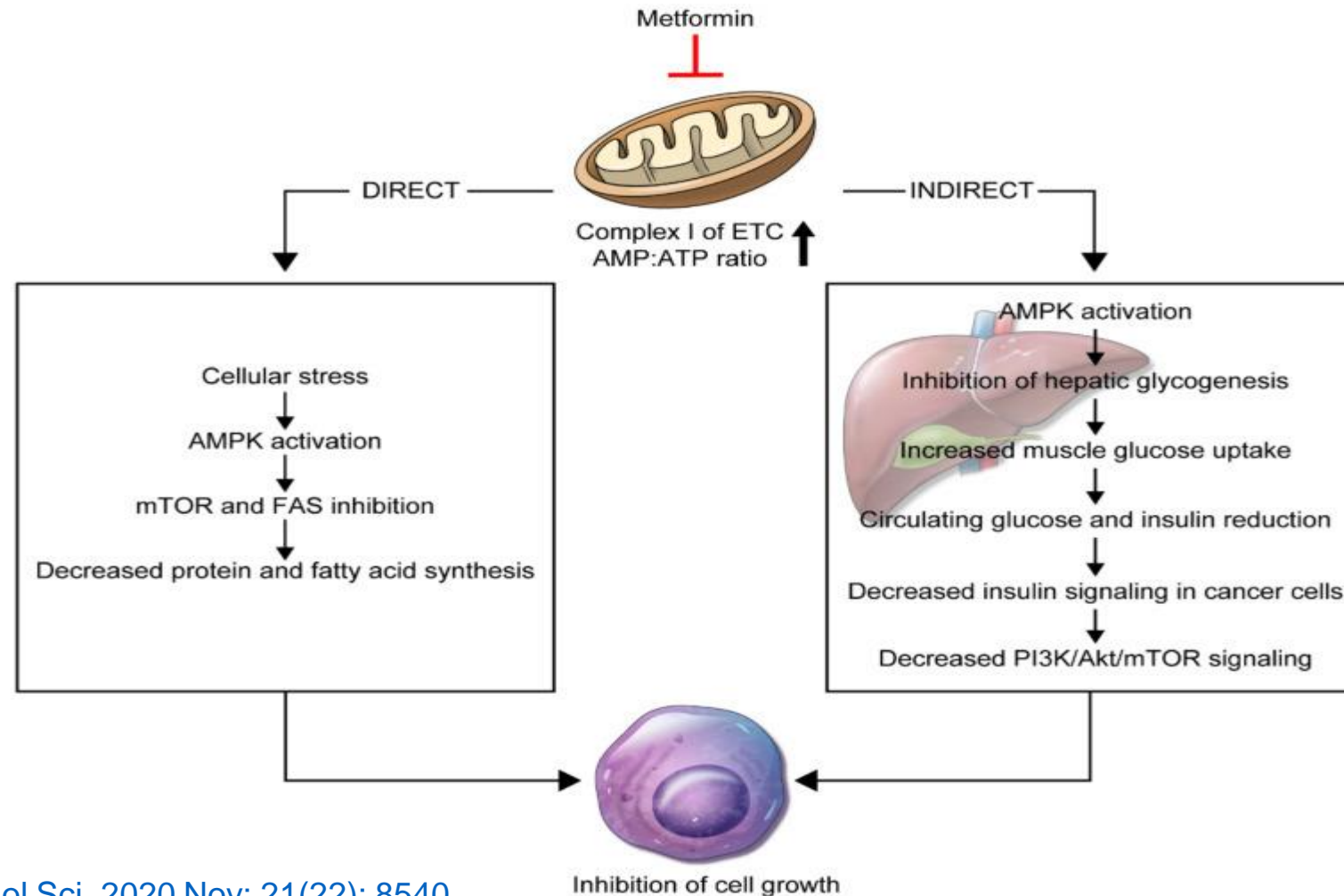


# Is there a Role for Metformin in Prostate Cancer Treatment?

Brian Mannion, MD  
Medical Oncologist  
The Christ Hospital Health Network

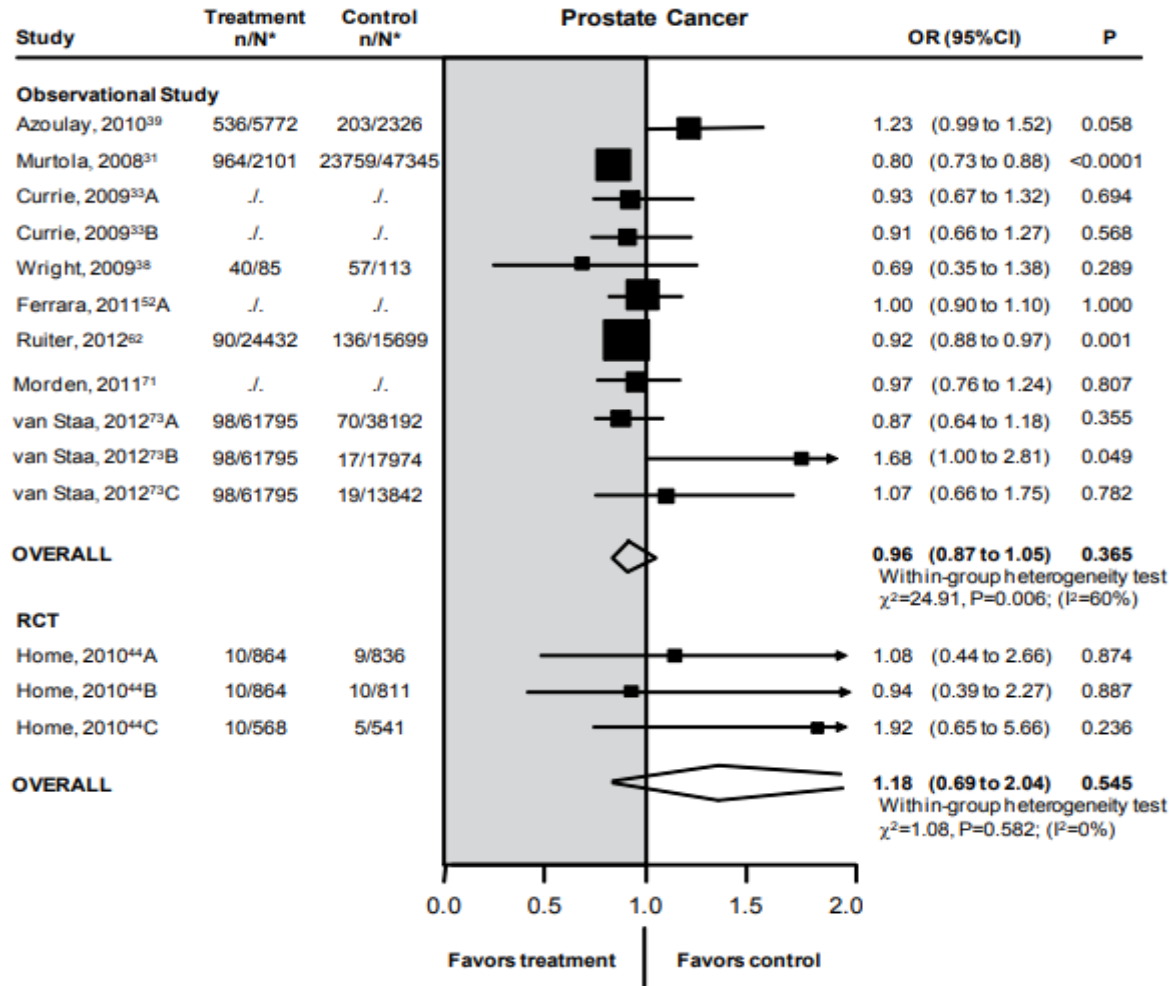
26 June 2024

# Potential Benefit of Using Metformin in Cancer