

Small Molecules prescribed on- and off-label for thoracic cancers during Pregnancy: A Combined VigiBase and Systematic Review Analysis

Roberta Nosedà^{1#}, Giuseppe Salfi^{2,3#}, Francesca Bedussi¹, Manuela Proietto², Martino Pedrani², Daniele Brenna², Luigi Tortola², Giulia Montelatici², Alessandro Santi⁴, Lise Selleret⁵, Patrizia Froesch², Alessandro Ceschi^{1,6,7}, Emanuel Raschi⁸, Marina Chiara Garassino⁹, Fedro Peccatori¹⁰, Giovanna Scarfone¹¹, Narjust Florez¹², Jacques Cadranel¹³, and Martina Imbimbo²

1. Division of Clinical Pharmacology and Toxicology, Institute of Pharmacological Sciences of Southern Switzerland, Ente Ospedaliero Cantonale (EOC), Lugano, Switzerland
2. Oncology Institute of Southern Switzerland (IOSI), Ente Ospedaliero Cantonale (EOC), Bellinzona, Switzerland
3. Institute of Oncology Research (IOR), Bellinzona, Switzerland
4. Ospedale Regionale di Locarno, Ente Ospedaliero Cantonale (EOC), Locarno, Switzerland
5. Service de gynécologie obstétrique et médecine de la reproduction, hôpital Tenon, AP-HP, Sorbonne université, Paris, France; Réseau Cancer associé à la Grossesse, CALG, Paris, France
6. Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland
7. Clinical Trial Unit, Ente Ospedaliero Cantonale, Lugano, Switzerland
8. Department of Medical and Surgical Sciences, Alma Mater Studiorum - University of Bologna, Bologna, Italy
9. Department of Medicine, University of Chicago Department of Medicine - Section of Hematology/Oncology, Chicago, IL, USA
10. Division of Gynecologic Oncology, European Institute of Oncology IRCCS, Via Ripamonti 435, Milan 20141, Italy
11. Division of Gynecology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
12. Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts
13. Department of Respiratory Medicine and Thoracic Oncology. Assistance Publique Hôpitaux de Paris, Hôpital Tenon and GRC012 Therascan, Sorbonne University, Paris, France

#RN and GS contributed equally to this work and share first authorship

Supplementary Materials

Supplementary Figure 1. VigiBase study flow-chart

Supplementary Table 1. List of the small molecules used to select the group of individual case safety reports of interest: active ingredients, chemical class and FDA-approved indication for non-small cell lung cancer vs off-label use

Supplementary Table 2. List of preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA) used to define the type of drug exposure for selecting individual case safety reports included in the study population

Supplementary Table 3. Pregnancy-related adverse drug reactions of interest and their classification into six main categories (abortion, delivery complications, congenital malformations, neonatal complications, pregnancy complications, stillbirth) along with corresponding subcategories

Supplementary Table 4. Description and disproportionality analyses of pregnancy-related adverse drug reactions reported with the small molecules of interest compared with other anticancer agents

Supplementary Table 5. Description of pregnancy-related adverse drug reactions reported with FDA-approved small molecules for non-small cell lung cancer compared with other anticancer agents

Supplementary Table 6. Description of pregnancy-related adverse drug reactions reported with FDA-approved small molecules for non-small cell lung cancer compared with other anticancer agents considering the subgroup of individual case safety reports without co-suspect drugs

Supplementary Table 7. Overview of all small molecules of interest with the reported pregnancy-related adverse drug reactions by small molecule chemical classes

Supplementary Table 8. Description of pregnancy-related adverse drug reactions reported with HER2-EGFR, BRAF, EGFR and mTOR inhibitors

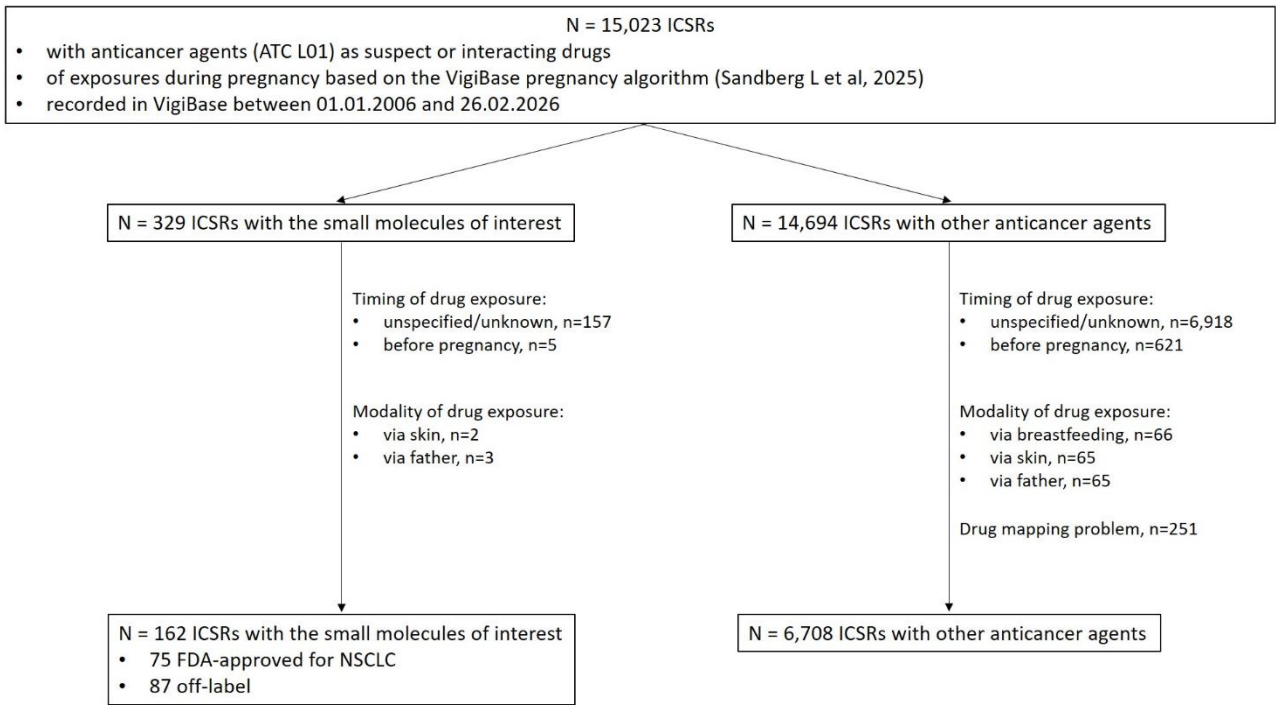
Supplementary Table 9. Description of pregnancy-related adverse drug reactions associated with single small molecules and reported in ≥ 5 individual case safety reports

Supplementary Table 10. Flow chart of literature search and article selection (PRISMA flow chart)

sAppendix 1. Literature search strategy

sAppendix 2. Exclusion criteria

Supplementary Figure 1 VigiBase study flow-chart



Abbreviations: ICSR, individual case safety report; ATC. Anatomical, therapeutic, chemical; NSCLC, non-small cell lung cancer

