



## Advances in Molecular Targeted Therapy May Expand the Scope of Fertility Preservation Counseling in Advanced Cancer: A Case in Which Brigatinib Achieved 5-Year Progression-Free Survival in a Patient with Stage IV ALK-Positive Non-Small Cell Lung Cancer and a Live Birth Following Embryo Transfer After Discontinuation of Treatment

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### Abstract

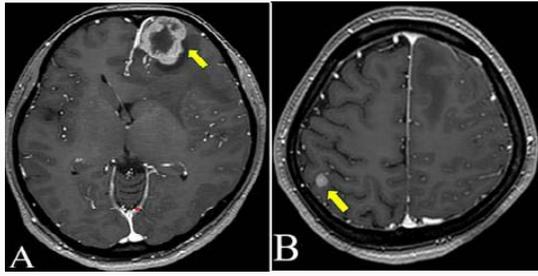
In Japan, Fertility Preservation (FP) counseling for cancer patients with poor prognoses appears to be done infrequently because of prohibitions on posthumous reproduction and surrogacy. A 31-year-old nulligravid woman diagnosed with Stage IV Anaplastic Lymphoma Kinase (ALK)-positive Non-Small Cell Lung Cancer (NSCLC) with brain metastases. Following craniotomy for tumor resection, embryo cryopreservation, and cranial radiotherapy, brigatinib (ALK inhibitor) was administered. Five years of progression-free survival was observed. The patient requested Embryo Transfer (ET). After a planned 7-month treatment interruption (washout period) and multidisciplinary counselling, ET was performed. This resulted in a live birth at 37 weeks' gestation with no tumor progression during pregnancy. Brigatinib was resumed postpartum. To our knowledge, this is the first report of a live birth following ET to herself during a planned interruption of molecular targeted therapy in a patient with potential residual cancer in advanced NSCLC. Advances in molecular targeted therapies may expand the scope of FP counselling in patients traditionally considered to have poor prognoses. However, ET performed in a patient with potential residual cancer is not a standard intervention. Determining the indication for such interventions requires a long-term observation of this patient, further accumulation of clinical evidence, and rigorous ethical consideration.

**Keywords:** Anaplastic Lymphoma Kinase (ALK); Fertility preservation; Molecular targeted therapy; Non-Small Cell Lung Cancer (NSCLC); Pregnancy

### Introduction

The Japan Society of Obstetrics and Gynecology (JSOG) prohibits posthumous reproduction-defined as the use of cryopreserved gametes, gonadal tissues, or embryos after a patient's death as well as oocyte donation and gestational surrogacy [1]. Consequently, the provision of Fertility Preservation (FP) information to cancer patients with poor prognoses appears to remain limited (further details are provided in the Discussion section).

We report a case involving a nulligravid woman with advanced lung cancer and brain metastases. Despite an initial poor prognosis, molecular targeted therapy achieved 5 years of progression-free survival. Following extensive counselling and a planned drug interruption, the patient underwent



**Figure 1:** Brain MRI. Pre-treatment brain metastatic lesions are shown by yellow arrows: (A) a 3-cm mass in the left frontal lobe, and (B) a small mass in the right temporal lobe. There lesion (A) was resected, and the lesion (B) was not resected.

Embryo Transfer (ET) and achieved a successful live birth. This case suggests that the remarkable efficacy of modern targeted therapies may necessitate a re-evaluation of FP counselling for a broader range of cancer patients.

### Case Presentation

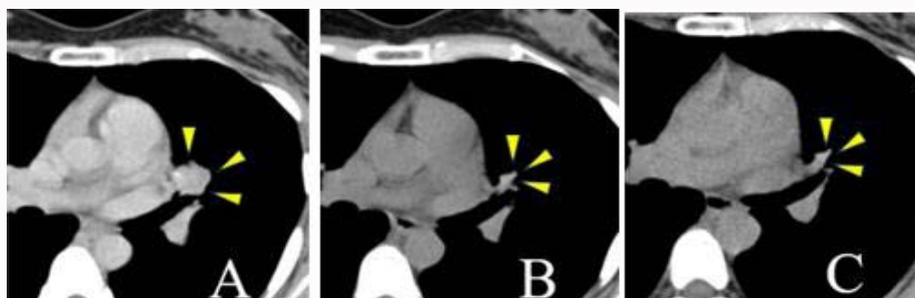
A 31-year-old nulligravid married woman presented with a 4-day history of severe headache. Her medical history was unremarkable, though her family history included various malignancies. Brain magnetic resonance imaging (MRI) revealed a 3-cm mass in the left frontal lobe with significant peritumoral edema and a small mass in the right temporal lobe (Figure 1), and chest Computed Tomography (CT) showed a 2 cm mass in the left hilar region (Figure 2A). She was diagnosed with lung cancer with brain metastases. An emergency craniotomy and tumor resection were done, and intraoperative

histopathology confirmed metastatic adenocarcinoma. The final diagnosis was cT1aN0M1c, Stage IVB, Anaplastic Lymphoma Kinase (ALK)- fusion gene-positive Non-Small Cell Lung Cancer (NSCLC).

