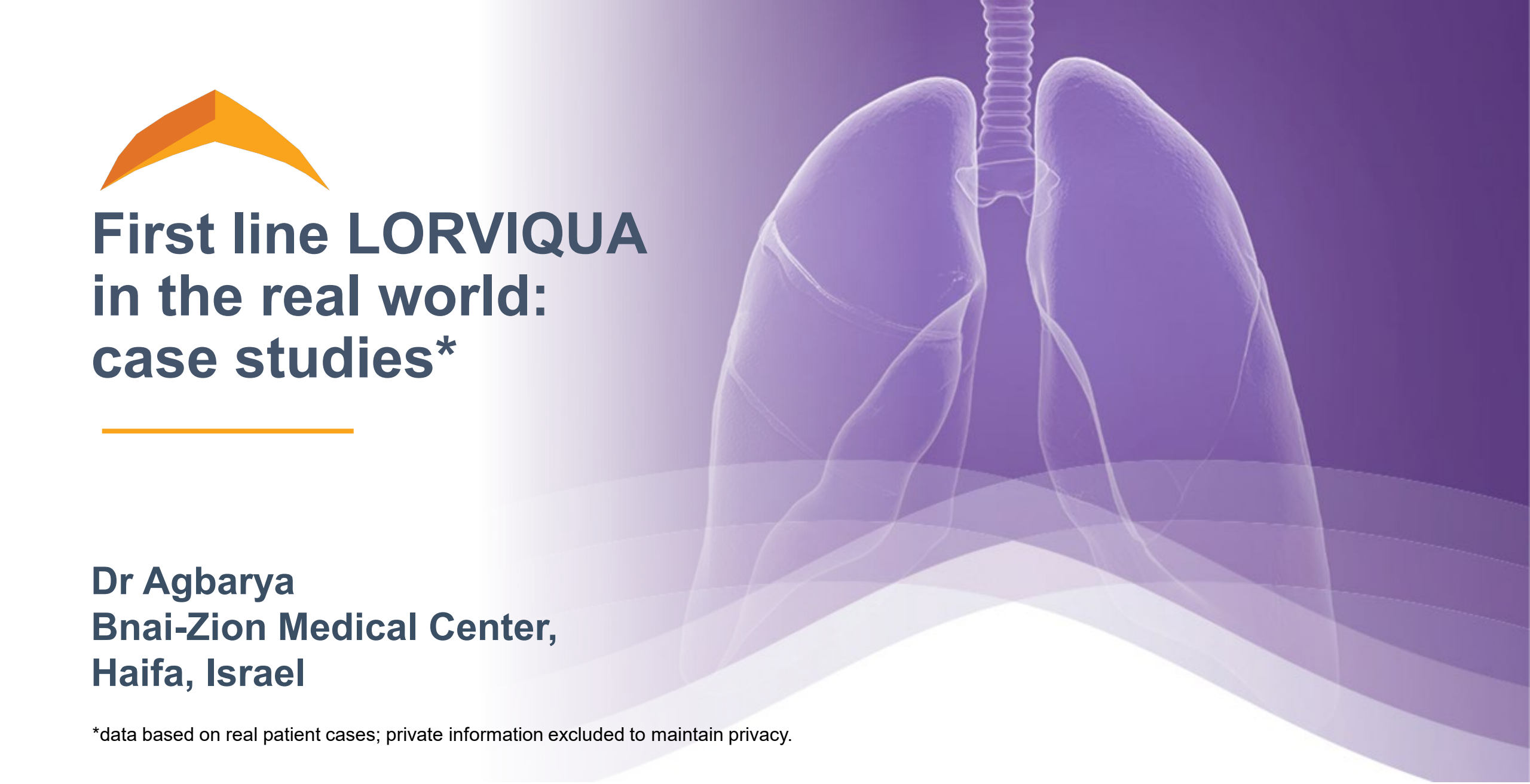


First line LORVIQUA in the real world: case studies*

Dr Agbarya
Bnai-Zion Medical Center,
Haifa, Israel

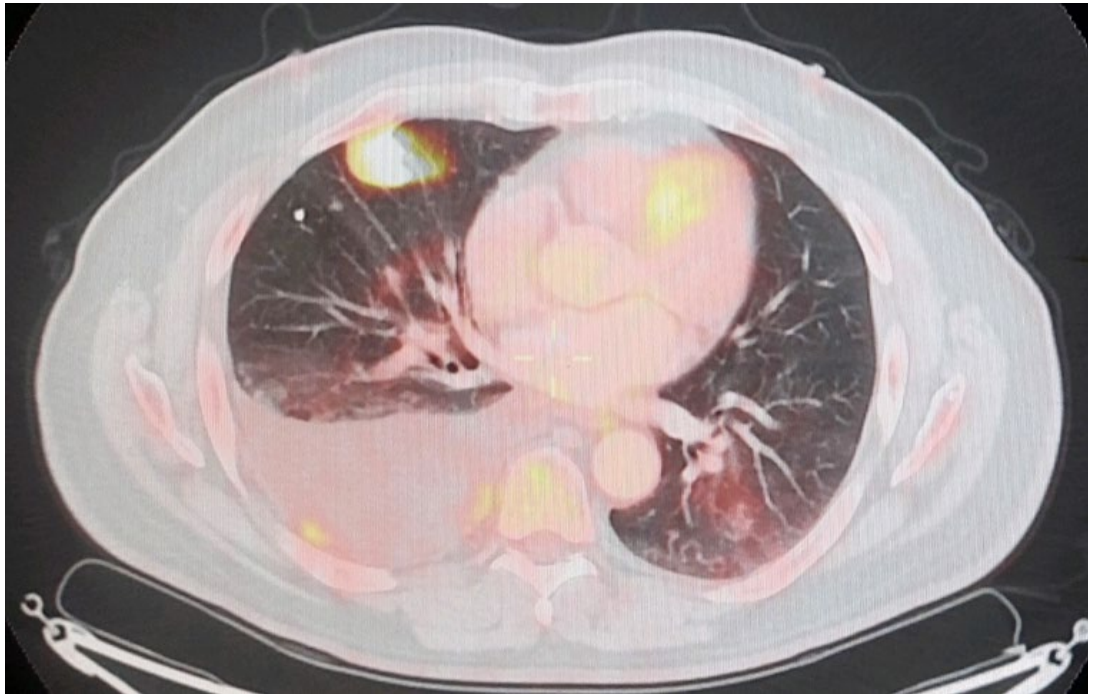
*data based on real patient cases; private information excluded to maintain privacy.

CASE 1

Case 1 - Initial presentation & Diagnosis

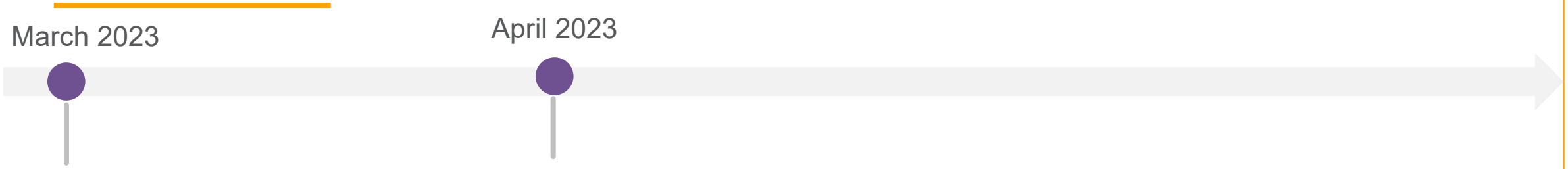
March 2023

- 61 y male
- Healthy, never smoker
- History of chemical Exposure
- Family history malignancies
- Admitted to hospital due to chest pain and shortness of breath - Diagnosed with MI
- PET-CT Pleural effusion+ RLL mass + bilateral lung Mets
- CT guided Biopsy- **Adenocarcinoma of Lung**
- Brain MRI clear



Dr Agbarya personal patient case
RLL- right lower lobe, MI myocardial infraction
Dr Agbarya personal patient case, images used with permission

Diagnosis & Course of Treatment



- PET-CT Pleural effusion+ RLL mass + bilateral lung Mets
- **Adenocarcinoma of Lung**

