# Second-line VEGF TKI after IO Combination Therapy:
## Results from the International mRCC Database Consortium (IMDC)

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## Background

- In metastatic renal cell carcinoma (mRCC), several first-line (1L) immuno-oncology (IO) combination therapies were shown to improve outcomes in comparison to Sunitinib monotherapy.
- Combined checkpoint inhibition with ipilimumab and nivolumab (IOIO) is a 1L treatment option for mRCC.
- Recent studies have shown various 1L PD(L)1-VEGF (IOVE) inhibitor combinations to be efficacious.
- Data on second-line (2L) therapy with vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (TKI) post-progression on IO-combination therapy are limited.

## Methods

- Using the IMDC dataset, we identified patients treated with 2L VEGF TKIs after receiving 1L IO combination therapy with either IOIO or IOVE.
- We compared the outcomes between the two groups.
  – Patients treated as part of a clinical trial were permitted for inclusion.
- Outcome measures of interest were:
  – 2L Overall Response Rate (ORR)
  – 2L Time to treatment failure (TTF)
  – 2L Overall survival (OS)
- Multivariable Cox regression analysis was performed to control for imbalances in IMDC risk factors.

## Results

- 142 patients with mRCC received 2L VEGF TKI after 1L IO-combination therapy

- 75 patients treated with 1L IOIO
  – Subsequent 2L VEGF inhibitors: 39 Sunitinib, 10 Cabozantinib, 4 Axitinib, 20 Pazopanib, 2 Lenvantinib + Everolimus

- 67 patients treated with 1L IOVE: IO (Nivolumab, Atezolizumab, Avelumab or Pembrolizumab) + VEGF (Bevacizumab, Sunitinib, Cabozantinib, Axitinib, Pazopanib or Lenvantinib + Everolimus) combinations
  – Subsequent 2L VEGF inhibitors: 22 Sunitinib, 21 Cabozantinib, 8 Axitinib, 6 Pazopanib, 10 Lenvantinib + Everolimus

### Table 1: Baseline Characteristics and IMDC Risk Factors

| | Post-IOIO (N=75) | Post-IOVE (N=67) | P-value |
|---|---|---|---|
| Age, median (IQR) | 58 (45-71) | 59 (45-73) | 0.68 |
| Male | 59/75 (79%) | 52/67 (78%) | 0.88 |
| ccRCC | 60/64 (94%) | 62/67 (93%) | 0.78 |
| Sarcomatoid features | 12/49 (24%) | 11/63 (17%) | 0.36 |
| **IMDC Risk Groups** | | | 0.86 |
| Favorable | 8/58 (14%) | 9/57 (16%) | |
| Intermediate | 30/58 (52%) | 31/57 (54%) | |
| Poor | 20/58 (34%) | 17/57 (30%) | |
| **IMDC Risk Factors** | | | |
| KPS < 80 | 21/67 (31%) | 12/63 (19%) | 0.11 |
| Diagnosis to therapy < 1 yr | 49/74 (66%) | 48/67 (72%) | 0.49 |
| Calcium > ULN | 10/61 (16%) | 7/59 (12%) | 0.48 |
| Hemoglobin < LLN | 37/69 (54%) | 30/65 (46%) | 0.39 |
| Neutrophils > ULN | 16/69 (23%) | 12/65 (18%) | 0.50 |
| Platelets > ULN | 10/69 (14%) | 14/65 (22%) | 0.29 |

### Table 2: Outcomes for 2L VEGF TKI after IO Combination Therapy

| | Post-IOIO (N=67) | Post-IOVE (N=63) | P-value |
|---|---|---|---|
| **Objective Response Rate** | 37% | 12% | |
| **Best Response** | | | <0.01 |
| CR | 1/46 (2%) | 0/57 (0%) | |
| PR | 16/46 (35%) | 7/57 (12%) | |
| SD | 20/46 (43%) | 31/57 (54%) | |
| PD | 9/46 (20%) | 19/57 (33%) | |
| **Time to Treatment Failure (months)** | 5.4 (4.1 – 8.3) | 4.6 (3.7 – 5.8) | 0.37 |
| **Overall Survival (months)** | 17.2 (10.8 – 35.1) | 11.8 (9.9 – 21.3) | 0.13 |
| **Hazard Ratios adjusted by IMDC Criteria** | | | |
| **Time to Treatment Failure** | 1.22 (0.73 – 2.07) | | 0.45 |
| **Overall Survival** | 1.43 (0.74 – 2.8) | | 0.29 |

