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Medical Second Opinion

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AGREEMENT TERMS AND CONDITIONS

Dear [redacted]
PlusOne provides second opinion services which are different from the primary diagnostic services typically provided by your treating physician. PlusOne contracts physicians that provide this service whom do not have the benefit of information that would be obtained by examining you in person to assess your physical condition. Therefore, the consulted physician may not be aware of facts or information that may affect his or her opinion of your diagnosis and treatment recommendations. This limitation may affect the accuracy of the consulting physician's opinion, and this is a risk to you.

Your involvement in the service will be considered **an indication of your acceptance to**:

1. The medical second opinion you will receive is limited, provisional and does not constitute a primary diagnosis;
2. The medical second opinion is not intended to replace a full medical evaluation or a face-to-face visit with a physician;
3. PlusOne contracted physicians will not have access to important information that is usually obtained through a physical examination; and as a result, this may affect the accuracy of the recommendations provided to your referring physician.

If you choose to provide us with personal information via email or postal mail/courier, or by filling out a form and submitting it through our web site, we use that information to respond to your request and to help us provide you with the information or material that you require. We do not give, share, sell, or transfer any personal information to a third party unless required by law.

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CONSULTATION PRIMARY PROVIDER(S)

LEADING MEMBERS OF THE INTERNATIONAL TUMOR BOARD [1]

MEDICAL ONCOLOGY:
- Dr Madeleine Radelle
- Dr Mercédès Herrera
- Dr Fernand Mondego
- Dr José Faria

SURGERY:
- Dr Eugénie Danglars

RADIOLOGY:
- Dr Edmond Dantès

INTERNATIONAL TUMOR DIRECTOR

Professor Maximilien Morrel

Professor Maximilien Morrel started his career as a medical oncologist and is currently the acting director of Gustave Roussy's international patient office. He has been an associate professor of medicine since 2014 and was the head of the Sarcomes committee of Gustave Roussy until 2019.
Prof. Morrel is a member of several international committees, including the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO). He is also an active member of the European Organization for Research and Treatment of Cancer of the Soft Tissue and Bone Sarcoma Group (STBSG). He is the co-president of the French sarcoma group and was a member of the board of directors of the Connective Tissue Oncology Society, from 2010 to 2013. Since 2014, Axel has been a member of the French Academy of Medicine.
His is the author of more than 320 research articles in the fields of sarcoma, gastrointestinal stromal tumours, lung and breast cancer, immunotherapy and genetic therapy

Gustave Roussy institute in a nutshell:
Is one of the top ten world leading cancer centers in the fight against cancer. Founded in 1926 by Professor Gustave Roussy, the institute distinguished itself from the very beginning by its wholly integrated approach to research, care and teaching[2]. Gustave Roussy takes pride in being the top ranked European cancer institute to have a dedicated Drug Development Department (DITEP) for early phase trials, to facilitate patient access to new medicines. Whereas the mean numbers of cancer patients recruited to clinical trials in France is between 4 and 10%, Gustave Roussy patients participating in such research is 27%[3].
Gustave Roussy is one of Europe's top referral centres for complex cases and rare tumours. Offering a wide ranging of cutting-edge medical services in the fields of chemotherapy, radiotherapy, interventional radiology, primary tumour surgery, and reconstruction. In 2018, 48000 patients were cared for at Gustave Roussy; of which 11000 were new patients. All these medical services are powered by 3100 employees with one goal to keep innovation at the heart of a human, scientific and technological revolution in the fight against cancer[4].

1. https://www.gustaveroussy.fr/en/international-department# website accessed 11.4.2023

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MEDICAL HISTORY EXECUTIVE SUMMARY

Date of history taking: 27th of March 2023

GENERAL INFORMATION			
Name	[redacted]	Occupation	Engineer
Age	[redacted]	Race/ethnicity	
Sex	Male	Nationality	Pangean
Marital status	Married	Address	Laurasia
Height, Weight & SA	85Kg, 180 cm	ECOG/PS	0

COMPLAINT

Treatment related symptoms (nausea, bony pains after Filgrastim)

PRESENT HISTORY

April 2022: The condition started by gradually progressing abdominal distension, for which he sought medical advice. Investigations were requested and frequent tapping to the ascitic fluid was done and cytological examination revealed nonspecific inflammatory and epithelial cells. At that time, it was thought to be related to a flair of his familial Mediterranean fever condition.

