendations for molecular testing considerably changed along the 10 years covered in this case-series – and in part for the lack of a family history suggestive for a *BRCA* mutation or because of the early TNM stage at the time of LC diagnosis. In this respect, it is worth to notice that many LC cases were diagnosed at early stages, probably because the lung lesions were detected as occasional radiological findings along the follow-up for the preceding OC. This could also explain the long survival time observed in this case series.

Beyond the findings and the limitations mentioned above, our report – which represents the largest patients' series of associated LC and OC – also outlines the clinical and pathologic diagnostic challenge of distinguishing secondary from primary ovarian neoplasms. This is true especially in the presence of synchronous tumors, where imaging techniques and conventional morphology alone may be often inadequate to obtain a reliable diagnosis.

In our report, the use of appropriate IHC markers in the pathology workup revealed that, in one case, the lung lesions deemed as primary lung adenocarcinoma were actually metastases from OC. It is worth mentioning that at the time of initial diagnosis, the biopsy specimen consisted of pleural cytology, which can often be misleading.

Lung represents the second preferential metastatic site for ovarian cancer (28.4% across 819 distant metastatic sites examined from SEER database) and, when present, has negative prognostic value (13). On the other hand, ovarian metastases from LC represent only 0.4-1.0% of all ovarian metastatic masses (14-16). However, such frequency is likely to increase due to the rising incidence of lung cancer in women (1). Surprisingly, several reports have described cases of ovarian metastases from lung adenocarcinoma associated with driver *EGFR* mutations, and even more commonly, with *ALK* rearrangements (17).

In conclusion, our study represents the largest case series of double LC and OC primaries, that not only underlines the key role of IHC in the differential diagnosis of metastatic disease, but also identifies common clinical and pathological features, with many cases driven by genetic alterations. As a future perspective, further analyses using an NGS panel could shed light on the biological mechanisms driving the occurrence of concomitant LC and OC, with beneficial repercussions on prevention and treatment strategies.

Conflicts of Interest

Mariniello A received financial support for travel and accommodation to participate to scientific events by Roche and Bristol Myers Squibb; Chiari R received speaker's fees from AstraZeneca, Roche, Takeda, Boheringer Ingelheim, Otsuka, Pfizer; Del Conte A received speaker's fees from AstraZeneca, BMS, Merck Sharp & Dome, Roche; Di Maio M received personal fees from Bristol Myers Squibb, Merck Sharp & Dohme, Roche, AstraZeneca, Janssen, Takeda, Pfizer and institutional research grant from Tesaro; Valabrega G received speaker's fees from AstraZeneca, Roche, PharmaMar, Tesaro; Novello S declares Speaker Bureau and/or Advisor for BMS, Eli Lilly, BI, Astra Zeneca, MSD, Takeda, Roche; Ghisoni E, Righi L, Gelibter A, Zichi C, Catino A, Barbieri F, Giaj Levra M and Cecere F declare no conflicts of interest.

Authors' Contributions

Conception and design: Novello S and Valabrega G. Acquisition of data: Mariniello A. Pathology revision and images of figures 2 and 3: Righi L. Analysis and interpretation of data: Mariniello A, Ghisoni E. Drafting the article: Mariniello A. Critically revising the article for important intellectual content: Novello S, Valabrega G, Righi L, Di Maio M. All Authors read and approved the final manuscript.

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References

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin *68(6)*: 394-424, 2018. PMID: 30207593. DOI: 10.3322/caac.21492

2 Torre LA, Trabert B, DeSantis CE, Miller KD, Samimi G, Runowicz CD, Gaudet MM, Jemal A and Siegel RL: Ovarian cancer statistics, 2018. CA Cancer J Clin *68(4)*: 284-296, 2018. PMID: 29809280. DOI: 10.3322/caac.21456

3 Vavalà T, Mariniello A, Reale ML and Novello S: Gender differences in lung cancer. Ital J Gender-Specific Med *2(3)*: 99-109, 2016.

4 Remon J, Isla D, Garrido P, de Castro J, Majem M, Viñolas N, Artal A, Carcereny E, García-Campelo MR, Lianes P, Provencio M, Juan O, Diz P, Blanco R, Lopez-Castro R, Maestu I, Vadell C and Felip E: Efficacy of tyrosine kinase inhibitors in EGFR-mutant lung cancer women in a real-world setting: the WORLD07 database. Clin Transl Oncol *19(12)*: 1537-1542, 2017. PMID: 28660482. DOI: 10.1007/s12094-017-1700-8

5 Lord CJ and Ashworth A: BRCAness revisited. Nat Rev Cancer *16(2)*: 110-120, 2016. PMID: 26775620. DOI: 10.1038/nrc.2015. 21

6 Cancer Genome Atlas Research Network: Integrated genomic analyses of ovarian carcinoma. Nature *474(7353)*: 609-615, 2011. PMID: 21720365. DOI: 10.1038/nature10166