### Figure 1: 2L Overall Survival



IOIO (N=67): 17.2 months (95% CI 10.8 – 35.1)
IOVE (N=63): 11.8 months (95% CI 9.9 – 21.3)
P = 0.13
Adjusted HR: 1.43 (95% CI 0.74 – 2.8; P = 0.29)

### Figure 2: 2L Time to Treatment Failure



IOIO (N=67): 5.4 months (95% CI 4.1 – 8.3)
IOVE (N=63): 4.6 months (95% CI 3.7 – 5.8)
P = 0.37
Adjusted HR: 1.22 (95% CI 0.73 – 2.07; P = 0.45)
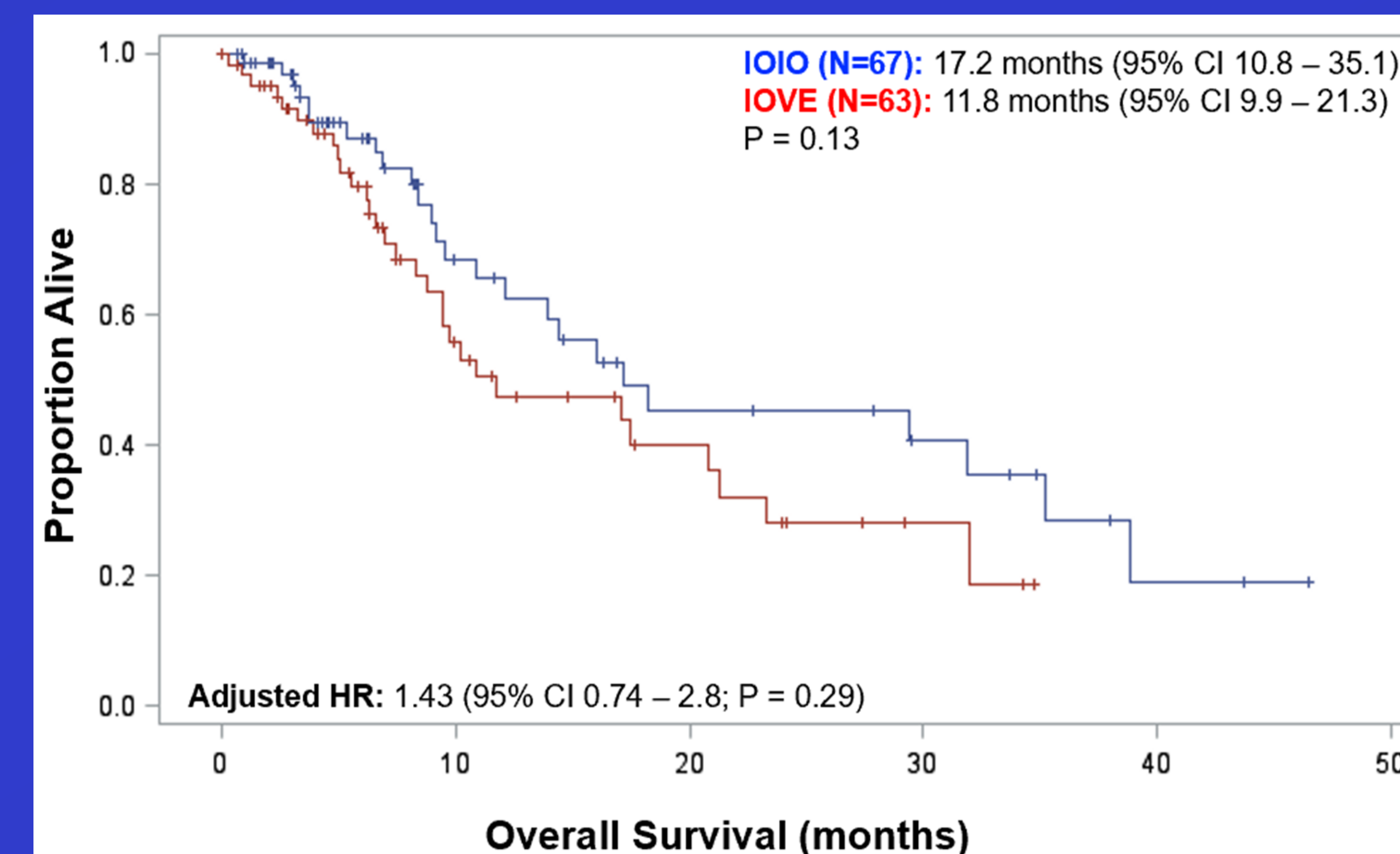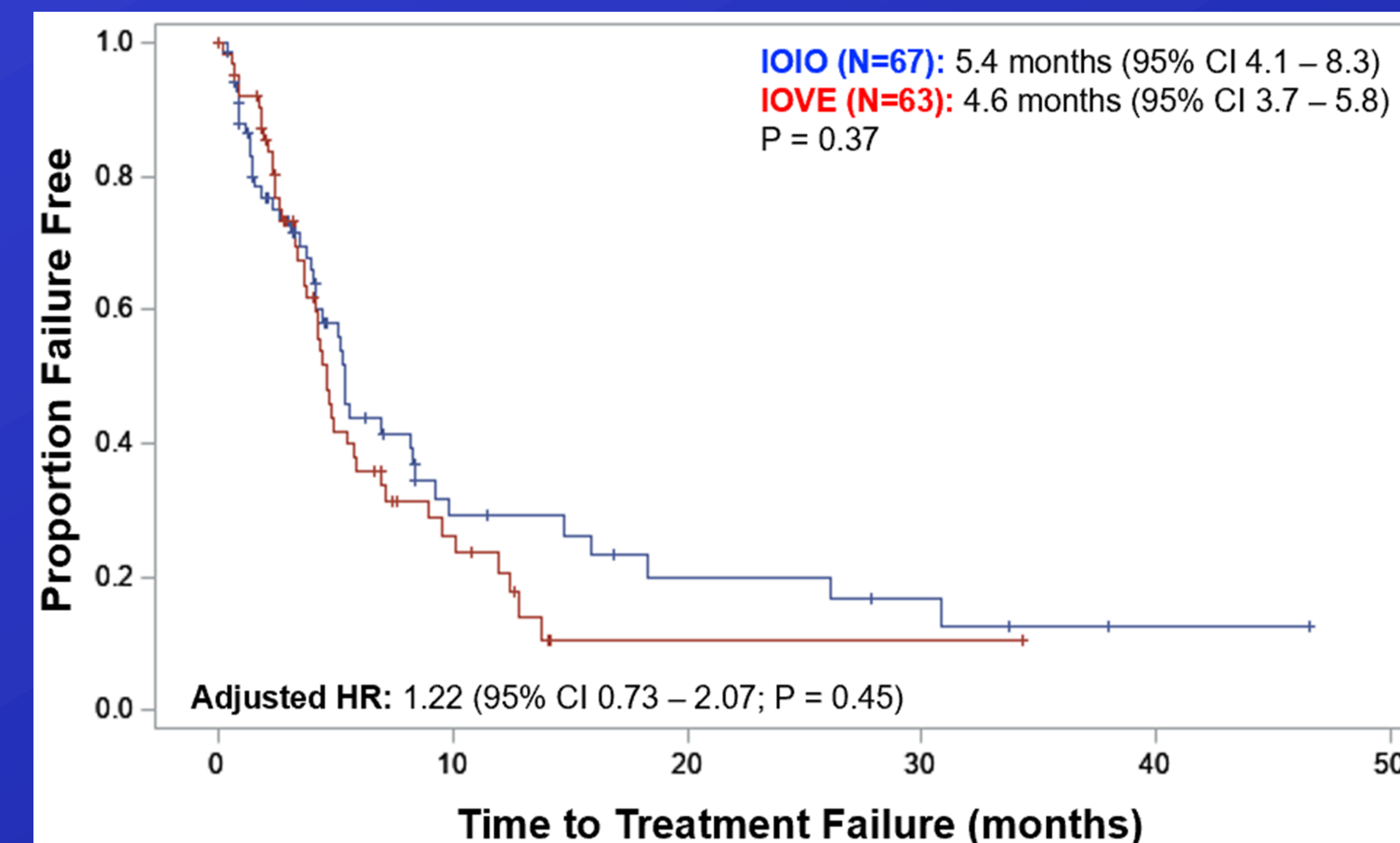
## Conclusions

- 2L VEGF TKIs show activity after 1L combination IO therapy.
- Response rates are higher in patients treated with 2L VEGF TKIs after 1L IOIO compared to after 1L IOVE.
- In patients with 2L VEGF TKI after 1L IOIO or 1L IOVE, no difference in OS and TTF was observed.