(PD42-02) Optimizing sequence of therapy and radiation delivery when combined with PD-L1 immune-checkpoint inhibition in bladder cancer

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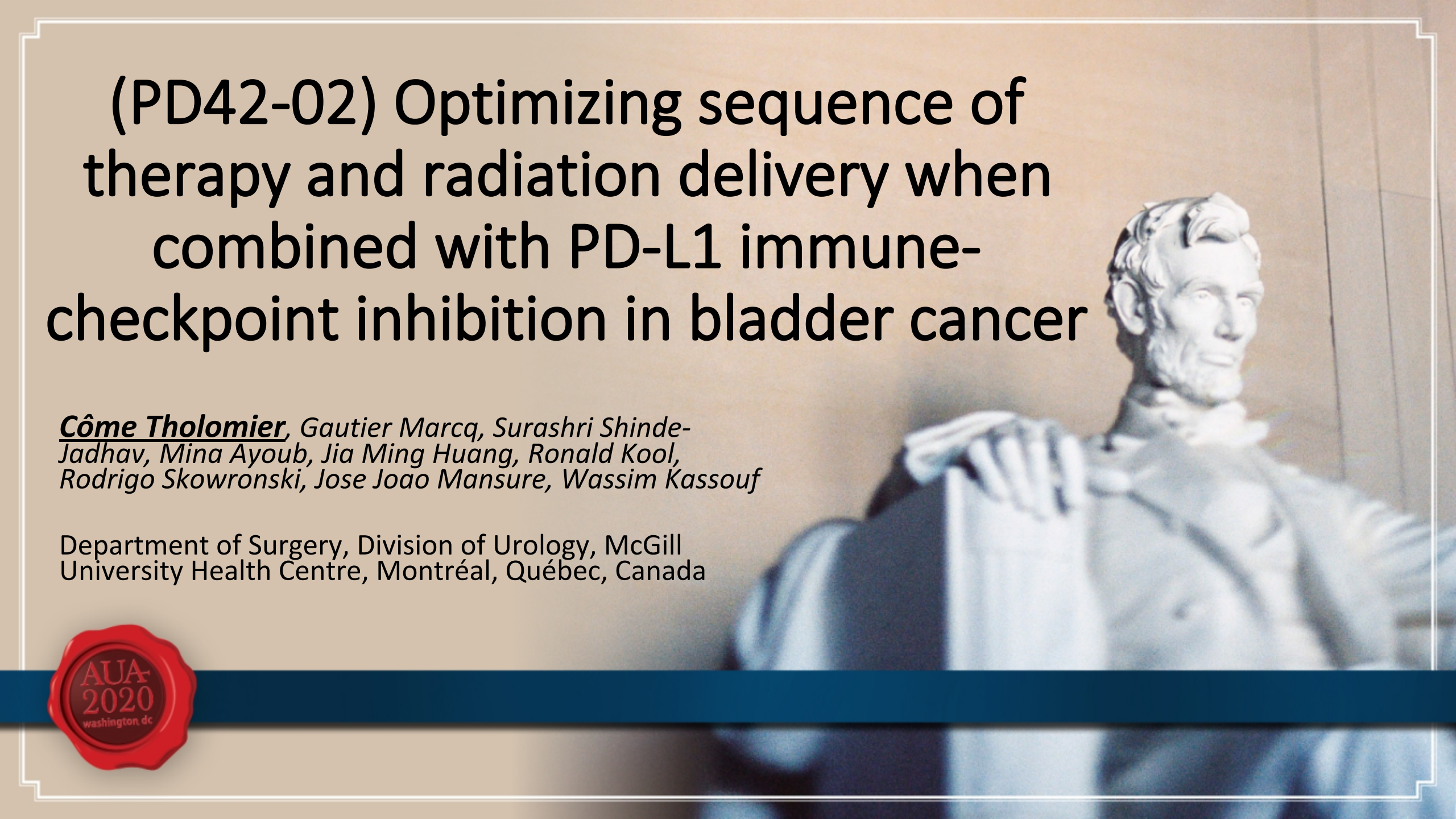

Introduction

- Treatment of muscle-invasive bladder cancer (MIBC)
  - →Neoadjuvant chemotherapy followed by radical cystectomy
  - →Bladder-preserving protocols (e.g. Trimodal therapy or **TMT**) in appropriately selected individuals: comparable oncological outcomes and avoid morbidity

Introduction

- Treatment of muscle-invasive bladder cancer (MIBC)
  - →Neoadjuvant chemotherapy followed by radical cystectomy
  - →Bladder-preserving protocols (e.g. Trimodal therapy or **TMT**) in appropriately selected individuals: comparable oncological outcomes and avoid morbidity
- Treatment of metastatic disease
  - →Platinum-based chemotherapy
  - → Immune checkpoint inhibitors: anti-PD-1 or anti-PD-L1

Introduction

- Combination of immunotherapy and radiation therapy shown to provide a **synergistic effect** → improve cancer control
  - E.g. Non-small cell lung cancer[1,2] and melanoma[3]

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- Combination of immunotherapy and radiation therapy shown to provide a **synergistic effect** → improve cancer control
  - E.g. Non-small cell lung cancer and melanoma
- Pre-clinical data in bladder cancer showed similar results[4,5]
  - Radiation → upregulation of PD-L1 expression in mice, peak at 72 hours
  - Combination therapy → improved overall survival and tumor growth rate + abscopal effect

Introduction

- Optimal sequencing of combination therapy?
  - Neoadjuvant vs. adjuvant vs. concurrent immunotherapy and radiotherapy
- Optimal radiation delivery?
  - Non-fractionated vs. hypo-fractionated vs. hyper-fractionated regimen

Introduction

- Optimal sequencing of combination therapy?
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- Optimal radiation delivery?
  - Non-fractionated vs. hypo-fractionated vs. hyper-fractionated regimen
- Aimed to compare different options of combination therapy and radiotherapy delivery on tumor growth and survival using an *in vivo* syngeneic MIBC mouse model