7 O'Sullivan CC, Moon DH, Kohn EC and Lee JM: Beyond breast and ovarian cancers: PARP inhibitors for BRCA mutation-associated and BRCA-like solid tumors. Front Oncol *4*: 42, 2014. PMID: 24616882. DOI: 10.3389/fonc.2014.00042

8 Marks JL, Golas B, Kirchoff T, Miller VA, Riely GJ, Offit K and Pao W: EGFR mutant lung adenocarcinomas in patients with germline BRCA mutations. J Thorac Oncol *3(7)*: 805, 2018. PMID: 18594331. DOI: 10.1097/JTO.0b013e31817e4664

9 Olaussen KA, Dunant A, Fouret P, Brambilla E, André F, Haddad V, Taranchon E, Filipits M, Pirker R, Popper HH, Stahel R, Sabatier L, Pignon JP, Tursz T, Le Chevalier T, Soria JC and IALT Bio Investigators: DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med *355(10)*: 983-991, 2006. PMID: 16957145.

10 Rosell R, Molina MA, Costa C, Simonetti S, Gimenez-Capitan A, Bertran-Alamillo J, Mayo C, Moran T, Mendez P, Cardenal F, Isla D, Provencio M, Cobo M, Insa A, Garcia-Campelo R, Reguart N, Majem M, Viteri S, Carcereny E, Porta R, Massuti B, Queralt C, de Aguirre I, Sanchez JM, Sanchez-Ronco M, Mate JL, Ariza A, Benlloch S, Sanchez JJ, Bivona TG, Sawyers CL and Taron M: Pretreatment EGFR T790M mutation and BRCA1 mRNA expression in erlotinib-treated advanced non-small-cell lung cancer patients with EGFR mutations. Clin Cancer Res *17(5)*: 1160-1168, 2011. PMID: 2133402. DOI: 10.1158/1078-0432.CCR-10-2158

11 Karachaliou N, Costa C, Gimenez-Capitan A, Molina-Vila MA, Bertran-Alamillo J, Mayo C, Massuti B, Majem M, Carcereny E, Moran T, Sanchez JJ, Viteri S, Gasco A, Wannesson L, Souglakos J, Jimeno J, Rosell R and Spanish Lung Cancer Group: BRCA1, LMO4, and CtIP mRNA expression in erlotinib-treated non-small-cell lung cancer patients with EGFR mutations. J Thorac Oncol *8(3)*: 295-300, 2013. PMID: 23407556. DOI: 10.1097/JTO.0b013e31827db621

12 Campelo RG, Felip E, Massuti B, Majem M, Carcereny E, Cardenal F, Molina-Vila MA, Martinez Marti A, Marti-Ciriquian JL, Alonso-Jaudenes Curbera G, Pallares C, Palmero R, Gonzalez-Arenas MC, Mayo-de las Casas C, Sanchez-Ronco M and Rosell R: Phase IB study of olaparib (AZD2281) plus gefitinib in EGFR-mutant patients (p) with advanced non-small-cell-lung cancer (NSCLC) (NCT 01513174/GECP- GOAL). J Clin Oncol *31*: abstr2581, 2013. DOI: 10.1200/jco.2013.31.15 _suppl.2581

13 Deng K, Yang C, Tan Q, Song W, Lu M, Zhao W, Lou G, Li Z, Li K and Hou Y: Sites of distant metastases and overall survival in ovarian cancer: A study of 1481 patients. Gynecol Oncol *150(3)*: 460-465, 2018. PMID: 30001833. DOI: 10.1016/j.ygyno. 2018.06.022

14 Fujiwara K, Ohishi Y, Koike H, Sawada S, Moriya T and Kohno I: Clinical implications of metastases to the ovary. Gynecol Oncol *59(1)*: 124-128, 1995. PMID: 7557597. DOI: 10.1006/ gyno.1995.1278

15 Kiyokawa T, Young RH and Scully RE: Krukenberg tumors of the ovary: a clinicopathologic analysis of 120 cases with emphasis on their variable pathologic manifestations. Am J Surg Pathol *30(3)*: 277-299, 2006. PMID:16538048. DOI: 10.1097/ 01.pas.0000190787.85024.cb

16 Irving JA and Young RH: Lung carcinoma metastatic to the ovary: a clinicopathologic study of 32 cases emphasizing their morphologic spectrum and problems in differential diagnosis. Am J Surg Pathol *29(8)*: 997-1006, 2005. PMID: 16006793.

17 Sasano H, Sekine A, Hirata T, Iwamoto K, Itou Y, Itani H, Kondou S, Tokui T and Tanigawa M: Ovarian metastases from ALK-rearranged lung adenocarcinoma: A case report and literature review. Intern Med *57(22)*: 3271-3275, 2018. PMID: 29984766. DOI: 10.2169/internalmedicine.0538-17

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