- Molecular Profile**:**

  ALK EML4 Fusion P

  PDL1=5% ; TMB=2.8 ; MSS
- **Started 1L treatment with 100mg LORVIQUA**
- 1st visit (1 week) blood test: Lipid profile and glucose normal

Dr Agbarya personal patient case
RLL- right lower lobe, PDL1- Programmed death-ligand 1, TBD- tumor mutational burden, MSS- Microsatellite Stability Biomarker, ALK, anaplastic lymphoma kinase, EML4, echinoderm microtubule-associated protein-like 4

Physician Checklist- prior to starting Lorviqua[1,2]

Perform investigations including:

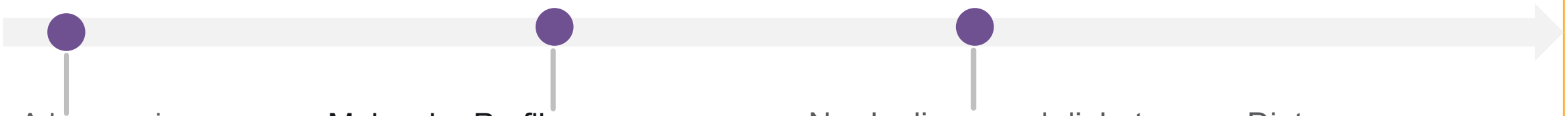
- ✓ Baseline serum cholesterol & Triglycerides
- ✓ Baseline Serum glucose
- ✓ Blood pressure
- ✓ ECG

Enquire about:

- ✓ Psychiatric history
- ✓ Baseline cognitive function, speech
- ✓ Independence with activities of daily living
- ✓ Use of CYP3A substrate drugs

1. Bauer, T. M., Felip, E., Solomon, B. J., et al. (2019). Clinical management of adverse events associated with lorlatinib. The oncologist, 24(8), 1103.
2. 1.LORVIQUA® Israeli latest approved PI

Diagnosis & Course of Treatment



March 2023

- Adenocarcinoma of Lung origin

April 2023

- Molecular Profile:

  ALK EML4 Fusion P
- **Started treatment with 100mg QD LORVIQUA**

June 2023

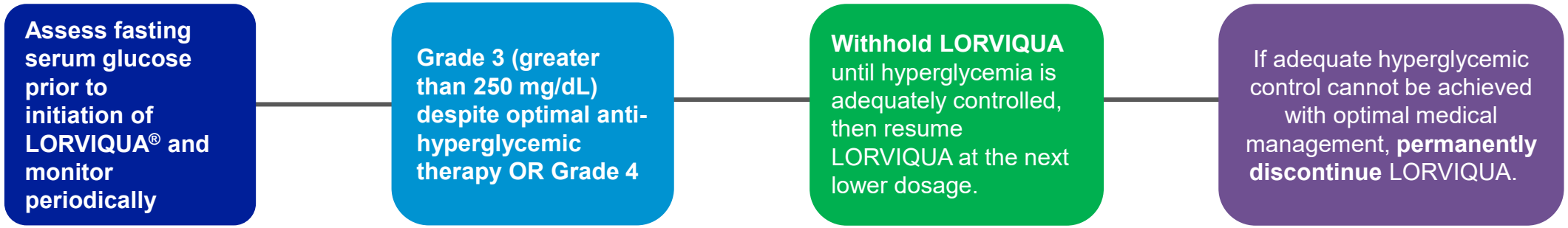
- Newly diagnosed diabetes → Diet
- Shortens of breath → Heart condition related
- **Depression grade 1-2 → Psychologic consultation - improved without intervention**
- **Edema grade 1 - No dose reduction needed**

Dr Agbarya personal patient case

ALK, anaplastic lymphoma kinase, EML4, echinoderm microtubule-associated protein-like 4

Management of Hyperglycemia[1]

- Hyperglycemia occurred in 9% of patients who received 100 mg LORVIQUA, including Grade 3 or 4 in 3.2% of patients.
- 0.8% of patients temporarily discontinued LORVIQUA for hyperglycemia.

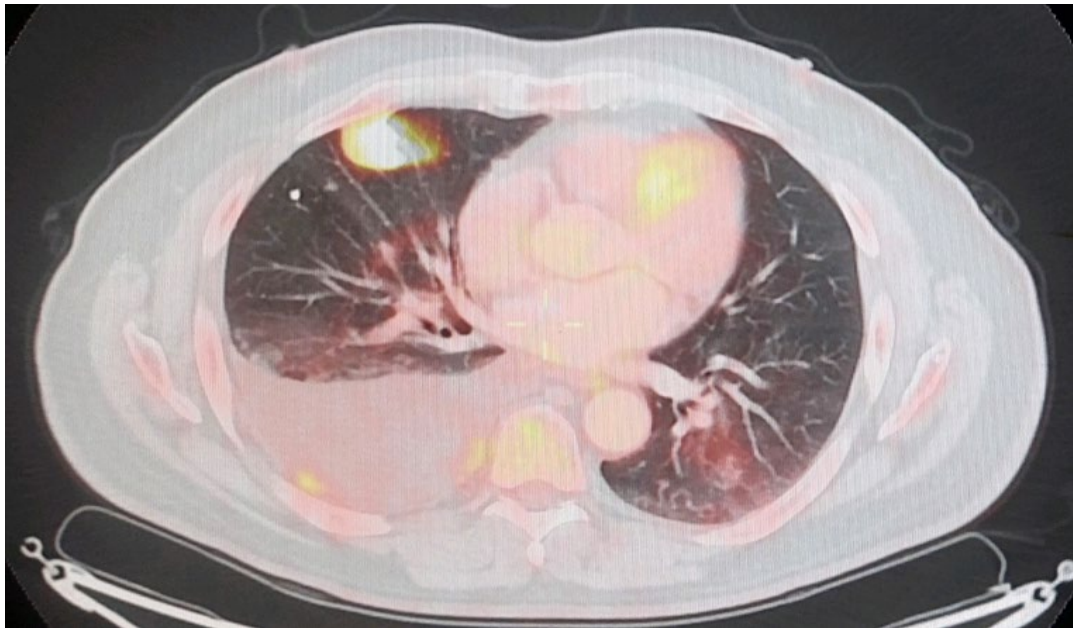


1.LORVIQUA® Israeli latest approved PI

PET/CT pre-treatment VS after 5 month on treatment

March 2023

Pleural effusion+
RLL mass +
bilateral lung Mets

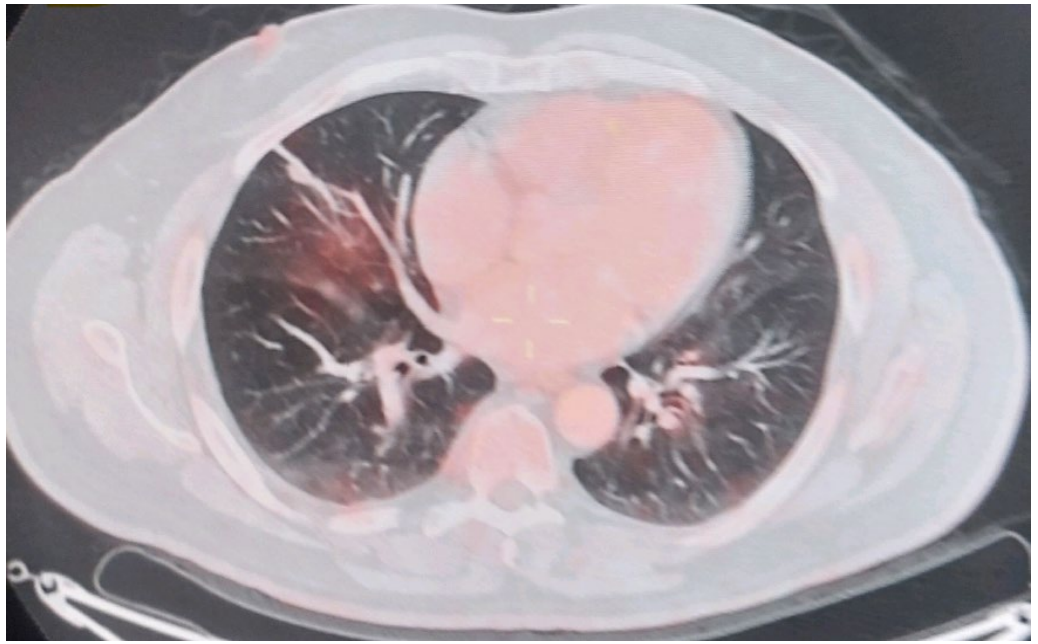


April 2023

Started treatment with 100mg QD LORVIQUA®

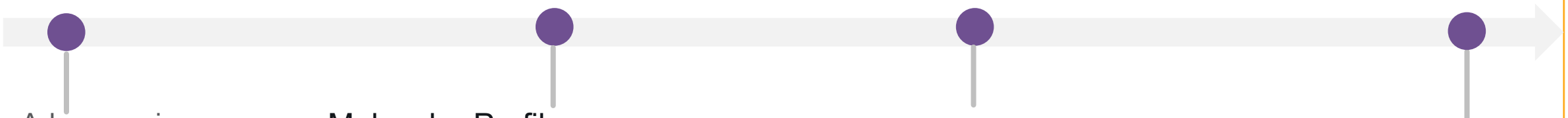
Aug 2023

CR- No pathological FDG uptake,
Pleural thickening with No FDG uptake in right hemi-thorax



