ESMO WORLD CONGRESS ON Gastrointestinal Cancer

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Oncodistinct study #5: Efficacy and Safety of Neoadjuvant Short-Course Radiation Followed by mFOLFOX-6 plus Avelumab for Locally-Advanced Rectal Adenocarcinoma: Averectal Study

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ONCO DISTINCT NETWORK

Study 5

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Disclosure

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Roche,Sanofi,Pharmamed,Bayer,MSD,Pfaizer, Merck,Lilly, Piere Fabre

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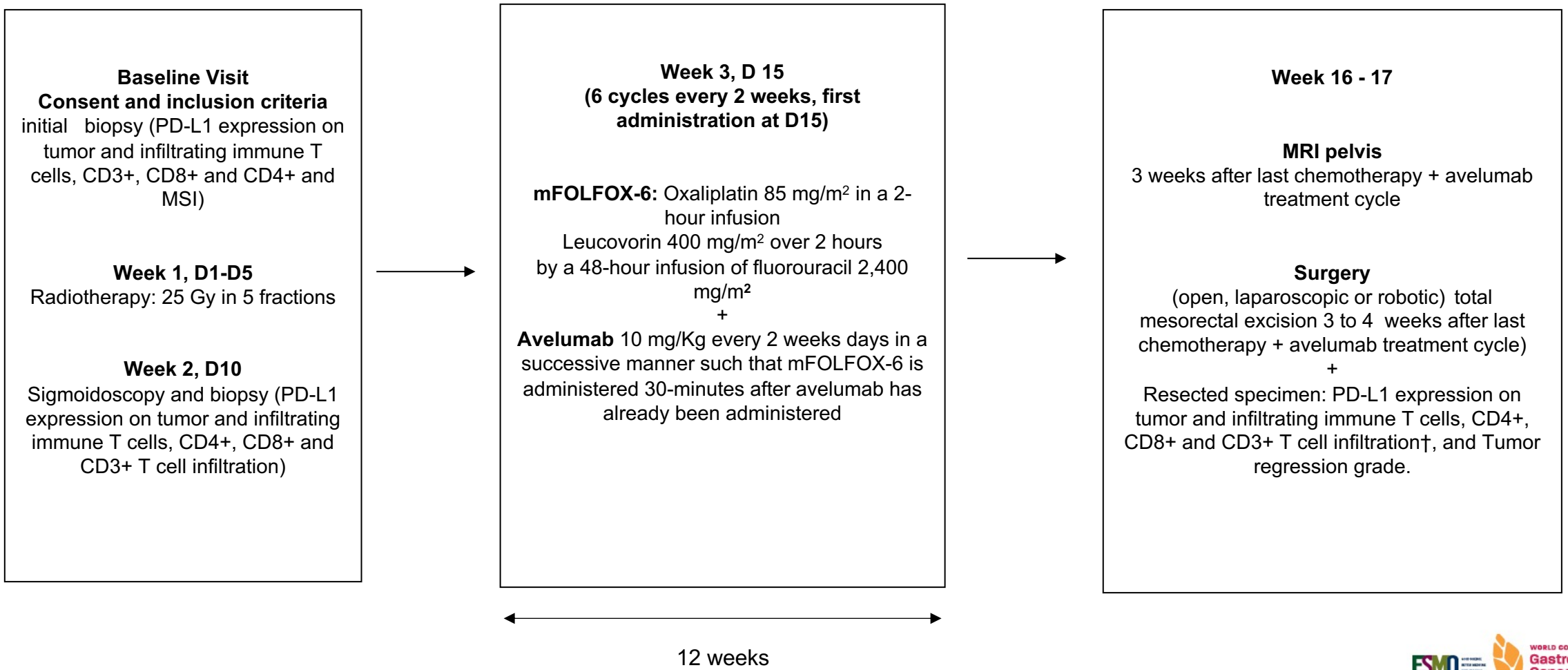
Background

- Total neoadjuvant therapy (TNT) for locally advanced rectal cancer is becoming an accepted approach over the last few years with increasing pathologic complete response (pCR) and compliance with chemotherapy in comparison with the current standard of care i.e., fluoropyrimidine-based chemoradiation followed by surgery and adjuvant chemotherapy[1].
- In the phase III RAPIDO Trial, TNT was shown to be associated with a lower rate of disease-related treatment failure and distant metastasis and a higher rate of pCR as compared to the current standard of care[2].
- Sequential use of anti–PD-1/PD-L1 antibody after radiation therapy has demonstrated synergistic effect in vivo models leading to decrease in size of irradiated and non-irradiated secondary tumors outside the radiation field (abscopal effect)[3].

