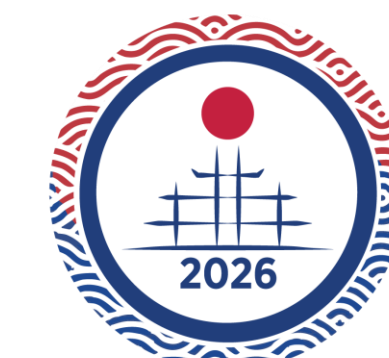


EP12.47: RIT1 Mutated Metastatic Lung Adenocarcinoma - A Case Series

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IASLC 2026 World Conference on Lung Cancer

SEPTEMBER 12 – 15, 2026
SEOUL, REPUBLIC OF KOREA

INTRODUCTION

- Aberrant functioning of the EGFR-RAS pathway leads to oncogenesis in over 75% of lung adenocarcinomas (LUAD)¹.
- RIT1 (Ras-like in all tissues) is a member of the RAS superfamily with GTP hydrolysis activity upon GTP binding.
- Approximately 2% of LUAD harbor point mutations in RIT1 and 14% exhibit amplification².
- RIT1 is a RAS-family GTPase with pathogenic variants often cluster near switch-II, activating MAPK signalling³.
- RIT1-M90I mutation is the most frequently observed alteration in LUAD, with no approved targeted therapies.
- RIT1 testing is not included on recommended lung biomarkers.

METHODS

Design:

- This was a retrospective review of patients with lung cancer referred to the The Australian Translational Genomics Centre (ATGC) for somatic whole-exome sequencing (WES) testing.
- The ATGC database was interrogated for patients with lung cancer harboring RIT1 mutations.
- This included patients from January 2020 to January 2026.
- Treatment outcomes were assessed including the presence of actionable genomic alterations (AGA), progression free survival (PFS) and overall survival (OS).

DISCUSSION AND CONCLUSION

- Patients harboring RIT1 mutations (or VUS) had poor outcomes on standard treatments.
- Case 1:** Despite high PD-L1 (TPS 90%), RIT1A77G & ARID1A mutations were confirmed with disease progression (new brain metastases) and stable extracranial disease requiring therapy change after 6 months.
 - Often feature a lower tumor mutational burden (TMB).
 - Associated with immune-excluded microenvironment.
- Cases 2 & 3:** EGFR Exon 19 deletion but progressed early on EGFR-TKI therapy and harbored a RIT1 VUS gain-of-function.
 - Possibly reflecting tumor clonality under drug pressure.
 - Experimental/preclinical data suggest RIT1 mutations can drive transformation and reduce sensitivity to EGFR inhibitors which may also result in targeted-therapy resistance^(7,8).

Actionable Take Away Message

- RIT1 mutations may confer resistance across standard lung adenocarcinoma treatments.
- This case series underscores the critical need for comprehensive molecular profiling.

Future Direction for Research

- Prospective studies are required to validate the prognostic & predictive value of RIT1 mutations in lung adenocarcinoma.

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Acknowledgements: Janssen Research & Development, LLC

RESULTS N = 3

CASE 1

11/2023	11/2023	12/2023	01/2024	03/2024	04/2023	05/2024	05/2024	07/2024	07/2024	08/2024	07/2025	12/2025
Diagnosis	SIADH	GK-SRS	Pembrolizumab	Brain PD	GK-SRS	Pembro-DKA	Pembro-Rash	Pembro-colitis	RIT-1 mutant	GK-SRS	Brain PD	LMD
T1cN2M1c (Stage IVb) RUL primary (26mm) • Left adrenal mets • Multiple brain mets • Core biopsy RUL primary • PD-L1 TPS = 90%	Na+ (plasma) = 130 mmol/L Na+ (urine) = 47 mmol/L Plasma Osmolality = 277 mOsm/L Urinary Osmolality = 690 mOsm/L	Completed to 7 Right frontal Left frontal Right occipital Right cerebellar Left cerebellar x 3 Largest lesion Right precentral gyrus frontal = 9mm	Completed CD13 18.01.24 CD13 - 08.02.2024 Mild treatment related dermatitis (arms) & fatigue	Six new supratentorial lesions with two on motor strip Pineal and R cerebellar met Pineal lesion increased in size Completed GK-SRS to 17/21 lesions identified on MRI Brain planning scan	24Gy / 3 fractions Pineal and R cerebellar met Stable - primary tumor & associated adenopathy Worsening rash, on prednisone 25mg for rash CS Pembro = 11.04.2024	Pembrolizumab induced Type I DM Polyuria & thirst BGL 38.5 mmol/L Ketones 1.6 mmol/L Commenced Insulin Pembrolizumab held	Biopsy proven Spongiotic drug reaction Widespread eczematous & lichenified rash	UV/ Phototherapy with Narrow band UVB 06/24 Grade 3 diarrhea Biopsy proven on colonoscopy Started 2mg/kg IVMP	WES testing Confirmed A77G mutation High TMB Commenced Carboplatin-Pemetrexed	New brain metastasis No recurrent lesions 9 lesions treated including 3 R frontal lesions	Maintenance Pemetrexed New left occipital lobe met 6mm. Radiation necrosis of right precentral gyrus & right frontal lesion. Started Bevacizumab	New cerebellar, supratentorial mets with LMD Functional decline Died 01/2026

