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Research Article,

Drug Utilization Pattern of World's First T-DM1 Biosimilar (UJVIRA$^{TM)}$ For Her2+ Breast Cancer in First Year of Its Availability – An Indian Context

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Abstract:

Cancer is a major contributor towards global disease burden and brings psychological as well as social distress to the patients and their relatives. In Indian context, breast cancer is still the most prevalent cancer among women with a higher mortality rate. Heterogeneity is observed among several subtypes of breast cancer and nearly 18%–20% of breast cancer patients were found to be HER2/neu positive, who will get benefitted with the targeted therapies. But due to constraint regarding availability as well as huge financial burden, limited patients get benefitted by the same. Ado-trastuzumab emtansine (T-DM1), is one of the cost-effective option available at present. Since 2013, T-DM1 has been US-FDA approved for its usage in treatment of advanced metastatic HER2 positive breast cancer and since, 2019 it got approval in early breast cancer setting. It was available after 2015, for the clinical use in India at an exorbitant price which limits its usage to the needy patients. Until 2020, only innovator drug was the option available for the T-DM1 usage in India while World's first biosimilar of T-DM1 got approved in December 2020 and It became available for the clinical use in India from May, 2021 by the name of UJVIRA^{TM} as a much more accessible option in comparison with the innovator molecule for the benefit of the patients. The present study aimed to analyse and evaluate the trend and usage patterns of Ujvira in the first year of its availability in Indian context. Obtained results states that with the availability of a targeted biosimilar drug with cost effectiveness and easy accessibility with proven efficacy as compared to reference product there will be an positive impact on the prescribing pattern among the clinicians as well as compliance of the patients and help curb the rising expense of treatment.

Keywords: T-DM1, HER2, Biosimilar, Breast cancer, drug utilization.

Introduction:

Cancer is a foremost burden and threat worldwide and one of the leading reasons of death in developed as well as developing countries. [WHO, 2008] It serve as a major contributor towards global disease burden and brings psychological as well as social distress to the patients and their relatives. [Pentareddy et al., 2015] WHO based on a survey state that nearly 8.2 million people surrendered to cancer in 2012, and number may rise upto 19 million by 2025. [WHO 2019] while as per data, nearly 45% of breast cancer cases and 55% of breast cancer deaths occur in low- and middle-income countries (LMICs). [Tfayli et al., 2010]

In Indian context, breast cancer is still the most prevalent cancer among women with a mortality rate of 12.7/100,000. [Malvia et al., 2017] In the developed nations like USA, the 5-year overall survival (OS) of breast cancer patients has increased upto 89%, but in India it is still only about 60%. [Hingmire et al., 2017] If diagnosed in early-stage breast cancer is potentially curable, but in LMICs mortality-to-incidence ratios for breast cancer are significantly worse in comparison to developed countries. [Martei et al., 2018]

Heterogeneity is observed among several subtypes of breast cancer and HER2/neu expression is found to be amplified in 18%–20% of breast cancer patients, indicating a close correlation between its role in disease prognosis and signifies its role as an attractive therapeutic target. [Revillion et al., 2008]

In case of HER2 positive breast cancer, there are options of treatment with HER2 targeted drug combination like Trastuzumab, lapatinib, capecitabine and pertuzumab. [Joensuu et al., 2006, Theriault et al., 2014] These drug combinations are having selective effect and shows benefit in many patients, but still there are large number of patients for whom this treatment fails. Also, there is a constraint regarding its availability as well as huge financial burden.

Ado-trastuzumab emtansine (T-DM1), an antibody-drug conjugate is one of the cost-effective option available at present, where trastuzumab is linked to the cytotoxic agent emtansine (DM1), a maytansine derivative and microtubule inhibitor. Since 2013, T-DM1 has been US-FDA approved for its usage in treatment of advanced metastatic HER2 positive breast cancer as a single therapeutic agent. [Indira et al., 2020, Boni et al., 2020] and since, 2019 it got approval in early breast cancer setting were, it has shown improved outcomes as an adjuvant therapeutic agent in residual invasive breast cancer patient post neoadjuvant treatment. [Indira et al., 2020, Paracha et al., 2020, Conte et al., 2020] It was available after 2015, for the clinical use in India at an exorbitant price which limits its usage to the needy patients.

