**Supplementary Table 1** Gene ontology (GO) summary of key transcriptional signatures driving each of the periphery-derived clusters (C1–C4) and the genesets significantly modulated by NRP1 within each cluster (by GSEA).

| Cluster ID | Datasets | Cluster specific signatures | Gene Set Enrichment Analysis (MsigDB:C7) |
|------------|----------|-----------------------------|-------------------------------------------|
| Cluster 1  | D12, D21 | 1. EIF2 signaling (10^{-3})  | 1. KAECCH_DAY15_EFF_VS_MEMORY_CD8_TCELL_UP |
|            |          | 2. Regulation of eIF4 and p70S6K signaling (10^{-3}) | 2. GSE10239_NAIVE_VS_DAY4.5_EFF_CD8_TCELL_DOWN |
|            |          | 3. mTOR signaling (10^{-4}); | 3. KAECCH_DAY8_EFF_VS_MEMORY_CD8_TCELL_UP |
|            |          |                             | 4. GSE9550_EFFECF_VS_MEMORY_CD8_TCELL_UP |
|            |          |                             | 5. GSE14699_NAIVE_VS_ACT_CD8_TCELL_UP |
| Cluster 2  | D12, D21 | 1. Estrogen-mediated S-phase entry; (10^{-4}); | 1. GOLDRATH_EFF_VS_MEMORY_CD8_TCELL_UP |
|            |          | 2. Mitotic Roles of Polo-like Kinase (10^{-4}); | 2. GSE23568_ID3_KO_VS_WT_CD8_TCELL_UP |
|            |          | 3. Cyclins and cell cycle regulation (10^{-5}); | 3. GSE30962_ACUTE_VS_CHRONIC_LCMV_SECONDARY_INF_CD8_TCELL_DOWN |
|            |          | 4. Cell cycle checkpoint control (10^{-6}) | 4. KAECCH_DAY8_EFF_VS_MEMORY_CD8_TCELL_UP |
|            |          | 5. G2/M DNA damage checkpoint regulation (10^{-5}); | |
| Cluster 3  | D35      | 1. NFAT in regulation of immune response (10^{-7}); | No significantly enriched pathway |
|            |          | 2. B cell receptor signaling (10^{-6}); | |
|            |          | 3. Phospholipase C signaling (10^{-6}); | |
|            |          | 4. PI3K signaling in B cells(10^{-5}); | |
| Cluster 4  | D63      | 1. Th1 activation (10^{-7}); | 1. GSE23568_ID3_KO_VS_WT_CD8_TCELL_DOWN |
|            |          | 2. T helper cell differentiation (10^{-6}); | 2. GSE15750_DAY6_VS_DAY10_EFF_CD8_TCELL_UP |
|            |          | 3. CD40 signaling (10^{-9}); | 3. GSE30962_PRIMARY_VS_SECONDARY_ACUTE_LCMV_INF_CD8_TCELL_DOWN |
|            |          | 4. ICOS-ICOSL signaling (10^{-9}); | 4. GSE15750_DAY6_VS_DAY10_EFF_CD8_TCELL_DOWN |

Red: Upregulated in the Nrp1^{-/-} datasets; Blue: Downregulated in the Nrp1^{-/-} datasets
**Supplementary Table 2** Gene ontology (GO) annotation for the pathways respectively enriched in the GSEA83978 (TCF1-associated) and GSE23568 (Id3-associated).

| GSEA dataset               | GO pathways                                      | pValue   | Enrichment | Genes               |
|----------------------------|--------------------------------------------------|----------|------------|---------------------|
| GSE83978_Chr_TCF1* vs. TCF1* | Cell Cycle: G2/M DNA Damage Checkpoint Regulation | 3.13E-05 | 8.3 % (4/48) | *Aurka, Ccnb1, Ccnb2, Plk1* |
|                            | Mitotic Roles of Polo-Like Kinase                | 7.11E-05 | 6.8 % 4/59 | *Ccnb1, Ccnb2, Plk1, Prc1* |
| GSE23568_Id3_WT vs. KO     | Mitotic Roles of Polo-Like Kinase                | 7.73E-08 | 10.2 % (6/59) | *Ccnb1, Ccnb2, Espl1, Kif11, Kif23, Prc1* |
|                            | DNA damage-induced 14-3-3 Signaling              | 3.79E-05 | 16.7 % (3/18) | *Ccnb1, Ccnb2, Cdk2* |
|                            | ATM Signaling                                    | 3.43E-04 | 4.4 % (4/90) | *Ccnb1, Ccnb2, Cdk2, Rad51* |
|                            | Cell Cycle: G2/M DNA damage checkpoint Regulation | 7.43E-04 | 6.2 % (3/48) | *Ccnb1, Ccnb2, Top2a* |
|                            | Cell Cycle: control of chromosomal replication   | 9.39E-04 | 5.8 % (3/52) | *Cdk2, Mcm3, Top2a* |
**Supplementary Table 3** Clinical information of the Head and neck squamous cell carcinoma (HNSCC) patients (Cohort A).