Methods

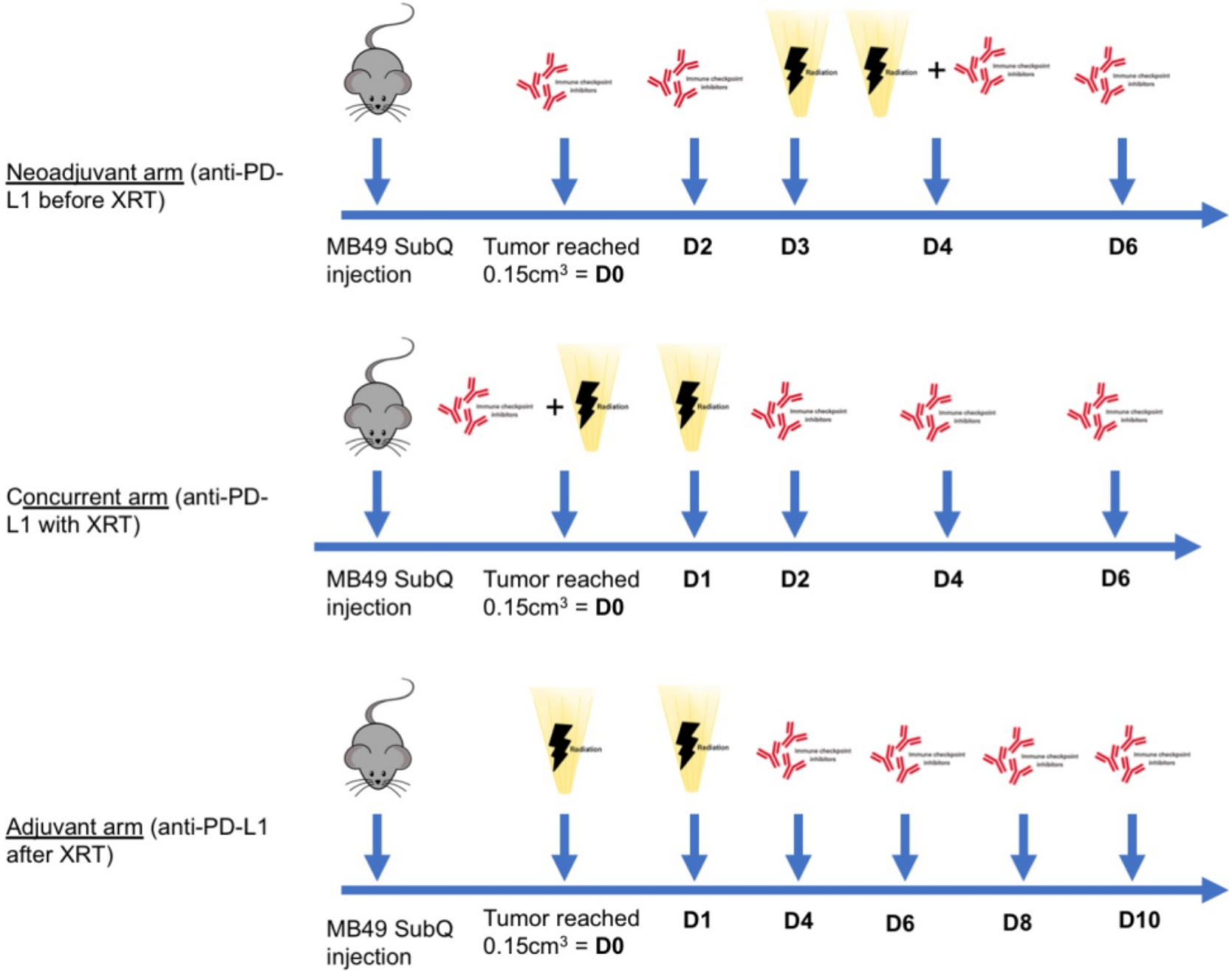
- Murine bladder cancer cell line MB49 (derived from C57BL/6 mice) were injected subcutaneously in the right flank of 6-8 weeks old C57BL/6 male mice
  - All mice received 5 x 10^5 MB49 cells
- All experiments followed all relevant guidelines and regulations as per the Facility Animal Care Committee at the McGill University Health Center Research Institute

Methods

- Tumor volume ≥ 0.15 cm^3 → randomization
- 115 mice were randomized
  1. Control
  2. Anti-PD-L1 alone (250µg q48 hours x4 doses)
  3. Radiotherapy (either 10 Gy x1, 6.25 Gy x2 or 3.3Gy x5 fractions) - bioequivalent
  4. Concurrent anti-PD-L1 and radiotherapy (same regimens as above)
  5. Sequence of therapy: anti-PD-L1 3 days before or 3 days after RT (6.25 Gy x2)

Methods

- Tumor growth monitored q48 hours with electronic caliper until primary endpoint was reached, at which mice were sacrificed
- Primary endpoint = tumor volume of 1.5 cm^3
- All statistical analyses were performed using Prism
  - Analysis of variance for repeated measurements were used to estimate differences between groups for tumor growth
  - Kaplan-Meier curves were used for time-to-endpoint analysis
  - Flow cytometry performed for concurrent combination therapy

