Supplementary Table 1. Baseline Characteristics of the Study Population (n=172), related to Figure 1

| Parameter                  | Number of Patients (%) |
|----------------------------|------------------------|
| Age (years)                | 65 (34-83)             |
| Sex                        |                        |
| male                       | 142 (83%)              |
| female                     | 30 (17%)               |
| smoker                     |                        |
| yes                        | 133 (70.7 %)           |
| no                         | 39 (29.3 %)            |
| Tumor histology            |                        |
| adenocarcinoma             | 59 (34.3 %)            |
| squamous carcinoma         | 81 (47.1%)             |
| Large cell                 | 25 (14.5 %)            |
| other                      | 7 ( 4.1 %)             |
| pT                          |                        |
| pT1                        | 62 (36.0 %)            |
| pT2                        | 91 (52.9 %)            |
| pT3+pT4                    | 19 (11.1 %)            |
| pN                          |                        |
| pN0                        | 106 (61.6 %)           |
| pN1-2                      | 66 (38.4 %)            |
| pStage                     |                        |
| Not Available              | 4 (2.3 %)              |
| pStage 1                   | 131 (76.2 %)           |
| pStage 2                   | 17 (9.9 %)             |
| pStage 3                   | 18 (10.4 %)            |
| pStage 4                   | 2 (1.2 %)              |
| Median Survival (months)   | 46.27 (±31 month)      |
| NOP10 expression           |                        |
| low                        | 31 (18.0 %)            |
| high                       | 141 (82.0 %)           |
Supplementary Table 2: Multivariate analysis of factors associated with overall survival in NSCLC patients, related to Suppl. Figure 1

| Risk Factor                                | HR (95% CI)        | p-value |
|--------------------------------------------|--------------------|---------|
| Staging (II-IV/ I)                         | 1.61 (1.09-2.38)   | 0.016   |
| NOP10 protein (low/high)                   | 0.35 (0.14- 0.92)  | 0.033   |
| Sex (male/ female)                         | 2.36 (1.04- 5.35)  | 0.039   |
| Smoking (no/ yes)                          | 0.65 (0.16- 1.38)  | 0.267   |
| Age at diagnosis (≤60/>60)                 | 1.0 (1.0- 1.0)     | 0.052   |
| Histological Grade (low malignancy/ moderate+ high malignancy) | 0.029 (0.001-1.623) | 0.085   |

Supplementary Table 3. SnoRNAs enriched and depleted in tumor vs. normal tissue, related to Figure 3

snoRNAs marked in red simultaneously promote higher pseudouridylation of their target sites in tumor vs. matched normal (see Suppl. Table 3)

| snoRNA name                      | average (T) | average (N) | T/N  | Log2FC(T/N) |
|----------------------------------|-------------|-------------|------|-------------|
| U18C                             | 82,20848    | 21,76697    | 3.776753 | 1.917146    |
| U78                              | 491,1726    | 85,73821    | 5.728748 | 2.51822     |
| U44                              | 23720.85    | 12567.17    | 1.887524 | 0.916495    |
| U74                              | 1009.356    | 440.0391    | 2.293787 | 1.197731    |
| mgU12-22/U4-8                    | 11,30278    | 19,15246    | 0.590148 | -0.76085    |
| U14A                             | 10,90798    | 4,464924    | 2.443039 | 1.288677    |
| HBII-289                         | 162,5246    | 459,6242    | 0.353603 | -1.4998     |
| HBI-6 (SNORA26)                  | 6,373157    | 1,297656    | 4.911285 | 2.296101    |
| HBII-13                          | 226,289     | 390,7374    | 0.579133 | -0.78803    |
| U77                              | 102,1291    | 10,84975    | 9.413036 | 3.23466     |
| ACA9 (SNORA9)                    | 13,36415    | 4,390575    | 3.043827 | 1.605886    |
| U28                              | 485,9898    | 122,5038    | 3.967141 | 1.9881      |
| U75                              | 496,3789    | 161,6574    | 3.070561 | 1.618502    |
| U18B                             | 545,7946    | 273,8575    | 1.992988 | 0.994933    |
| U36B                             | 117,6763    | 55,62151    | 2.115661 | 1.081109    |
| U65 (SNORA65)                    | 17,2263     | 5,928249    | 2.905799 | 1.538935    |
| Z17B                             | 119,457     | 35,84094    | 3.329277 | 1.736812    |
| U52                              | 3067,941    | 1638,204    | 1.872747 | 0.905156    |
| U45C                             | 1666,919    | 554,1474    | 3.008079 | 1.588842    |
| snR38A                           | 12,24837    | 2,395322    | 5.113452 | 2.354298    |
Suppl. Table 4: Increase in pseudouridylation of respective snoRNA target sites as determined by \(\Psi\)-seq, related to Figure 3.