*Dr Agbarya personal patient case, images used with permission.
RLL- right lower lobe, PET/CT- positron emission tomography/computed tomography, FDG- F-fluorodeoxyglucose. CR- complete response

Diagnosis & Course of Treatment



March 2023

- Adenocarcinoma of Lung origin

April 2023

- Molecular Profile:

  ALK EML4 Fusion P
- **Started treatment with 100mg QD LORVIQUA®**

June 2023

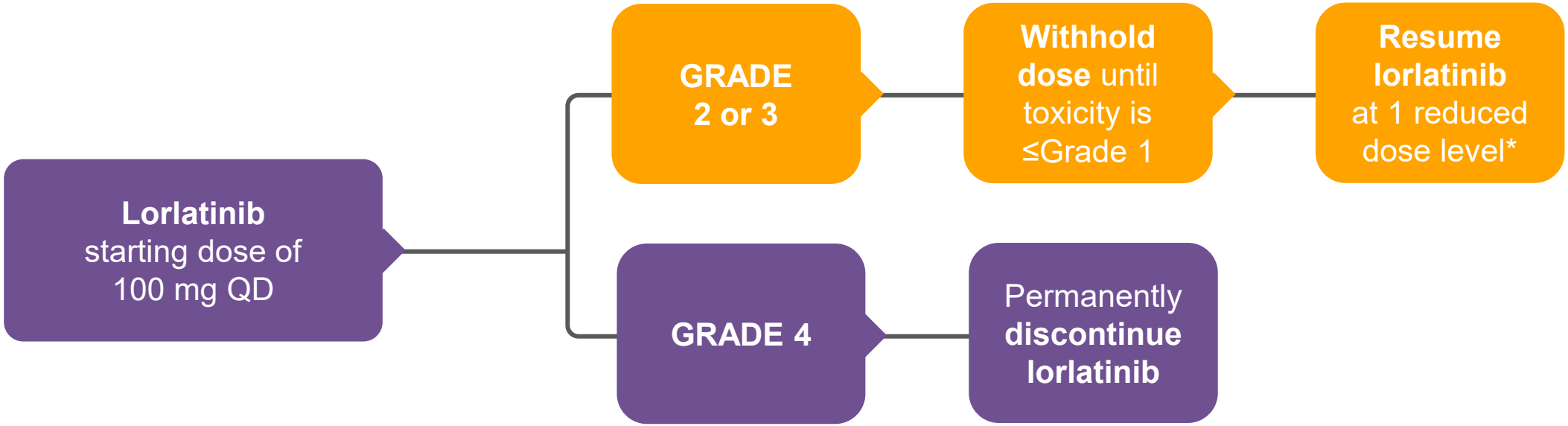
- Newly diagnosed diabetes → Diet
- Shortens of breath → Heart condition related
- **Depression grade 1-2 → Psychologic consultation and improvement.**
- **Edema grade 1 - No dose reduction needed**

Aug 2023

- **Mood changes → SSRI**

Dr Agbarya personal patient case
ALK, anaplastic lymphoma kinase, EML4, echinoderm microtubule-associated protein-like 4

Therapy management for CNS effects[1]



- A broad spectrum of CNS effects can occur in patients receiving lorlatinib, such as changes in cognitive function, mood and speech[2]
- Ask patients and inform caregivers and family members to report changes in mood, cognitive functioning and speech[2].
- Dose interruptions should be considered in the presence of Grade 1 CNS effects. LORVIQUA can be restarted at the same or lower dose after the patient returned to baseline.

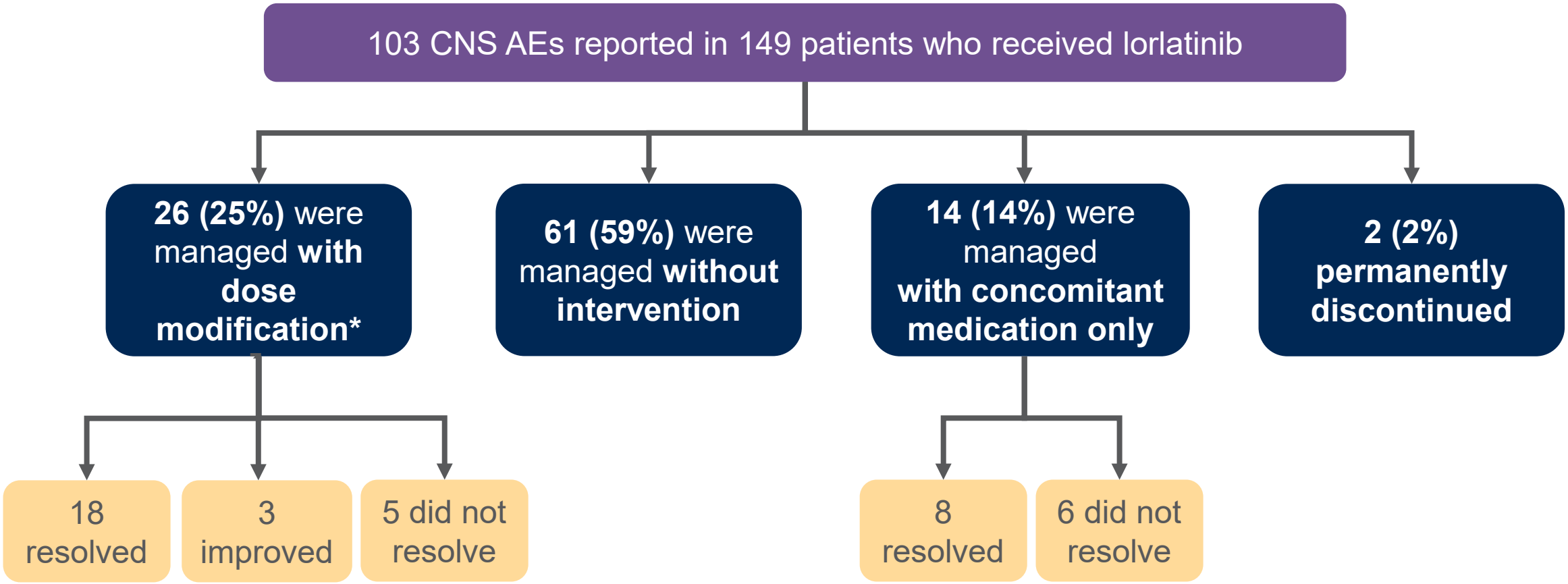
Grade 1- Mild, Grade 2- Moderate, Grade 3- Severe Grade 4- life threatening

*The recommended dose of lorlatinib is 100 mg taken orally, QD. The first dose-reduction level is 75 mg QD.[1]
AE, adverse event; CNS, central nervous system; QD, once daily.
1. LORVIQUA® Israeli latest approved PI 2. Bauer TM, et al. *Oncologist* 2019;24:1103–10.

Take home message:

- ✓ CNS side effects- mood disorders were treated successfully with SSRI – consider choosing a treatment that is not a cytochrome P450 substrate, such as Escitalopram.
- ✓ Adverse events were grade 1-2 and easily manageable.
- ✓ No dose reduction or dose interruptions were needed.

CROWN results- CNS tolerability and management[1]



*Dose modification = reduction and/or interruption, +/- concomitant medication.
AE, adverse event; CNS, central nervous system.
1. Solomon BJ, et al. *Lancet Respir Med* 2023;11(4):354–66.

