**Prof. Nir Peled** LN 26519 Specialist License 22022, 25714, 12815

**Internal Medicine, lung and oncology Specialist**

**Director of Oncological array, Soroka Hospital.**

**Assuta Hospital, Ramat Hahayal 10 HaBarzel St., Tel Aviv Yafo** [**peled.nir@gmail.com**](mailto:peled.nir@gmail.com)

Hello,

June 19, 2017

**Re: Shahar Yael ID 5392057-5 Mobile phone 052-8444550**

**June 2017: RLL sup. Segmentectomy pT2N0M0 (10 mm) stage IB Lipidic ADC NSCLC**

**August 2017: Exon20 on ALK rearrangement; PDL1>50%**

**January 2018: Increased CA19-9; CT-PET normal**

**February 2019: Mild growing RLL suture related collection**

61 years old, married +3, native of Israel, psychology lecturer, smoking until 5 years ago, 3-5 cigarettes per day. Generally, usually healthy. Slight joint pain in the arms. Untreated.

In the family, father with TCC, mother with MDS.

Contacted ER about two weeks ago due to pain in the left chest. Finding of spot on the left therefore performed CT PET. In imaging, lump in the upper segment of RLL diameter or 14 mm uptake of PET. Performed PET but no result yet, I don’t see pathological uptake beyond that. Note very very delicate peripheral GGO on the left.

, stable weight. Thickening of the wrists.

**In conclusion, RLL findings highly suspect as BAC tumor. Therefore, I recommend wedge resection using thoracoscopy and later segmentectomy with full node removal.**

Pre-surgery must complete:

 1. Brain MRI

2. Markers including CA19-9 CYFRA21 CA15-3 CA125 CEA

3. Breathing functions.

Inspection about a month after surgery with the pathological report.

**July 13, 2017 -**

1. Underwent surgery on June 29, 2017 – in Beilinson – resection in single port VATS with normal margins, segmentectomy of upper RLL, visceral pleura involvement only, gate node negative. Lipid tumor, 10 mm diameter. T1aN0M0 but due to visceral pleura involvement the pathological rating is T2N0M0 (stage IB)

2. Therefore, there is no need for complementary treatment.

3. Note marker test pre-surgery 19-9CA increased (74 there instead of 37), therefore, this marker should be followed in the future as well.

4. Pre-surgery brain MRI without tumor illness, meningioma on the left IAC. Bony frontal finding not clear.

5. Will complete hybrid sequence test (foundation) though this has no treatment impact at the moment.

6. In examination, general state is excellent, very small but normal surgical wound.

7. In conclusion, normal course with lesion resection as aforesaid.

8. Recommend monitoring of CA19-9 in about a month and a half and 3 months from now, as well as chest CT imaging in 3 months.

**October 2, 2017-**

1. Three months post-surgery, normal course. CT chest typical for post-surgery without additional lumps. Glands seem normal (pre-result).

2. Markers 19-9 which was pathological is now normal.

3. Note ALK positive. PDL1 over 50%.

4. Performed brain MRI. No significant findings but no final result yet.

5. Therefore, normal course, will transfer CT result and continued monitoring with current CT PET in 3 months as well as markers. Brain MRI in 6 months.

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**January 1, 2018-**

1. Feels well. PS=0.

2. Markers on the rise including 19-9CA which rose to the value before surgery (now 62 and was 79 in the past, in the middle declined to normal).

3. Current PET CT normal without change. No pathological uptake.

4. Brain MRI from September 2017 Ichilov without tumor findings.

5. PS=0 asymptotic,Test - Nothing to report test.

6. Therefore now without explanation for the rise in the markers. Will continue monitoring of markers in Hadassah (Dr. Nisman) now and in two months, and in addition another inspection in three months with repeated brain MRI and CT PET. Abdomen Nothing to report. If the markers return to normal in about two months, may continue monitoring with chest CT only.

8. No clinic of the digestive system.

**April 16, 2018 –**

1. Asymptotic.

2. Markers including CA19-9 back to normal (15).

3. Chest CT without contrast material normal without new findings.

4. Therefore, continued monitoring in 6 months with PET CT and brain MRI.

5. Continued markers one every 3 months and update if there is a rise.

**August 16, 2018 –**

1. One year and two months removed from surgery. ALK positive. Normal course so far.

2. Current brain MRI without tumor findings. Known Meningioma.

3. PET CT in Beilinson July 2018 normal without uptake and no lung findings. Stump seems normal.

Markers normal. 19-9CA which was 83 before surgery declined to 12 today. CYFRA 21 was normal even before surgery.

In conclusion, normal course. Monitoring with chest CT in six months. Markers CA 19-9 once every 3 months.

