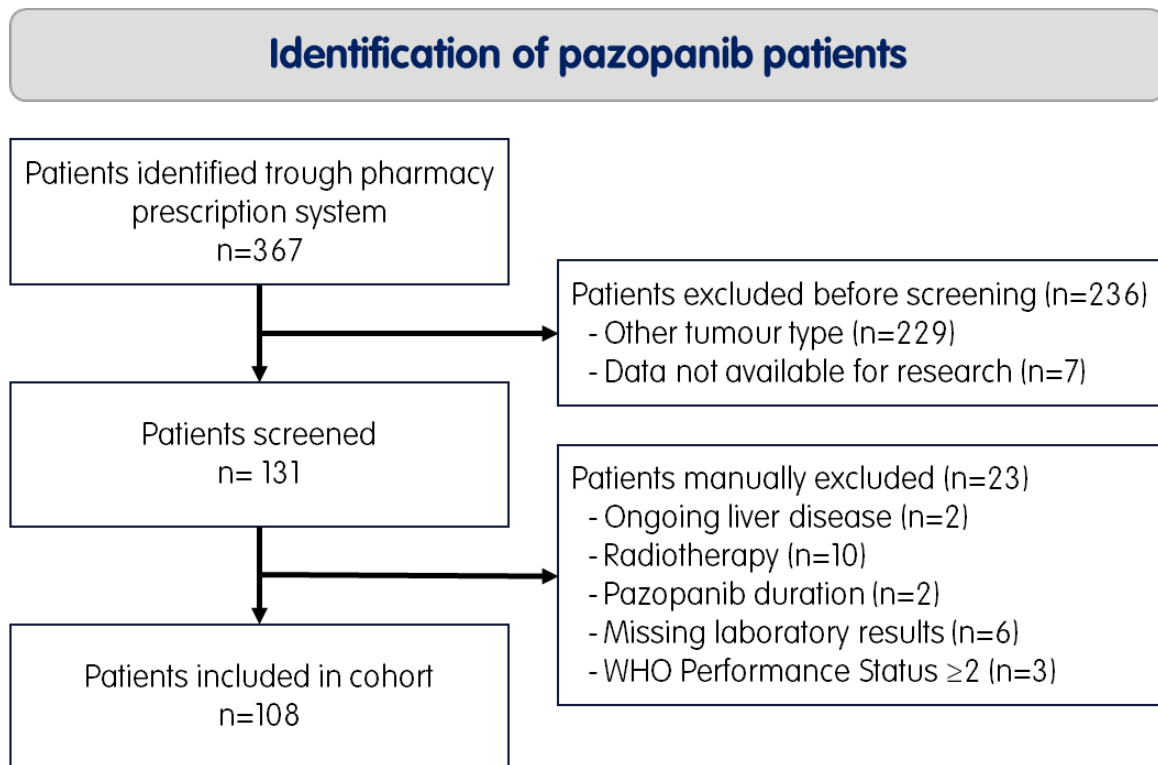


# The Impact of Pazopanib and Extremity Radiotherapy on Transaminase Elevations

## Supplementary tables and Figures

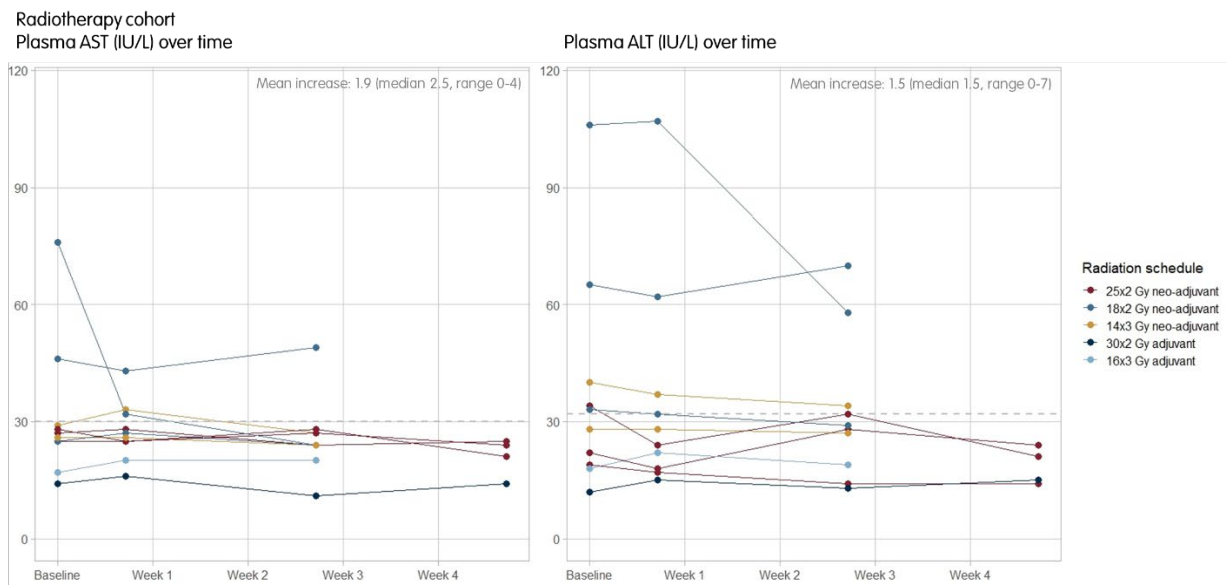
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**Supplementary Figure 1. Flow diagram of patient selection pazopanib cohort**