Supplementary Table 1 List of the small molecules used to select the group of individual case safety reports of interest: active ingredients, chemical class and FDA-approved indication for non-small cell lung cancer vs off-label use

Active ingredient	Chemical class	FDA-approved for NSCLC
Alectinib	ALK inhibitors	yes
Ceritinib	ALK-ROS inhibitors	yes
Lorlatinib	ALK-ROS inhibitors	yes
Brigatinib	ALK-ROS inhibitors	yes
Crizotinib	ALK-ROS inhibitors and MET inhibitors	yes
Entrectinib	ALK-ROS-NTRK inhibitors	yes
Repotrectinib	ALK-ROS-NTRK inhibitors	yes
Dabrafenib	BRAF inhibitors	yes
Encorafenib	BRAF inhibitors	yes
Vemurafenib	BRAF inhibitors	no
Palbociclib	CDK inhibitors	no
Erlotinib	EGFR inhibitors	yes
Gefitinib	EGFR inhibitors	yes
Afatinib	EGFR inhibitors	yes
Osimertinib	EGFR inhibitors	yes
Pozotinib	EGFR inhibitors	no
Dacomitinib	EGFR inhibitors	yes
Lazertinib	EGFR inhibitors	yes
Mobocertinib	EGFR inhibitors	no
Tucatinib	HER2 inhibitors	no
Lapatinib	HER2-EGFR inhibitors	no
Neratinib	HER2-EGFR inhibitors	no
Adagrasib	KRAS inhibitors	yes
Trametinib	MEK inhibitors	yes
Binimetinib	MEK inhibitors	yes
Cobimetinib	MEK inhibitors	no
Capmatinib	MET inhibitors	yes
Tepotinib	MET inhibitors	yes
Savolitinib	MET inhibitors	no
Everolimus	mTOR inhibitors	no
Larotrectinib	NTRK inhibitors	yes
Selpercatinib	RET inhibitors	yes
Pralsetinib	RET inhibitors	yes
Cabozantinib	RET inhibitors and VEGFR-TRK inhibitors	no
Lenvatinib	VEGFR-TRK inhibitors	no
Sunitinib	VEGFR-TRK inhibitors	no
Sunvozertinib	EGFR inhibitors	yes
Zongertinib	HER2 inhibitors	yes
Sevabertinib	HER2 inhibitors	yes

Abbreviations: FDA, Food and Drug Administration; NSCLC, non-small cell lung cancer; ALK, anaplastic lymphoma kinase; ROS, reactive oxygen species; NTRK, neurotrophic tyrosine receptor kinase; BRAF, B-

Raf serine-threonine kinase; CDK, cyclin-dependent kinase; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma viral oncogene homolog; MEK, mitogen-activated protein kinase; MET, c-mesenchymal-epithelial transition; mTOR, mechanistic (mammalian) target of rapamycin; RET, rearranged during transfection gene; VEGFR-TRK, vascular endothelial growth factor receptor-tropomyosin receptor kinase

Supplementary Table 2 List of preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA) used to define the type of drug exposure for selecting individual case safety reports included in the study population

MedDRA preferred term	Type of drug exposure
Exposure during pregnancy	exposure during pregnancy
First trimester pregnancy	exposure during pregnancy
Fetal exposure during delivery	exposure during pregnancy
Fetal exposure during pregnancy	exposure during pregnancy
High risk pregnancy	exposure during pregnancy
Maternal exposure during delivery	exposure during pregnancy
Maternal exposure during pregnancy	exposure during pregnancy
Pregnancy	exposure during pregnancy
Pregnancy on contraceptive	exposure during pregnancy
Pregnancy on oral contraceptive	exposure during pregnancy
Pregnancy with advanced maternal age	exposure during pregnancy
Pregnancy with contraceptive device	exposure during pregnancy
Pregnancy with injectable contraceptive	exposure during pregnancy
Unintended pregnancy	exposure during pregnancy
Unwanted pregnancy	exposure during pregnancy
Drug exposure before pregnancy	exposure before pregnancy
Maternal exposure before pregnancy	exposure before pregnancy
Exposure via breast milk	exposure via breast milk
Maternal exposure during breast feeding	exposure via breast milk
Exposure via body fluid	exposure via semen
Exposure via father	exposure via semen
Exposure via partner	exposure via semen
Maternal exposure via partner during pregnancy	exposure via semen
Paternal drugs affecting foetus	exposure via semen
Paternal exposure before pregnancy	exposure via semen
Paternal exposure during pregnancy	exposure via semen
Paternal exposure timing unspecified	exposure via semen
Pregnancy of partner	exposure via semen
Accidental exposure to product	exposure via skin
Exposure via direct contact	exposure via skin
Exposure via skin contact	exposure via skin
Occupational exposure to product	exposure via skin

Abbreviations: MedDRA, medical dictionary for regulatory activities

Supplementary Table 3 Pregnancy-related adverse drug reactions of interest and their classification into six main categories (abortion, delivery complications, congenital malformations, neonatal complications, pregnancy complications, stillbirth) along with corresponding subcategories

Category of pregnancy-related ADR	Subcategory of pregnancy-related ADR	MedDRA preferred term
Abortion	Abortion (Spontaneous abortion)	Abortion spontaneous
	Abortion (Spontaneous abortion)	Abortion spontaneous complicated
	Abortion (Induced abortion)	Abortion induced
	Abortion, not otherwise specified	Aborted pregnancy
	Abortion, not otherwise specified	Abortion
	Abortion, not otherwise specified	Abortion incomplete
Delivery complications		Amniorrhexis
		Arrested labour
		Breech presentation
		Caesarean section
		Cephalo-pelvic disproportion
		Complication of delivery
		Delayed delivery
		Episiotomy
		Induced labour
		Labour complication
		Post procedural haemorrhage
		Postpartum haemorrhage
		Postpartum sepsis
		Premature delivery
		Premature labour
		Premature rupture of membranes
		Preterm premature rupture of membranes
		Procedural haemorrhage
		Prolonged labour
		Threatened labour
		Uterine dilation and curettage
		Vaginal haemorrhage
		Wound dehiscence
Congenital malformations	Cardiovascular malformations	Aorta hypoplasia
		Atrial septal defect
		Bicuspid aortic valve
		Cardiac disorder
		Cardiac septal defect
		Cardiac ventricular disorder
		Cardiomegaly
		Haemangioma
		Heart disease congenital
		Left atrial enlargement
		Left ventricular dilatation
		Left ventricular dysfunction
		Left ventricular enlargement