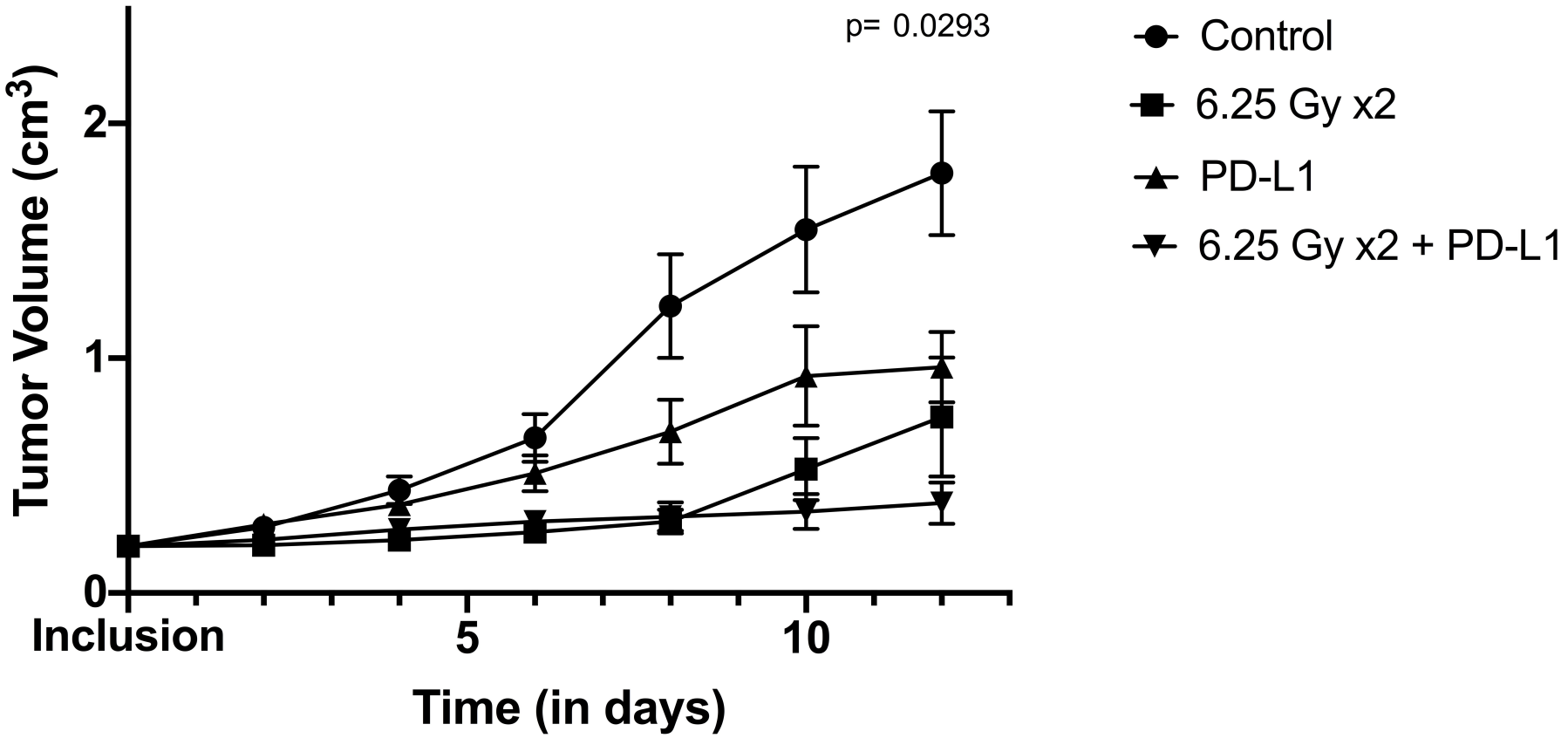

Neoadjuvant arm (anti-PD-L1 before XRT)
Radiation
Radiation
MB49 SubQ injection
Tumor reached 0.15cm3 = D0
D2
D3
D4
D6
Concurrent arm (anti-PD-L1 with XRT)
Radiation
Radiation
MB49 SubQ injection
Tumor reached 0.15cm3 = D0
D1
D2
D4
D6
Adjuvant arm (anti-PD-L1 after XRT)
Radiation
Radiation
MB49 SubQ injection
Tumor reached 0.15cm3 = D0
D1
D4
D6
D8
D10