Treatment



# Metformin Therapy and Risk of Cancer in Patients with Type 2 Diabetes: Systematic Review

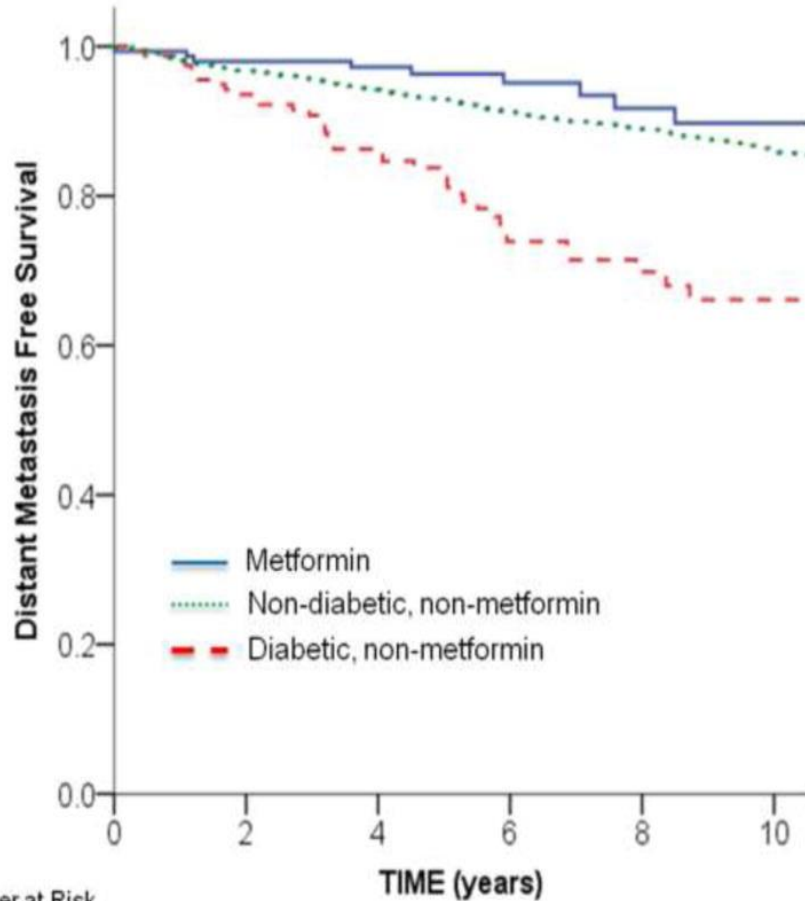
**Figure S5: Prostate cancer: results of Meta-analyses based on 8 observational studies (521667 patients) and 2 RCTs (3620 patients)**