27th May 2022: In an attempt to investigate more the reason of the recollecting ascites a laparoscopy was done showing minimal peritoneal deposits (the endoscopy report is not available). However a biopsy was taken from one of the nodules and pathologically examined reporting the following:

Multi-cystic mesothelioma (multi/ocular peritoneal inclusion cysts).

Ascitic fluid, cytology: Mild inflammatory changes, negative for malignant cells.

6th June 2022: A follow up PET CT was requested to identify the extent of the disease reporting the following:

- Marked free abdomino-pelvic ascites seen displaying mild increased tracer uptake more pronounced at pelvic region eliciting SUVmax of 3.
- Associated greater omental minimally tracer avid streaky-like thin densities seen beneath the anterior abdominal wall eliciting SUVmax of 1.5.

9th June 2022: In an attempt to confirm the diagnosis a slide revision was done reporting the following:

Peritoneal and omental nodules, Referred block and slides [Biopsies], CHRONIC INFLAMMATORY PROCESS WITH OVERLYING PAPILLARY MESOTHELIAL HYPERPLASIA.

June2022: With suspicion about the actual nature of the sample, patient was managed as being FMF and started Colchicine and corticosteroids.

18th October 2022: Patient went on for 6 months on anti FMF treatment with no improvement and numerous tpping was done to relief his dyspnea.

A follow up Abdominopelvic U/S was done still showing the following:

- Marked ascites.
- Much gaseous distention.
- 26th November 2022: A second Pathology report (revision of slides) was done in an attempt to re – confirm the diagnosis. Pathological examination reported the following:
- **Picture Compatible with Multi-cystic Mesothelioma, Amenable for Local Recurrences. Associated Dense Chronic Non-Specific Inflammation.**
- Inflammatory Ascitic Fluid, Negative for Cytologically Malignant Cells.

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MEDICAL HISTORY EXECUTIVE SUMMARY (continued)

5th December 2022: Patient was also complaining of epigastric pain so an upper GI was done and a biopsy was taken reporting the following:
Chronic Gastritis, With Moderate Intensity, Mild to Moderate Activity, Associated with H. Pylori. No Malignancy.
14th December 2022: Also, another ascitic tapping cytological examination was done reporting the following:
Atypical mesothelial cell proliferation (neoplastic versus Reactive) Associated with marked inflammatory exudate.
Pathology report (revision of slides): **1 &2: Ascetic Fluid Aspiration Cytology and Omental Tissue Biopsy (Referred Slides and Paraffin Tissue Block): Consistent with low grade mesothelial neoplasm (likely non-Asbestos related tumor).**
15th December 2022: IHC was carried out on the of initial biopsy reporting the following:

- Positive for WT-1, D2-40, EMA
- Weakly occasionally positive for p53
- Negative for MOC-31
- Ki-67: 15%
- **Picture compatible with epithelial mesothelioma.**

23rd December 2022: Another 3rd slide revision of the IHC of initial biopsy and reported the following:

- Positive for D2-40, EMA denoting mesothelial origin
- Negative for P53 & Ki-67: 2% denoting bland pathology
- Negative for MOC-31 excluding carcinoma
- The tumour is considered benign versus low grade tendency to reoccur.
- Picture compatible with multi-cytic mesothelioma.

21st December 2022: Another follow PET CT was done reporting the following:

- Still noted mildly avid marked dense pelvi-abdominal ascites is noted achieving SUVmax 2.69 in the peri-hepatic region (compared to SUV max 3 previously). Associated mildly avid omental thickening that shows metabolic progression, currently achieving SUVmax 4.45 (compared to SUVmax 1.5 previously).
- Newly developed few small low-grade epi-phrenic lymph nodes are noted measuring up to 25x11mm and achieving SUVmax 2.