1. *Benson, Al B., et al. "NCCN Guidelines Insights: Rectal Cancer, Version 6.2020: Featured Updates to the NCCN Guidelines." Journal of the National Comprehensive Cancer Network 18.7 (2020): 806-815.*
2. *Hospers, Geke, et al. "Short-course radiotherapy followed by chemotherapy before TME in locally advanced rectal cancer: The randomized RAPIDO trial." (2020): 4006-4006.*
3. *Trommer, Maike, et al. "Abscopal Effects in Radio-Immunotherapy—Response Analysis of Metastatic Cancer Patients With Progressive Disease Under Anti-PD-1 Immune Checkpoint Inhibition." Frontiers in pharmacology 10 (2019): 511.*

Averectal Study Design

- This is a multicenter phase II study involving 3 different centers: the American University of Beirut Medical Center and Hotel-Dieu de France in Lebanon and King Hussein Cancer Center in Jordan



Averectal Study: Endpoints

- **Primary endpoint:**
  - The proportion of patients who achieve a pathological complete response (pCR), defined as no viable tumor cells on the resected specimen.

- **Secondary endpoints:**
  - Progression-free survival (PFS) at 3 years will be estimated with the Kaplan-Meier method and presented with the 95% confidence interval (CI).
  - Evaluation of response by obtaining Tumor Regression Grade (TRG).
  - Evaluation of biomarkers: CD4+, CD8+ and CD3+ T cell infiltration, and changes in PD-L1 expression.
  - Determination of immunoscore at baseline using the percentiles of CD8+ and CD3+ T cell infiltration and assessing its correlation to pCR.
  - Frequency, severity, and attribution of AEs related to avelumab in neoadjuvant setting.
  - Quality of life assessment using the questionnaire for the functional assessment of cancer therapy for patients with colorectal cancer (FACT-C, English version 4 of 16 November 2007 or Arabic version 4 of 03 September 2014).

Averectal Study: Key Eligibility

* INCLUSION CRITERIA	*EXCLUSION CRITERIA
□ Written Informed consent	□ Distant metastasis
□ Age ≥ 18	□ T2N0 and cT4b
□ Newly diagnosed locally advanced rectal adenocarcinoma (cT2 N1-3, cT3 /cT4a N0-3, and M0)	□ Recurrent rectal cancer
□ Tumor <15 cm from anal verge	□ Prior radiotherapy or chemotherapy
□ Potentially resectable tumor	□ Prior organ or stem cell transplantation
□ Performance Status ≤1	□ Presence of peripheral neuropathy
□ Negative pregnancy test	□ Presence of an active cardiovascular disease or a recent cerebrovascular event
□ Effective contraception	□ Presence of an active autoimmune disease
□ Normal Lab Tests (CBC, Chem9, LFT, Thyroid tests and Virology)	□ History of positive HIV test or known AIDS
□ Additional Criteria may apply	□ History of complications following exposure to a component of the tested formulation
	□ Vaccination 4 weeks or less prior to first dose of Avelumab or during trial

Averectal Study: Statistical Consideration

- A Simon's two-stage optimal design with a null hypothesis pCR rate ≤ 16% versus the alternative that pCR rate ≥ 35%, a type I error of 0.05 and a power of 80%.
- The results of the first 13 patients eligible for the primary efficacy analysis will be assessed in stage 1.
- If 2 or less patients achieved pCR, the study will be stopped, otherwise another 23 (eligible) patients will be added to the study (stage 2) for a total of 36 eligible for the primary efficacy analysis.
- If overall 10 or more patients achieved pCR, then the null hypothesis (the percentage of pCR is ≤16%) will be rejected.
- In total, 44 patients will be enrolled into the study considering that 15 to 20% of the patients might be not eligible for the primary analysis. .
- Then, the percentage of patients achieving pCR will be calculated along with its one-sided 95% confidence interval.
- Also using Kaplan-Meier method, the median PFS will be estimated along with its 95% confidence interval. Exploratory variables will be analyzed according to their scale of measurement by using mean ± standard deviation or frequency distribution for numeric and categorical variables respectively.

