Poster 20: Molecular Pathway Analysis of NSMP Endometrial Cancers Reveals Distinct Subtypes

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Topic
Endometrial

Objectives
We aimed to further characterize the FIGO 2023 NSMP (“No Specific Molecular Phenotype”) endometrial cancers and identify molecular pathways and targetable mutations.

Methods
Genomic data from the AACR GENIE database were analyzed to identify uterine tumors lacking POLE mutations, mismatch repair deficiency (dMMR), and TP53 alterations, which define the NSMP cohort. dMMR status was defined by somatic alterations in mismatch repair genes (MLH1, MSH2, MSH6, and PMS2), as microsatellite instability, MLH1 promoter hypermethylation, and germline data were not available. Recurrent genomic alterations (>2% frequency) were used to construct a binary feature matrix, and unsupervised clustering was performed to identify molecular subtypes. Tumors were stratified into genomically “quiet” (≤1 alteration) and “active” (>1 alteration) groups. Cluster centroids derived from GENIE were applied to an independent TCGA cohort for validation. Overall survival (OS) was evaluated using Kaplan–Meier methods.

Results
Among 7,873 total uterine tumors, 3,837 (48.7%) were classified as NSMP, while 2,750 (34.9%) harbored TP53 alterations, 676 (8.6%) were dMMR, and 610 (7.7%) were POLE-mutated. Within the NSMP cohort, the median age was 63 years (IQR 57–70), and most tumors were primary (66.6%), with 16.8% metastatic. Histologically, NSMP tumors were predominantly endometrioid (86.2%), followed by serous (5.0%), carcinosarcoma (4.8%), clear cell (2.7%), and mixed carcinoma (1.3%) subtypes. Genomically active tumors (>1 alteration) comprised approximately 70% of NSMP cases (n=2,672), while 30% were genomically quiet (n=1,165). Among active tumors, four molecular subtypes were identified: a PI3K–MAPK co-activated subtype, a chromatin-remodeling subtype, a PIK3R1-dominant regulatory subtype, and a WNT/β-catenin–activated subtype. These subtypes were defined by majority enrichment of PTEN/PIK3CA with KRAS alterations, ARID1A and KMT2D alterations, PIK3R1 alterations, and CTNNB1 alterations, respectively. In TCGA (n=266 NSMP tumors), the median age and stage distribution were comparable to the GENIE cohort. Eighty percent (n=214) were classified as active and 20% (n=52) as quiet. Subtype-specific genomic patterns were preserved. Genomically quiet tumors demonstrated lower overall survival compared with active tumors (log-rank p = 0.046). Among active tumors, survival varied across subtypes, with WNT/β-catenin tumors demonstrating a trend towards higher survival and PIK3R1-dominant tumors demonstrating lower survival, while PI3K–MAPK and chromatin subtypes showed intermediate outcomes; however, this was not powered for statistical significance (log-rank p=0.073).

Conclusions
Our data suggests that the NSMP molecular subgroup can be further refined into four molecular subclasses, including PI3K–MAPK co-activated, chromatin-remodeling, PIK3R1-dominant regulatory, and WNT/β-catenin–activated subtypes. Genomically active tumors demonstrated improved survival compared to quiescent tumors. These pathway-defined groups warrant further validation in prospective clinical studies.