**February 25, 2019 –**

1. Feels well, no cough or mucus. Stable weight.

2. Current chest CT overall without change but in RLL (deformation ? distortion ?) of RLL with impression of nodes compared to March 2018.

3. Markers CA 19-9 low and normal.

4. Therefore, it is likely that the finding on the right is a benign finding, secondary to the (deformation ? distortion ?) of the lobe, but recommended completion of bronchoscopy to sample the area, preferably with radial sonar.

5. If normal, then monitoring with chest CT in 6 months, if positive for tumor cells then CT PET must be completed.

6. In genetic inquiry, note that presence of DNMT3A at a frequency of MAF 2% is very likely somatic, but mutations in this gene are also related to MDS, and therefore completion of germinal inquiry is in place in this direction, such as the Invita test.

7. Completion of MRI in about two months (towards meningioma monitoring).

**August 8, 2019 –**

1. After discussion regarding the imaging, concluded along with the team in Carmel Hospital to continue conservative monitoring.

2. PET CT from March 18 without pathological uptake of FDG.

3. Markers CA19-9 last April 18, normal 11.94.

4. Brain MRI from April 29 – stable meningioma on the left.

5. Normal listening, lately cough.

6. In conclusion, normal course, I recommend:

a. Poster 100/6 twice a day.

b. Chest CT PET in the upcoming two months.

c. Continued monitoring of markers CA19-9 once every two months.

**November 11, 2019 –**

1. Without clinical change. Asymptotic.

2. PET CT with uptake in mediastinal glands which seem like tumors. Uptake in supraclavicular gland on the right. Uptake also in adjacent nodular infiltrate in the remaining lung base on the right. No other uptake outside the chest area.

3. Current markers 19-9CA which was 73 at the peak is now 13 (normal). CEA which was 1.8 is now 11.5.

4. Preparing for brain MRI in the upcoming days.

5. Treatment options include systemic treatment dependent on ALk positive  and I have preferred XalKori 250 mg twice a day. We have spoken about recommended second generation options, but if there are no metastases to the brain, I have preferred to start with XalKori and brain follow up every three months with brain MRI. Additionally, we will consider definitive radiation for the current illness volume.

6. In conclusion,

a. Progress of the illness which requires systemic treatment, must start XalKori 250 mg twice a day with functional monitoring every two weeks.

b. Referred to consultation on the matter of definitive radiation without chemotherapy, including the surgery bed. During the radiation treatment, we will discuss the systemic treatment according to the radiation plan.

c. Follow-up in 3 months with current PET CT and MRI and markers CEA, CA19-9.

d. Regardless, follow-up in a month and a half with blood tests and liver function monitoring.

December 23, 2019 –

1. Guardant without discovery of tumorous DNA cells.
2. Commenced with XalKori on November 14, 2019, twice a day with light nausea and occasional diarrhea.
3. Commenced radiation on December 1, 2019, and simultaneously decreased to 250 mg once a day with decline in the aforementioned complaints.
4. After 8 days of radiation, began coughing, therefore stopped with XalKori and started with Prednisone 20 mg per day with improvement. Still taking Prednisone 20 mg per day.
5. Now under listening observation, aeration completely normal without wheezing or crepitations or rhonchus.
6. In conclusion, in my opinion it is likely that the cough is collateral to the XalKori in itself and less likely related to radiation. Therefore, I recommend:
   1. Waiting period with renewal of XalKori.
   2. In order to maximize the treatment, I recommend provision of Carboplatin AUC 5 along with Pemetrexed 500 mg per sqm, once every three weeks in 2-3 cycles. Therefore, folic acid 400 mg should be commenced and a one time shot of B12 1000 microgram.
   3. Treatment of FOSTER 100/6 twice a day.
   4. Decrease in Prednisone 10 mg per day for three days and then 5 mg per day for three days and then stop.
   5. Follow up with chest CT in about 6 weeks.
   6. Completion of CA 19-9 in about a month and a half. *+CEA*