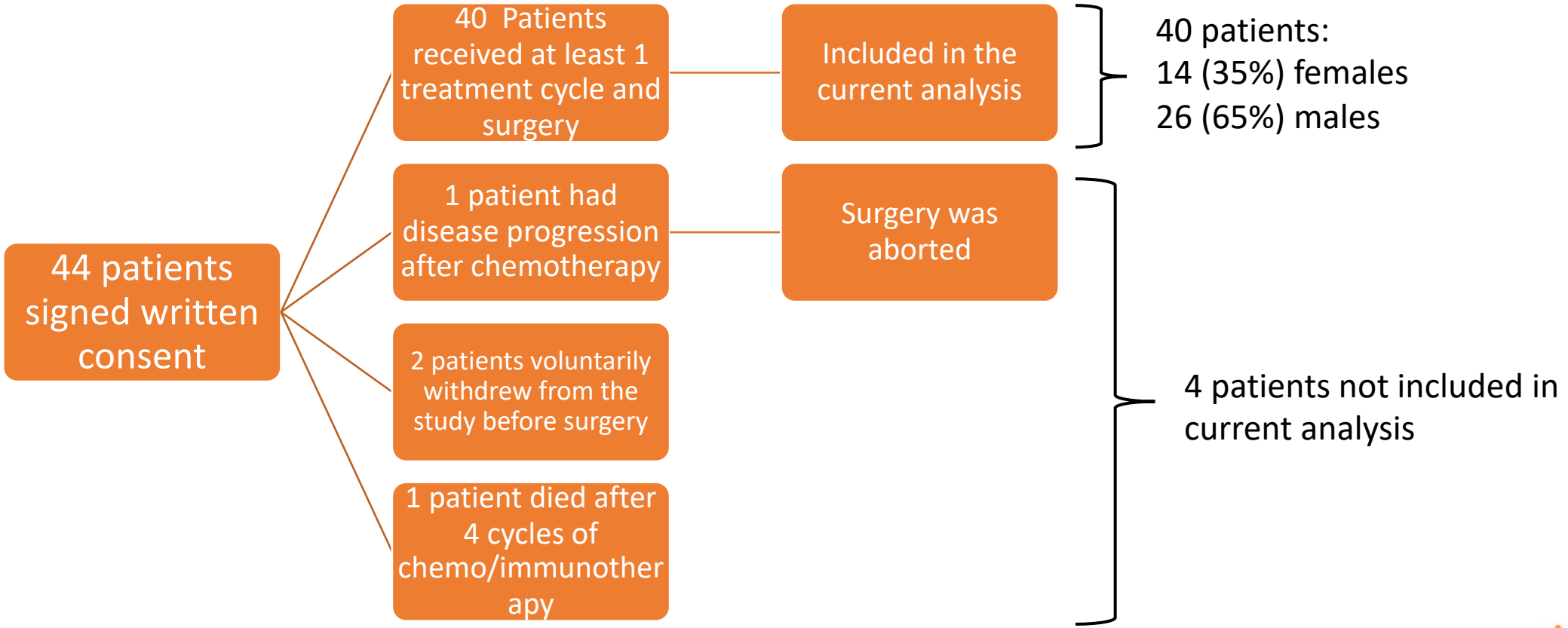
Stage 1 analysis

- 13 out of 44 patients were enrolled in the first stage of the study (30% from total sample size).
- All patients met the inclusion criteria and received the full short-course radiation course followed by 6 cycles of mFOLFOX6 plus avelumab. 12 out of the 13 patients completed TME while one patient had progression of disease and was dropped out of the study.
- The sample consisted of 9 (69%) males and 4 (31%) females with median age of 62 (33–73) years.
- The first interim analysis revealed **that 3 (25%) patients achieved pathologic complete response (pCR) (tumor regression grade, TRG 0) out of 12**. Another 3 (25%) patients had near pCR with TRG 1.
- **In total, 6 out of 12 patients (50%) had a major pathologic response.** The protocol regimen was well tolerated with no serious adverse events of grade 4 reported.
- As such, we proceeded with the second stage of the study

Shamseddine, Ali, et al. "Short-course radiation followed by mFOLFOX-6 plus avelumab for locally-advanced rectal adenocarcinoma." *BMC cancer* 20.1 (2020): 1-11.
Shamseddine, Ali, et al. "Efficacy and safety-in analysis of short-course radiation followed by mFOLFOX-6 plus avelumab for locally advanced rectal adenocarcinoma." *Radiation Oncology* 15.1 (2020): 1-7.
Shamseddine, Ali, et al. "Short-course radiation followed by mFOLFOX-6 plus avelumab for locally advanced rectal adenocarcinoma." Journal of Clinical Oncology 2020 38:4_suppl, 139-139