		Patent ductus arteriosus
		Right ventricular dilatation
		Right ventricular dysfunction
		Transposition of the great vessels
		Univentricular heart
		Vein disorder
		Ventricular septal defect
	Endocrine malformations	Congenital hypothyroidism
	Gastrointestinal malformations	Congenital diaphragmatic hernia
		Congenital umbilical hernia
		Diaphragmatic hernia
		Duodenal atresia
		Exomphalos
		Pyloric stenosis
		Small intestinal obstruction
	Musculoskeletal malformations	Adactyly
		Brachydactyly
		Congenital hand malformation
		Congenital musculoskeletal disorder of skull
		Congenital nose malformation
		Craniosynostosis
		Foot deformity
		Polydactyly
	Neurological malformations	Cerebellar hypoplasia
		Cerebral haemorrhage
		Cerebral infarction
		Cerebral ventricle dilatation
		Congenital hydrocephalus
		Congenital spinal cord anomaly
		Hydrocephalus
		Intervertebral disc disorder
	Congenital respiratory tract disorders	Congenital pulmonary airway malformation
		Lung disorder
	Genitourinary malformations	Congenital renal disorder
		Double ureter
		Hypospadias
		Renal dysplasia
		Urethral repair
	Other congenital malformations, not otherwise specified	Blindness
		Congenital skin dimples
		Ear malformation
		Hypertelorism
		Microphthalmos
		Nose deformity
		Pigmentation disorder
		Strabismus

		Tuberous sclerosis complex
		Amniocentesis abnormal
		Cleft palate
		Congenital anomaly
		Cytogenetic abnormality
		Cytogenetic analysis abnormal
		Deafness bilateral
		Dysmorphism
		Fistula
		Fetal malformation
		Gene mutation
		Gene mutation identification test positive
		General physical condition abnormal
		Hair texture abnormal
		Ultrasound Doppler abnormal
		Ultrasound antenatal screen abnormal
		Ultrasound scan abnormal
Neonatal complications	Neonatal complications, Haematological disorder	Neutropenia neonatal
	Neonatal complications, Cardiovascular disorder	Bradycardia neonatal
		Tachycardia fetal
	Neonatal complications, Metabolic and endocrine disorder	Metabolic acidosis
	Neonatal complications, Infection	Immunodeficiency
		Infection
		Puerperal infection
		Sepsis
		Sepsis neonatal
		Septic shock
	Neonatal complications, Neuronal disorder	Haemorrhage intracranial
		Hypotonia neonatal
		Neonatal seizure
		Seizure
	Neonatal complications, Respiratory disorder	Apnoea
		Fetal distress syndrome
		Hypoxia
		Immature respiratory system
		Infantile apnoea
		Neonatal aspiration
		Neonatal dyspnoea
		Neonatal respiratory distress syndrome
		Neonatal respiratory failure
		Neonatal tachypnoea
		Newborn persistent pulmonary hypertension

		Pulmonary oedema neonatal
		Respiratory disorder
		Respiratory distress
		Respiratory failure
		Respiratory tract infection
	Other neonatal complications, not otherwise specified	Apgar score low
		Endotracheal intubation
		Grey syndrome neonatal
		Hyperbilirubinaemia neonatal
		Jaundice
		Jaundice neonatal
		Large for dates baby
		Low birth weight baby
		Neonatal disorder
		Perinatal depression
		Small for dates baby
		Sudden infant death syndrome
Pregnancy complications	Pregnancy complications, Gestational diabetes	Diabetes mellitus
		Gestational diabetes
		Type 2 diabetes mellitus
	Pregnancy complications, Gestational hypertension and preeclampsia	Blood pressure increased
		Eclampsia
		Gestational hypertension
		Hypertension
		Pre-eclampsia
	Pregnancy complications, Intrauterine growth restriction	Fetal growth restriction
		Growth retardation
	Other pregnancy complications, not otherwise specified	Abortion threatened
		Amniotic cavity infection
		Amniotic fluid index decreased
		Amniotic fluid volume decreased
		Anaemia of pregnancy
		Bacterial vaginosis
		Disseminated intravascular coagulation
		Ectopic pregnancy
		Fetal heart rate abnormal
		Fetal monitoring abnormal
		Haemorrhage in pregnancy
		Hydrops fetalis
		Hyperemesis gravidarum
		Morning sickness
		Oligohydramnios
		Placenta praevia
		Placental disorder

		Placental insufficiency
		Polyhydramnios
		Premature baby
		Premature separation of placenta
		Rubella in pregnancy
		Status epilepticus
		Umbilical cord abnormality
		Urinary tract infection
		Urinary tract infection pseudomonal
		Uterine contractions during pregnancy
Stillbirth		Death
		Death neonatal
		Fetal death
		Premature baby death
		Stillbirth

Abbreviations: ADR, adverse drug reaction; MedDRA, medical dictionary for regulatory activities

Supplementary Table 4 Description and disproportionality analyses of pregnancy-related adverse drug reactions reported with the small molecules of interest compared with other anticancer agents

	ICSRs with the small molecules of interest (N=162)		ICSRs with other anticancer agents (N=6,708)				
Pregnancy-related ADR	n	%	n	%	ROR *	LCL	UCL
<u>Abortion</u>	16	9.9	731	10.9	0.90	0.53	1.51
Spontaneous abortion (MedDRA PT)	10	6.2	535	8.0	0.76	0.40	1.45
Abortion induced (MedDRA PT)	3	1.9	124	1.9	-		
Abortion (MedDRA PT)	3	1.9	74	1.1	-		
<u>Stillbirth</u>	1	0.6	177	2.6	-		
<u>Delivery complications</u>	20	12.4	653	9.7	1.31	0.81	2.10
Premature delivery (MedDRA PT)	8	4.9	396	5.9	0.83	0.40	1.70
Premature labour (MedDRA PT)	7	4.3	113	1.7	2.64	1.21	5.75
Caesarean section (MedDRA PT)	5	3.1	107	1.6	1.97	0.79	4.89
Prolonged labour (MedDRA PT)	1	0.6	3	0.0	-		
Vaginal haemorrhage (MedDRA PT)	2	1.2	48	0.7	-		
Threatened labour (MedDRA PT)	1	0.6	3	0.0	-		
<u>Congenital malformations</u>	8	4.9	418	6.2	0.78	0.38	1.60
<i>Cardiovascular malformations</i>	1	0.6	122	1.8	-		
Left ventricular dilatation (MedDRA PT)	1	0.6	0	0.0	-		
Left ventricular dysfunction (MedDRA PT)	1	0.6	1	0.0	-		
Cardiac ventricular disorder (MedDRA PT)	1	0.6	1	0.0	-		
<i>Musculoskeletal malformations</i>	3	1.9	90	1.3	-		
Polydactyly (MedDRA PT)	1	0.6	7	0.1	-		
Foot deformity (MedDRA PT)	1	0.6	5	0.1	-		
Adactyly (MedDRA PT)	1	0.6	14	0.2	-		
<i>Neurological malformations</i>	2	1.2	36	0.5	-		
Cerebral infarction (MedDRA PT)	1	0.6	3	0.0	-		
Cerebral ventricle dilatation (MedDRA PT)	1	0.6	9	0.1	-		
<i>Congenital respiratory tract disorders</i>	1	0.6	17	0.3	-		
Congenital pulmonary airway malformation (MedDRA PT)	1	0.6	0	0.0	-		
<i>Genitourinary malformations</i>	1	0.6	30	0.5	-		
Renal dysplasia (MedDRA PT)	1	0.6	3	0.0	-		
<i>Other congenital malformations</i>					-		
Hypertelorism (MedDRA PT)	1	0.6	12	0.2	-		
Nose deformity (MedDRA PT)	1	0.6	6	0.1	-		
Ear malformation (MedDRA PT)	1	0.6	8	0.1	-		
Tuberous sclerosis complex (MedDRA PT)	1	0.6	1	0.0	-		
Dysmorphism (MedDRA PT)	1	0.6	19	0.3	-		
Cytogenetic abnormality (MedDRA PT)	1	0.6	6	0.1	-		
Fistula (MedDRA PT)	1	0.6	2	0.0	-		
<u>Pregnancy complications</u>	45	27.8	1,417	21.1	1.44	1.01	2.04