CASE 2

Case 2 - Initial presentation & Diagnosis

Oct 2022

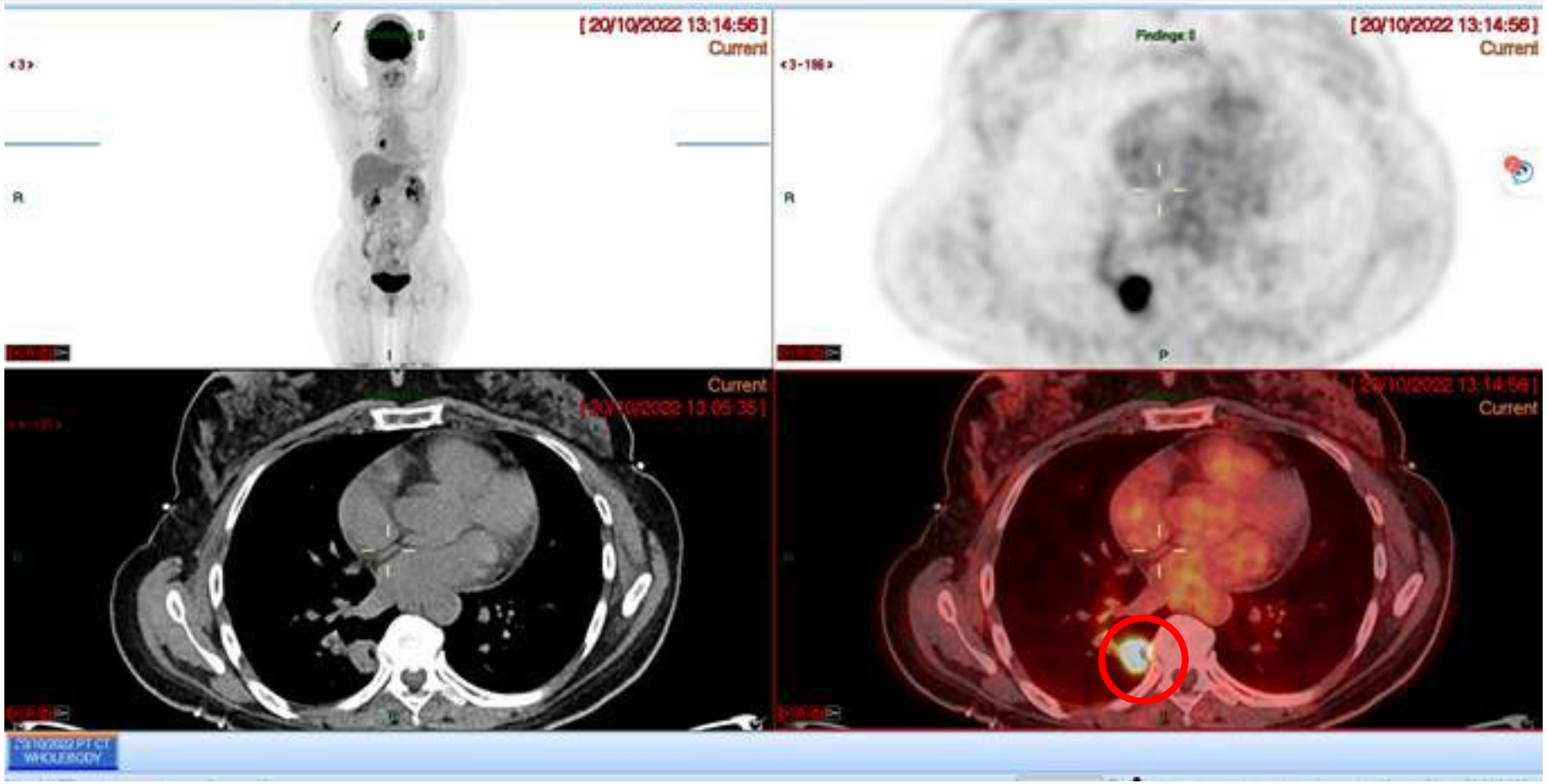
- 58 y Female, married +4
- Never smoker
- S/P Splenectomy due to ITP
- Family history of ovarian malignancies
- Presented with dry cough
- **PET-CT- solitary 2.5 cm** nodule detected in the medial RLL
- CT guided Biopsy- Adenocarcinoma
- Brain MRI- clear

Dr Agbarya personal patient case
ITP= Idiopathic thrombocytopenic purpura

PET-CT and Diagnosis

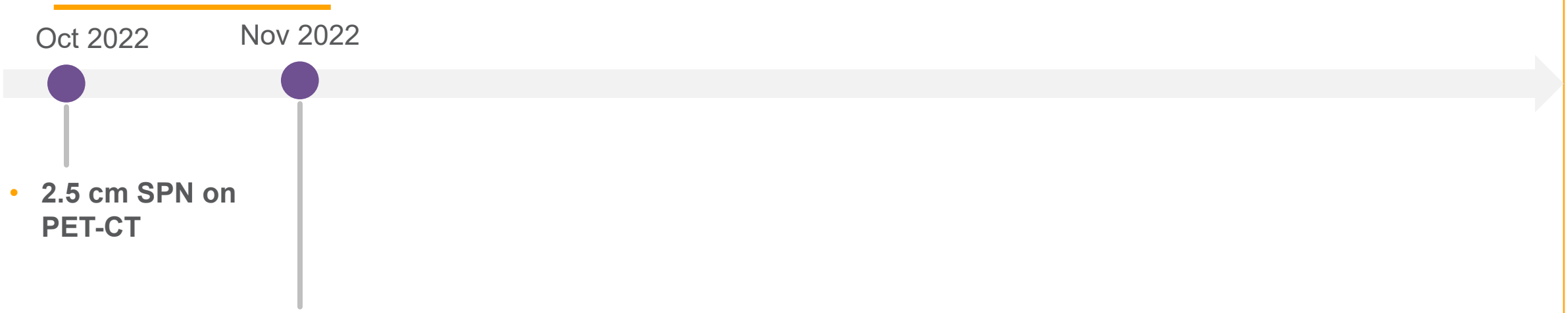
Oct 2022

- 2.5 cm SPN on PET-CT



SPN- solitary pulmonary nodule.
*Dr Agberya personal patient case, images used with permission.

Diagnosis & therapy

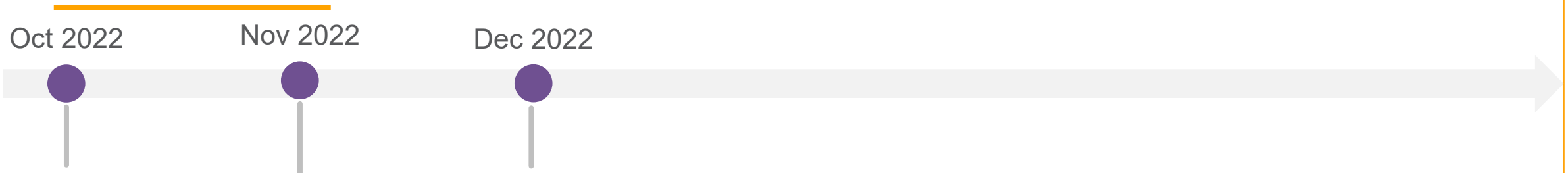


- **2.5 cm SPN on PET-CT**

- Stage IIIC
- RL Lobectomy
- Pathological report: **PD 1.5 cm Adenocarcinoma lesion** . 32 hilar and mediastinal lymph nodes were involved with metastatic adenocarcinoma.
- Lymphovascular invasion and extracapsular extension were identified.
- Post operative re-hospitalization due to Pneumonia and Empyema.