Stage 2: Patients' Flowchart

- Median age of 58.5 (31,74) years
- Median follow-up of 13.2 (3.6, 31.9) months



Patient Demographics and Characteristics

Patients Characteristics (N 40)	Descriptive Analysis	
Gender n(%)		
Male	26	(65)
Female	14	(35)
Age(year)		
Median/(min,max)	58.5	(31,74)
Nationality n(%)		
Iraq	3	(7.5)
Jordan	23	(57.5)
Lebanon	13	(32.5)
Syria	1	(2.5)
Smoking n(%)		
Never	26	(65)
Ever	14	(35)
Family History of Malignancy n(%)		
Yes	24	(60)
No	16	(40)

Tumor characteristics (N40)	Descriptive Analysis	
Grade n(%)		
1	1	(2.5)
2	2	(5)
3	31	(77.5)
4	5	(12.5)
Stage n(%)		
T2N1	1	(2.5)
T2N2	1	
T3N0	2	(7.5)
T3N1	4	(57.5)
T3N2	28	(32.5)
T4aN1	1	(2.5)
T4aN2	1	(2.5)
Primary site distance from anal verge median in cm (range)	6.75	(2.6, 14)

Primary End Point Result

Tumor Regression Grade (TRG)	N (%)
pCR (TRG=0; no viable tumor cells in tumor bed)	**15 (37.5%)***
1 (< 10% viable tumor cells)	12 (30%)
2 (10-50% viable tumor cells)	9 (22.5%)
3 (> 50% viable tumor cells)	4 (10%)

Median follow up 13.2 M(3.6-31.9)
mDFS: NR

Major pathologic response rate (mpRR)
(TRG 0 + 1): 67.5%

TNM Stage	Total Number	T1-T2N0 Downstaging n(%)	T0N0 Downstaging n(%)
T3/T4 N+	35	6(17%)	13(37%)

Survival in Rectal Cancer is Driven by Post Therapy Pathologic Stage

Primary end point of the study was met

** As compared to historical control group with a pCR of 16% (p=0.025, 95% CI. 24% -53%)*

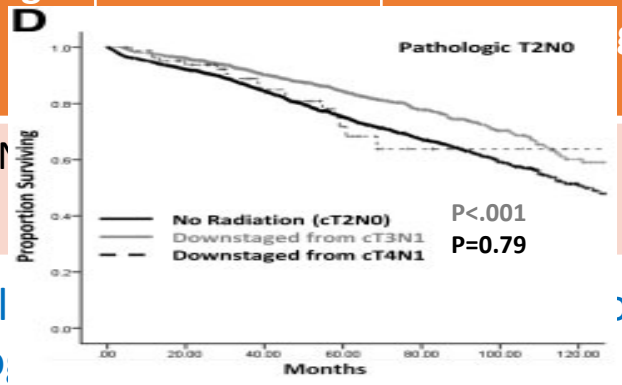
Primary End Point Result

Tumor Regression Grade (TRG)	N (%)
pCR (TRG=0; no viable tumor cells in tumor bed)	**15 (37.5%)***
1 (< 10% viable tumor cells)	12 (30%)
2 (10-50% viable tumor cells)	9 (22.5%)
3 (> 50% viable tumor cells)	4 (10%)

Median follow up 13.3 M(4.1-31.9)
mDFS: NR

Major pathologic response rate (mpRR)
(TRG 0 + 1): 67.5%

TNM Stage	Total	T1-T2N0	T0N0 Downstaging n(%)
T3/T4 N			13(37%)



Survival ost Therapy
Patholo

Primary end point of the study was met

** As compared to historical control group with a pCR of 16% (p=0.025, 95% CI. 24% -53%)*

Delitto D, et al. JNCI Natl Cancer Inst, 2018;110(5)

Major Adverse Events Occurring in relation with Avelumab and Surgery None exceeded 10%