Until 2020, only innovator drug was the option available for the T-DM1 usage in India while World's first biosimilar of T-DM1 got approved in December 2020 by CDSCO, India after various pre-clinical assays and a phase-3 clinical trial in Indian breast cancer patients and demonstrating its noninferiority with the reference standard product. (Thungappa et al., 2021) It became available for the clinical use in India from May, 2021 by the name of UJVIRA^{TM} as a much more accessible option for the benefit of the patients.

The present study aimed to analyse and evaluate the trend and usage patterns of Ujvira in the first year of its availability in Indian context. It also aimed to provide a review of prescribing practices to cancer care clinicians, which can be used to propagate better health care delivery among deserving patients.

The objectives of the study were to assess the practice pattern of this drug, identify the patients & disease characteristics where it was used and find the proportion of patients taking benefit of patient assistance program (PAP).

Material and Methods:

The study was conducted after one year of the clinical use and availability of Ujvira in India. This observational, retrospective study was conducted based on the drug (Ujvira) usage in HER2 positive breast cancer patients across various hospitals and centres across India. The data was taken from the repository of Healthcare at Home (HCAH), Noida, India, who were appointed to execute PAP since the availability of Ujvira in India. As a part of availing PAP, patients register to HCAH with required details and documents. And the assistance was given for one free of cost Ujvira cycle after every 7 cycles of treatment with the same in breast cancer. Total 470 patients were registered for patient assistance program and out of that 342 patients (72.8 %) could avail the assistance with at least one free of cost cycle of Ujvira. A total of 167 patients' basic disease characteristic and treatment line details were retrieved from the data of those patient who registered for patient assistance program.

The inclusion criteria were PAP registered HER2-positive breast cancer patients of all age groups in which Ujvira was given for the treatment. Patients whose forms are having insufficient records and data were excluded from the study. An Excel-based tool was used for systematic data sampling and analysis. Data was collected and entered in excel sheet and necessary parameters needed for the study were observed. The obtained results were presented in numbers and visualised in various histograms. The collected data was analysed using descriptive statistics such as frequencies and percentage were calculated for selected variables and were represented in graphs.

Results and Discussion:

During the study period of one year, majority of the patients who got Ujvira were in metastatic breast cancer setting that too in later lines followed by early breast cancer patients on adjuvant therapy. From the estimated 2000 breast cancer patients who got access to Ujvira for their treatment, 470 patients did registration for assistance. Out of total 470 registered patients, nearly 342 patients took assistance of free cycle under PAP programme. In the breakup study of the patients who took benefit of free drug, 71 patients

(21%) were of Early Breast cancer setting and got benefit of free drug in Adjuvant therapy. While 268 patients (79%) were of Metastatic Breast cancer setting and out of those 245 patients (72%) got one cycle free while 23 patients (7%) got two free cycles of Ujvira. (Graph 1)