Dr Agbarya personal patient case
SPN-solitary pulmonary nodule, PD -purely differentiated

Diagnosis & Course of Treatment



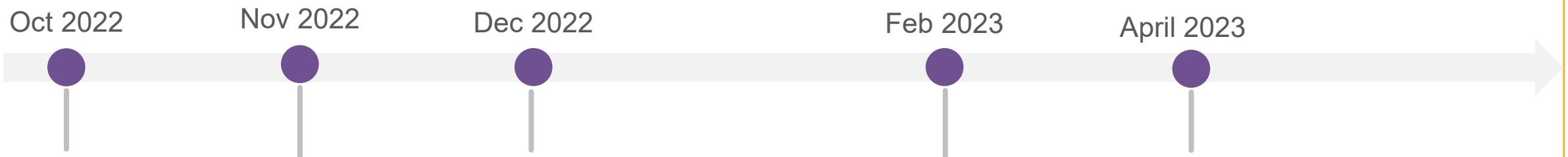
- 2.5 cm SPN on PET-CT

- Stage IIIC
- RL Lobectomy
- PD Adenocarcinoma 1.5 cm

- Due to Lesions undetectable in PET-CT Multidisciplinary team -**Restaging to Stage IV**
- Liquid BX- Negative for targeted mutations
- **Tissue NGS-** ALK +, PDL1 -, MSS, TMB 5.7
- **Diagnosis:** *ALK*+ NSCLC
- **Started treatment with 100mg QD LORVIQUA**

Dr Agbarya personal patient case
SPN- solitary pulmonary nodule, PD -purely differentiated , TMB-tumor mutational burden, MSS- Microsatellite Stability Biomarker, ALK, anaplastic lymphoma kinase, NSCLC non small cell lung cancer, PDL1- Programmed death-ligand NGS-New generation sequencing, MSS- Microsatellite Stability Biomarker TBD- tumor mutational burden.

Diagnosis & Course of Treatment



- 2.5 cm SPN on PET-CT

- Stage IIIC
- RL Lobectomy
- PD Adenocarcinoma 1.5 cm

- **Stage IV**
- ***ALK*+ NSCLC**
- **Lorviqua 100 mg QD**

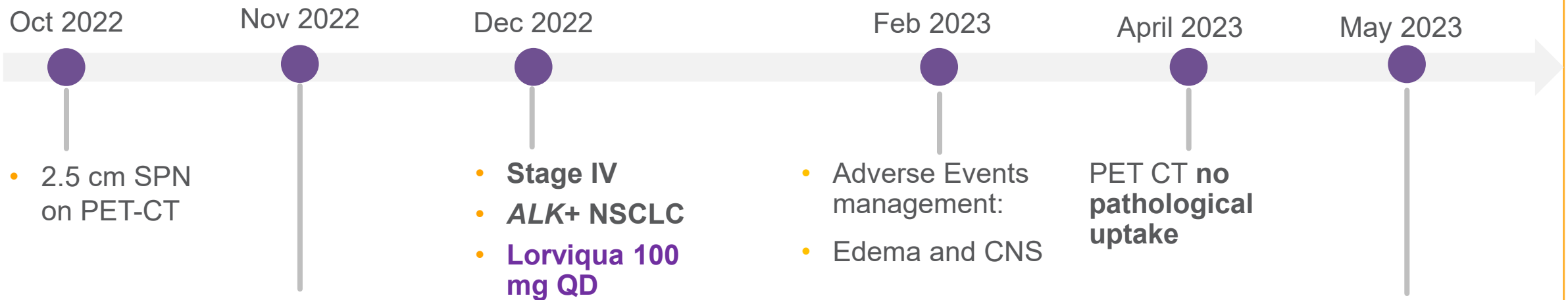
Follow up:

- Edema grade 2-3 :
- weight gain 4 kg → Diuretics + lymphatic massage
- Periorbital edema → Laser treatment
- Depression grade 1-2 → Phycological counselling

PET CT **no pathological uptake**

Dr Agbarya personal patient case
SPN- solitary pulmonary nodule, PD -purely differentiated , ALK, anaplastic lymphoma kinase, NSCLC non small cell lung cancer, PDL1- Programmed death-ligand NGS-New generation sequencing, MSS- Microsatellite Stability Biomarker TBD- tumor mutational burden.

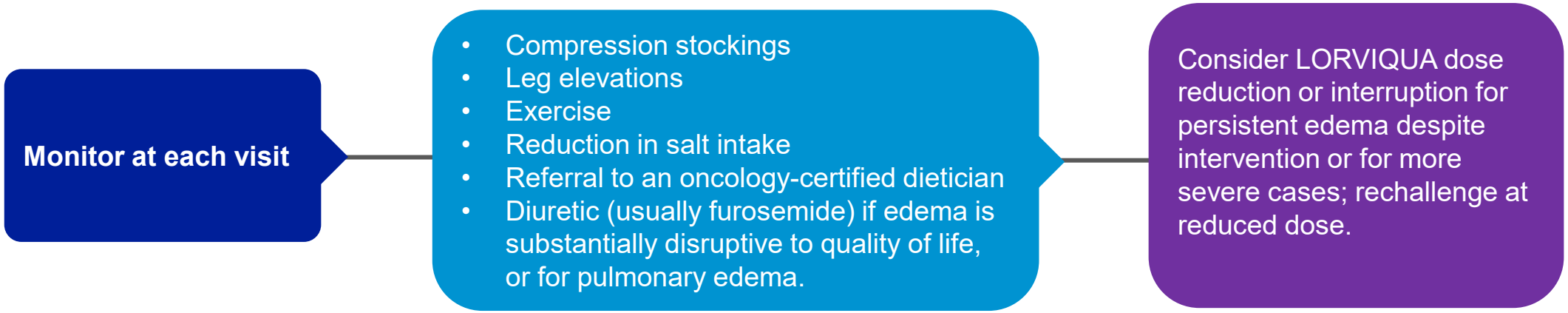
Diagnosis & Course of Treatment



Dr Agbarya personal patient case
SPN- solitary pulmonary nodule, PD -purely differentiated , TMB-tumor mutational burden, MSS- Microsatellite Stability Biomarker, ALK, anaplastic lymphoma kinase, NSCLC non small cell lung cancer, PDL1- Programmed death-ligand NGS-New generation sequencing, MSS- Microsatellite Stability Biomarker TBD- tumor mutational burden.

Therapy management for Edema

- Patients should be informed that weight gain and swelling of the arms, legs, hands, and feet may occur due to the excess fluid in body tissue associated with edema
- Body weight should be monitored during each office visit, and patients should be instructed to report any changes in the fit of rings, clothes, shoes, etc.
- Pharmacists can help to monitor and counsel patients about edema and should coordinate with dieticians as needed



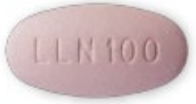
Reed M, et al. *Adv Ther* 2020;37(6):3019–30.

Lorlatinib dose modification[1]

1

Recommended dose

100 mg QD



2

First dose reduction
(if needed)

75 mg QD

3

Second dose reduction
(if needed)

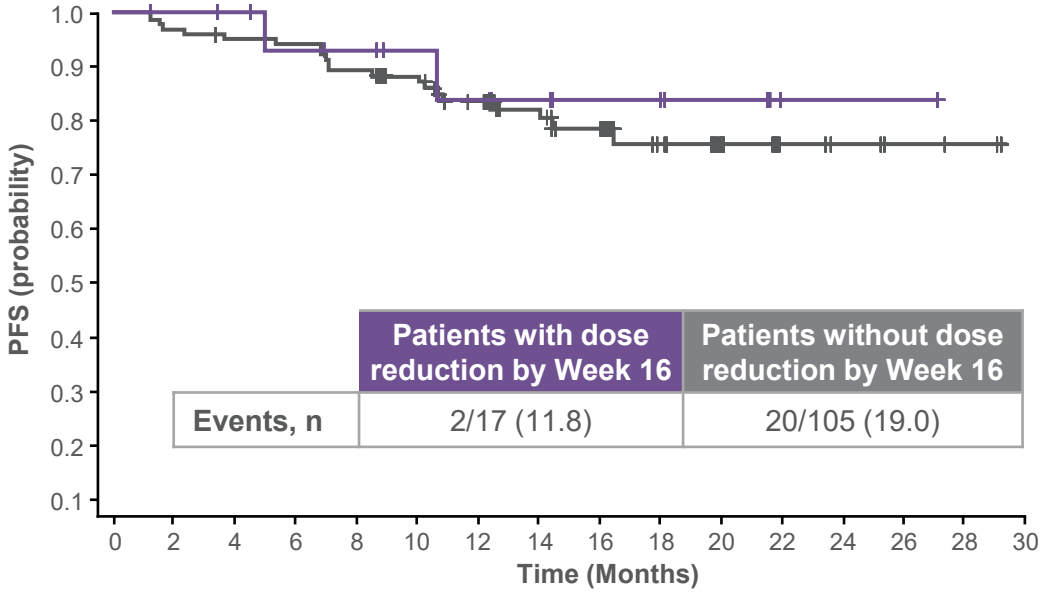
50 mg QD

AEs are usually **mild to moderate** in severity, but **dose modification may be required to support management** based on individual safety and tolerability*,[1,2]

*Guidance for clinical management of AEs associated with lorlatinib is based on the safety data from the Phase 1/2 study (NCT01970865).
AE, adverse event; QD, once daily.
1 LORVIQUA® Israeli latest approved PI. January 2022; 2. Bauer TM, et al. Oncologist 2019;24:1103–10.