snoRNAs marked in red are enriched in tumor vs. matched normal (see Suppl. Table 2). Target rRNA positions for individual snoRNAs have been annotated based on Modomics [1]. SnOPY [2] annotations are given in column 3.

| SnoRNA            | Target RNA [1] | Target RNA [2] | Log2FC(T/N)  | P Value     |
|-------------------|----------------|----------------|--------------|-------------|
| ACA36 (SNORA36A)  | 18S 105        | 18S 105        | 0.506507616  | 0.001191381 |
| ACA36B (SNORA36B) | 18S 105        | 18S 105        | 0.506507616  | 0.001191381 |
| ACA50 (SNORA50)   | 18S 105        | 18S 105        | 0.506507616  | 0.001191381 |
| ACA62 (SNORA76)   | 18S 105        | 18S 105        | 0.506507616  | 0.001191381 |
| ACA9 (SNORA9)     | 28S 1662       | 28S 1670       | 0.607931071  | 0.003773914 |
| ACA43 (SNORA43)   | 28S 4928       | 28S 4938       | 0.274478767  | 0.004214525 |
| ACA42 (SNORA42)   | 18S 109        | 18S 109        | 0.32715463   | 0.005317231 |
| ACA67 (SNORA80)   | 18S 109        | 18S 109        | 0.32715463   | 0.005317231 |
| ACA67B (SNORA80B) | 18S 109        | 18S 109        | 0.32715463   | 0.005317231 |
| U66 (SNORA66)     | 18S 119        | 18S 119        | 0.266072956  | 0.01166257  |
| ACA52 (SNORA52)   | 28S 1723       | 28S 1731       | 0.197505127  | 0.013975514 |
| ACA31 (SNORA31)   | 18S 218        | 18S 218        | 0.1227333    | 0.037129618 |
| ACA7 (SNORA7A)    | 28S 1771       | 28S 1779       | 0.150068195  | 0.038973871 |
| ACA7B (SNORA7B)   | 28S 1771       | 28S 1779       | 0.150068195  | 0.038973871 |
| U19-2 (SNORA74A (B)) | 28S 3731   | 28S 3741       | 0.258519692  | 0.040174303 |

Supplementary Table 5. Composition of the CRISPR/Cas9 KO Library (in separate Excel file), related to Figure 4