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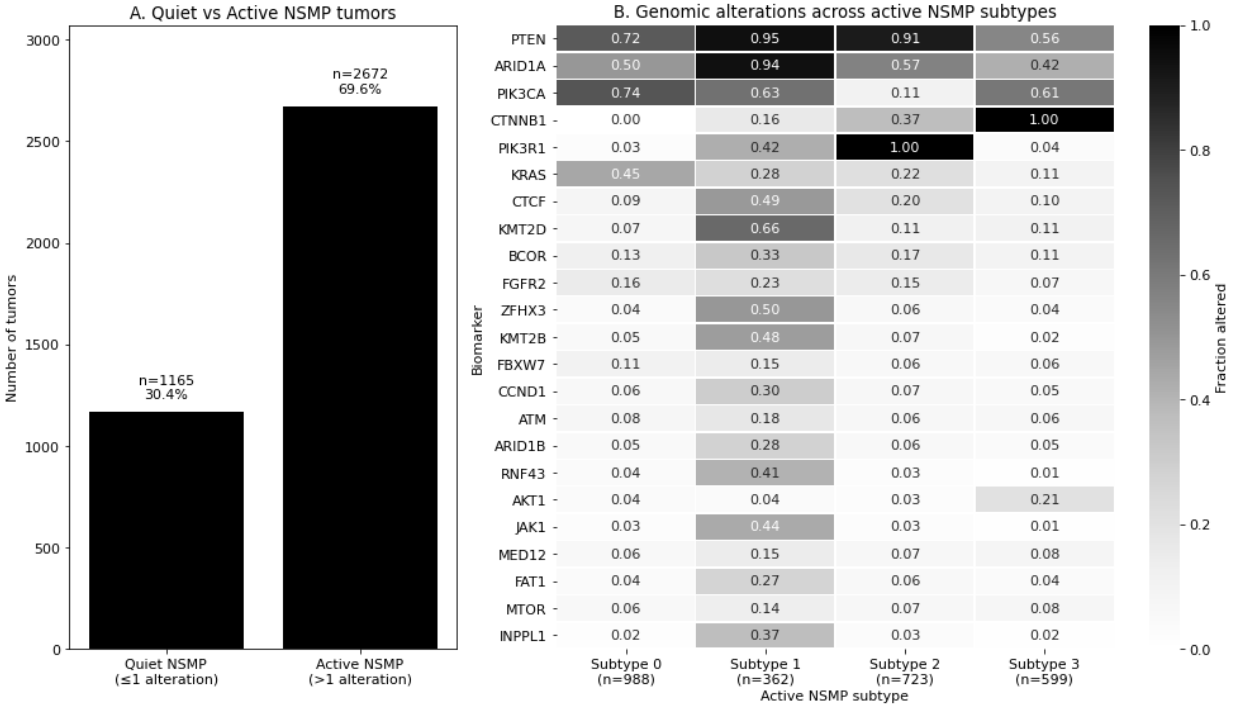
Abstract Table or Graph


A. Quiet vs Active NSMP tumors
Number of tumors
3000
2500
2000
1500
1000
500
0
n=1165
30.4%
n=2672
69.6%
Quiet NSMP
(≤1 alteration)
Active NSMP
(>1 alteration)
B. Genomic alterations across active NSMP subtypes
Biomarker
PTEN 0.72 0.95 0.91 0.56
ARID1A 0.50 0.94 0.57 0.42
PIK3CA 0.74 0.63 0.11 0.61
CTNNB1 0.00 0.16 0.37 1.00
PIK3R1 0.03 0.42 1.00 0.04
KRAS 0.45 0.28 0.22 0.11
CTCF 0.09 0.49 0.20 0.10
KMT2D 0.07 0.66 0.11 0.11
BCOR 0.13 0.33 0.17 0.11
FGFR2 0.16 0.23 0.15 0.07
ZFHX3 0.04 0.50 0.06 0.04
KMT2B 0.05 0.48 0.07 0.02
FBXW7 0.11 0.15 0.06 0.06
CCND1 0.06 0.30 0.07 0.05
ATM 0.08 0.18 0.06 0.06
ARID1B 0.05 0.28 0.06 0.05
RNF43 0.04 0.41 0.03 0.01
AKT1 0.04 0.04 0.03 0.21
JAK1 0.03 0.44 0.03 0.01
MED12 0.06 0.15 0.07 0.08
FAT1 0.04 0.27 0.06 0.04
MTOR 0.06 0.14 0.07 0.08
INPPL1 0.02 0.37 0.03 0.02
Subtype 0
(n=988)
Subtype 1
(n=362)
Subtype 2
(n=723)
Subtype 3
(n=599)
Active NSMP subtype
Fraction altered
1.0
0.8
0.6
0.4
0.2
0.0