Post hoc analysis in Phase 3 CROWN study: BICR-assessed PFS and IC-TPP by dose reduction

PFS by BICR by first lorlatinib dose reduction within 16 weeks[1]

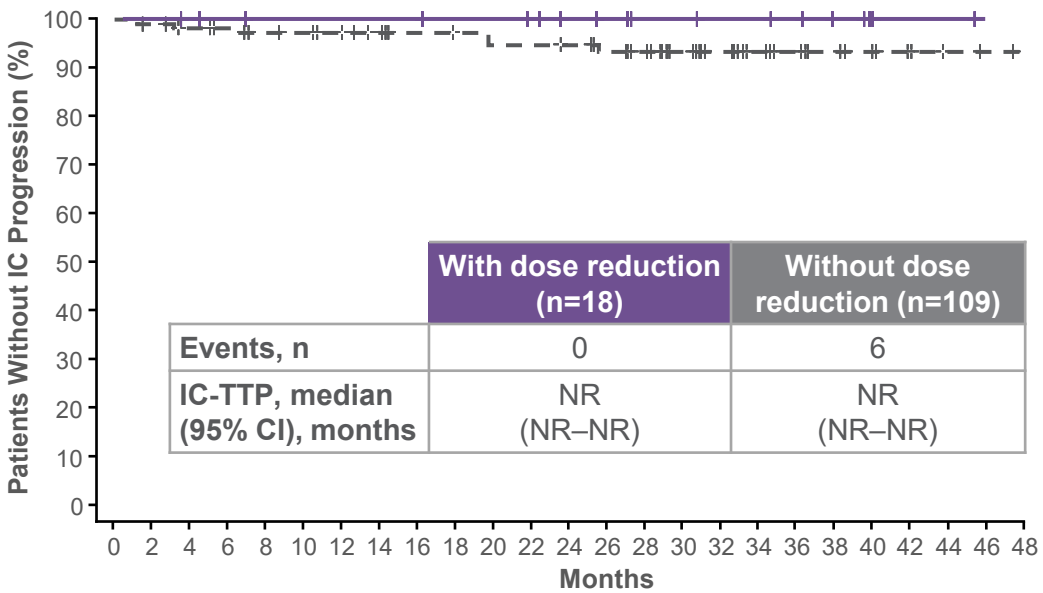


	Patients with dose reduction by Week 16	Patients without dose reduction by Week 16
Events, n	2/17 (11.8)	20/105 (19.0)

Number at risk

Patients with reduction	17	17	16	14	13	10	9	8	6	6	4	1	1	1	0	0
Patients without reduction	105	101	98	97	92	82	63	51	36	25	16	10	7	3	2	0

IC-TTP by BICR by first lorlatinib dose reduction within 16 weeks[2,*]



	With dose reduction (n=18)	Without dose reduction (n=109)
Events, n	0	6
IC-TTP, median (95% CI), months	NR (NR–NR)	NR (NR–NR)

Number at risk

Patients with reduction	18	18	17	16	15	15	15	15	15	14	14	13	11	10	8	8	7	7	6	4	2	1	1	0	0
Patients without reduction	109	104	100	98	94	93	90	87	83	82	80	80	79	76	67	54	47	32	28	21	15	7	3	1	0

In patients **with or without dose reduction** within 16 weeks of lorlatinib initiation, both **PFS** and **time to intracranial progression** were **comparable**[1,2]

*Patients with IC-TTP ≤16 weeks were excluded. For patients included in the analysis, IC-TTP was recalculated starting at the landmark time1.
BICR, blinded independent central review; CI, confidence interval; IC, intracranial; NR, not reached; PFS, progression-free survival; TTP, time to progression.
1. Solomon BJ, et al. J Clin Oncol 2022;40:3593–602; 2. Bearz A, et al. 979P. Poster presented at ESMO Annual Meeting, April 9–13, 2022; Paris, France.

Take home messages:

- ✓ Edema grade 2-3 led to dose reduction.
- ✓ Mood changes were managed with psychological counselling.
- ✓ Proactive management of potential toxicities is important for compliance and achieving clinical benefits of treatment.
- ✓ In patients with or without dose reduction within 16 weeks of lorlatinib initiation, both PFS and time to intracranial progression were comparable[1,2].

1. Solomon BJ, et al. J Clin Oncol 2022;40:3593–602; 2. Bearz A, et al. 979P. Poster presented at ESMO Annual Meeting, April 9–13, 2022; Paris, France.

CASE 3

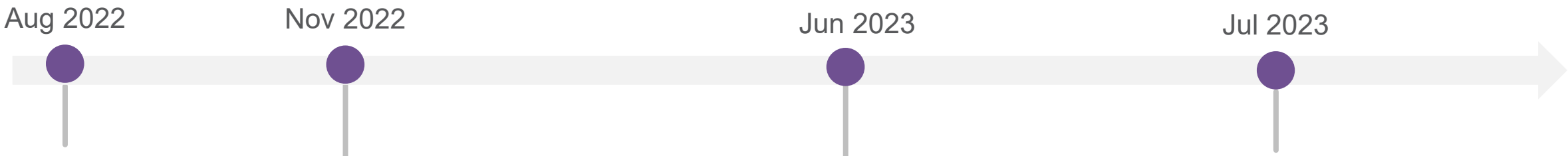
Case 3 - Initial presentation & treatment course

Aug 2022

- 49 y Male, married +3
- Past smoker, 15 y ago, generaly healthy
- Admitted due to back pain complains
- PET-CT- **advanced LC**, huge RUL mass with involvement of hilar and mediastinal lymph nodes, **metastases to bone and liver**.
- Biopsy- **Adenocarcinoma** WILD TYPE for all targeted mutations.
- PDL1- intermediate
- KN 189: Carbo Alimta Kytruda each 3 weeks up to 6 cycles and then Kytruda maintenance

Dr Agbarya personal patient case
KN- KEYNOTE -189 study(carboplatin/pemetrexed/pembrolizumab), PDL1- Programmed death-ligand

Initial presentation & treatment course



- PET-CT: large mass
- **WILD TYPE aNSCLC**
- PDL1 intermediate
- **KN 189**. Carbo Alimta KYTRUDA
- ZOMERA

- 5th cycle, no DLT
- Overall good wellbeing
- **PET-CT showed improvement in all sites**

- PET: **Disease progression in all sites**: Lungs, abdomen, liver, bones.
- PS=3

- **Completed palliative radiation**: C6-DL1, D11, L1, D4-6
- **What's next?**

Dr Agbarya personal patient case
KN- KEYNOTE -189 study, SPN- solitary pulmonary nodule, PD -purely differentiated , ALK, anaplastic lymphoma kinase, NSCLC non small cell lung cancer, PDL1- Programmed death-ligand NGS-New generation sequencing, DLT – Dose Limiting Toxicities

Restaging

Aug 2023

- Liquid biopsy by *Foundation (BAFST research):*

  ALK+ rearrangement, ALK fusion
- **23/8/2023 LORVIQUA 100mg QD**

Nov 2023

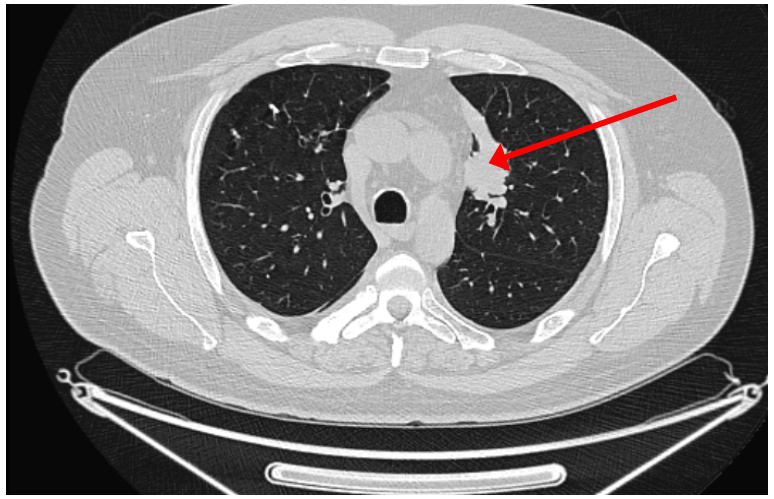
- PET-CT results: **Very impressive response in all sites**
- Clinical improvement **PS=0**