Supplementary Table 6. SnoRNAs enriched and depleted in A549 cells as identified by the CRISPR/Cas9 KO screen, related to Figure 4.
| id               | num | Neg. p-value | Neg. fdr  | Neg. rank |
|------------------|-----|--------------|-----------|-----------|
| SNORD14D         | 4   | 0.0040414    | 0.228342  | 8         |
| SNORD76          | 3   | 0.011686     | 0.360726  | 14        |
| **SNORA7A**      | 2   | 0.014621     | 0.388759  | 17        |
| SNORA3_SNORA45A  | 6   | 0.025377     | 0.528128  | 20        |
| SNORA5A          | 5   | 0.02553      | 0.528128  | 21        |
| SNORD109A_SNORD109B | 4    | 0.025705   | 0.528128  | 22        |
| SNORD94          | 5   | 0.029736     | 0.560025  | 23        |
| SNORD51          | 2   | 0.033241     | 0.591965  | 25        |
| SNORD11B         | 3   | 0.035694     | 0.597543  | 27        |
| SNORD67          | 4   | 0.050064     | 0.701499  | 30        |
| SNORD7           | 5   | 0.060709     | 0.707667  | 38        |
| SNORD43          | 2   | 0.064126     | 0.724629  | 40        |
| SNORA59A         | 5   | 0.070304     | 0.727925  | 42        |
| **SNORA65**      | 7   | 0.073195     | 0.727925  | 43        |
| SNORD9           | 6   | 0.075254     | 0.727925  | 45        |
| SNORD59A         | 2   | 0.078693     | 0.727925  | 48        |
| SNORD58C         | 1   | 0.092362     | 0.750512  | 55        |
| SNORD14C         | 3   | 0.094925     | 0.750512  | 56        |
| SNORA70C         | 3   | 0.096305     | 0.750512  | 58        |
| **SNORA7B**      | 1   | 0.1011       | 0.774543  | 59        |
| id               | num | Pos. p-value | Pos. fdr  | Pos. rank |
|------------------|-----|--------------|-----------|-----------|
| SNORA76          | 5   | 0.00040524   | 0.15099   | 1         |
| SNORD86          | 7   | 0.0006681    | 0.15099   | 2         |
| SNORA31          | 3   | 0.0026614    | 0.40099   | 3         |
| SNORA63          | 4   | 0.0035595    | 0.402228  | 4         |
| SNORA52          | 10  | 0.0045014    | 0.406931  | 5         |
| SNORD50A         | 2   | 0.0087072    | 0.512101  | 7         |
| SNORA71B         | 4   | 0.0099996    | 0.512101  | 8         |
| SNORD88A         | 5   | 0.017272     | 0.624646  | 11        |
| SNORD103A_SNORD103B | 4   | 0.024216   | 0.624646  | 14        |
| SNORA68          | 3   | 0.024501     | 0.624646  | 15        |
| SNORA45B         | 2   | 0.024742     | 0.624646  | 16        |
| SNORA13          | 4   | 0.029079     | 0.624646  | 18        |
| SNORA80A         | 4   | 0.029473     | 0.624646  | 19        |
| SNORA70E         | 4   | 0.033788     | 0.624646  | 21        |
| SNORA79          | 6   | 0.034029     | 0.624646  | 22        |
| SNORD68          | 3   | 0.034183     | 0.624646  | 23        |
| SNORA73A         | 9   | 0.035168     | 0.624646  | 24        |
| SNORA32          | 3   | 0.03703      | 0.624646  | 25        |
| SNORD88B         | 3   | 0.0376       | 0.624646  | 26        |
| SNORA19          | 2   | 0.038213     | 0.624646  | 27        |
| SNORA26          | 1   | 0.038695     | 0.624646  | 28        |
| SNORA77          | 5   | 0.050283     | 0.773833  | 29        |
| target/ gRNA name | gRNA sequence                           |
|------------------|----------------------------------------|
| SNORA7A7B-sgRNA-1-S | CACCGTCTGGCCAGCTTCCGAAAGGG            |
| SNORA7A7B-sgRNA-1-AS | AAACCCCTTTCCGAGCTGGCAGAc             |
| SNORA7A7B-sgRNA-2-S  | CACCGTACCTCTGGGATCGCAGTC             |
| SNORA7A7B-sgRNA-2-AS  | AAACGATGCGATCCACAGGAGGTCC             |
| SNORA7A7B-sgRNA-3-S  | CACCGTATTTGGCCAGTTCCGAA              |
| SNORA7A7B-sgRNA-3-AS  | AAACCTCTCGAAGCTGGCAGAAC              |
| SNORA7A7B-sgRNA-4-S  | AAACCCCTTTCCGAGCTGGCAGAc             |
| SNORA7A7B-sgRNA-4-AS  | AAACCCCTTTCCGAGCTGGCAGAc             |
| NOP10-sgRNA-1-S    | CACCGCAGTTATTACCTCAACGGAC             |
| NOP10-sgRNA-1-AS    | AAACGCTCGTGGAGTAAATCTGGG             |
| NOP10-sgRNA-2-S    | CACCGAGATCGAGTCTATACGCTG             |
| NOP10-sgRNA-2-AS    | AAACCTCGAGTTATAGACCTCGATCTC           |
| NOP10-sgRNA-3-S    | CACCGGAGGAAATTCTGGAC                 |
| NOP10-sgRNA-3-AS    | AAACCTCGGCTCAAATTCTGCTCC             |
| NOP10-sgRNA-4-S    | CACCGCTCTCGACCCCCATCTGCT             |
| NOP10-sgRNA-4-AS    | AAACAGCAGGATGGGCTGAGCAGGC            |
| NOP10-sgRNA-5-S    | CACCGCAGCAGGCTCCTGTCCT              |
| NOP10-sgRNA-5-AS    | AAACGAGGACAGGGCCCCCGGTGGTC           |
| NOP10-sgRNA-6-S    | CACCGGAGACAGGCGGCGGTGGTC             |
| NOP10-sgRNA-6-AS    | AAACAGCAACACGGGCCTCGTCTC             |
| NOP10-sgRNA-7-S    | CACCGTACCTGGGAGAACCAGGAC             |
| NOP10-sgRNA-7-AS    | AAACGCTCGTCTGCCAGATCCAG             |
| NOP10-sgRNA-8-S    | CACCGACCCCTGAGAGACGGGGGC             |
| NOP10-sgRNA-8-AS    | AAACGCGGCTTCTGCCTTGAGGTC             |
| SNORA65-sgRNA-1-S  | CACCGTGGTGGCTGTAATCCAG              |
| SNORA65-sgRNA-1-AS  | AAACCTGGATTGCCACCAAGCCCAACA          |
| SNORA65-sgRNA-2-S  | CACCGAAACAGGGTTCTTTTCTCATG           |
| SNORA65-sgRNA-2-AS  | AAACCATGAGAGAACACCGCTGGT            |