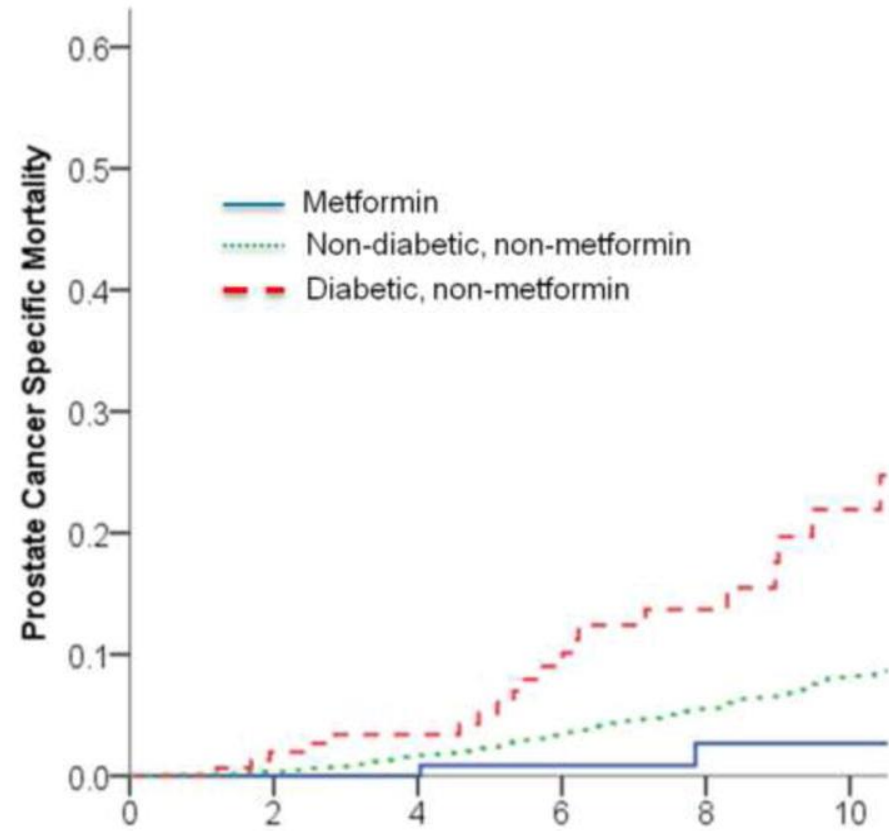
\*Number of events and total patients per arm where reported when available from the original articles

# Metformin and Prostate Cancer: Benefit for Development of Castration-resistant Disease and Prostate Cancer Mortality

[Daniel E. Spratt](#),<sup>1</sup> [Chi Zhang](#),<sup>2</sup> [Zachary S. Zumsteg](#),<sup>1</sup> [Xin Pei](#),<sup>1</sup> [Zhigang Zhang](#),<sup>3</sup> and [Michael J. Zelefsky](#)<sup>1,\*</sup>

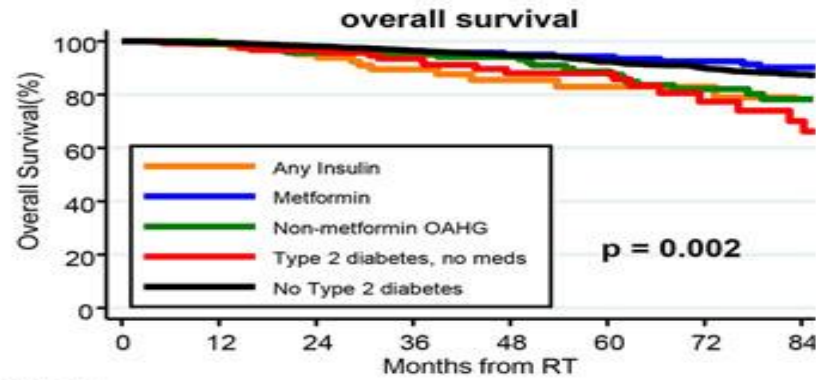


| Number at Risk                |      | TIME (years) |      |      |     |    |
|-------------------------------|------|--------------|------|------|-----|----|
|                               | 0    | 2            | 4    | 6    | 8   | 10 |
| <b>Metformin</b>              | 138  | 114          | 79   | 50   | 21  |    |
| <b>Diabetic Non-metformin</b> | 138  | 105          | 64   | 41   | 25  |    |
| <b>Non-diabetic</b>           | 2340 | 1982         | 1523 | 1090 | 704 |    |