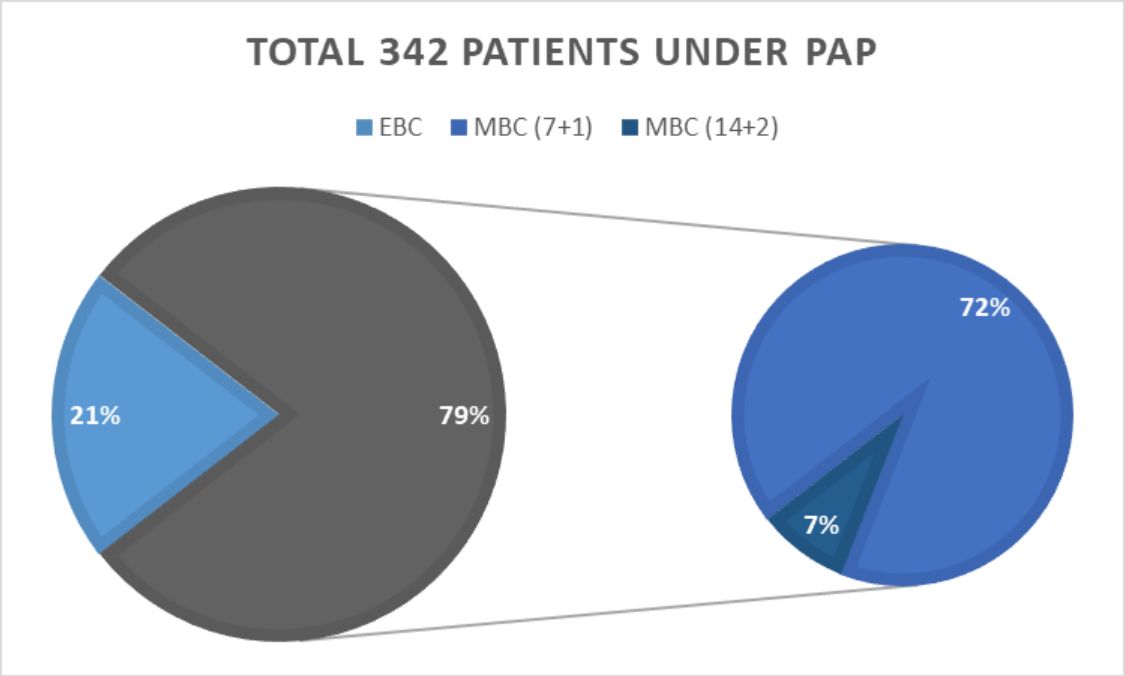

Figure 1 - Distribution pattern of patients benefited under PAP

For outlining the drug use, we selected prescriptions containing at least minimal details which can help out to understand several parameters like age, stage of cancer and further line of treatment. 167 Rx was found to be appropriate containing major details, so further variable-based analysis was carried out using the same. (Table 1)

Table 1 - Variable based data of selected Rx

Sr.no	Variable	Sub-category	Frequency (n)	Percentage (%)
1	**Age (yrs.)**	**20 - 30**	1	0.8
		30 - 40	14	11.2
		40 - 50	35	28
		50 - 60	52	41.6
		60 - 70	16	12.8
		70 - 80	7	5.6
2	**Side of breast affected**	**Left**	39	59
		Right	27	41
3	**Hormone receptor status**	**ER-/PR-/Her2+**	109	69.9
		ER+/PR+/HER2 +	32	20.5
		ER+/PR-/Her2+	15	9.6
4	**Usage of Ujvira**	**MBC**	123	73.65
		EBC	20	11.98
		LABC	19	11.38
5	**Pattern of usage of Ujvira**	**Adjuvant**	39	36.45

		2nd Line	30	28.03
		3rd Line	20	18.69
		4th Line and Beyond	12	11.22
		1st Line	6	5.61
6	**Sites of Metastasis**	**Brain**	19	31.14
		Liver	17	27.86
		Bone	15	24.60
		Lung	10	16.40

The age (yrs.) wise distribution pattern reveals that the majority of participants were belonging to age-group of 50-60 years, followed by those belonging to the bracket of 40-50 years and 60-70 years, in the descending order. Those in the age-groups of 70-80 years were the least ones. (Graph 2)