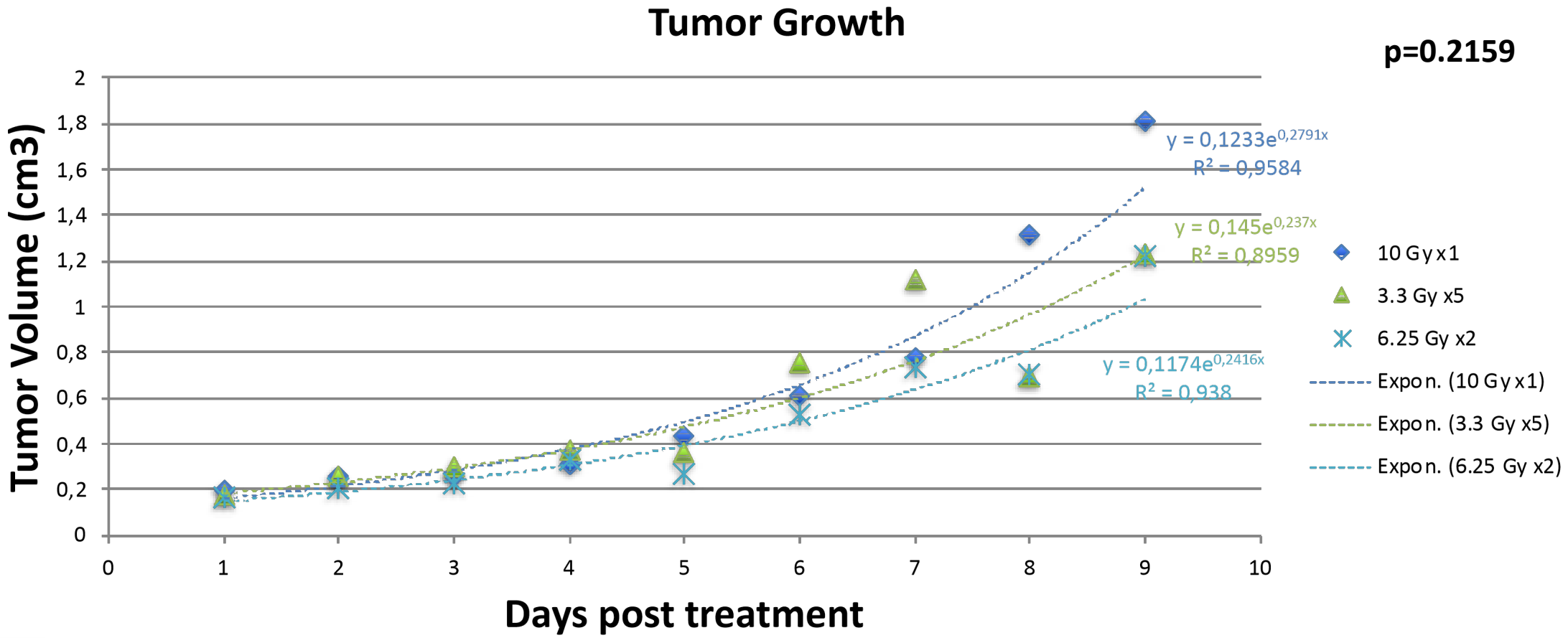
Results

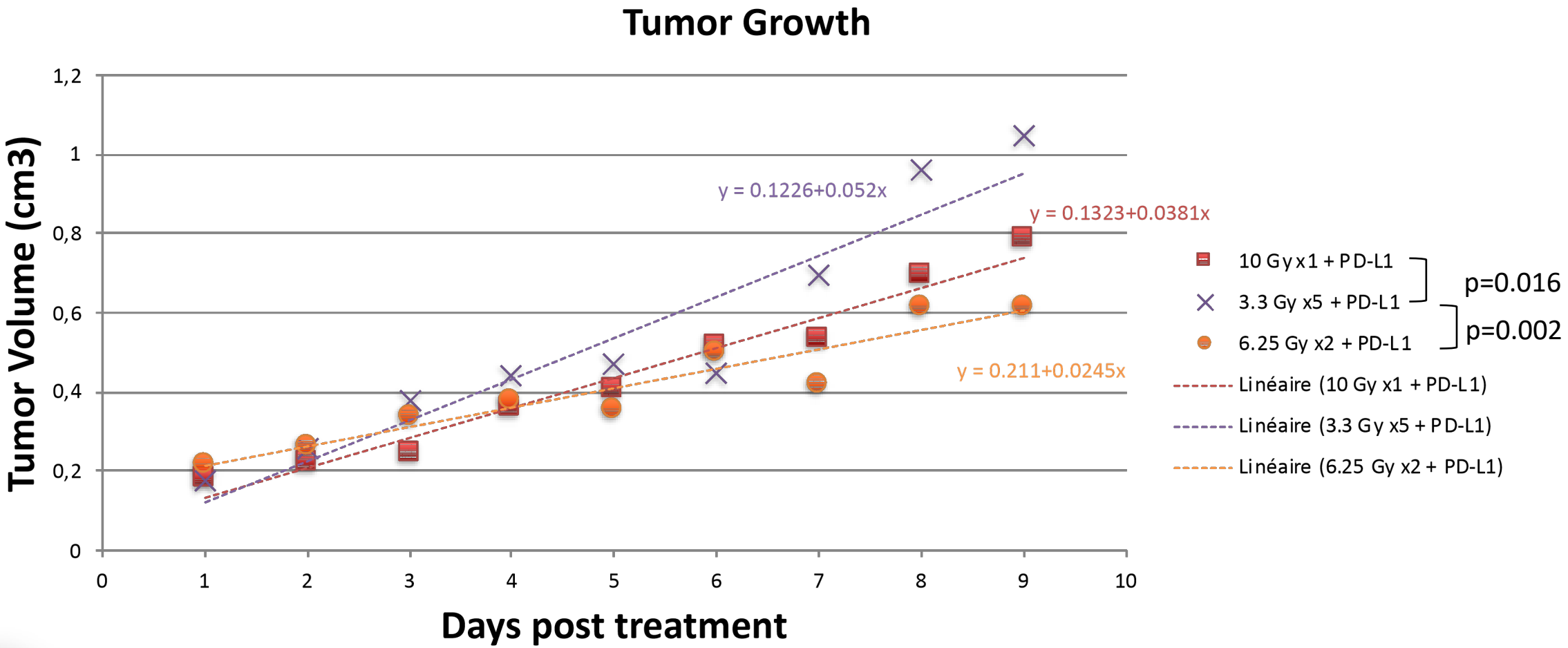
- Previously shown that combination therapy led to a statistically significant slower tumor growth rate than monotherapy
- ANOVA: statistically significant difference in tumor growth across treatment arms (p=0.029)
- Combination therapy → most favorable curve