<i>Gestational diabetes</i>	1	0.6	62	0.9	-		
<i>Gestational hypertension and pre-eclampsia</i>	7	4.3	181	2.7	1.63	0.75	3.52
Hypertension (MedDRA PT)	2	1.2	56	0.8	-		
Blood pressure increased (MedDRA PT)	1	0.6	10	0.1	-		
Pre-eclampsia (MedDRA PT)	4	2.5	100	1.5	-		
<i>Intrauterine growth restriction</i>	13	8.0	259	3.9	2.17	1.22	3.88
Fetal growth restriction (MedDRA PT)	12	7.4	246	3.7	2.10	1.15	3.84
Growth retardation (MedDRA PT)	1	0.6	14	0.2	-		
<i>Other pregnancy complications</i>							
Premature baby (MedDRA PT)	23	14.2	734	10.9	1.35	0.86	2.11
Placental insufficiency (MedDRA PT)	1	0.6	14	0.2	-		
Oligohydramnios (MedDRA PT)	4	2.5	124	1.8	-		
Anaemia of pregnancy (MedDRA PT)	1	0.6	4	0.0	-		
Fetal monitoring abnormal (MedDRA PT)	1	0.6	2	0.0	-		
Status epilepticus (MedDRA PT)	1	0.6	1	0.0	-		
Umbilical cord abnormality (MedDRA PT)	1	0.6	5	0.1	-		
<u>Neonatal complications</u>	22	13.6	647	9.7	1.47	0.93	2.32
<i>Neonatal respiratory complications</i>	9	5.6	182	2.7	2.11	1.06	4.20
Neonatal respiratory distress syndrome (MedDRA PT)	5	3.1	56	0.8	3.78	1.50	9.57
Hypoxia (MedDRA PT)	1	0.6	8	0.1	-		
Infantile apnoea (MedDRA PT)	1	0.6	10	0.1	-		
Neonatal aspiration (MedDRA PT)	1	0.6	1	0.0	-		
Neonatal respiratory failure (MedDRA PT)	1	0.6	6	0.1	-		
Respiratory distress (MedDRA PT)	1	0.6	25	0.4	-		
Respiratory failure (MedDRA PT)	1	0.6	27	0.4	-		
<i>Neonatal neuronal disorders</i>	2	1.2	28	0.4	-		
Hypotonia neonatal (MedDRA PT)	1	0.6	13	0.2	-		
Neonatal seizure (MedDRA PT)	1	0.6	2	0.0	-		
<i>Neonatal cardiovascular disorders</i>	1	0.6	1	0.0	-		
Bradycardia neonatal (MedDRA PT)	1	0.6	1	0.0	-		
<i>Neonatal haematological disorders</i>	1	0.6	17	0.3	-		
Neutropenia neonatal (MedDRA PT)	1	0.6	17	0.3	-		
<i>Neonatal infection</i>	3	1.9	153	2.3	-		
Sepsis	3	1.9	27	0.4	-		
<i>Other neonatal complications</i>							
Low birth weight baby (MedDRA PT)	10	6.2	189	2.8	2.27	1.18	4.37
Small for dates baby (MedDRA PT)	1	0.6	61	0.9	-		
Jaundice neonatal (MedDRA PT)	1	0.6	50	0.7	-		

* ROR computation was performed for pregnancy-related ADRs with at least five ICSRs involving the small molecules of interest. Disproportionate reporting signals were considered when the LCL was greater than 1

Abbreviations: ADR, adverse drug reaction; ICSR, individual case safety report; ROR, reporting odds ratio; LCL, lower confidence limit; UCL, upper confidence limit; MedDRA, medical dictionary for regulatory activities; PT, preferred term

Supplementary Table 5 Description of pregnancy-related adverse drug reactions reported with FDA-approved small molecules for non-small cell lung cancer compared with other anticancer agents

Pregnancy-related ADR	ICSRs with FDA-approved small molecules for NSCLC n (%) (N=75)	ICSRs with other anticancer agents n (%) (N=6,708)
<u>Abortion</u>	7 (9.3)	731 (10.9)
Spontaneous abortion (MedDRA PT)	6 (8.0)	535 (8.0)
Abortion induced (MedDRA PT)	1 (1.3)	124 (1.9)
<u>Delivery complications</u>	9 (12.0)	653 (9.7)
Premature delivery (MedDRA PT)	3 (4.0)	396 (5.9)
Premature labour (MedDRA PT)	5 (6.7)	113 (1.7)
Caesarean section (MedDRA PT)	3 (4.0)	107 (1.6)
Threatened labour (MedDRA PT)	1 (1.3)	3 (0.0)
<u>Congenital malformations</u>	4 (5.3)	418 (6.2)
<i>Musculoskeletal malformations</i>	1 (1.3)	90 (1.3)
Adactyly (MedDRA PT)	1 (1.3)	14 (0.2)
<i>Neurological malformations</i>	1 (1.3)	36 (0.5)
Cerebral infarction (MedDRA PT)	1 (1.3)	3 (0.0)
<i>Genitourinary malformations</i>	1 (1.3)	30 (0.5)
Renal dysplasia (MedDRA PT)	1 (1.3)	3 (0.0)
<i>Other congenital malformations</i>		
Fistula (MedDRA PT)	1 (1.3)	2 (0.0)
<u>Pregnancy complications</u>	17 (22.7)	1,417 (21.1)
<i>Gestational diabetes</i>	1 (1.3)	62 (0.9)
Gestational diabetes (MedDRA PT)	1 (1.3)	37 (0.6)
<i>Gestational hypertension and pre-eclampsia</i>	1 (1.3)	181 (2.7)
Pre-eclampsia (MedDRA PT)	1 (1.3)	100 (1.5)
<i>Intrauterine growth restriction</i>	5 (6.7)	259 (3.9)
Fetal growth restriction (MedDRA PT)	4 (5.3)	246 (3.7)
Growth retardation (MedDRA PT)	1 (1.3)	14 (0.2)
<i>Other pregnancy complications</i>		
Premature baby (MedDRA PT)	9 (12.0)	734 (10.9)
Placental insufficiency (MedDRA PT)	1 (1.3)	14 (0.2)
Oligohydramnios (MedDRA PT)	3 (4.0)	124 (1.8)
<u>Neonatal complications</u>	12 (16.0)	647 (9.7)
<i>Neonatal respiratory complications</i>	5 (6.7)	182 (2.7)
Neonatal respiratory distress syndrome (MedDRA PT)	3 (4.0)	56 (0.8)
Hypoxia (MedDRA PT)	1 (1.3)	8 (0.1)
Infantile apnoea (MedDRA PT)	1 (1.3)	10 (0.1)
Respiratory distress (MedDRA PT)	1 (1.3)	25 (0.4)
<i>Neonatal infection</i>	2 (2.7)	153 (2.3)
Sepsis (MedDRA PT)	2 (2.7)	27 (0.4)
<i>Other neonatal complications</i>		
Low birth weight baby (MedDRA PT)	7 (9.3)	189 (2.8)
Small for dates baby (MedDRA PT)	1 (1.3)	61 (0.9)
Jaundice neonatal (MedDRA PT)	1 (1.3)	50 (0.7)