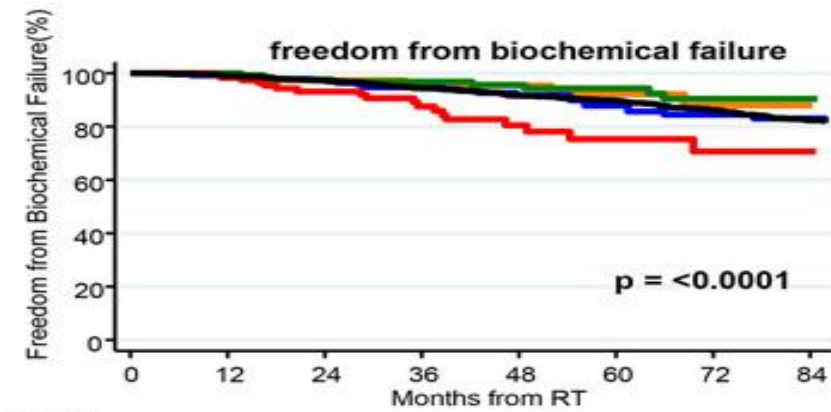


| Number at Risk                |      | TIME (years) |      |      |     |    |
|-------------------------------|------|--------------|------|------|-----|----|
|                               | 0    | 2            | 4    | 6    | 8   | 10 |
| <b>Metformin</b>              | 116  | 116          | 81   | 52   | 22  |    |
| <b>Diabetic Non-metformin</b> | 144  | 117          | 80   | 82   | 31  |    |
| <b>Non-diabetic</b>           | 2409 | 1982         | 2072 | 1179 | 776 |    |

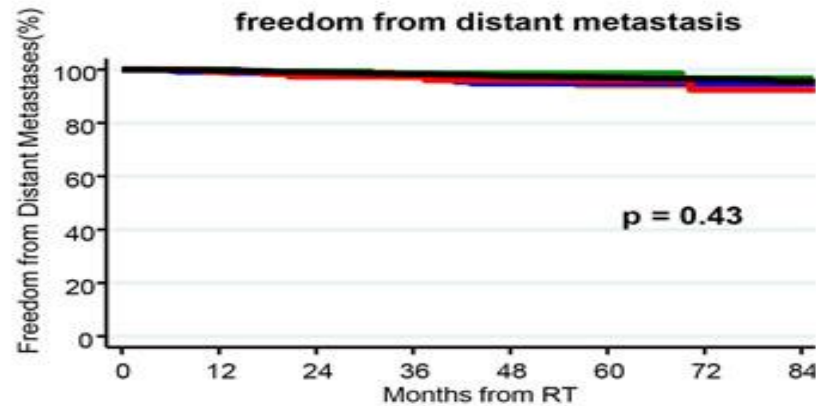
# Prostate cancer patients with unmanaged diabetes or on insulin have worse outcomes and toxicities after treatment with radiation therapy



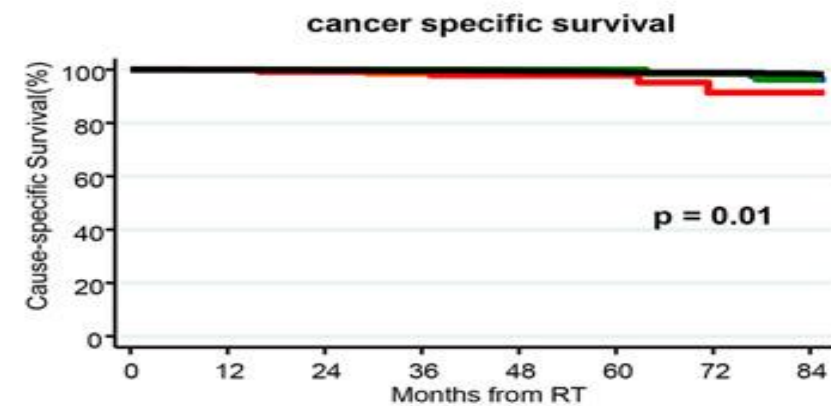
| N at risk   | 0    | 12   | 24   | 36   | 48   | 60   | 72  | 84 |
|-------------|------|------|------|------|------|------|-----|----|
| Insulin     | 89   | 85   | 73   | 54   | 36   | 29   | 22  | 16 |
| Metformin   | 251  | 246  | 218  | 181  | 132  | 113  | 88  | 70 |
| Oral DM med | 148  | 144  | 130  | 116  | 92   | 72   | 53  | 32 |
| Med Hx DM   | 126  | 119  | 103  | 80   | 54   | 41   | 24  | 18 |
| No Diab     | 2603 | 2512 | 2298 | 1932 | 1535 | 1235 | 947 | 69 |



| N at risk   | 0    | 12   | 24   | 36   | 48   | 60  | 72  | 84  |
|-------------|------|------|------|------|------|-----|-----|-----|
| Insulin     | 87   | 77   | 56   | 43   | 31   | 26  | 18  | 15  |
| Metformin   | 249  | 227  | 195  | 155  | 106  | 83  | 66  | 52  |
| Oral DM med | 147  | 132  | 116  | 98   | 72   | 56  | 41  | 32  |
| Med Hx DM   | 124  | 104  | 80   | 57   | 34   | 21  | 14  | 13  |
| No Diab     | 2584 | 2366 | 2039 | 1657 | 1218 | 939 | 668 | 471 |



| N at risk   | 0    | 12   | 24   | 36   | 48   | 60   | 72  | 84 |
|-------------|------|------|------|------|------|------|-----|----|
| Insulin     | 89   | 85   | 72   | 54   | 36   | 29   | 22  | 16 |
| Metformin   | 251  | 244  | 217  | 178  | 126  | 109  | 85  | 70 |
| Oral DM med | 148  | 144  | 130  | 116  | 92   | 72   | 52  | 32 |
| Med Hx DM   | 126  | 118  | 101  | 78   | 53   | 40   | 24  | 18 |
| No Diab     | 2603 | 2504 | 2280 | 1910 | 1511 | 1217 | 929 | 68 |