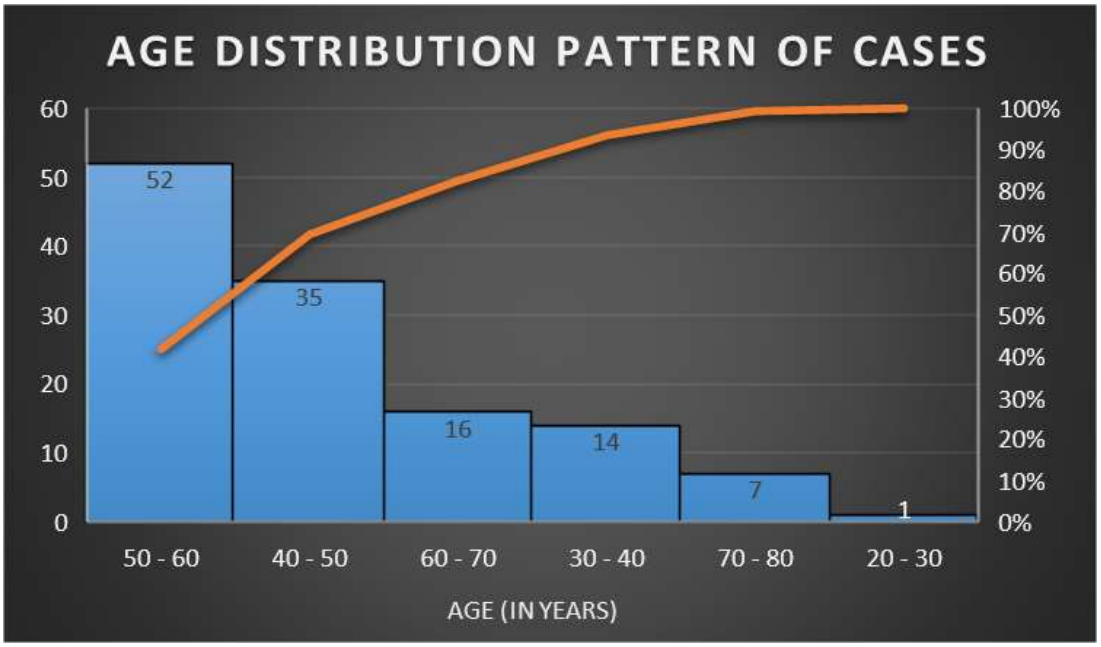

Figure 2 – Age distribution pattern of patients

Among the study group, in context to the sidedness of the breast affected among females, majority were having left side breast getting affected more (59%) in comparison with right side. (Graph not shown) The details about the Hormone receptor status were obtained in nearly half of the prescriptions. While, further analysis of it reveals that nearly 20% patients were found to be triple positive i.e., HER2 Receptor was positive along with Estrogen receptor (ER) and Progesterone receptor (PR) positive status. While, 70 % were found to be positive for only HER2 and rest two receptors were negative. (Graph not shown)

Analysis of selected Rx (n=167) showed that a greater number of usages was done in metastatic as well as palliative setting among Breast cancer patients in the initial few months of Ujvira availability. It was also revealed that it was used in later lines after the initial standard therapy fails and patients are in disease progression stage. While adjuvant use in case of early breast cancer (EBC) and locally advance Breast cancer (LABC) was almost in equal number. (Graph 3)

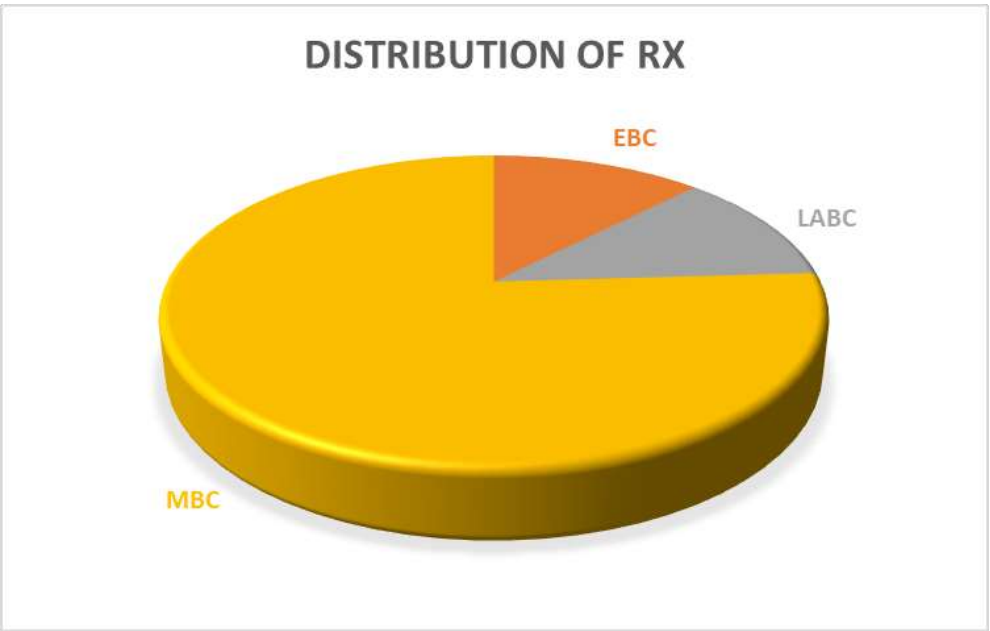

Figure 3 – Distribution pattern of analysed Rx

T-DM1 has been approved by the US-FDA for treatment of advanced metastatic HER2 positive breast cancer in 2nd line and beyond since 2013. While, in 2019 it also got approval for the usage in Adjuvant treatment of HER2 positive breast cancer who did not achieve pathological complete response post-surgical treatment. Based on the analysis of selected Rx, majority of the patients got benefitted in PAP were in the adjuvant setting, followed by 2nd line treatment of MBC. Fewer patients were observed to be treated in 1st line in case if they were not suitable for conventional chemotherapy. (Graph 4)

