Figure S1

**Disease-free survival**

![Disease-free survival graph](image1)

**Overall survival**

![Overall survival graph](image2)

| Population | Median DFS (years) (95% CI) | 1-year DFS rate (%) (95% CI) | 5-year DFS rate (%) (95% CI) |
|------------|-----------------------------|------------------------------|------------------------------|
| Overall (91) | 3.21 (2.62-NA) | 82.4 (74.6-90.9) | 40.0 (29.2-54.8) |
| OAC (75) | 3.53 (2.31-NA) | 80.2 (71.5-90.1) | 39.0 (27.1-56.1) |
| OSCC (16) | 2.95 (2.05-NA) | 93.8 (82.6-100) | 41.7 (20.6-84.3) |

| Population | Median OS (years) (95% CI) | 1-year OS rate (%) (95% CI) | 5-year OS rate (%) (95% CI) |
|------------|-----------------------------|------------------------------|------------------------------|
| Overall (91) | 4.29 (2.85-NA) | 85.3 (78.3-93.0) | 43.1 (32.1-58.0) |
| OAC (75) | 4.29 (2.70-NA) | 86.3 (78.8-94.6) | 41.5 (29.4-58.6) |
| OSCC (16) | 3.08 (1.57-NA) | 81.2 (64.2-100) | 48.4 (27.0-86.6) |
Figure S2A,B

A

Mandard TRG in OAC & OSCC

P = 0.022

Disease-free survival

Time (years)

Mandard TRG in OAC & OSCC

P < 0.0001

Overall survival

Time (years)

TRG1 25 22 19 12 6 3
TRG2 13 10 6 6 5 4
TRG3 22 15 11 4 2 1
TRG4 27 19 11 8 4 2
TRG5 1 0 0 0 0

Number at risk

Mandard TRG in OAC

P = 0.033

Disease-free survival

Time (years)

Mandard TRG in OAC

P = 0.17

Overall survival

Time (years)

TRG1 15 14 12 9 3 1
TRG2 11 8 5 5 4 3
TRG3 20 13 9 4 2 1
TRG4 26 19 11 8 4 2
TRG5 1 0 0 0 0

Number at risk

B

PRSC in OAC & OSCC

P = 0.0015

Disease-free survival

Time (years)

PRSC in OAC & OSCC

P = 0.0065

Overall survival

Time (years)

A 30 23 19 14 8 5
B 41 32 22 12 8 4
C 17 11 6 4 1 1

Number at risk

PRSC in OAC

P = 0.0014

Disease-free survival

Time (years)

PRSC in OAC

P = 0.017

Overall survival

Time (years)

A 22 17 14 12 6 4
B 34 26 17 10 6 2
C 16 11 6 4 1 1

Number at risk
Figure S2C

ypN in OAC & OSCC

\[ P = 0.00017 \]

ypN0

tyN1–3

54 43 33 24 15 9
35 24 15 7 3 2

ypN in OAC & OSCC

\[ P < 0.0001 \]

ypN0

tyN1–3

54 45 36 28 18 10
35 28 19 9 4 3

ypT in OAC & OSCC

\[ P = 0.014 \]

ypT0–2

tyT3–4

42 32 26 19 12 7
46 34 21 12 6 4

ypT in OAC & OSCC

\[ P = 0.11 \]

ypT0–2

tyT3–4

42 33 28 22 14 7
46 39 26 15 8 6

TRG1/2/3 vs 4/5 in OAC & OSCC

\[ P = 0.0017 \]

TRG1/2/3

TRG4/5

60 47 36 22 13 8
28 19 11 8 4 2

TRG1/2/3 vs 4/5 in OAC & OSCC

\[ P = 0.031 \]

TRG1/2/3

TRG4/5

60 49 38 27 15 8
28 23 16 9 6 4
Figure S3
Figure S4

![Box plot showing methylation index comparison between OSCC and OAC.

- OSCC group shows a lower mean methylation index compared to the OAC group.
- The difference is statistically significant with a p-value of < 0.0001.

The box plot indicates variability within each group, with the median methylation index for OSCC being lower than that for OAC.

- OSCC: Median = 0.25, Interquartile Range (IQR) = 0.25
- OAC: Median = 0.75, IQR = 0.75

Overall, the findings suggest a significant difference in methylation patterns between the two groups, with OSCC displaying lower methylation levels.
Figure S5

| Mandard 1 | Mandard 2 | Mandard 3 | Mandard 4 |
|-----------|-----------|-----------|-----------|
| CDK4/6 inh. | CDKN2A | KRAS | CDK4 | CDKN2A | KRAS | CDK4 | CDKN2A | KRAS | CDK4 | CDKN2A | KRAS | CDK4 | CDKN2A | KRAS | CDK4 | CDKN2A |
| BET inh. | K-RAS | MYC | CCND2 | CCND3 | CDK4 | CCND2 | CCND3 | CDK4 | CCND2 | CCND3 | CDK4 | CCND2 | CCND3 | CDK4 | CCND2 | CCND3 | CDK4 |
| Parp inh. | BRCA1 | BRCA2 | VEGFA | MYC | PIK3CA | MET | FGFR2 | MET | FGFR2 | MET | FGFR2 | MET | FGFR2 | MET | FGFR2 | MET | FGFR2 |
| Anti-EGFR mAb | EGFR | EGFR | EGFR | EGFR | EGFR | EGFR | EGFR | EGFR | EGFR | EGFR | EGFR | EGFR | EGFR | EGFR | EGFR | EGFR | EGFR |
| VEGF inh. | VEGFA | VEGFA | VEGFA | VEGFA | VEGFA | VEGFA | VEGFA | VEGFA | VEGFA | VEGFA | VEGFA | VEGFA | VEGFA | VEGFA | VEGFA | VEGFA | VEGFA |
| PI3K/AKT inh. | MYC | PIK3CA | MYC | PIK3CA | MYC | PIK3CA | MYC | PIK3CA | MYC | PIK3CA | MYC | PIK3CA | MYC | PIK3CA | MYC | PIK3CA | MYC |
| MET inh. | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET |

Any targetable event

Mandard 1: 86.7%
Mandard 2: 72.7%
Mandard 3: 70.0%
Mandard 4: 73.1%

OSCC

Node positive (ypN)
- Yes
- No

Recurrence < 1 yr
- Yes
- No

Any targetable event
- Yes
- No
Figure S6

- NEIL2 (amplification): Overall survival in OAC
  - No CNV: 70, 5, 3, 58, 45, 31, 18, 10
  - Amp: 5, 3, 0, 0, 0, 0, 0, 0
  - P = 0.011

- CTSB (amplification): Overall survival in OAC
  - No CNV: 71, 4, 3, 58, 45, 31, 18, 10
  - Amp: 4, 3, 0, 0, 0, 0, 0, 0
  - P = 0.0093