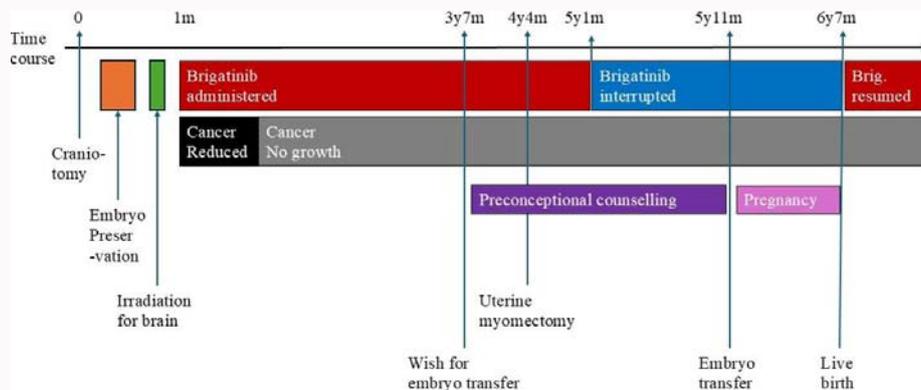
Ten days post-surgery, the patient was referred for Fertility Preservation (FP) counselling. Despite being informed that a complete cure was unlikely, the couple expressed a strong desire for biological parenthood. After multidisciplinary consultation, it was determined that a brief delay for FP would not compromise her oncological outcome. With an Anti-Müllerian Hormone (AMH) level of 5.33 ng/mL, she underwent a random-start antagonist protocol. Ten oocytes were retrieved, and two blastocysts (Gardner’s classification 4AA and 4CC) were cryopreserved. After FP, she underwent cranial radiotherapy and initiated the ALK inhibitor brigatinib.

The patient showed an excellent response to brigatinib, with no brain lesions detectable (data not shown) and pulmonary lesion regressing to a few millimeters after 4 months (Figure 2B), and the lesions remained stable for 5 years. At 3 years and 7 months post-diagnosis, she wished to undergo Embryo Transfer (ET). After multidisciplinary consultation, it was determined that interruption of brigatinib for pregnancy may be accepted with a thorough informed consent. At 4 years and 4 months, she underwent laparoscopic resection of the uterine submucous myoma to reduce the risk of implantation failure.

After 5 years of stable disease, brigatinib was discontinued. Following a 7-month washout period, no tumor progression was observed. Extensive counselling was provided regarding the risks of recurrence during pregnancy. A management plan was informed: in the event of symptomatic progression (headache or dyspnea),



**Figure 2:** Thoracic CT. The lung cancer is shown by yellow triangles: (A) the tumor was 2 cm in size before treatment, then (B) reduced in size after 4 months administration of brigatinib, and (C) the tumor showed no growth at 25 weeks of gestation.



**Figure 3:** Summary of clinical timeline.

the pregnancy would be terminated to prioritize maternal life; in the event of asymptomatic progression, molecular targeted therapy would be resumed with delivery planned at a viable gestational age (approximately 30-32 weeks), although the effects of brigatinib for the mother and fetus are unknown.

The couple consented after 3 months of deliberation and support from the Cancer Support Center. ET was performed 10 months after drug discontinuation. A single blastocyst (4AA) was transferred during a hormone replacement cycle, resulting in a singleton pregnancy. No tumor growth occurred during gestation, the brain lesions were not detected (not shown), and the pulmonary lesion showed no growth (Figure 2C). An elective cesarean section was performed at 37 weeks because of the previous myomectomy, and a healthy 2,765 g female infant was born. Brigatinib was resumed postpartum, and formula feeding was initiated. Both the mother and baby were in a good condition at 2 months postpartum. The clinical timeline was summarized in Figure 3.

## Discussion

First, we examined the international status of FP counselling for cancer patients with poor prognoses. The legal and ethical landscape regarding posthumous reproduction, the use of donor gametes, and surrogacy varies significantly by country, which in turn influences clinical practice.

In Japan, JSOG strictly prohibits posthumous reproduction, oocyte donation, and surrogacy [1]. The 2024 Clinical Practice Guidelines for Fertility Preservation in Cancer Patients, published by the Japan Society of Clinical Oncology (JSCO), state: "If a planned cancer treatment is expected to result in loss of gonadal function or fertility, opportunities for discussion regarding future FP must be provided as early as possible. However, providing information to patients with a high risk of recurrence or mortality remains a matter of ethical debate [2]. To our knowledge, no large-scale domestic surveys have evaluated the frequency of FP counselling for patients with poor prognoses. While some reports suggest that advanced age and poor prognosis are factors in withholding FP information, specific data—such as the percentage of poor-prognosis cases receiving information or the precise definition of "poor prognosis" are lacking. In personal communication, many reproductive specialists in Japan consider a 5-year survival rate of at least 50% as an indication for providing FP information.