Dr Agbarya personal patient case
ALK, anaplastic lymphoma kinase, BFAST, blood first screening trial

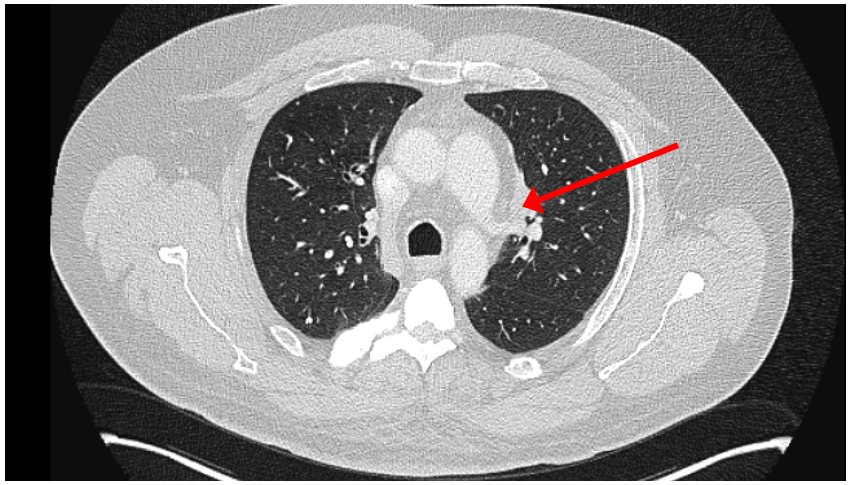
PET-CT before and after initiation of therapy

Aug 2023

Nov 2023



Large tumor in left pericardium, detectable in PET-CT

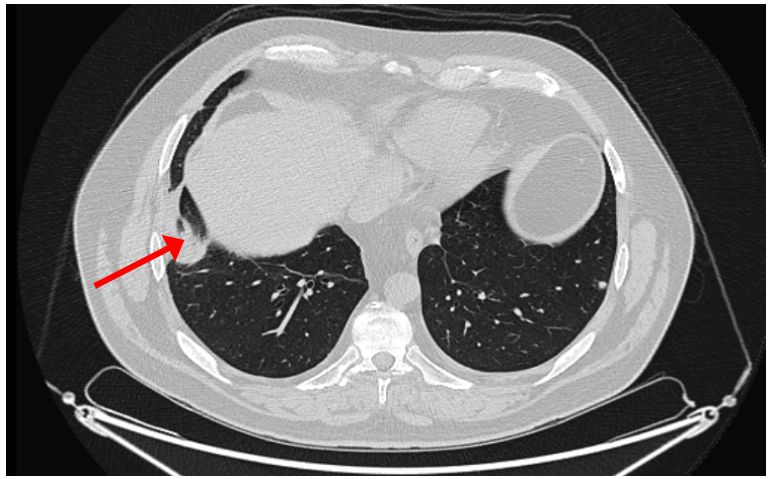


Reduced size tumor in left pericardium, undetectable in PET-CT

Dr Agbarya personal patient case, images used with permission
SPN- solitary pulmonary nodule, PD -purely differentiated , ALK, anaplastic lymphoma kinase, NSCLC non small cell lung cancer, PDL1- Programmed death-ligand NGS-New generation sequencing, MSS- Microsatellite Stability Biomarker TBD- tumor mutational burden.

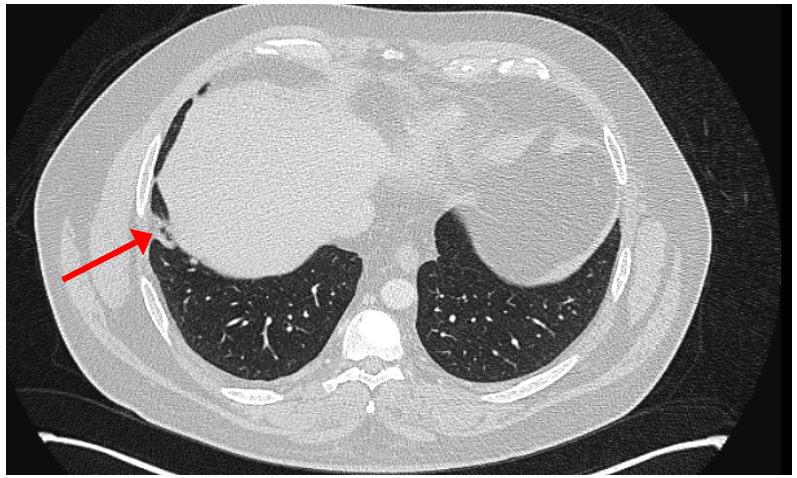
PET-CT before and after initiation of therapy

Aug 2023



RLL lymph

Nov 2023

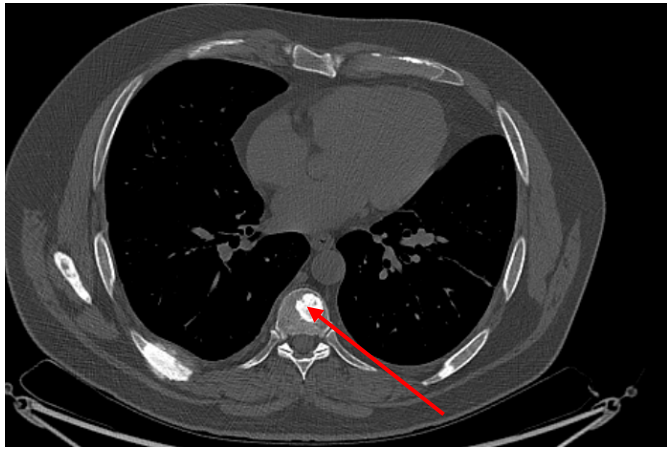


RLL lymph reduced significantly and undetectable in PET

Dr Agbarya personal patient case, images used with permission
SPN- solitary pulmonary nodule, PD -purely differentiated , ALK, anaplastic lymphoma kinase, NSCLC non small cell lung cancer, PDL1- Programmed death-ligand NGS-New generation sequencing, MSS- Microsatellite Stability Biomarker TBD- tumor mutational burden.

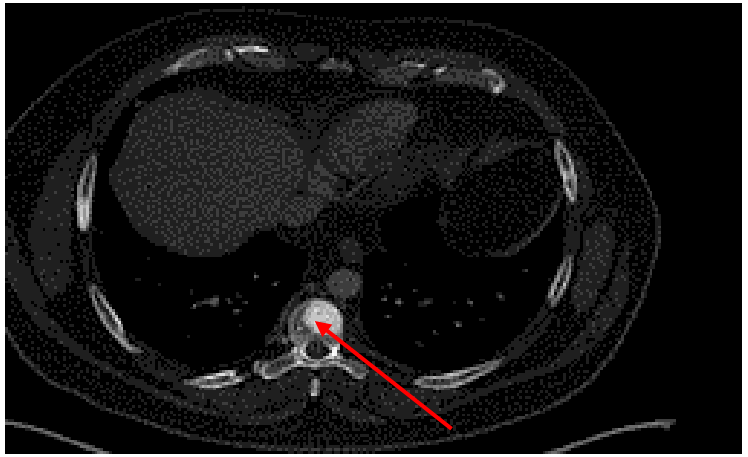
PET-CT before and after initiation of therapy

Aug 2023



Osteolytic lesion in thoracic spine

Nov 2023



Sclerotic lesion

Undetectable in PET-CT

Jan 2023

?

Dr Agbarya personal patient case, images used with permission
SPN- solitary pulmonary nodule, PD -purely differentiated , ALK, anaplastic lymphoma kinase, NSCLC non small cell lung cancer, PDL1- Programmed death-ligand NGS-New generation sequencing, MSS- Microsatellite Stability Biomarker TBD- tumor mutational burden.