31st December 2022: The patient stopped his FMF medications and started **1L Pemetrexed/Cisplatin.**
1st February 2023: Abdominopelvic U/S:

- A SOLITARY SMALL STONE LOWER CALYX OF THE LEFT KIDNEY, WITH NO APPARENT BACK PRESSURE Manifestation.
- A LARGE AMOUNT OF CLEAR ASCETIC FLUIDS IS COLLECTED WITHIN THE ABDOMINAL GUTTERS, AND IN THE SUPRAPUBIC AREA, WITH FLOATING INTESTINAL LOOPS.

6th March 2023: The patient received his 4th cycle. The patient received 7 times Filgrastim due to repeated grade 3 nuetropenia, last two were on the 21st and 23rd of March.
22nd March 2023: PET CT:

- Rather stationary course of the omental/peritoneal soft tissue density, eliciting SUV max ~ 2.6 (as before).
- Progression of the low grade FDG-avid currently marked ascites with SUVmax ~ 2.4 (as before).
- Resolution of the low grade FDG-avid peri-phrenic lymph node.

Metabolic progression of generalized FDG-avid bone marrow, with SUV-max ~12.3 (was 3).
Nb.: Its worth mentioning that the patient has received GCSF at the night of the PETCT which might explain the hyperactivity of the bone marrow and high SUV

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MEDICAL HISTORY EXECUTIVE SUMMARY (continued)

23 March 2023: Full labs were done reporting severe bone marrow suppression (from cis/pemetrexed)
Hb: 8.6 g/dl
TLC: 1.880 x 10^3 /cmm
Platelets: 24 x10^3/cmm

His first dose has been postponed till bone marrow recovery and deciding on the next type of therapy

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SECOND OPINION RESPONSE (1 of 2)

Date of response: 11th of April 2023
RESPONDING EXPERT/S:
Medical records discussed with Gustave Rosussy's entire international tumor board & Dr Eugénie Danglars, specialist in CHIP procedure for abdominal mesothelioma
This consultation was facilitated through Prof. Dr. Morrel International clinic Director

QUESTION 1:
With this evident progression what would you recommend as the upcoming treatment option. Should we consider ipilimumab + nivolumab? Would his familial Mediterranean fever be an issue with this combo?

GUSTAVE ROUSSY MDT RESPONSE:
Yes this combination can be an option. There are not a lot of data regarding the potential interaction between immunotherapy and FMF. The combination can be proposed according to us

QUESTION 2:
If the patient's general condition does not allow, especially that he suffers from repeated bone marrow suppression Grade 2-3. Would it be reasonable to offer him Atezo + Bev (as per the reported 20 patients at Basket study study at MD Anderson by Kanwal Raghav et al Cancer Discov. 2021 Nov;11(11):2738-2747) ?

GUSTAVE ROUSSY MDT RESPONSE:
Yes, this combination is an alternative option if first combo is not so well tolerated

QUESTION 3:
Would you agree to offer him alternatively carboplatin + pemetrexed + bevacizumab (as cisplatin is causing intolerable Bone marrow suppression)?

GUSTAVE ROUSSY MDT RESPONSE:
From our experience, carboplatine can give more myelosuppression than cisplatine. We are more in favor to proceed with cisplatin (lower dose)

QUESTION 4:
Do you have any other recommendations?

GUSTAVE ROUSSY MDT RESPONSE:
CHIP procedure (operative cytoreduction plus hyperthermia plus local chemotherapy) can be proposed to this young patient. Indication could be discussed in our pluridisciplinary team with the recent CDRom (to be sent to us)

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SECOND OPINION RESPONSE (2 of 2)

QUESTION 5:
Would you recommend we offer the patient NGS MI profile or Foundation medicine?

GUSTAVE ROUSSY MDT RESPONSE:
Indeed, Always useful in rare malignancies

Nb.: File discussed with the entire international tumor board plus Dr E. Danglars, surgeon specialist in CHIP procedure for abdominal mesothelioma

Maximilien Morrel

International Department
French Sarcoma Group
Académie de Médecine