July 13, 2020

1. Completed six courses of chemotherapy
2. Under prednisone, respiratory improvement. Without prednisone for the last two months and reports having difficulty with deep breathing and dry cough.
3. ENT exam rules out disturbance in swallowing mechanism.
4. Markers CA19-9 normal (20), CA 125 (48.6) mildly increased.
5. Updated PET-CT with post radiation changes, organized bronchiectasis at the location of the primary tumor. Uptake in the sigmoid specifically, likely inflammatory, for follow-up.
6. On examination, clinical condition excellent, head and neck normal, good aeration, no rhonchi or wheezing.
7. Respiratory function with diffusion of 60% (June 14, 2020).
8. A trial with Foster did not help with the way she feels.
9. MRI of brain July 5, 2020 - answer not yet received. Observation without new irregular findings.
10. In summary, completed six chemotherapy courses (two more than recommended for her condition), without Xalkori (crizotinib) in coordination with Prof. Ross Gamidge, USA). At present, mild pneumonitis and mild uptake in the sigmoid. Recommend:
    1. Despite making an appointment for a colonoscopy, recommend waiting in order to create distance from the chemotherapy and deciding according to PET in three more months.
    2. At this stage, I do not see the need for steroids, in light of the potential side effects. Therefore, at present, I recommend taking Azenil (azithromycin) 250 mg a day for a week, once every six weeks.
    3. Follow up in six weeks with updated chest X-ray and respiratory functions.
    4. ALK may be monitored in a specific fluid exam as well as CA 19-9 CEA in approximately six more months.

Aug. 24, 2020

1. Without prednisone since May 2020.
2. Under Azenil (azithromycin), improvement in cough and presently coughs primarily upon exposure to salt. Feels well during walking.
3. Without Xalkori (crizotinib) since stopping it during radiation.
4. Updated Chest X-ray.
5. Respiratory functions excellent and normal, FEV1 112%, ratio 88% to FVC, Diffusion 77% normal. TLC 86%.
6. Chest X-ray without pleural fluid and without interstitial changes.
7. Upon auscultation, completely normal aeration.
8. In summary, normal process, Azenil (azithromycin) may be stopped. For follow up with PET-CT in about another two months. MRI of brain six months after the last one.

**January 28, 2021**

1. PET/CT October was without dynamics.
2. PET/CT of Jan. 18, 2021 with progression of the disease in the mediastinum (station 7 and at the hilum to the right).
3. Without Xalkori since radiation (stopped due to cough).
4. EBUS at Carmel Hospital with positive endocarcinoma. The material was sent to Foundation One .
5. Experienced an episode of herpes zoster which was treated with Zovirax.
6. MRI of brain without metastases.
7. On examination, general good condition, head, neck, heart, lungs, abdomen, and extremities normal.
8. Markers at present – rise in CA125 at present, where as it was normal in the past. In the past, a rise of CA 19-5 as well in 2017 and also CEA in 2019.
9. In summary, progression of local disease, but resistant to radiation, especially in light of past pneumonitis, recommend return to ALK treatments, preferably with Brigatinib 180 mg a day in light of previous treatment with Xalkori.
10. Follow-up with PET/CT approximately two months after start of treatment.
11. Follow-up – liver and kidney functions, every week in the coming month.

April 01, 2021

1. On Brigatinib for the last two months. Suffers mainly from pricking sensations

throughout the body. Started acupuncture with improvement in complaints.

2. FOUNDATION test with Intron10 of ALK, MSS. Specific mutation of PMS2 but it does

not impact the MSI.

3. Updated PET/CT (Ichilov) March 29, with excellent metabolic response and contraction

of the nodes that were enlarged beforehand. Known post-radiation changes.

4. To the family’s question, the presence of PMS is somatic according to the report and is

not germinal, but an exam such as INVITE may be completed for assessment of the

germinal presence, and genetic consultation accordingly.

5. Therefore, recommended to continue Brigatinib without change, 180 mg a day and

PET/CT follow-up in another 3 months.

**Apr. 6, 2021**

1. Is very concerned about the feeling of paresthesia. Telfast does not help even after taking it for 10 days.
2. She thought about adding Cipralex or Lyrica, but in light of the low volume of disease and the excellent response, suggest first reducing the dosage to 90 mg a day for three weeks. In the event that the symptom subsides, then we can try to increase to 90 mg a day routinely, except for twice a week when 180 mg can be taken. In the event it does not subside, then return to 180 mg a day.
3. Liver functions AST increase by approximately 1.5. Overall, normal
4. Follow-up with PET in another three months. Follow-up of liver functions, once every three months.

**July 8, 2021**

1. Underwent a period of difficult adaptation with mouth sores, paresthesia, which now has been reduced, and takes 180 mg brigatinib a day.

2. Updated Chest CT without contrast material with post-radiation changes and without new findings.

3. Examination of ecchymosis in the lips, bleeding skin sores, heart, lung, abdomen, extremities, normal.

4. In summary, had side effects which stabilized, and presently continues with 180 mg brigatinib a day.

5. Recommend:

a. Continue 180 mg brigatinib a day.

b. Attempt to treat the lips with Aquaphor.

c. Follow-up with PET/CT in another 3 months.

Sincerely,

Prof. Nir Peled L.N. 26519

Director, Oncology Division and Wing

Internal Medicine, Pulmonary and Oncology Specialist

Shaare Zedek Hospital