Course of Treatment and AE management

Aug 2023

- Liquid biopsy by *Foundation (BAFST research):*

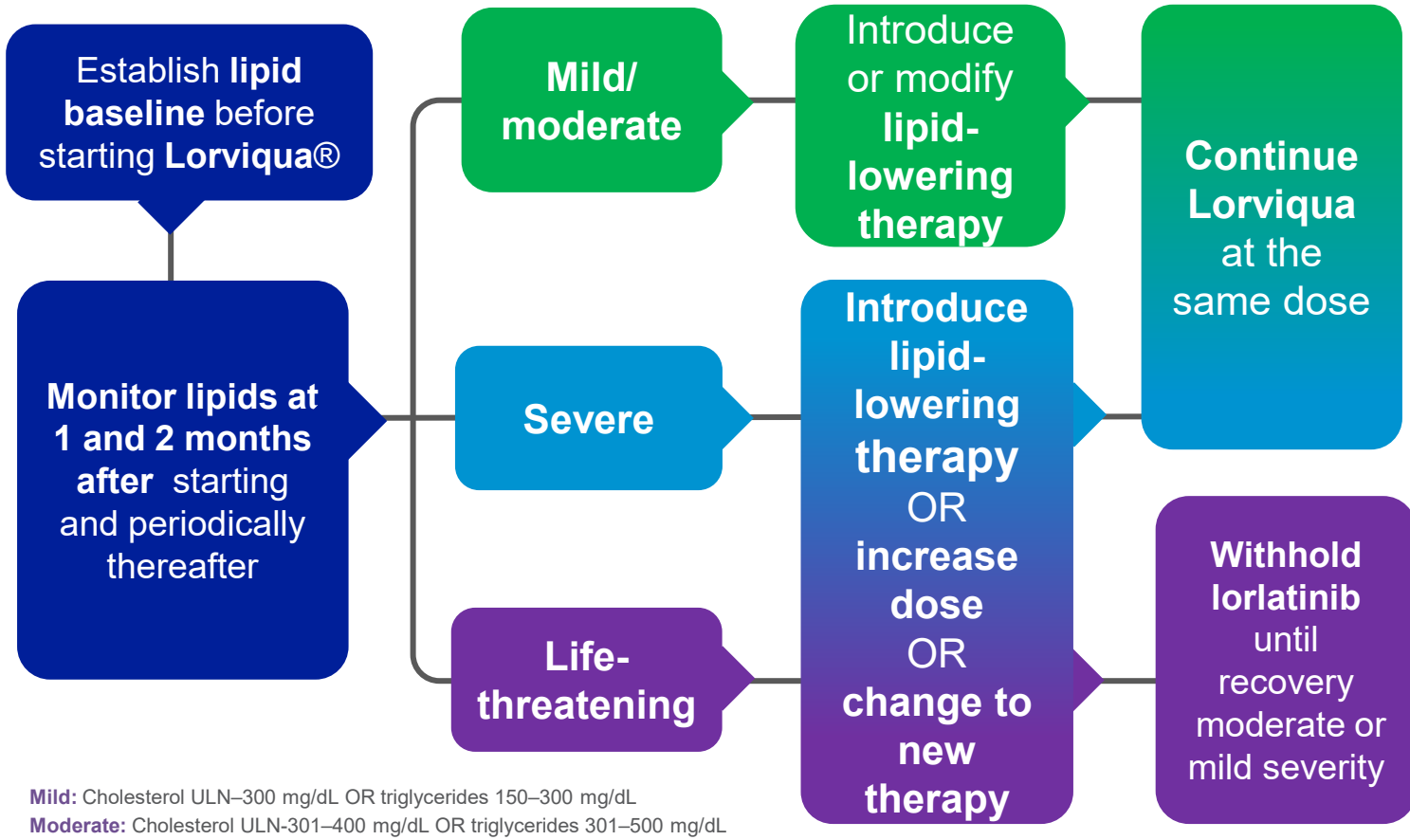
  ALK+ rearrangement, ALK fusion
- **23/8/2023 LORVIQUA 100mg QD**

Nov 2023

- AE: Oedema grade 1, generally well tolerated
- 10 Kg weight gain
- Improvement in mood and general well being…
- Clinically significant improvement in pain and breathing.
- Increase in cholesterol levels- to be closely monitored
- **To be continued…**

Dr Agbarya personal patient case
SPN- solitary pulmonary nodule, PD -purely differentiated , ALK, anaplastic lymphoma kinase, NSCLC non small cell lung cancer, PDL1- Programmed death-ligand NGS-New generation sequencing, MSS- Microsatellite Stability Biomarker TBD- tumor mutational burden.

Therapy management for hyperlipidaemia[1,2]



- Choice and dosage of statins may be based on their differential **metabolism by the CYP** pathway[2]
- Recommended statins* for the treatment of LORVIQUA-associated hyperlipidemia: Rosuvastatin, Pravastatin, Pitavastatin[2]
- If other lipid-lowering agents, such as fibrates or fish oils, are required, it is important to consider which is the most appropriate[2]

Mild: Cholesterol ULN–300 mg/dL OR triglycerides 150–300 mg/dL
Moderate: Cholesterol ULN-301–400 mg/dL OR triglycerides 301–500 mg/dL
Severe: Cholesterol ULN-401–500 mg/dL OR triglycerides 501–1000 mg/dL
Life-threatening: Cholesterol >500 mg/dL OR triglycerides >1000 mg/dL

*The recommended dose of lorlatinib is 100 mg taken orally, QD. The first dose-reduction level is 75 mg QD.
CYP, cytochrome P450; HCL, hypercholesterolaemia; HMG CoA, 3-hydroxy-3-methylglutaryl coenzyme A; HTG, hypertriglyceridaemia; QD, once daily; ULN, upper limit of normal.
1.LORVIQUA® Israeli latest approved PI, 2. Bauer, T. M., Felip, E., Solomon, B. J., et al. (2019). Clinical management of adverse events associated with lorlatinib. The oncologist, 24(8), 1103.

Take home messages:

- ✓ Hyperlipidemia is a common AE with Lorlatinib and regular monitoring of serum cholesterol and triglyceride levels is needed[1].
- ✓ In the clinical trial, hyperlipidemia was generally managed and resolvable through lipid-lowering therapy and/or dose modifications and/or interruptions[1].
- ✓ Once hyperlipidemia develops during treatment , formal consultation should be performed.
- ✓ The importance of molecular testing and liquid biopsy

1. Solomon BJ, et al. J Clin Oncol 2022;40:3593–602;

INDICATIONS: LORVIQUA® is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive.
CONTRAINDICATIONS: LORVIQUA is contraindicated in patients taking strong CYP3A inducers, due to the potential for serious hepatotoxicity. Hypersensitivity to the active substance or to any of the excipients
WARNINGS AND PRECAUTIONS: Risk of Serious **Hepatotoxicity** with Concomitant Use of Strong CYP3A Inducers
LORVIQUA® is contraindicated in patients taking strong CYP3A inducers. Discontinue strong CYP3A inducers for 3 plasma half-lives of the strong CYP3A inducer prior to initiating LORVIQUA. **CNS Effects:** These include seizures, Psychotic effects, and changes in cognitive function, mood (including suicidal ideation), speech, mental status, and sleep.
Hyperlipidemia, Atrioventricular Block, Interstitial Lung Disease/Pneumonitis: Permanently discontinue LORVIQUA® for treatment-related ILD/pneumonitis of any severity. **Embryo-Fetal Toxicity,** LORVIQUA can cause fetal harm when administered to a pregnant woman.
Lactose Intolerance: contains lactose as an excipient.
ADVERSE EFFECTS: The most common (≥20%) adverse reactions in clinical trials were: edema, peripheral neuropathy, cognitive effects, dyspnea, fatigue, weight gain, arthralgia, mood effects, and diarrhea; the most common (≥20%) laboratory abnormalities were hypercholesterolemia, hypertriglyceridemia, anemia, hyperglycemia, increased AST, hypoalbuminemia, increased ALT, increased lipase, and increased alkaline phosphatase.
For further information on Warnings, precautions and full list of Adverse effects please refer to the Full prescribing information

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Thank you for listening