Therapy-related Myeloid Neoplasms Following PARP Inhibitors—Response

Vincent Marmouset[1], Pierre-Marie Morice[2], Arnaud Pagès[3], Alexandra Leary[4], and Jean-Baptiste Micol[5]

In their letter addressed to *Clinical Cancer Research*, Batalini and colleagues discuss the limitations of our study (1) and we thank them for their comments, which give us the opportunity to clarify some points.

Firstly, the definition of t-MN is chronologic, based on history of cancer treatment with cytotoxic therapy and the 2022 WHO Classification added exposure to PARP inhibitors (PARPi) as a qualifying criterion for t-MN (2). Secondly, our work was descriptive and we did not aim to assess an increased risk of t-MN induced by PARPi as it has already been published (3). That being said, in our center we described an increase of t-MN in ovarian cancer survivors by 52% between 2010–2015 and 2016–2021, as the incidence (normalized to the number of patients with ovarian cancer during the same period) increased from 6,53‰ to 9,91‰. Thirdly, if we agree that we cannot conclude that all these cases are causally linked to PARPi exposure, recent publications (**Table 1**) describe a higher incidence of t-MN post PARPi (2%–8%) than reported in earlier trials. In addition, the clear association between prior PARPi exposure and unfavorable t-MN characteristics and poor outcome underline the importance of identifying these patients.

In our national cohort, more than 70% of patients who developed post-PARPi t-NM had a germline *BRCA1/2* mutation, this could be explained by the fact that PARPi's primary indications were restricted to *BRCA1/2* mutated patients. However, in a recent update of the ARIEL 3 study (4), a randomized trial of rucaparib versus placebo as maintenance therapy in recurrent ovarian carcinoma, the incidence of t-MN in patients with a germline or somatic *BRCA* mutation treated with rucaparib for more than 2 years was 15.2% compared with 6.1% for *BRCA*wt patients who received more than 2 years. These data may also suggest that duration of PARPi therapy is associated with a significant rate of t-MN, and BRCAm patients are most likely to be exposed for prolonged periods.

We are relieved to see that in other indications, with other prior chemotherapy regimens and shorter duration of PARPi, the incidence of t-MN seems to be lower. However, a recent literature review of 8 randomized clinical trials of PARPi maintenance in ovarian cancer, reported a relatively high incidence of t-MN [in total 2.1% in PARPi arms and 1.2% in placebo (5)] confirming the importance of identifying these patients at risk.

Similar to our colleagues from the Mayo Clinic, at Gustave Roussy Cancer Center, access to combined expertise from oncologists, hematologists and appropriate technical support allows us to thoroughly investigate cytopenias in cancer survivors. We believe that our study provides insight for the management of t-MN risk under PARPi. We also believe that clinical, translational and basic research is needed to

Table 1. Characteristics of t-MN following PARPi from recent retrospective studies.

Study reference	t-MN	Type of primary cancer	BRCA1/2 status	Incidence of MDS/AML	*TP53* presence
Marmouset et al. Clin Cancer Research, 2022	69 (28 AML, 41 MDS)	Ovarian, breast	48/67 germline BRCAm	3.5% (13/373 from 2015 to 2021)	*TP53* : 32/45 (71.1%)
Morice et al. Br Journ Haematol, 2022	21 (7 AML, 14 MDS)	Ovarian, breast, fallopian tube	12/21 BRCAm	Not specified	*TP53* : 6/20 (30%)
Oliveira et al. Blood Cancer J., 2022	9 (4 MDS and 5 AML)	Ovarian, breast, fallopian tube	6/9 BRCAm	Not specified	*TP53* : 4/8 (50%)
Todisco et al. Int J Cancer, 2020	9 (1 CCUS, 5 MDS, 2 AML, 1 ALL)	Ovarian	7/9 BRCAm	6.9% (9/130 from 2010 to 2018)	*TP53* : 5/9 (55.6%)
Zhu et al. Clinical Genitourinary Cancer, 2017	1 (AML)	Prostate	BRCA2m	Not available	Not available
Todisco et al. Int J Cancer, 2022	16 (12 MDS, 4 AML)	Ovarian	9/14 BRCAm	8.7% (16/182 from 2010 to 2021)	*TP53* : 12/13 (92.3%)
Kwan et al. JAMA oncology	22 (types not specified)	Ovarian	13/22 BRCAm	2.1% (22/1052 from 2013 to 2019)	*TP53* : 9/22 (41%)
Chiusolo et al. Amer Journal of Haematology, 2022	13 (8 MDS, 5 AML)	Ovarian	13/13 BRCAm	4.3% (13/300 from 2019 to 2022)	*TP53* : 13/13 (100%)
Total :	160	-	109/156 (70%)	From 2.1% to 8.7%	81/130 (62%)

[1]Gustave Roussy, Villejuif, France. [2]Caen University Hospital, Caen, France. [3]Gustave Roussy, Villejuif, France. [4]Gustave Roussy, Villejuif, France. [5]Gustave Roussy, Villejuif, France.

Corresponding Author: Jean-Baptiste Micol, Gustave Roussy Institute, Villejuif 94805, France. E-mail: Jeanbaptiste.MICOL@gustaveroussy.fr

Clin Cancer Res 2023;29:1158–9

doi: 10.1158/1078-0432.CCR-23-0164

clarify the physiopathology of t-MN in this setting. This was our aim in this large cohort of t-MN post PARPi and one will pursue in ongoing research programs.

Authors' Disclosures

A. Leary reports grants, nonfinancial support, and other support from AZ; grants and other support from Clovis, MSD, Onxeo; and grants and other support from GSK during the conduct of the study; other support from Ability Pharmaceuticals, Owkin, Apmonia Therapeutics; and grants and other support from Zentalis outside the submitted work. J.B. Micol reports personal fees from AbbVie, Jazz Pharmaceuticals, Astellas; and personal fees from Gilead outside the submitted work. No disclosures were reported by the other authors.

Received January 18, 2023; revised January 25, 2023; accepted January 25, 2023; published first March 14, 2023.

References

1. Marmouset V, Decroocq J, Garciaz S, Etienne G, Belhabri A, Bertoli S, et al. Therapy-related myeloid neoplasms following PARP inhibitors: real-life experience. Clin Cancer Res 2022;28:5211–20.
2. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the world health organization classification of hematolymphoid tumors: myeloid and histiocytic/dendritic neoplasms. Leukemia 2022;36:1703–19.
3. Morice PM, Leary A, Dolladille C, Chrétien B, Poulain L, González-Martín A, et al. Myelodysplastic syndrome and acute myeloid leukemia in patients treated with PARP inhibitors: a safety meta-analysis of randomized controlled trials and a retrospective study of the WHO pharmacovigilance database. Lancet Haematol 2021;8:e122–34.
4. O'Malley DM, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, et al. Clinical and molecular characteristics of ARIEL3 patients who derived exceptional benefit from rucaparib maintenance treatment for high-grade ovarian carcinoma. Gynecol Oncol 2022;167:404–13.
5. Armstrong DK. AML and MDS associated with PARP inhibitor treatment of ovarian cancer. Gynecol Oncol 2022;S0090–8258:01961–8.