Supplementary Figure 1. Flow chart of patient identification and selection pazopanib monotherapy (PAZ) cohort.

## Supplementary Figure 2. Plasma transaminases over time radiotherapy cohort



Supplementary Figure 2. Plasma AST and ALT levels over time in patients receiving radiotherapy. Horizontal dashed lines indicate thresholds for upper limit of normal.

AST, alanine aminotransferase; ALT, aspartate aminotransferase

## Supplementary Table 1. Multivariate logistic regression grade ≥3 transaminase elevations

### Univariate logistic regression

| Covariate | Comparison    | N (grade ≥3 events) | Grade ≥3          |         |
|-----------|---------------|---------------------|-------------------|---------|
|           |               |                     | OR (95% CI)       | p-value |
| Treatment | PAZ+RT vs PAZ | 36 (13) vs 108 (7)  | 8.16 (3.01–23.92) | <0.001  |

### Multivariate logistic regression

| Covariate                                    | Comparison    | N (grade ≥3 events) | Grade ≥3          |         |
|----------------------------------------------|---------------|---------------------|-------------------|---------|
|                                              |               |                     | OR (95% CI)       | p-value |
| Treatment                                    | PAZ+RT vs PAZ | 24 (9) vs 87 (7)    | 5.44 (1.66–18.24) | 0.005   |
| Pazopanib geometric mean C <sub>trough</sub> | per 10 mg/L   | 111 (16)            | 1.34 (1.02–1.82)  | 0.045   |