|                      | Early (n=23) | Advanced (n=25) |
|----------------------|--------------|-----------------|
| **Sex**              |              |                 |
| Male                 | 15           | 20              |
| Female               | 8            | 5               |
| **Smoking History**  |              |                 |
| Yes                  | 19           | 23              |
| No                   | 4            | 2               |
| **Nodes Positive**   |              |                 |
| Yes                  | 0            | 10              |
| No                   | 19           | 6               |
| NA                   | 4            | 9               |
| **Pathology Stage**  |              |                 |
| NA                   | 1            | 0               |
| T1, N0               | 10           | 0               |
| T1, N1               | 0            | 3               |
| T1, NX               | 4            | 0               |
| T2, N0               | 8            | 0               |
| T2, N1               | 0            | 1               |
| T2, N2A              | 0            | 2               |
| T2, N2B              | 0            | 1               |
| T3, N0               | 0            | 4               |
| T3, N2C              | 0            | 1               |
| T4A, N0              | 0            | 2               |
| T4A, N2B             | 0            | 1               |
| T4A, N2C             | 0            | 1               |
| TX, TX               | 0            | 9               |
| **Tumor Site**       |              |                 |
| Cheek - Mucosa       | 1            | 1               |
| Gum - Lower          | 4            | 2               |
| Hypopharynx          | 0            | 1               |
| Larynx - Glottis     | 5            | 0               |
| Larynx - Overlap     | 0            | 2               |
| Lesion               |              |                 |
| Larynx - Supraglottis| 2            | 6               |
| Mouth, Floor         | 4            | 3               |
| Palate - Soft        | 1            | 1               |
| Tongue - Base        | 0            | 6               |
| Tongue - Dorsal      | 1            | 0               |
| Surface              |              |                 |
| Tongue               | 2            | 1               |
| Tonsil               | 3            | 2               |
**Supplementary Table 4** Clinical information of the advanced skin cancer patients (Cohort B).

|                       | Responder (n=20) | Progressor (n=20) |
|-----------------------|-----------------|-------------------|
| **Sex**               |                 |                   |
| Male                  | 14              | 11                |
| Female                | 6               | 9                 |
| **Age**               |                 |                   |
| >75yr                 | 7               | 6                 |
| <75yr                 | 13              | 14                |
| **Histology**         |                 |                   |
| Melanoma              | 19              | 13                |
| Cutaneous SCC         | 1               | 0                 |
| Basal Cell            | 0               | 2                 |
| Mucosal Melanoma      | 0               | 3                 |
| Uveal Melanoma        | 0               | 1                 |
| Merkel Cell           | 0               | 1                 |
| **Therapy**           |                 |                   |
| Pembrolizumab         | 6               | 5                 |
| Nivolumab             | 8               | 6                 |
| Cemiplimab            | 1               | 0                 |
| Nivolumab+Ipilimumab  | 3               | 8                 |
| proprietary anti-PD1-based ICB combination | 2 | 1 |
| **Treatment History** |                 |                   |
| Treatment-naive       | 17              | 12                |
| Pretreated            | 3               | 8                 |
| **Race**              |                 |                   |
| White                 | 19              | 20                |
| Asian                 | 0               | 0                 |
| Black                 | 1               | 0                 |
| **BRAF mutation**     |                 |                   |
| Mutation +            | 7               | 4                 |
| Mutation –            | 10              | 12                |
| Unknown               | 3               | 4                 |
| **Stage**             |                 |                   |
| III                   | 6               | 2                 |
| IV                    | 14              | 18                |
| **Response**          |                 |                   |
| CR                    | 6               | N/A               |
| PR                    | 14              | N/A               |
| PD                    | N/A             | 20                |
Supplementary Figure 1

Gating strategy and purity check for \( Nrp1^{+/+} \) and \( Nrp1^{-/-} \) pMel-T cells purified from CD45.1 recipient for transcriptomic (RNAseq) analysis.

**a** Pre-sort

**b** Post-sort

\( Nrp1^{+/+} \)

\( Nrp1^{-/-} \)