In contrast, the 2019 American Society for Reproductive Medicine (ASRM) guidelines do not specify prognostic limits and advocate for discussing all family-building options, including donor gametes, surrogacy, and adoption. They also emphasize documenting the patient's wishes regarding posthumous reproduction in the event of death [3]. Similarly, the American Society of Clinical Oncology (ASCO) (2025) and European Society of Human Reproduction and Embryology (ESHRE) (2020) guidelines do not define eligibility based on stage or prognosis [4, 5]. The European Society for Medical Oncology (ESMO) guidelines (2020) clearly state that FP information should be provided regardless of cancer type or stage [6]. However, the reality of clinical practice in the West remains complex. A review by Jones et al. indicated that over half of physicians hesitate to provide FP information to patients with poor prognoses. While only 16.2% of physicians "supported" posthumous reproduction (with 51.5% "unsure"), many still provided FP information ("always" 43%; "mostly" 41%), suggesting a discrepancy between personal conviction

and clinical practice [7]. Furthermore, a U.S. interview study of 43 non-physician professionals (nurses, psychologists, social workers) revealed significant distress and confusion regarding the complexities of these options, highlighting a pressing need for institutional guidelines and specialized training [8].

Second, from an ethical standpoint, we discuss the decision to perform ET in a patient with a potential residual cancer lesion. In this case, the primary lung cancer lesion had regressed from 2 cm to a few millimeters following brigatinib treatment and remained stable for five years thereafter. Our multidisciplinary team-comprising respiratory oncologists, reproductive specialists, and perinatologists hypothesized that the lesion represented a clinical scar devoid of viable malignant cells. However, a definitive diagnosis was impossible as biopsy (bronchoscopic, CT-guided, or ultrasound-guided) was difficult. Consequently, prior to the ET, the patient and her family were informed of the risk of tumor recurrence secondary to the discontinuation of brigatinib. They were further counselled that medical managements would vary depending on the gestational stage at the time of any potential recurrence.

A review by Simons et al. [9] on pregnancy in oncogene-driven NSCLC identified 11 cases where molecular targeted therapies were used during the first trimester (organogenesis period) or later. No significant adverse maternal effects or major congenital anomalies were reported among the 12 infants (including one set of twins), although in 3 cases Fetal Growth Restriction (FGR) occurred, but the relation of FGR and molecular targeted medicines are not defined. All the 12 infants were normally developed. Based on this, we counselled the family that if tumor progression occurred, therapy would be resumed, and pregnancy would be maintained until a viable gestational age (approximately 30-32 weeks).

The patient's husband expressed profound anxiety regarding the risks associated with interrupting brigatinib. His concerns included the possible severe maternal depression if a pregnancy had to be terminated before 22 weeks due to tumor progression, and the fear of being unable to maintain his career if a premature birth resulted in neonatal disability. Continuous counselling by nurses from the Cancer Support Center was helpful in addressing these fears. The husband eventually consented after the patient's mother and sister promised their support for childcare and after seeing the patient's unwavering desire to conceive.

The 2024 JSCO guidelines address this specific clinical question: "Is interrupting molecular targeted therapy for pregnancy/delivery acceptable in lung cancer patients?" The guidelines state that while evidence is insufficient, decisions must balance the risk of cancer progression against the potential impact of the drugs on the pregnancy [10]. In the absence of clear evidence, we believe that allowing pregnancy after thorough informed consent is reasonable in practice. A long-term follow-up of this patient and further accumulation of cases are required to determine which cancer types and stages are suitable for such interventions.

Third, it may be questioned whether FP was truly necessary here, because that cranial radiotherapy and brigatinib have low gonadotoxicity. However, the patient was diagnosed at age 31 and cleared for pregnancy at age 36. Because of the well-documented decline in female fertility after age 35, the cryopreservation of embryos at age 31 clearly constitutes "fertility preservation.

Finally, we consider how FP information should be provided

to poor-prognosis patients in Japan. We previously encountered a case of a married woman in her 30s with stage IV rectal cancer who strongly desired embryo cryopreservation. When she later requested ET at a stage where her prognosis was estimated at 1-2 years, a multidisciplinary team (oncologists, reproductive specialists, nurses, and psychologists) conducted months of counselling, eventually leading the patient to decline ET (presented at the 15<sup>th</sup> Japan Society for Fertility Preservation meeting, 2025). Importantly, she did not regret the initial embryo cryopreservation, stating that it served as a psychological "pillar" that helped her endure difficult chemotherapy.

We believe that FP information should be provided to any patient with a strong desire for future biological parenthood, even if the prognosis is poor. Particularly in rare cases like young-onset advanced NSCLC, the possibility of an extraordinary response to specific molecular targeted therapies must be considered when counselling patients on their reproductive future.

## Conclusion

Advances in molecular targeted therapies are transforming advanced cancer into a manageable chronic condition for some patients, thereby expanding the scope of FP counselling. While this case resulted in a successful live birth without tumor progression, such interventions require intensive multidisciplinary counselling and a rigorous informed consent process to navigate the inherent oncological and obstetric risks.

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