| N at risk   | 0    | 12   | 24   | 36   | 48   | 60   | 72  | 84  |
|-------------|------|------|------|------|------|------|-----|-----|
| Insulin     | 89   | 85   | 73   | 54   | 36   | 29   | 22  | 16  |
| Metformin   | 251  | 246  | 218  | 181  | 132  | 113  | 88  | 70  |
| Oral DM med | 148  | 144  | 130  | 116  | 92   | 72   | 53  | 32  |
| Med Hx DM   | 126  | 119  | 103  | 80   | 54   | 41   | 24  | 18  |
| No Diab     | 2603 | 2512 | 2298 | 1932 | 1535 | 1235 | 947 | 695 |

# Conclusions

- **Observational Studies** suggest possible protective effect of metformin in developing prostate cancer
- **Retrospective Studies** of Prostate Cancer Patients treated with radiation
  - One study (MSKCC) suggested metformin lowered recurrence risk
  - Second study (Fox Chase) suggested it was uncontrolled DM and not specifically metformin causing inferior outcomes
- What About **Prospective Trials**?
  - Combine it with ADT? With chemo? With enzalutamide?

# Metformin to treat prostate cancer (PCa) and prevent metabolic syndrome associated with androgen deprivation therapy (ADT): Results of a randomized double-blind placebo-controlled study of metformin in non-diabetic men initiating ADT for advanced PCa.

[Devalingam Mahalingam](#), [Hanni Salih](#), [Christos Fountzilas](#), [Joel Michalek](#), [John Sarantopoulos](#), [Paromita Datta](#), [Ofelia Romero](#), [Sureshkumar Mulampurat](#)  
[h Achutan Pillai](#), [John G. Kuhn](#), [Michael N. Pollak](#), and [Ian Murchie Thompson](#)

Publication: Journal of Clinical Oncology  
[Volume 35, Number 15\\_suppl](#)

**Results:** 36 men were randomized to metformin or placebo, mean age 68.4; 50% in MET and 53.3% in P cohort achieved undetectable PSA at wk 28; difference not statistically significant.

**Conclusions:** This study detected **no impact of metformin addition to ADT on the risk of metabolic syndrome and no additional anti-tumor effects.**

# The Effect of Metformin Use during Docetaxel Chemotherapy on Prostate Cancer Specific and Overall Survival of Diabetic Patients with Castration Resistant Prostate Cancer

The Journal of Urology  
Volume 197, Issue 4, April 2017, Pages 1068-1075

## Results

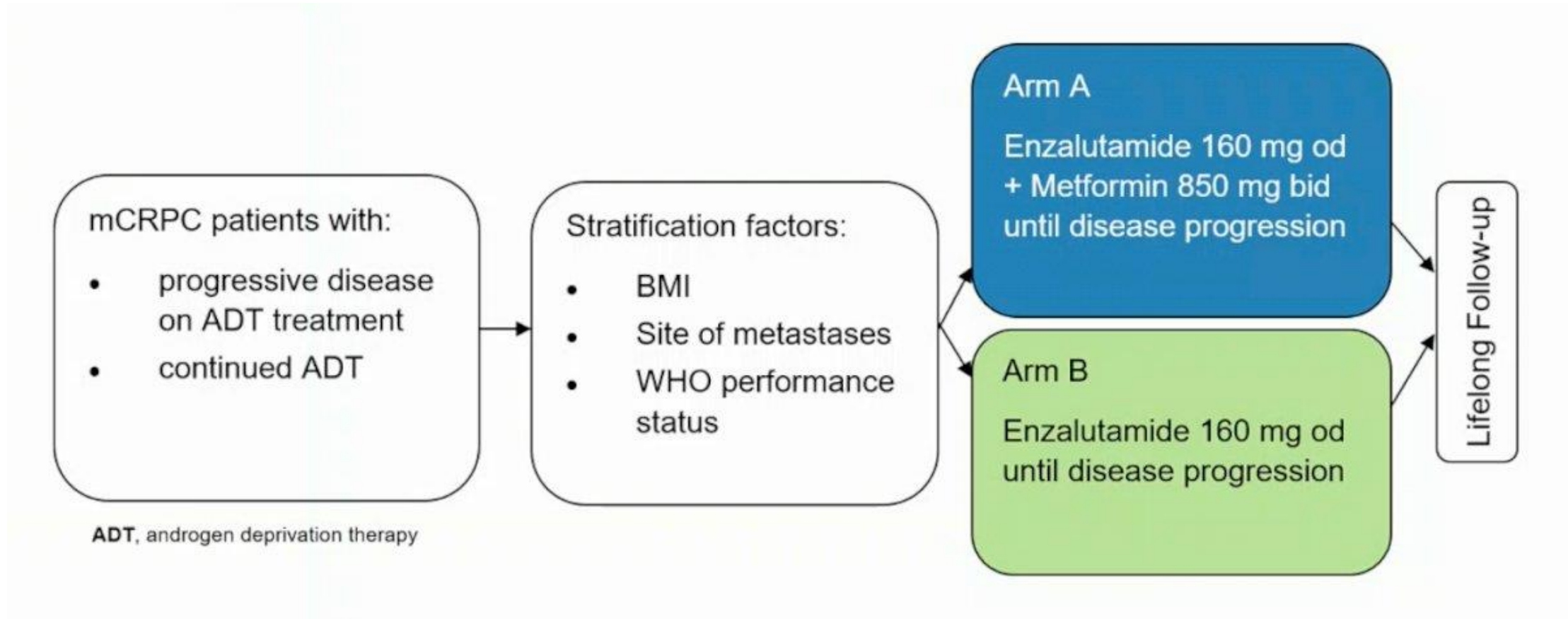
- Survival curves showed that metformin use with docetaxel did not improve prostate cancer specific survival ( $p = 0.9562$ ) or overall survival ( $p = 0.9927$ ).