In bold, pregnancy-related ADRs with ≥ 5 ICSRs involving FDA-approved small molecules for NSCLC for which disproportionality analyses were performed

Abbreviations: ADR, adverse drug reaction; FDA, Food and Drug Administration; ICSR, individual case safety report; NSCLC, non-small cell lung cancer; MedDRA, medical dictionary for regulatory activities; PT, preferred term

Supplementary Table 6 Description of pregnancy-related adverse drug reactions reported with FDA-approved small molecules for non-small cell lung cancer compared with other anticancer agents considering the subgroup of individual case safety reports without co-suspect drugs

Pregnancy-related ADR	ICSRs with FDA-approved small molecules for NSCLC without co-suspect drugs n (%), N=61	ICSRs with other anticancer agents without co-suspect drugs n (%), N=4,716
<u>Abortion</u>	6 (9.8)	543 (11.5)
Spontaneous abortion (MedDRA PT)	5 (8.2)	407 (8.6)
Abortion induced (MedDRA PT)	1 (1.6)	77 (1.6)
<u>Delivery complications</u>	6 (9.8)	386 (8.2)
Premature delivery (MedDRA PT)	2 (3.3)	211 (4.5)
Premature labour (MedDRA PT)	3 (4.9)	75 (1.6)
Caesarean section (MedDRA PT)	3 (4.9)	70 (1.5)
Threatened labour (MedDRA PT)	1 (1.6)	3 (0.1)
<u>Congenital malformations</u>	2 (3.3)	267 (5.7)
<i>Neurological malformations</i>	1 (1.6)	19 (0.4)
Cerebral infarction (MedDRA PT)	1 (1.6)	1 (0.0)
<i>Genitourinary malformations</i>	1 (1.6)	17 (0.4)
Renal dysplasia (MedDRA PT)	1 (1.6)	3 (0.1)
<u>Pregnancy complications</u>	13 (21.3)	874 (18.5)
<i>Gestational diabetes</i>	1 (1.6)	27 (0.6)
Gestational diabetes (MedDRA PT)	1 (1.6)	23 (0.5)
<i>Gestational hypertension and pre-eclampsia</i>	1 (1.6)	102 (2.2)
Pre-eclampsia (MedDRA PT)	1 (1.6)	72 (1.5)
<i>Intrauterine growth restriction</i>	4 (6.6)	143 (3.0)
Fetal growth restriction (MedDRA PT)	3 (4.9)	136 (2.9)
Growth retardation (MedDRA PT)	1 (1.6)	8 (0.2)
<i>Other pregnancy complications</i>		
Premature baby (MedDRA PT)	7 (11.5)	421 (8.9)
Placental insufficiency (MedDRA PT)	1 (1.6)	6 (0.1)
Oligohydramnios (MedDRA PT)	1 (1.9)	87 (1.8)
<u>Neonatal complications</u>	9 (14.8)	305 (6.5)
<i>Neonatal respiratory complications</i>	3 (4.9)	96 (2.0)
Neonatal respiratory distress syndrome (MedDRA PT)	2 (3.3)	33 (0.7)
Hypoxia (MedDRA PT)	1 (1.6)	4 (0.1)
Infantile apnoea (MedDRA PT)	1 (1.6)	7 (0.1)
<i>Neonatal infection</i>	2 (3.3)	38 (0.8)
Sepsis	2 (3.3)	10 (0.2)
<i>Other neonatal complications</i>		
Low birth weight baby (MedDRA PT)	5 (8.2)	89 (1.9)
Small for dates baby (MedDRA PT)	1 (1.6)	25 (0.5)
Jaundice neonatal (MedDRA PT);	1 (1.6)	14 (0.3)

In bold, pregnancy-related ADRs with ≥ 5 ICSRs involving FDA-approved small molecules for NSCLC for which disproportionality analyses were performed

Abbreviations: ADR, adverse drug reaction; FDA, Food and Drug Administration; ICSR, individual case safety report; NSCLC, non-small cell lung cancer; MedDRA, medical dictionary for regulatory activities; PT, preferred term

Supplementary Table 7 Overview of all small molecules of interest with the reported pregnancy-related adverse drug reactions by small molecule chemical classes

Small molecule chemical class	Detailed information on correspondent ICSRs (suspect small molecules and reported ADRs)
ALK-ROS-NTRK inhibitors (N=0)	-
KRAS inhibitors (N=0)	-
NTRK inhibitors (N=3)	3 ICSRs with larotrectinib (all of drug exposure during pregnancy, without pregnancy-related ADRs of interest)
MET inhibitors (N=4)	4 ICSRs with crizotinib : • 2 ICSRs of drug exposure during pregnancy, without pregnancy-related ADRs of interest • 1 ICSR of cerebral infraction, hypoxia, sepsis, premature baby • 1 ICSR of renal dysplasia, growth restriction, premature baby
RET inhibitors (N=4)	4 ICSRs with cabozantinib : • 3 ICSRs of drug exposure during pregnancy, without pregnancy-related ADRs of interest • 1 ICSR of spontaneous abortion
HER2 inhibitors (N=5)	5 ICSRs with tucatinib : • 3 ICSR of drug exposure during pregnancy, without pregnancy-related ADRs of interest • 1 ICSR of abortion induced • 1 ICSR of hypertelorism, dysmorphism, nose deformity, congenital pulmonary airway malformation, ear malformation, polydactyly and induced abortion
VEGF-TRK inhibitors (N=6)	4 ICSRs with cabozantinib , 1 ICSR with lenvatinib , 1 ICSR with sunitinib : • 4 ICSRs of drug exposure during pregnancy, without pregnancy-related ADRs of interest • 1 ICSR of spontaneous abortion • 1 ICSR of premature baby and respiratory failure
ALK-ROS inhibitors (N=8)	4 ICSRs with crizotinib , 2 ICSRs with brigatinib , 1 ICSR with crizotinib , alectinib, 1 ICSR with lorlatinib : • 4 ICSRs of drug exposure during pregnancy, without pregnancy-related ADRs of interest • 1 ICSR of spontaneous abortion • 1 ICSR of abortion induced • 1 ICSR of cerebral infraction, hypoxia, sepsis, premature baby • 1 ICSR of renal dysplasia, growth restriction, premature baby
MEK inhibitors (N=8)	6 ICSRs with dabrafenib, trametinib , 2 ICSR with binimetinib , encorafenib: • 5 ICSRs of drug exposure during pregnancy, without pregnancy-related ADRs of interest • 1 ICSR of spontaneous abortion • 1 ICSR of premature labour • 1 ICSR of gestational diabetes
CDK inhibitors (N=9)	9 ICSRs with palbociclib : • 6 ICSRs of drug exposure during pregnancy, without pregnancy-related ADRs of interest • 1 ICSR of abortion • 1 ICSR of prolonged labour • 1 ICSR of premature baby and neonatal death
ALK inhibitors (N=19)	18 ICSRs with alectinib , 1 ICSR with crizotinib , alectinib : • 15 ICSRs of drug exposure during pregnancy, without pregnancy-related ADRs of interest • 1 ICSR of spontaneous abortion • 1 ICSR of fistula • 1 ICSR of low birth weight baby • 1 ICSR of premature delivery and respiratory distress