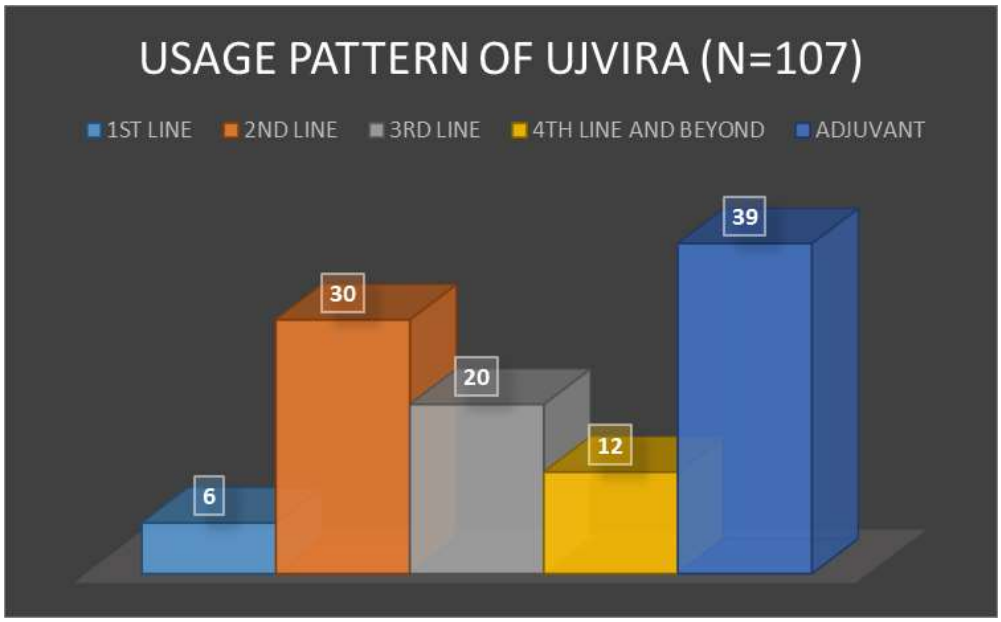

Figure 4 – Pattern of usage of UJVIRA among patients

While analysing the sites of metastasis involved in case of advanced Breast cancer patients, were T-DM1 was used. Majority of the patients were found to be having involvement of Brain metastasis (31%) followed

by liver metastasis. Bone and lung were also found to be involved as major metastasis site, in decreasing order. (Graph 5)