CASE 2

08/2021	09/2021	09/2022	11/2022	03/2023	03/2023	06/2023	09/2023	10/2023	11/2023	11/2023	03/2024
Diagnosis	MARIPOSA	Oligoprogression	NGS-WES	PD	ABCP	Transaminitis	Arthritis	PD	Docetaxel	LMD	Brain metastasis
T1cN2M1c (Stage IVb) LLL primary (18mm) • Bilateral supraclavicular LN mets • Multiple bone mets • EBUS FNA • EGFR Exon 19 deletion • PD-L1 TPS = 40%	Lazertinib / placebo (240mg) plus Osimertinib / placebo (80mg) 25 Gy / 5 Fractions External Beam Radiation Therapy (EBRT)	Left supraclavicular & left hilar lymph node 25 Gy / 5 Fractions External Beam Radiation Therapy (EBRT)	TMB (13.2 Muts/Mbp) myc gain of function RIT1 gain of function (variance of unknown significance)	Right Infracavicular, Right adrenal & Right superior iliac crest Right anterior acetabular lytic bone met Left iliacium 19 Gy/1Fraction EBRT to right acetabular metastasis	Atezolizumab-Bevacizumab-Carboplatin-Paclitaxel	Grade 2 transaminitis due to Paclitaxel Replaced with Pemetrexed from C4 onwards.	Grade 2 immunotherapy related arthritis Affecting shoulder and hips Atezolizumab stopped from C8	Increase in primary lung cancer	One cycle Stopped due to Grade 2 peripheral neuropathy bilateral lower limbs	Leptomeningeal disease L & S- spine Completed 20 Gy/5Fractions Opted for Best supportive care	New symptomatic brain metastasis Died later in month

CASE 3

04/2020	05/2020	10/2020	10/2020	09/2021	11/2021	11/2021	03/2022	03/2022	07/2022	10/2022	12/2022
Diagnosis	Erlotinib	Skin toxicity	Osimertinib	PD	ABCP	NGS-WES	PD	Carbo-Etop	PD	Irinotecan	Brain metastases
T1cN2M1c (Stage IVa) Bilateral lung metastases WES testing - EGFR Exon 19 deletion • PD-L1 TPS = 20%	Developed florid pustular rash on face, non-pustular acneiform rash on chest/back. required doxycycline & topical steroids.	Stopped Erlotinib 5 months later due to Grade 3 rash in addition to palmar planar erythrodysesthesia Refractory to topical tacrolimus	No skin toxicities PD after 11 months.	Pulmonary, hepatic & LN. Mediastinal LN biopsy -> predominantly adenocarcinoma plus clusters of small cell carcinoma	Atezolizumab-Bevacizumab-Carboplatin-Paclitaxel	TMB (6.6 Muts/Mbp) Loss-of: function RB1. Gain-of-function PIK3CA. EGFR Exon 19 del Gain-of-function RIT1 mutation with 8 copies (variance of unknown significance).	Progression of liver metastases	Carboplatin-Etoposide	Stable initial scan Progression of known liver metastases. New brain metastases and proceeded to WBRT	Completed 1 cycle of docetaxel with disease progression Started Irinotecan & further progression liver metastases.	Died later in month

LEGEND

Pembrolizumab	MARIPOSA	Atezolizumab-Bevacizumab-Carboplatin-Paclitaxel (Pemetrexed)	Docetaxel	Best Supportive Care
Carboplatin-Pemetrexed	Erlotinib	Osimertinib	Carboplatin-Etoposide	Irinotecan

Fig 1 Summary of treatment courses in three patients harboring a RIT1 mutation.

Note: RUL – right upper lobe, PD-L1 TPS – programmed death-ligand 1 tumor proportion score; GK-SRS -Gamma Knife - Stereotactic Radiosurgery; SIADH –Syndrome of Inappropriate Antidiuretic Hormone, PD – progression of disease; NGS-WES - Next-generation sequencing- whole exome sequencing; LLL – left lower lobe; LN – lymph node; mets – metastasis(es); TMB – tumor mutational burden; EBRT – external beam radiation therapy; LMD – leptomeningeal disease; WBRT – whole brain radiation therapy.

Table 2 Summary of patient treatment outcomes with confirmed RIT1 mutations from WES testing.

Note: Expected First PFS is based on data from relevant clinical trials.

Case Number (Biomarker used for initial treatment)	Core Biopsy (Timing)	Classification	VAF/ (Copy Number)	Relevant Treatment Regimen	Expected First PFS (months)	Observed First PFS (months)	No. of treatment lines	OS (months)
1. (PD-L1 TPS = 90)	Tumour Mutational Burden (Diagnosis) ARID1A p.(Glu1444Ter) ARID1A p.(Pro1898HisfsTer23) RIT1 p.(Ala77Gly) PT53 p.(Pro85LeufsTer38)	10.6 Muts/Mbp Loss-of-function Loss-of-function Gain-of- function Loss-of-function	- 15.6% 14.5% 6.8% 28.7%	Pembrolizumab (First line)	10.3 ⁽⁴⁾	6	2	26
2. (EGFR Exon 19 deletion)	Tumour Mutational Burden (Oligoprogression on Mariposa) PIK3CA p.(Gln75Glu) TP53 p.(Arg110TrpfsTer12) myc PTP4A3 CCNE1 AKT2 RIT1 VUS	13.2 Muts/Mbp Gain-of- function Loss-of-function Gain-of- function Gain-of-function Gain-of-function Gain-of-function Gain-of-function	- 18.8% 49.6% (15) (13) (7) (16) (7)	Mariposa trial (First line)	16.6 ⁽⁵⁾	11	3	31
3. (EGFR Exon 19 deletion)	Tumour Mutational Burden (Progression on Osimertinib) PIK3CA p.(His1047Arg) RB1 splice acceptor variant RIT1 VUS	5.6 Muts/Mbp Gain-of- function Gain-of- function Gain-of- function	- 92.4% 79.8% (6)	Erlotinib -> Osimertinib (First line)	24.9 ⁽⁶⁾	16	5	32