HER2-EGFR inhibitors (N=19)	17 ICSRs with lapatinib , 2 ICSRs with neratinib : • 7 ICSRs of drug exposure during pregnancy, without pregnancy-related ADRs of interest • 12 ICSRs of pregnancy-related ADRs of interest (Supplementary Table 8 and Figure 2A)
BRAF inhibitors (N=23)	11 ICSRs with vemurafenib , 6 ICSRs with dabrafenib , trametinib, 4 ICSRs with dabrafenib , 2 ICSR with binimetinib, encorafenib : • 12 ICSRs of drug exposure during pregnancy, without pregnancy-related ADRs of interest • 11 ICSRs of pregnancy-related ADRs of interest (Supplementary Table 8 and Figure 2B)
EGFR inhibitors (N=34)	14 ICSRs with erlotinib , 9 ICSRs with gefitinib , 10 ICSRs with osimertinib , 1 ICSR with osimertinib , afatinib : • 12 ICSRs of drug exposure during pregnancy, without pregnancy-related ADRs of interest • 22 ICSRs of pregnancy-related ADRs of interest (Supplementary Table 8 and Figure 2C)
mTOR inhibitors (N=37)	37 ICSRs with everolimus : • 14 ICSRs of drug exposure during pregnancy, without pregnancy-related ADRs of interest • 23 ICSRs of pregnancy-related ADRs of interest (Supplementary Table 8 and Figure 2D)

Abbreviations: ICSR, individual case safety report; ADR, adverse drug reaction; ALK, anaplastic lymphoma kinase; ROS, reactive oxygen species; NTRK, neurotrophic tyrosine receptor kinase; BRAF, B-Raf serine-threonine kinase; CDK, cyclin-dependent kinase; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma viral oncogene homolog; MEK, mitogen-activated protein kinase; MET, c-mesenchymal-epithelial transition; mTOR, mechanistic (mammalian) target of rapamycin; RET, rearranged during transfection gene; VEGFR-TRK, vascular endothelial growth factor receptor-tropomyosin receptor kinase

Supplementary Table 8 Description of pregnancy-related adverse drug reactions reported with HER2-EGFR, BRAF, EGFR and mTOR inhibitors

Pregnancy-related ADR	HER2-EGFR inhibitors n (%), N=19	BRAF inhibitors n (%), N=23	EGFR inhibitors n (%), N=34	mTOR inhibitors n (%), N=37
<u>Abortion</u>	2 (10.5)	2 (8.7)	2 (5.9)	3 (8.1)
Spontaneous abortion (MedDRA PT)	1 (5.3)	2 (8.7)	2 (5.9)	2 (5.4)
Abortion (MedDRA PT)	1 (5.3)	-	-	1 (2.7)
<u>Delivery complications</u>	3 (15.8)	4 (17.4)	6 (17.6)	5 (13.5)
Premature delivery (MedDRA PT)	2 (10.5)	3 (13.0)	1 (2.9)	1 (2.7)
Premature labour (MedDRA PT)	-	1 (4.3)	4 (11.8)	2 (5.4)
Caesarean section (MedDRA PT)	1 (5.3)	-	3 (8.8)	-
Vaginal haemorrhage (MedDRA PT)	-	-	-	2 (5.4)
Threatened labour (MedDRA PT)	-	1 (4.3)	-	-
<u>Congenital malformations</u>	-	-	1 (2.9)	3 (8.1)
<i>Cardiovascular malformations</i>	-	-	-	1 (2.7)
Left ventricular dilatation (MedDRA PT)	-	-	-	1 (2.7)
Left ventricular dysfunction (MedDRA PT)	-	-	-	1 (2.7)
Cardiac ventricular disorder (MedDRA PT)	-	-	-	1 (2.7)
<i>Musculoskeletal malformations</i>	-	-	1 (2.9)	1 (2.7)
Foot deformity (MedDRA PT)	-	-	-	1 (2.7)
Adactyly (MedDRA PT)	-	-	1 (2.9)	-
<i>Neurological malformations</i>	-	-	-	1 (2.7)
Cerebral ventricle dilatation (MedDRA PT)	-	-	-	1 (2.7)
<i>Other congenital malformations</i>	-	-	-	1 (2.7)
Tuberous sclerosis complex (MedDRA PT)	-	-	-	1 (2.7)
Dysmorphism (MedDRA PT)	-	-	-	-
Cytogenetic abnormality (MedDRA PT)	-	-	-	1 (2.7)
<u>Pregnancy complications</u>	10 (52.6)	5 (21.7)	12 (35.3)	14 (37.8)
Gestational diabetes (MedDRA PT)	-	1 (4.3)	-	-
<i>Gestational hypertension and pre-eclampsia</i>	-	2 (8.7)	-	5 (13.5)
Hypertension (MedDRA PT)	-	-	-	2 (5.4)
Blood pressure increased (MedDRA PT)	-	-	-	1 (2.7)
Pre-eclampsia(MedDRA PT)	-	2 (8.7)	-	2 (5.4)
<i>Intrauterine growth restriction</i>	8 (42.1)	-	4 (11.8)	-
Fetal growth restriction (MedDRA PT)	8 (42.1)	-	4 (11.8)	-
<i>Other pregnancy complications</i>				
Anaemia of pregnancy (MedDRA PT)	-	1 (4.3)	-	-
Fetal monitoring abnormal (MedDRA PT)	-	-	-	1 (2.7)
Oligohydramnios (MedDRA PT)	-	-	3 (8.8)	1 (2.7)
Placental insufficiency (MedDRA PT)	-	-	1 (2.9)	-
Premature baby (MedDRA PT)	4 (21.1)	2 (8.7)	6 (17.6)	7 (18.9)
Status epilepticus (MedDRA PT)	-	-	-	1 (2.7)
Umbilical cord abnormality (MedDRA PT)	-	-	-	1 (2.7)
<u>Neonatal complications</u>	1 (5.3)	3 (13.0)	8 (23.5)	6 (16.2)
<i>Neonatal respiratory complications</i>	-	2 (8.7)	2 (5.9)	2 (5.4)
Infantile apnoea (MedDRA PT)	-	-	1 (2.9)	-