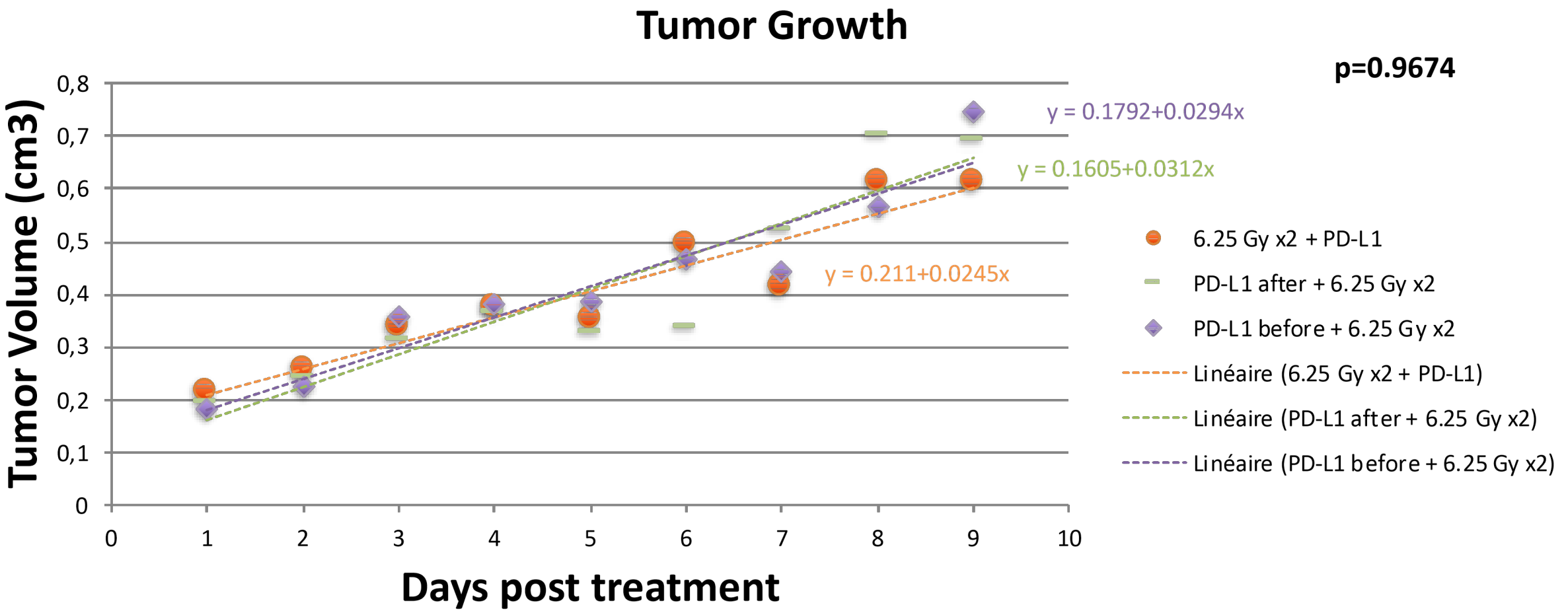
ANOVA: Analysis of variance

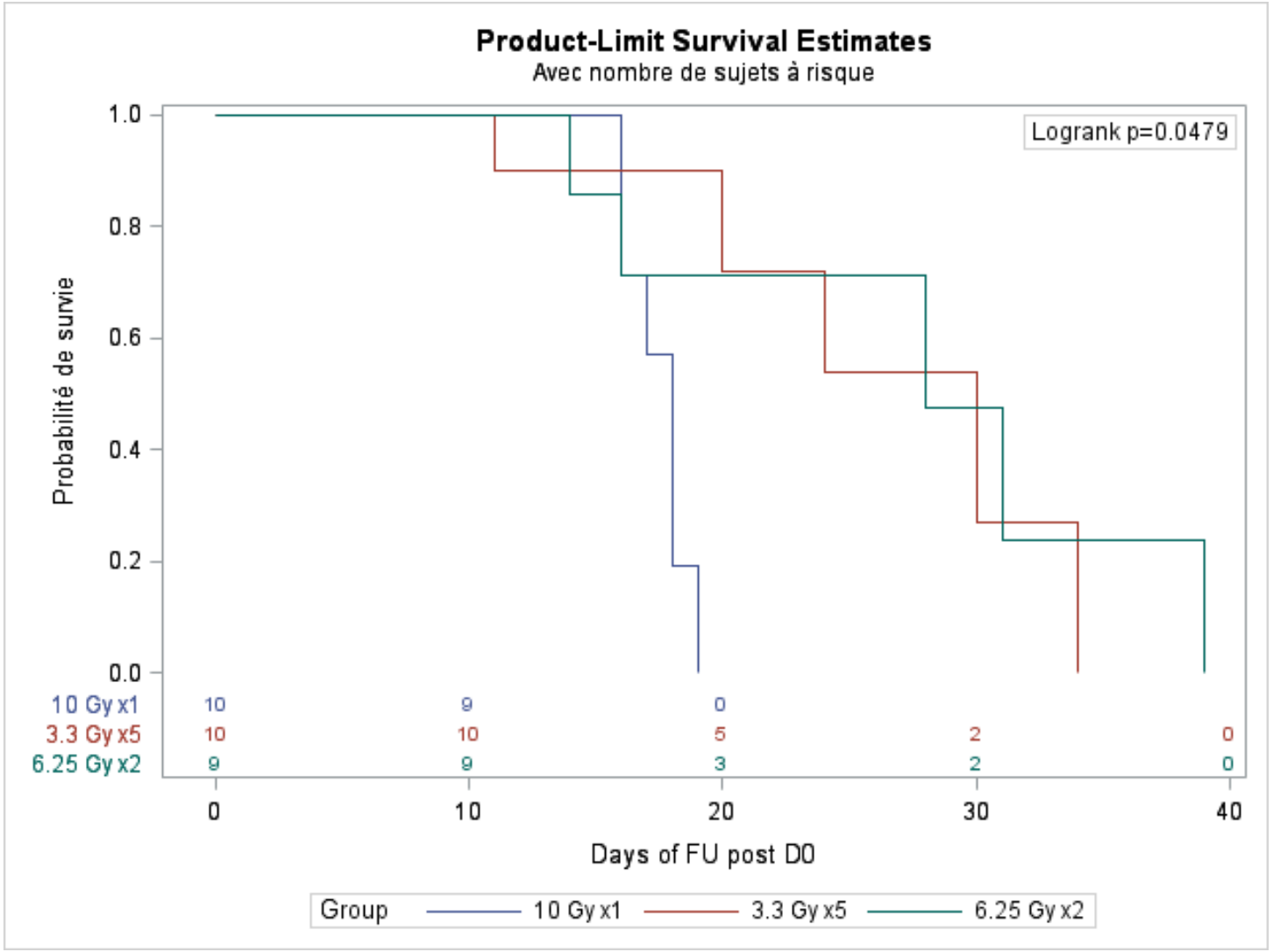
Tumor Growth

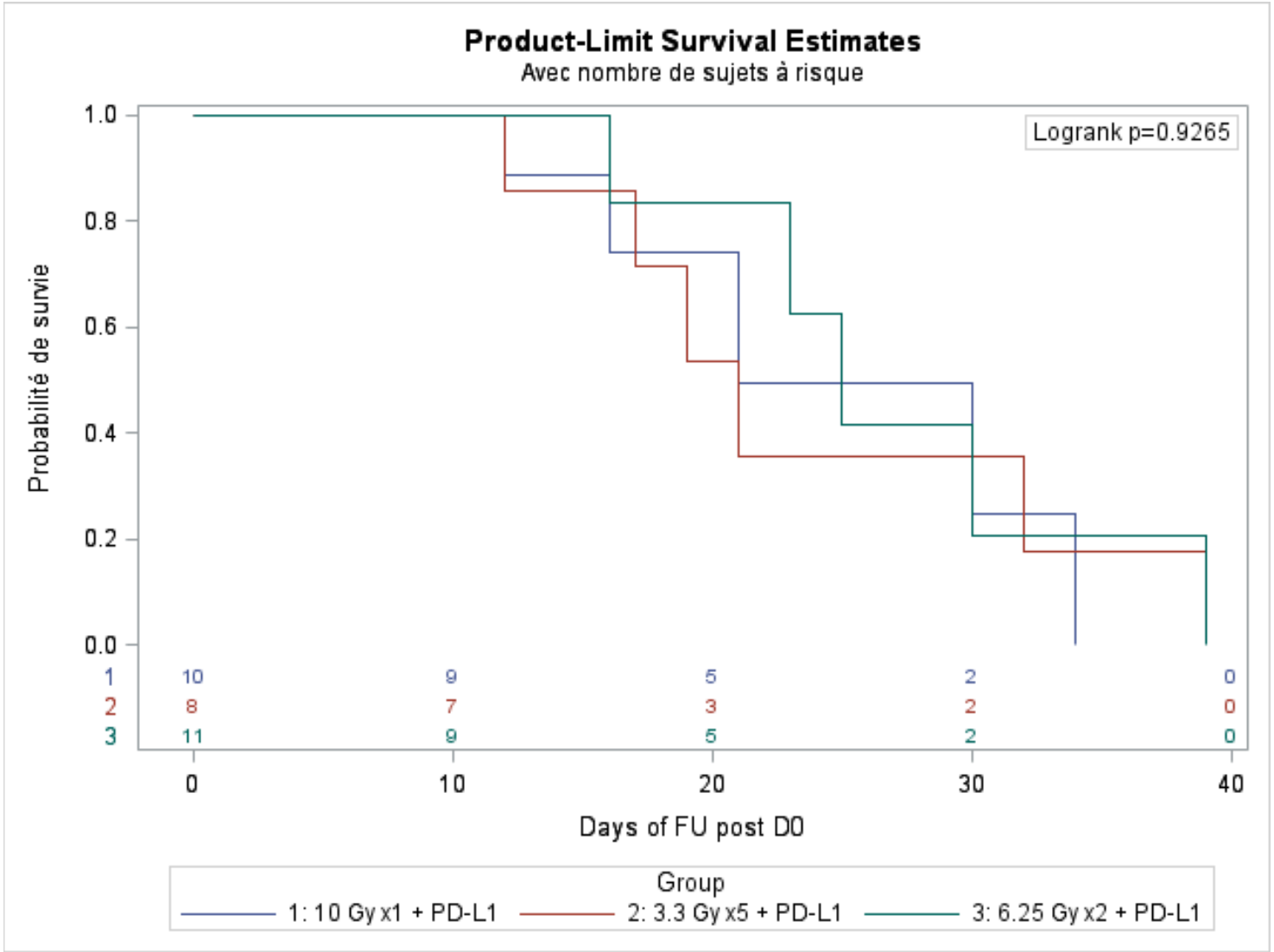


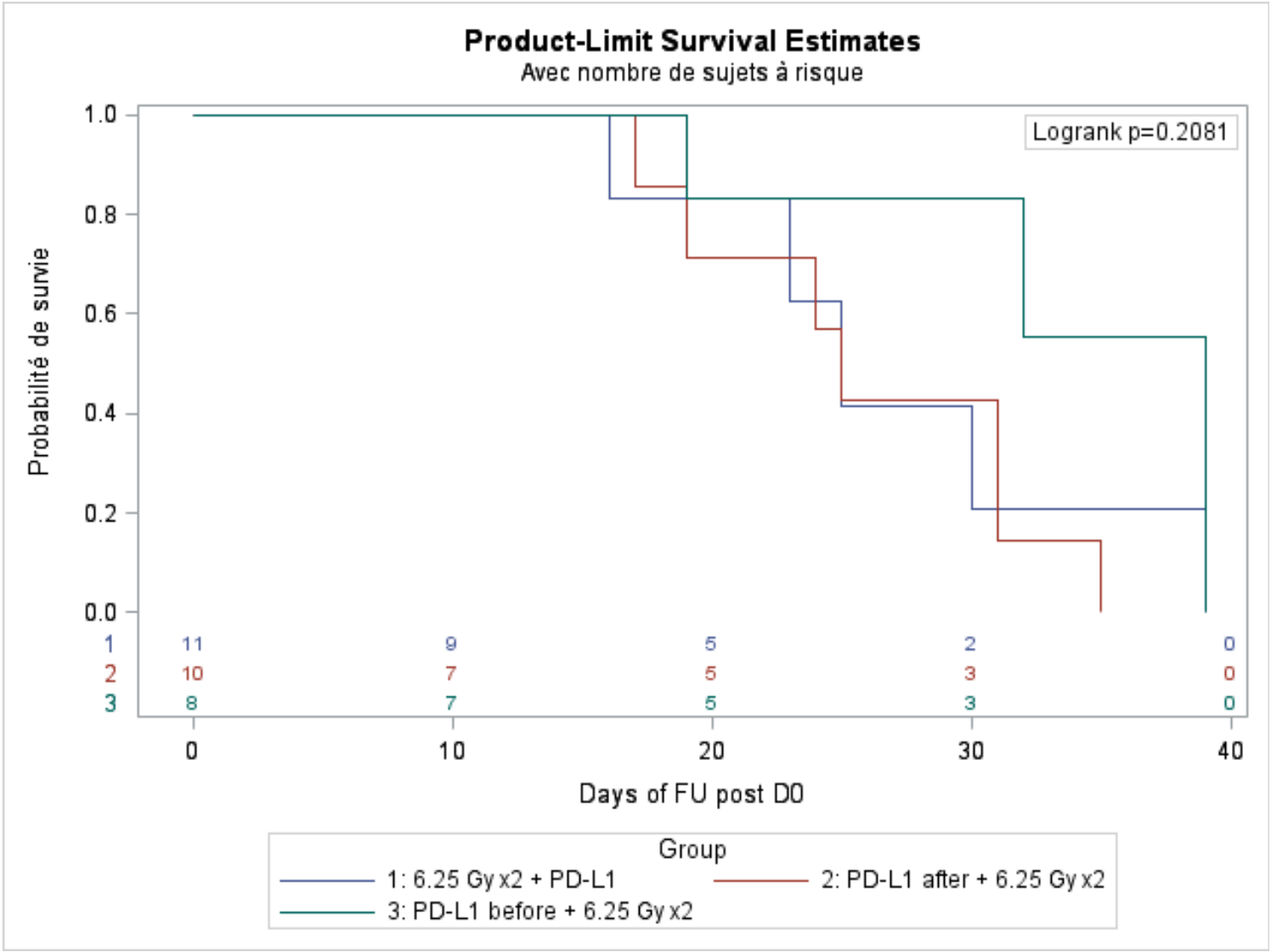

Tumor Growth
p=0.2159
Tumor Volume (cm3)
Days post treatment
y = 0,1233e0,2791x
R² = 0,9584
y = 0,145e0,237x
R² = 0,8959
y = 0,1174e0,2416x
R² = 0,938
10 Gy x1
3.3 Gy x5
6.25 Gy x2
Expon. (10 Gy x1)
Expon. (3.3 Gy x5)
Expon. (6.25 Gy x2)