## Conclusions

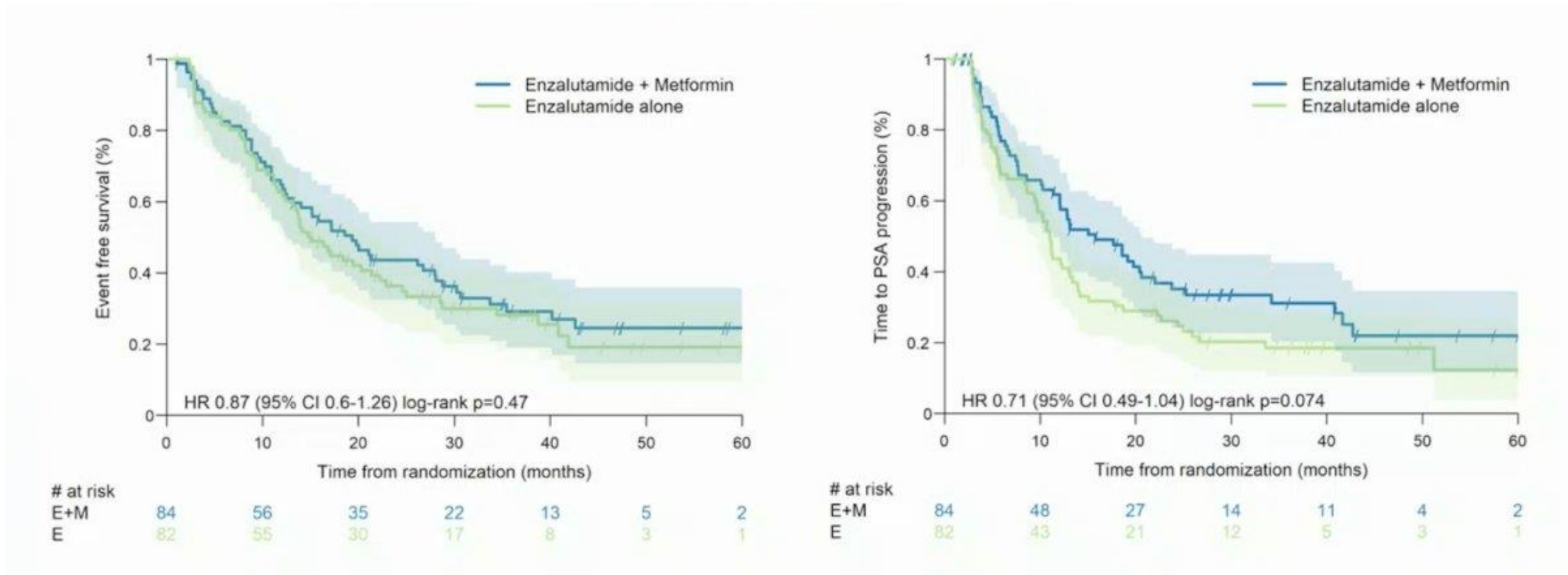
- Metformin use during docetaxel chemotherapy did not significantly improve prostate cancer specific or overall survival in diabetic patients with metastatic castration resistant prostate cancer.



# IMPROVE Investigation of Metformin in Patients with mCRPC in Combination with Enzalutamide Versus Enzalutamide Alone: A Randomized, Open Label, Phase II Trial