Neonatal aspiration (MedDRA PT)	-	-	-	1 (2.7)
Neonatal respiratory distress syndrome (MedDRA PT)	-	2 (8.7)	2 (5.9)	1 (2.7)
Neonatal respiratory failure (MedDRA PT)	-	-	-	1 (2.7)
<i>Neonatal neuronal disorders</i>	-	-	-	2 (5.4)
Hypotonia neonatal (MedDRA PT)	-	-	-	1 (2.7)
Neonatal seizure (MedDRA PT)	-	-	-	1 (2.7)
<i>Neonatal cardiovascular disorders</i>	-	1 (4.3)	-	-
Bradycardia neonatal (MedDRA PT)	-	1 (4.3)	-	-
<i>Neonatal haemathological disorders</i>	-	1 (4.3)	-	-
Neutropenia neonatal (MedDRA PT)	-	1 (4.3)	-	-
<i>Neonatal infection (sepsis)</i>	-	-	1 (2.9)	1 (2.7)
<i>Other neonatal complications</i>				
Low birth weight baby (MedDRA PT)	1 (5.3)	1 (4.3)	6 (17.6)	1 (2.7)
Small for dates baby (MedDRA PT)	-	-	1 (2.9)	-
Jaundice neonatal (MedDRA PT)	-	-	1 (2.9)	-

In bold, pregnancy-related ADRs with ≥ 5 ICSRs involving small molecules of interest for which disproportionality analyses were performed

Abbreviations: ADR, adverse drug reaction; MedDRA, medical dictionary for regulatory activities; PT, preferred term; HER2, human epidermal growth factor receptor 2; EGFR, epidermal growth factor receptor; BRAF, B-Raf serine-threonine kinase; mTOR, mechanistic (mammalian) target of rapamycin

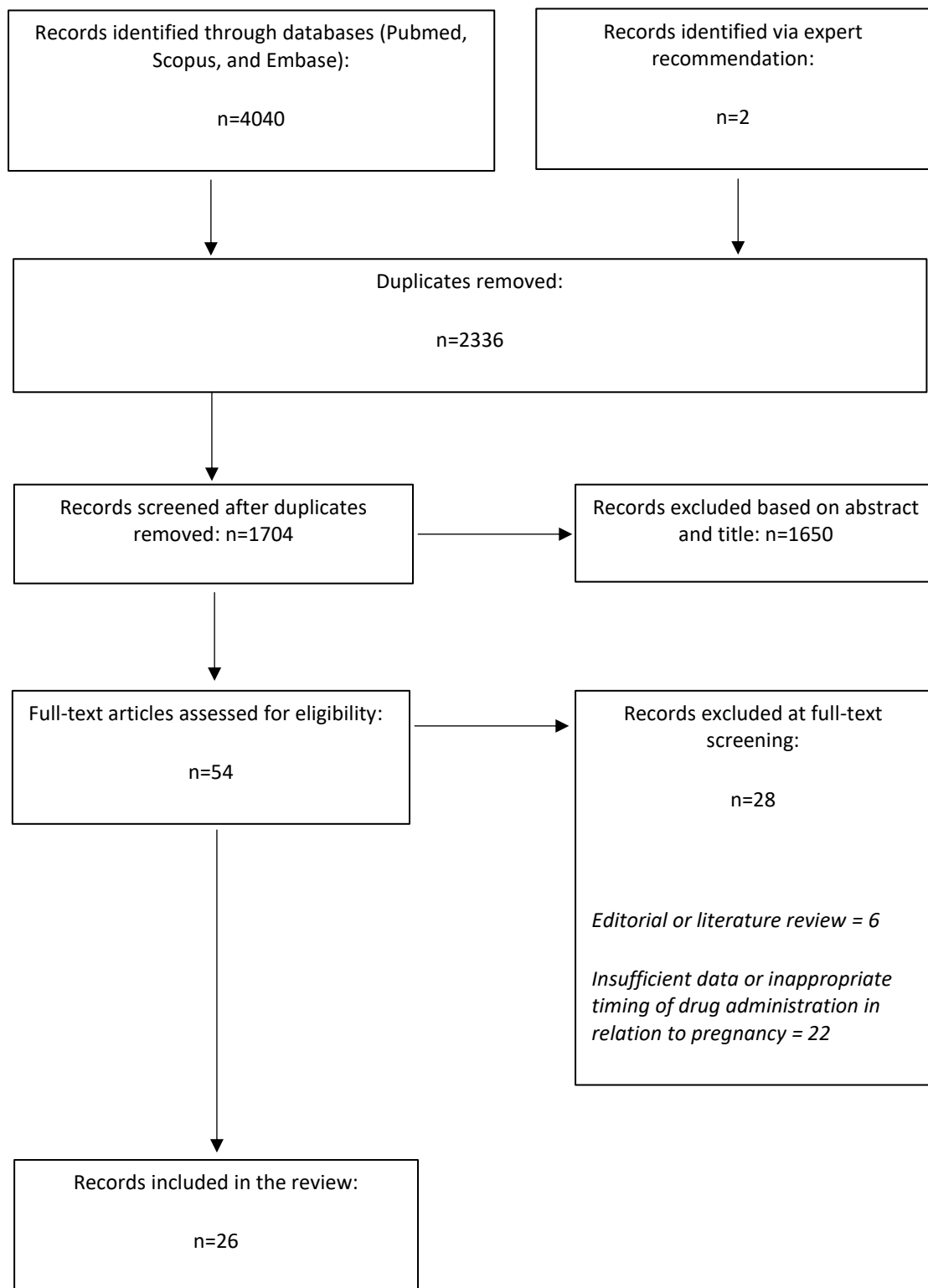
Supplementary Table 9 Description of pregnancy-related adverse drug reactions associated with single small molecules and reported in ≥ 5 individual case safety reports