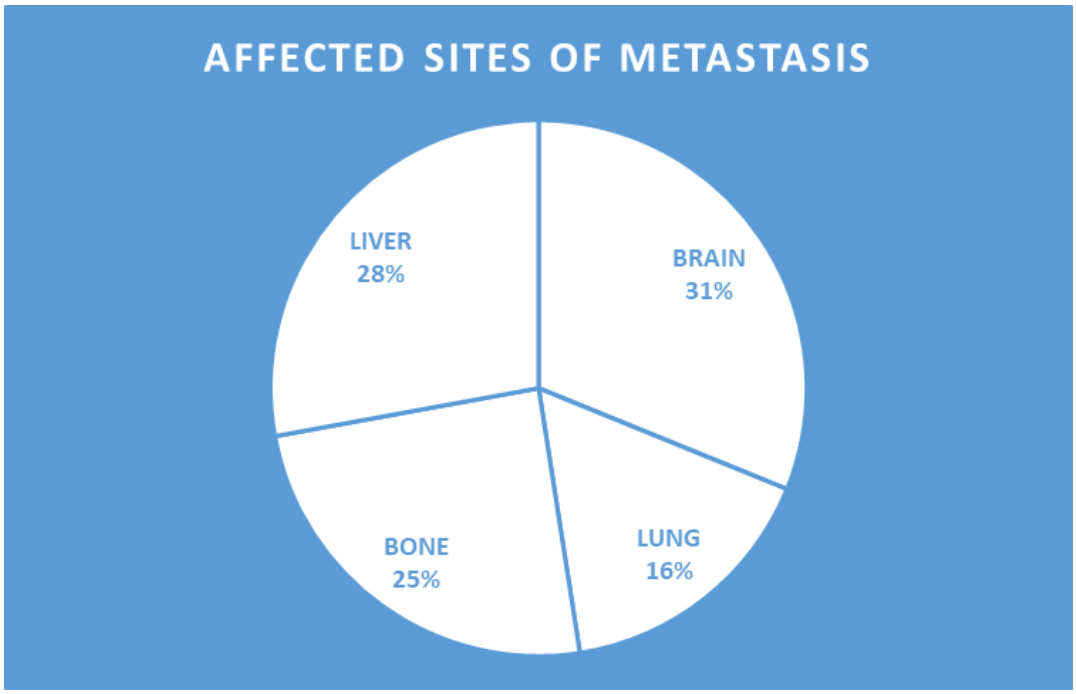

Figure 5 – Metastatic sites observed among Advance Breast cancer patients

Discussion:

In India, breast cancer has overtaken all other cancers very rapidly in a decade in context of mortality as well as in rate of incidence. Women in India are getting breast cancer at a younger, premenopausal age and a huge part of the patients present at an advance stage. Considering the epidemiological data, in India breast cancer becomes the most common cause of cancer-related mortality. While other major concern is the rise in incidence among younger population were almost half the cases occurs in females less than 50 years of age [Ferlay et al., 2012]. Thus, as per the data breast cancer occurrence is decade earlier at a more advance stage among Indian females as compared to the western population.

The higher prevalence of cancer along with the increased cost of therapeutic treatment and management imparts a significant challenge to the patients [Wani et al., 2013]. Thus, the availability of option of cost effective biosimilar for the treatment will be in benefit of the patient for the best possible management of cancer.

T-DM1 was the first antibody drug conjugate approved for usage in Breast cancer in 2013 by US Food and Drug Administration (FDA) after publication of Preclinical data regarding T-DM1 in 2008 followed by the first clinical trial data publication in 2010. T-DMI was granted approval only within 5 years after the first publication reflecting both need as well as excitement towards the targeted therapy which can cause relatively lower toxicities and showed improved efficacy in comparison with traditional chemotherapy.

The analysed data in this study also revealed that the average cost of the innovator T-DM1 drug is very high which makes it unaffordable to the usage of common people in a developing country like India. It also states that, with a high cost, the patients who needs this drug will have a limited usage considering the financial constraints and ultimately suffers from the compromised treatment.

As per the IPSOS W2 2021-22 data (July-June), with the availability of biosimilar of T-DM1, out of total 1400 patients benefitted from T-DM1 nearly 62% patients were on UJVIRA post launch as compared to the innovator molecule. In context of cancer, significant cost of health care is incurred by the usage of targeted drugs. Thus, the availability of a targeted biosimilar drug with cost effectiveness and easy accessibility with proven efficacy as compared to reference product is of utmost importance. This will impact positively on the prescribing pattern among the clinicians as well as compliance of the patients and help curb the rising expense of treatment.

Conclusion:

Drug utilization study is an inevitable tool in the health economics to understood the usage of any drug. It also provides the insights about the efficacy and pattern of drug used as well as preferences and outcome of use. Present study also suggests that with the availability of the first biosimilar of T-DM1 (UJVIRA[TM]) as a more accessible option in India, a higher number of patients are able to take the benefit of it. It is enabling the clinicians to increase its usage as the standard of care in adjuvant setting and in second-line metastatic breast cancer in accordance with international guidelines on HER2-positive breast cancer management.

Author Contributions:

Conception and Design: VT and PM
Collection of Patient Data: GT and VJ
Data Assembly, Analysis and Interpretation: All Authors
Manuscript Writing: VT and PM
Final Approval of Manuscript: All Authors
Accountable For All Aspects Of The Work: All Authors

DATA AVAILABILITY: Patient Data Were Retrieved From Electronic Database Of HCAH And Any Further Queries Can Be Directed To The Corresponding Author.

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Conflict Of Interest: Authors Declare That There Are No Potential Conflicts Of Interest.

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