**Supplementary Table 2. Clinical characteristics of patients with grade  $\geq 3$  transaminase elevations**

| Cohort | Treatment & exposure |                                       |                            | Toxicity Grade $\geq 3$ |     | Patient characteristics |        |        |            |                  | Normal baseline laboratory liver parameters <sup>a</sup> |            |                          |               | Co medication |                            | Toxicity markers                          |          |
|--------|----------------------|---------------------------------------|----------------------------|-------------------------|-----|-------------------------|--------|--------|------------|------------------|----------------------------------------------------------|------------|--------------------------|---------------|---------------|----------------------------|-------------------------------------------|----------|
|        | Pazopanib dose (mg)  | Radiotherapy schedule (fraction x Gy) | C <sub>trough</sub> (mg/L) | AST                     | ALT | Age (years)             | Sex    | WHO PS | Tumor site | Liver metastases | AST (IU/L)                                               | ALT (IU/L) | Bilirubin ( $\mu$ mol/L) | Albumin (g/L) | NSAID         | Gastric suppressive agents | Notable inflammatory markers <sup>b</sup> | Hy's law |
| PAZ    | 800                  | NA                                    | 41                         | No                      | Yes | 79                      | Female | 0-1    | Thorax     | No               | Yes                                                      | Yes        | Yes                      | Yes           | No            | No                         | No                                        | No       |
| PAZ    | 400                  | NA                                    | 27                         | No                      | Yes | 71                      | Female | 0-1    | Abdomen    | Yes              | Yes                                                      | Yes        | Yes                      | Yes           | No            | No                         | No                                        | No       |
| PAZ    | 800                  | NA                                    | 63                         | No                      | Yes | 64                      | Female | 0-1    | Abdomen    | Yes              | Yes                                                      | Yes        | Yes                      | Yes           | Yes           | No                         | No                                        | No       |
| PAZ    | 800                  | NA                                    | 44                         | Yes                     | Yes | 43                      | Male   | 0-1    | Abdomen    | Yes              | No (47)                                                  | No (35)    | Yes                      | Yes           | No            | Yes                        | No                                        | No       |
| PAZ    | 800                  | NA                                    | 51                         | Yes                     | Yes | 61                      | Female | 0-1    | Abdomen    | No               | No (54)                                                  | No (50)    | Yes                      | Yes           | Yes           | No                         | No                                        | No       |
| PAZ    | 800                  | NA                                    | 17                         | Yes                     | Yes | 73                      | Female | 0-1    | Abdomen    | No               | No (37)                                                  | Yes        | Yes                      | Yes           | No            | No                         | No                                        | No       |
| PAZ    | 800                  | NA                                    | 47                         | Yes                     | Yes | 75                      | Male   | 0-1    | Abdomen    | Yes              | Yes                                                      | Yes        | Yes                      | Yes           | No            | No                         | No                                        | No       |
| PAZ+RT | 800                  | 25x2                                  | 121                        | No                      | Yes | 39                      | Female | 0-1    | Extremity  | No               | Yes                                                      | Yes        | Yes                      | Yes           | No            | No                         | No                                        | No       |
| PAZ+RT | 800                  | 25x2                                  | 24                         | No                      | Yes | 44                      | Male   | 0-1    | Extremity  | No               | Yes                                                      | Yes        | Yes                      | Yes           | No            | No                         | No                                        | No       |
| PAZ+RT | 800                  | 25x2                                  | 47                         | Yes                     | Yes | 72                      | Female | 0-1    | Extremity  | No               | Yes                                                      | Yes        | Yes                      | Yes           | No            | No                         | No                                        | No       |
| PAZ+RT | 800                  | 25x2                                  | 31                         | Yes                     | Yes | 61                      | Male   | 0-1    | Extremity  | No               | Yes                                                      | Yes        | Yes                      | Yes           | No            | No                         | No                                        | No       |
| PAZ+RT | 800                  | 25x2                                  | 92                         | Yes                     | Yes | 50                      | Female | 0-1    | Extremity  | No               | Yes                                                      | Yes        | Yes                      | Yes           | Yes           | No                         | No                                        | No       |
| PAZ+RT | 800                  | 25x2                                  | NA                         | Yes                     | Yes | 61                      | Male   | 0-1    | Extremity  | No               | Yes                                                      | Yes        | Yes                      | Yes           | No            | No                         | No                                        | No       |
| PAZ+RT | 800                  | 25x2                                  | 30                         | Yes                     | Yes | 53                      | Female | 0-1    | Thorax     | No               | Yes                                                      | Yes        | Yes                      | Yes           | No            | No                         | No                                        | No       |
| PAZ+RT | 800                  | 18x2                                  | 42                         | Yes                     | Yes | 71                      | Female | 0-1    | Extremity  | No               | Yes                                                      | No (51)    | Yes                      | Yes           | No            | No                         | No                                        | No       |
| PAZ+RT | 600                  | 25x2                                  | NA                         | Yes                     | Yes | 74                      | Male   | 0-1    | Extremity  | No               | Yes                                                      | Yes        | Yes                      | Yes           | No            | No                         | No                                        | No       |
| PAZ+RT | 800                  | 25x2                                  | NA                         | Yes                     | Yes | 78                      | Female | 0-1    | Extremity  | No               | Yes                                                      | Yes        | Yes                      | Yes           | No            | No                         | No                                        | No       |
| PAZ+RT | 800                  | 25x2                                  | 56                         | Yes                     | Yes | 71                      | Female | 0-1    | Extremity  | No               | Yes                                                      | Yes        | Yes                      | Yes           | Yes           | No                         | No                                        | No       |
| PAZ+RT | 600                  | 25x2                                  | NA                         | Yes                     | Yes | 60                      | Male   | 0-1    | Thorax     | No               | Yes                                                      | Yes        | Yes                      | Yes           | No            | No                         | No                                        | No       |
| PAZ+RT | 800                  | 25x2                                  | 55                         | Yes                     | Yes | 55                      | Male   | 0-1    | Extremity  | No               | Yes                                                      | No (43)    | Yes                      | Yes           | No            | No                         | No                                        | No       |

AST, aspartate aminotransferase; ALT, alanine aminotransferase; C<sub>trough</sub>, geometric mean pazopanib trough level; Gy, Gray; PAZ, pazopanib; PAZ+RT pazopanib + radiotherapy (PASART); WHO PS, World Health Organization performance status; NA, not applicable.

<sup>a</sup> Normal baseline laboratory parameters indicate laboratory values within the upper limit of normal at baseline, abnormal values are provide in parenthesis.

<sup>b</sup> Inflammatory markers include leukocytes and other notable inflammatory markers when available