Small molecule	Detailed information on correspondent ICSRs (suspect small molecule and reported ADRs)
Everolimus (mTOR inhibitor, N=37)	• 14 ICSRs of drug exposure during pregnancy, without pregnancy-related ADRs of interest • 23 ICSRs of pregnancy-related ADRs of interest (Supplementary Table 8 and Figure 2D)
Alectinib (ALK inhibitor, N=18)	• 14 ICSRs of drug exposure during pregnancy, without pregnancy-related ADRs of interest • 1 ICSR of premature delivery, respiratory distress • 1 ICSR of low birth weight baby • 1 ICSR of fistula • 1 ICSR of spontaneous abortion
Lapatinib (HER2-EGFR inhibitor, N=17)	• 6 ICSRs of drug exposure during pregnancy, without pregnancy-related ADRs of interest • 3 ICSRs of fetal growth restriction • 2 ICSRs of fetal growth restriction, premature delivery • 2 ICSRs of premature baby • 1 ICSR of fetal growth restriction, premature baby • 1 ICSR of abortion • 1 ICSR of fetal growth restriction, low birth weight baby • 1 ICSR of fetal growth restriction, caesarean section, premature baby (Supplementary Table 8 and Figure 2E)
Erlotinib (EGFR inhibitor, N=14)	• 8 ICSRs of drug exposure during pregnancy, without pregnancy-related ADRs of interest • 2 ICSRs of low birth weight baby • 2 ICSRs of fetal growth restriction • 1 ICSR of adactyly • 1 ICSR of small for dates baby
Vemurafenib (BRAF inhibitor, N=11)	• 6 ICSRs of drug exposure during pregnancy, without pregnancy-related ADRs of interest • 2 ICSRs of premature delivery • 1 ICSR of pre-eclampsia, anaemia of pregnancy • 1 ICSR of low birth weight baby • 1 ICSR of premature baby, neonatal neutropenia, respiratory distress syndrome, bradycardia neonatal
Osimertinib (EGFR inhibitor, N=10)	• 1 ICSR of drug exposure during pregnancy, without pregnancy-related ADRs of interest • 2 ICSRs of spontaneous abortion • 1 ICSR of premature labour • 1 ICSR of premature labour, oligohydramnios • 1 ICSR of oligohydramnios • 1 ICSR of premature baby • 1 ICSR of premature baby, low birth weight baby • 1 ICSR of placental insufficiency, premature labour, caesarean section • 1 ICSR of fetal growth restriction, premature baby, low birth weight baby, neonatal respiratory distress syndrome (Figure 2F)
Gefitinib (EGFR inhibitor, N=9)	• 4 ICSRs of drug exposure during pregnancy, without pregnancy-related ADRs of interest • 2 ICSRs of premature baby, low birth weight baby • 1 ICSR of premature delivery • 1 ICSR of premature labour, caesarean section • 1 ICSR of caesarean section, premature baby, jaundice, apnoea, sepsis neonatal, neonatal respiratory distress syndrome

Palbociclib (CDK inhibitor, N=9)	• 6 ICSRs of drug exposure during pregnancy, without pregnancy-related ADRs of interest • 1 ICSR of abortion • 1 ICSR of prolonged labour • 1 ICSR of premature baby, neonatal death
Dabrafenib, trametinib (BRAF and MEK inhibitors, N=6)	• 4 ICSRs of drug exposure during pregnancy, without pregnancy-related ADRs of interest • 1 ICSRs of spontaneous abortion • 1 ICSR of premature labour
Tucatinib (HER2 inhibitors, N=5)	• 3 ICSR of drug exposure during pregnancy, without pregnancy-related ADRs of interest • 1 ICSR of abortion induced • 1 ICSR of hypertelorism, dysmorphism, nose deformity, congenital pulmonary airway malformation, ear malformation, polydactyly and induced abortion

Abbreviations: ICSR, individual case safety report; ADR, adverse drug reaction; ALK, anaplastic lymphoma kinase; BRAF, B-Raf serine-threonine kinase; CDK, cyclin-dependent kinase; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; mTOR, mechanistic (mammalian) target of rapamycin

Supplementary Table 10. Flow chart of literature search and article selection (PRISMA flow chart)



sAppendix 1. Literature search strategy

Pubmed:

("pregnancy" OR "delivery" OR "pregnant" OR "birth" OR "embryo" OR "fetus") AND ("lung cancer" OR "lung adenocarcinoma" OR "lung squamous cell carcinoma" OR "lung neoplasm" OR "nslc" OR "sclc" OR "lung carcinoma" OR "lung tumor" OR "lung malignancy" OR "thoracic tumor" OR "thoracic cancer" OR "thymic tumor" OR "thymoma" OR "thymic carcinoma") AND ("tki" OR "thyrosine kinase inhibitor" OR "egfr inhibitor" OR "erlotinib" OR "gefitinib" OR "afatinib" OR "osimertinib" OR "poziotinib" OR "dacomitinib" OR "amivantamab" OR "lazertinib" OR "mobocertinib" OR "alk inhibitor" OR "alectinib" OR "crizotinib" OR "ceritinib" OR "lorlatinib" OR "brigatinib" OR "entrectinib" OR "LAROTRECTINIB" OR "Repotrectinib" OR "Selpercatinib" OR "Pralsetinib" OR "Capmatinib" OR "Tepotinib" OR "Savolitinib" OR "Dabrafenib" OR "Encorafenib" OR "Vemurafenib" OR "Trametinib" OR "Binimetinib" OR "Cobimetinib" OR "Larotrectinib" OR "Entrectinib" OR "tucatinib" OR "lapatinib" OR "Sunitinib" OR "Cabozantinib" OR "Lenvatinib" OR "neratinib" OR "everolimus" OR "palbociclib")

Embase and Scopus:

("pregnancy" OR "delivery" OR "pregnant" OR "birth" OR "embryo" OR "fetus") AND ("lung cancer" OR "lung adenocarcinoma" OR "lung squamous cell carcinoma" OR "lung neoplasm" OR "nslc" OR "sclc" OR "lung carcinoma" OR "lung tumor" OR "lung malignancy" OR "thoracic tumor" OR "thoracic cancer" OR "thymic tumor" OR "thymoma" OR "thymic carcinoma") AND ("tki" OR "thyrosine kinase inhibitor" OR "egfr inhibitor" OR "erlotinib" OR "gefitinib" OR "afatinib" OR "osimertinib" OR "poziotinib" OR "dacomitinib" OR "amivantamab" OR "lazertinib" OR "mobocertinib" OR "alk inhibitor" OR "alectinib" OR "crizotinib" OR "ceritinib" OR "lorlatinib" OR "brigatinib" OR "entrectinib" OR "LAROTRECTINIB" OR "Repotrectinib" OR "Selpercatinib" OR "Pralsetinib" OR "Capmatinib" OR "Tepotinib" OR "Savolitinib" OR "Dabrafenib" OR "Encorafenib" OR "Vemurafenib" OR "Trametinib" OR "Binimetinib" OR "Cobimetinib" OR "Larotrectinib" OR "Entrectinib" OR "tucatinib" OR "lapatinib" OR "Sunitinib" OR "Cabozantinib" OR "Lenvatinib" OR "neratinib" OR "everolimus" OR "palbociclib")

In EMBASE and Scopus, the research was limited to studies conducted on humans, written in english, with an abstract available.

sAppendix 2. Exclusion criteria

Studies were excluded from the systematic review based on the following criteria:

- (a) Articles not relevant to the clinical question, including those not involving tyrosine kinase inhibitors (TKIs), pregnancy, or thoracic malignancies;
- (b) Study types not reporting original patient data, such as systematic reviews, meta-analyses, narrative reviews, editorials, comments, letters to the editor;
- (c) Case reports or case series in which TKIs were not administered during pregnancy, or were given for indications other than thoracic malignancies;
- (d) Studies involving patients with thoracic malignancies who were not pregnant at the time of TKI administration;
- (e) Insufficient or missing data on TKI exposure timing relative to pregnancy, cancer diagnosis, or maternal/fetal outcomes;
- (g) Duplicate or overlapping datasets—when identified, only the most comprehensive or recent report was included.