Supplementary Table 7. Small guide RNA sequences used for knockout of individual snoRNAs and target genes

Supplementary Table 8. Sequences of primers used in PCR and quantitative RT-PCR
| Primer name              | Primer sequence                      |
|-------------------------|--------------------------------------|
| NOP10 (hum)-RT-AS       | TACCTCAACGAGCAGGGAGA                 |
| NOP10 (hum)-RT-AS       | CTGGGTCATGAGCACCTTGA                 |
| DKC1 (hum)-RT-S         | CCGTCACTCTACCTGCAGAC               |
| DKC1 (hum)-RT-AS        | TGGCGAGACTCAGTGAGTCAA               |
| ACTIN (hum)-RT-S        | AGGCACCGGGGCGTGAT                  |
| ACTIN (hum)-RT-AS       | GCGCAGCTAGGAATCTTTCTGAC             |
| SNORA7A/7B-genomic-S    | GATTTGCTCAGCTGTGGCATTTC             |
| SNORA7A/7B-genomic-S    | ACGATCTTTGGGCTTCACAAAGG             |
| NOP10-Genomic-1-S       | GACGAACACGTGACGCAGGG               |
| NOP10-Genomic-1-AS      | CACGTATGACCTCACCCACT                |
| NOP10-Genomic-2-S       | TTTGCCCTTTTCTGCGCTG                |
| NOP10-Genomic-2-AS      | TCAATCGCCACGAGAGACTG                |
| SNORA7A/B-RT-S          | GTATTCTGCCAGCTTCGGGAAAGG             |

References

1 Boccaletto P, Machnicka MA, Purta E, Piatkowski P, Baginski B, Wirecki TK et al. MODOMICS: a database of RNA modification pathways. 2017 update. *Nucleic acids research* 2018; 46: D303-d307.

2 Yoshihama M, Nakao A, Kenmochi N. snOPY: a small nucleolar RNA orthological gene database. *BMC research notes* 2013; 6: 426.