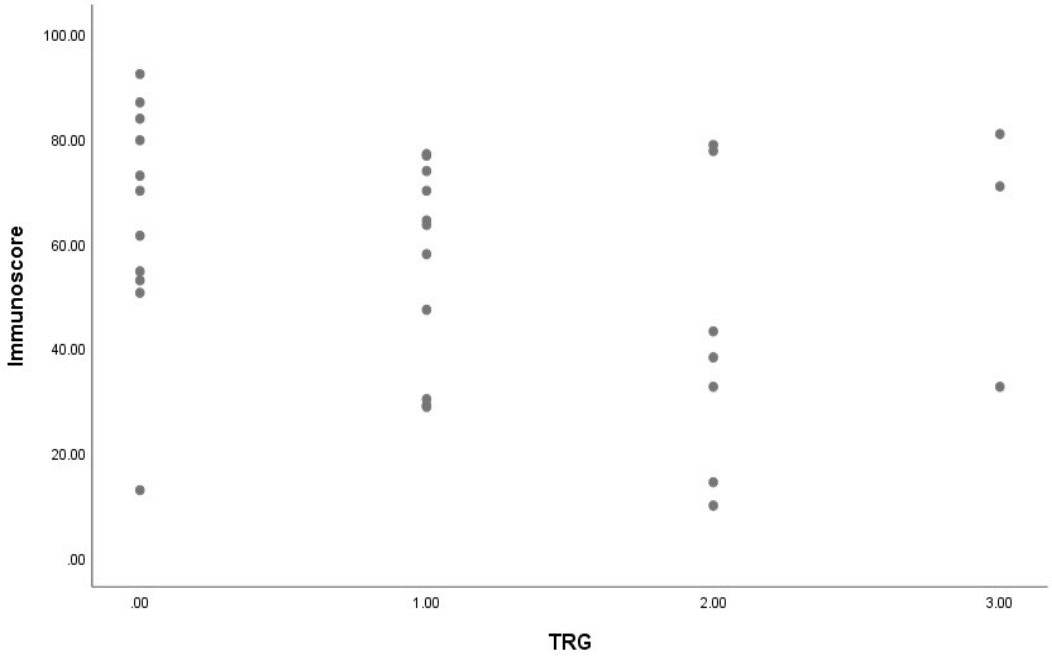
N=291	ALL Grades	Grade 3/4
Avelumab related (total) (15, 5.1%)	15 (5.1%)	None
Nausea	6 (2%)	-
Rash	3 (1%)	-
Chills/Fever	2 (<1%)	-
Hypothyroidism	1(<1%)	-
Elevated LFTs	1(<1%)	-
Hypotension	1(<1%)	-
Mild Transient reaction	1(<1%)	-
Surgery-related (total) (35, 12%)	23 (9.5 %)	12 (5%)
Electrolyte imbalance	6(2%)	4(1.3 %)
Pelvic Abscess	2(<1%)	2(<1%)
Perforation and anastomosis Leak	2(<1%)	2(<1%)
Infection	2(<1%)	_
Small Bowel Obstruction	2(<1%)	2(<1%)

Preliminary Immunoscore Results

- For each case, the densities of CD3+ and CD8+ cells at the tumor margin and within the core of the tumor were calculated on the baseline pathology specimen and transformed to percentiles based on our population.
- The mean of the 4 percentiles (2 markers, 2 regions) was calculated and converted into an immunoscore (IS).
- 32 (80%) out of 40 patients have their IS reported until date
- **The mean IS was 56.72 and the median IS was 62.45**

TRG	N(%)	Median IS	Median IS
0	11 (34%)	70	63.91
1	11 (34%)	63.5	
2	7 (22%)	38.2*	40.69
3	3 (10%)	61.42	
Total	32 (100%)	70	62.45

** IS data showed a statistically significant difference between TRG 0 and TRG 2 where a high IS can predict higher pCR as compared to a lower IS with p= 0.045*



Scatter plot showing the distribution of the immunoscores of patients in the different TRG groups.

Khalifeh, I., El Husseini, Z., Zeidan, Y., Turfa, R., Kattan, J., Mukherji, D., ... & Shamseddine, A. (2020). P-51 Immunoscore in rectal cancer patients receiving radiation followed by mFOLFOX with avelumab. *Annals of Oncology*, *31*, S106.

Pagès, F., Mlecnik, B., Marliot, F., Bindea, G., Ou, F. S., Bifulco, C., ... & Galon, J. (2018). International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study. *The Lancet*, *391*(10135), 2128-2139.

Conclusion

- Based on this analysis, the primary endpoint was successfully met with significant improvement in pCR (37.5% vs 16% in historical control, p=0.025) rate in the setting of an acceptable safety profile.

- High immunoscore performed on initial biopsy is significantly associated with increasing pCR(p=0.045), warranting further study in a larger cohort.

- 3-year disease-free survival, overall survival and quality of life data will be reported later in the final study manuscript.

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