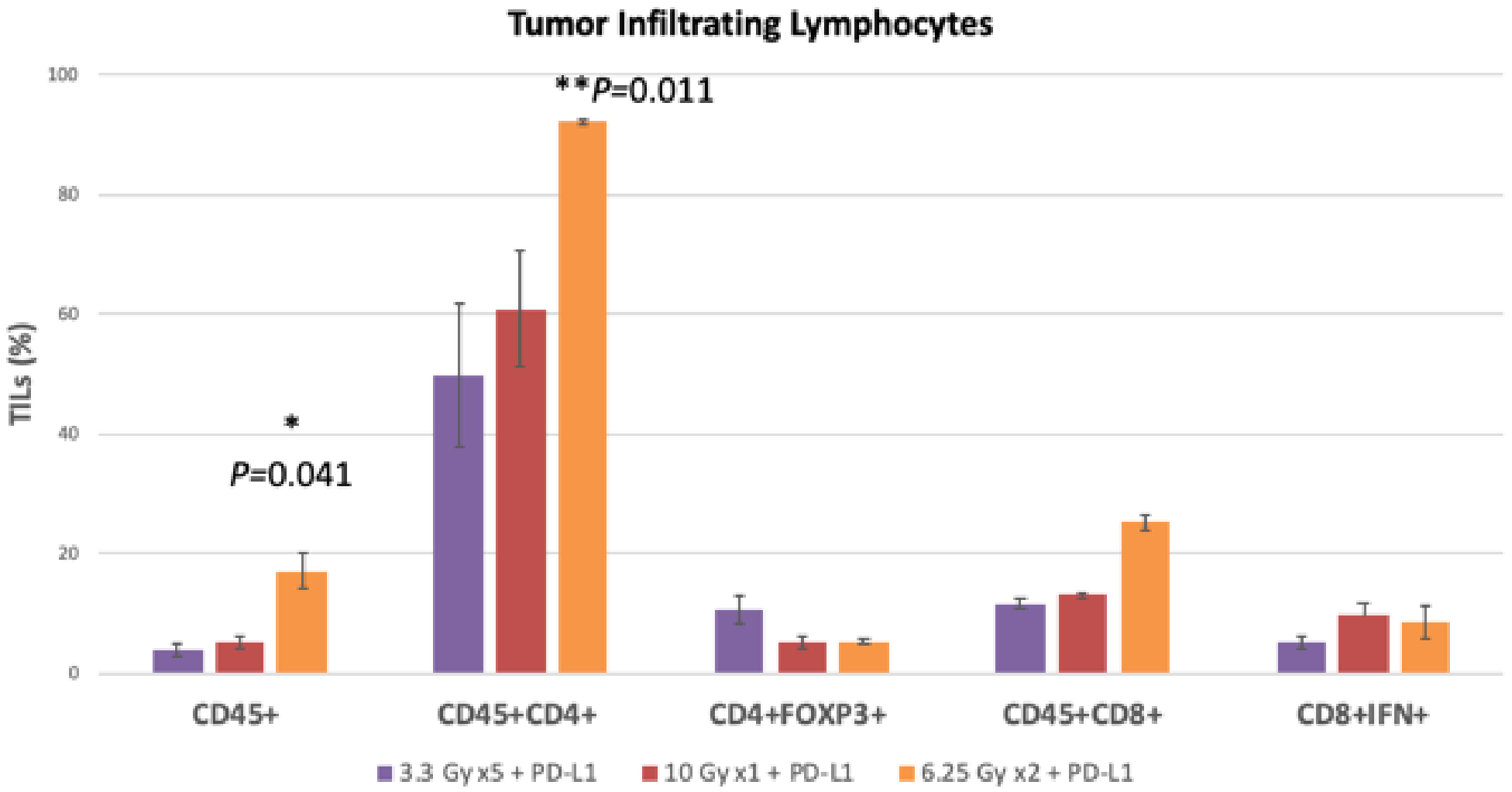


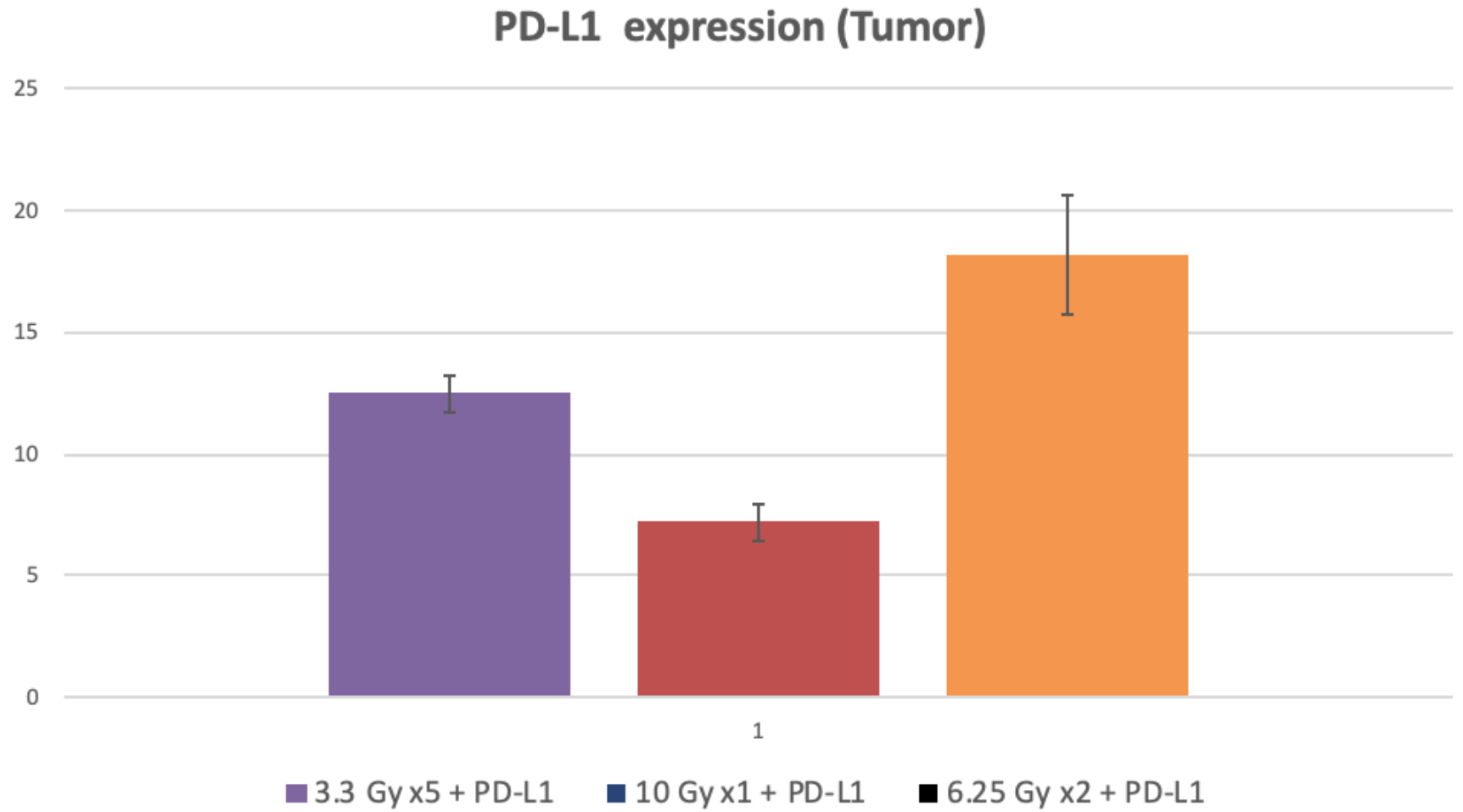



Product-Limit Survival Estimates
Avec nombre de sujets à risque
Logrank p=0.0479
Probabilité de survie
1.0
0.8
0.6
0.4
0.2
0.0
10 Gy x1 10 9 0
3.3 Gy x5 10 10 5 2 0
6.25 Gy x2 9 9 3 2 0
0
10
20
30
40
Days of FU post D0
Group 10 Gy x1 3.3 Gy x5 6.25 Gy x2


Product-Limit Survival Estimates
Avec nombre de sujets à risque
Logrank p=0.9265
Probabilité de survie
1.0
0.8
0.6
0.4
0.2
0.0
1 10 9 5 2 0
2 8 7 3 2 0
3 11 9 5 2 0
0
10
20
30
40
Days of FU post D0
Group
1: 10 Gy x1 + PD-L1
2: 3.3 Gy x5 + PD-L1
3: 6.25 Gy x2 + PD-L1


Product-Limit Survival Estimates
Avec nombre de sujets à risque
Logrank p=0.2081
Probabilité de survie
1.0
0.8
0.6
0.4
0.2
0.0
1 11 9 5 2 0
2 10 7 5 3 0
3 8 7 5 3 0
0
10
20
30
40
Days of FU post D0
Group
1: 6.25 Gy x2 + PD-L1
2: PD-L1 after + 6.25 Gy x2
3: PD-L1 before + 6.25 Gy x2




PD-L1 expression (Tumor)
25
20
15
10
5
0
1
3.3 Gy x5 + PD-L1
10 Gy x1 + PD-L1
6.25 Gy x2 + PD-L1

Discussion

- Ongoing clinical trials on immunotherapy combined with TMT
  - Concurrent atezolizumab or pembrolizumab
  - Neoadjuvant durvalumab
  - Adjuvant durvalumab

TMT: Trimodal therapy

Discussion

- Ongoing clinical trials on immunotherapy combined with TMT
- PLUMMB trial: concurrent combination therapy
  - Pembrolizumab + concurrent radiotherapy (6 Gy x6 fractions)
  - Significant toxicity → trial was paused and protocol will be amended

TMT: Trimodal therapy

Discussion

- Ongoing clinical trials on immunotherapy combined with TMT