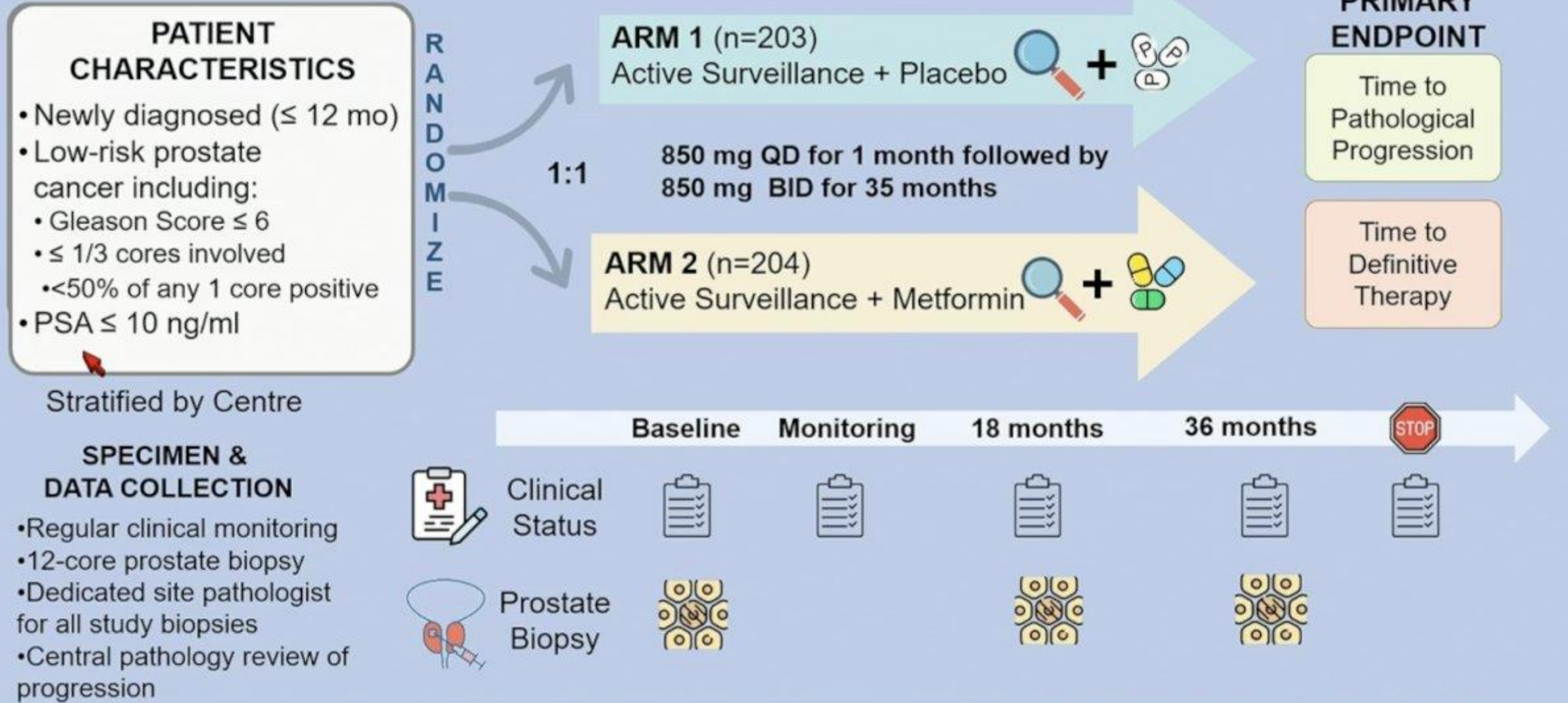
# IMPROVE Investigation of Metformin in Patients with mCRPC in Combination with Enzalutamide Versus Enzalutamide Alone: A Randomized, Open Label, Phase II Trial

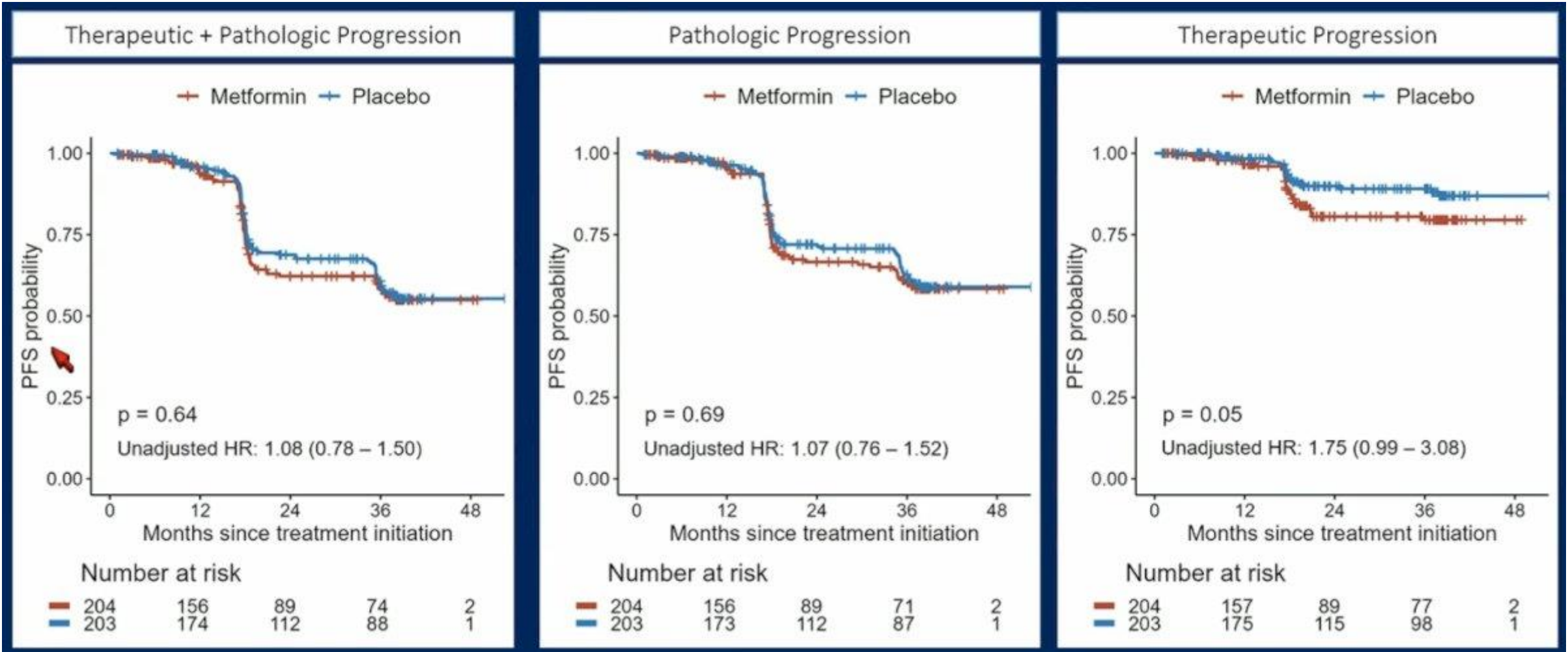


# Conclusions

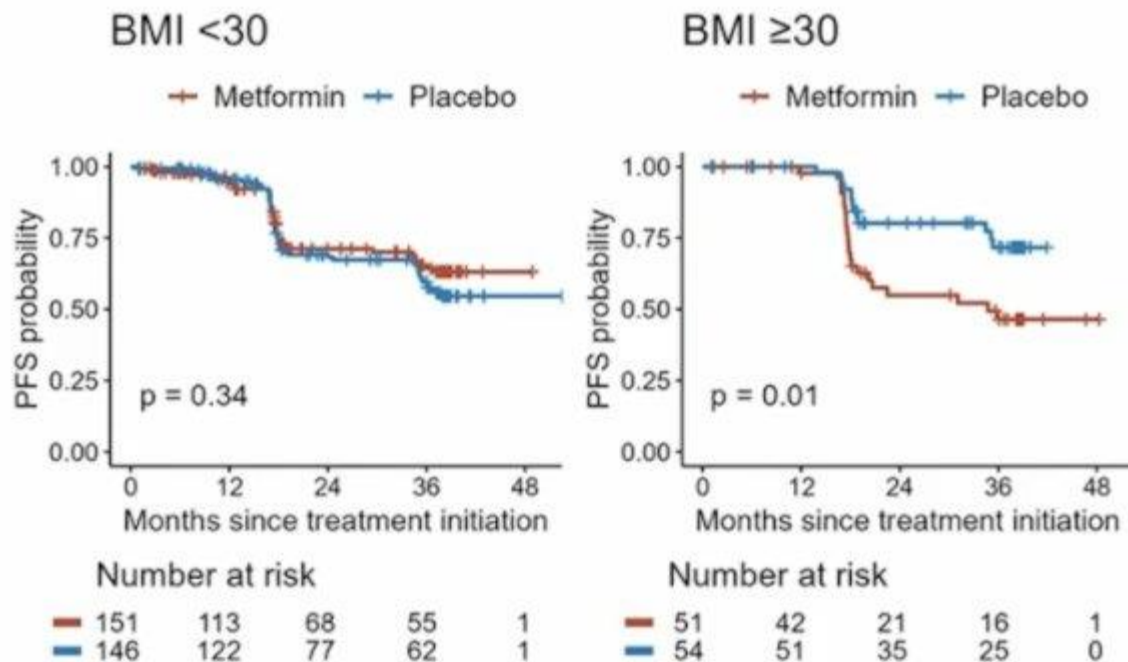
- In prospective trials, no clear benefit of metformin in **advanced disease**, including:
  - Castrate-sensitive disease, when added to ADT
  - Castrate resistant disease when added to docetaxel
  - Castrate resistant disease when added to enzalutamide
- Potential Role in **early disease**?
  - Any benefit in active surveillance population?

# Study Schema









- Previous meta-analysis has shown an inverse association between BMI and PSA:
  - Each 5 kg/m increase in BMI associated with 6% drop in PSA<sup>1</sup> in screening assessments

1) Harrison S, et al. Cancer Causes Control 2020;31:431-449.  
 2) Zhang E, et al. Nat Commun 2022;13:1135.

|                             | Metformin<br>(n=62)<br>(%) | Placebo<br>(n=67)<br>(%) | Log-rank<br>p-value |
|-----------------------------|----------------------------|--------------------------|---------------------|
| % Cores Involved >33.3%     | 30 (48.4)                  | 32 (47.8)                | 0.77                |
| Max % Core Involvement ≥50% | 28 (45.2)                  | 30 (44.8)                | 0.78                |
| Gleason ≥7                  | 43 (69.4)                  | 44 (65.7)                | 0.6                 |
| Gleason ≥8                  | 8 (12.9)                   | 3 (4.5)                  | 0.082               |

Anthony M. Joshua, ASCO 2024

# Conclusions

- Some retrospective studies suggest metformin has a positive benefit in prostate cancer
- Prospective studies have failed to show benefit of metformin in advanced prostate cancer
- New study (MAST) shows no benefit using metformin in patients who are undergoing active surveillance
- There might be a detriment to using metformin in active surveillance patients
  - high BMI subpopulation
  - More pts in metformin group with GG4 disease at progression