- PLUMMB trial: concurrent combination therapy
- Adjuvant setting: decreasing toxicity, improving safety profile, maintaining efficacy – avoid interruption of TMT

TMT: Trimodal therapy

Conclusion

- Combination of anti-PD-L1 immunotherapy and radiation therapy offers **optimal antitumoral** responses
  - Hypo-fractionation regimen appears to be superior
- Timing of immunotherapy (neoadjuvant, concurrent or adjuvant) does not appear to modify this added benefit

Conclusion

- Optimize sequence of combination therapy and fractionation of radiation
  → **Minimize toxicity** while **maximizing clinical benefit**
- Ongoing clinical trials and pre-clinical studies would be beneficial to improve tumor control

References

1. Shaverdian N, Lisberg AE, Bornazyan K, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. Lancet Oncol 2017;18(7):895-903.
2. Antonia SJ, Villegas A, Daniel D, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl J Med 2018;379(24):2342-50.
3. Kiess AP, Wolchok JD, Barker CA, et al. Stereotactic radiosurgery for melanoma brain metastases in patients receiving ipilimumab: safety profile and efficacy of combined treatment. *Int J Radiat Oncol Biol Phys* 2015;92(2):368-75.
4. Solanki AA, Bossi A, Efstathiou JA, et al. Combining Immunotherapy with Radiotherapy for the Treatment of Genitourinary Malignancies. Eur Urol Oncol 2019;2(1):79-87.
5. Rompre-Brodeur A, Shinde-Jadhav S, Ayoub M, et al. PD-1/PD-L1 Immune Checkpoint Inhibition with Radiation in Bladder Cancer: In Situ and Abscopal Effects. Mol Cancer Ther 2020;19(1):211-20.