SUMMER Trial for Adjuvant Treatment of NSCLC

Survival Upgrade for Major Malignancy by Eliminating Relapse

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Standard of care and Goal of SUMMER

Standard of care for NSCLC stage IIA, IIB and IIIA is surgery followed by platinum based adjuvant therapy (+/- radiation).

40% of patients are alive at 5 years.

30% relapse within 12 months.

The objective of SUMMER is to explore the usefulness of targeted therapies selected by SIMS in the adjuvant setting.

The overarching goal is to decrease the number of patients relapsing at 12 months.

Detterbeck et al, Chest, 2009
Current landscape of adjuvant NSCLC investigation

- Targeted agents are being tested in the adjuvant setting for established driver DNA mutations, e.g. EGFR$^{mt}$ and ALK translocation.

- Single agent immune checkpoint inhibitors, e.g. anti-PDL1 or –PD1, are demonstrating significant activity in refractory metastatic disease.

- Nivolumab (anti-PD1; NCI ALCHEMIST; non-squamous only) and MEDI4736 (anti-PD-L1; NCIC CTG BR.31) are being tested as single agent therapy in the adjuvant setting for driver negative NSCLC.
SUMMER overview workflow

Inclusion: NSCLC stage II A&B, IIIA

Curative Surgery Tumor and Normal tissues obtained from resection

NGS CNV
Expression mRNA miRNA Protein
SIMS integrative algorithm & score

Randomization

N=200
4 cycles standard adjuvant platinum based followed by observation
Arm A

Arm B
N=200
4 cycles standard adjuvant platinum based followed by anti-PD1/PDL1

Arm C (*)
N=200
4 cycles standard adjuvant platinum based followed by anti-PD1/PDL1 combined with SIMS directed targeted therapy

Liquid biopsies

(*) the number of specific targeted + immunotherapy combinations is yet to be determined in Arm C
Statistical Design/Considerations

- First, assume a 2-arm trial (say Arm A and Arm B)
- Assume the 12-month RFS rate in Arm A is 70% (average all stages: IIA, IIB, and IIIA) and in Arm B, it is increased to 80%.
- Assume RFS follow the exponential survival distribution.
- Assume accrual rate is 20 patients/month and after the last patient accrued, there is an additional 12-month follow-up.
- We need 380 patients to achieve 80% power using the log-rank test to test the null hypothesis of no difference between Arm A and Arm B.
- Assume 5% patients are inevaluable, need 400 patients.
- Total study duration = 20 months enrollment + 12 months follow-up = 32 months
- To compare Arm B vs. Arm A and Arm C vs. Arm A, assume the 12 RFS rates are 70%, 80%, and 80% respectively.
- There are two tests but we do not correct for type I error due to multiplicity.
- We need 200 patients per arm. Total sample size = 600.
  Total study duration = 30 + 12 months = 42 months.
Tissue Profiling

Tissue collection from standard of care surgery

Fresh frozen to store for future ancillary studies

FFPE for analysis

FFPE blocks sent to Central Platforms

Central Platforms

Tumor Tissue (T)

Normal Tissue (N)

T - 2 blocks fresh frozen for storage

N - 2 blocks fresh frozen for storage

T 3 blocks in FFPE

N 3 blocks in FFPE

- Genomics & transcriptomics Central Platform (2 blocks FFPE T&N)
- Proteomics Central Platform (1 block FFPE T&N)

- Histological control to determine percentage of tumor cells and characterize the content of other components of the specimen
- Macrodissection, if necessary, to ensure tumor specimens reach threshold of 50% tumor cell content

- DNA sequencing 183 genes for SIMS (+ other genes for research)
- Differential mRNA and miRNA expression arrays T & N for 183 genes for SIMS (+ other genes for research)
- Reverse Phase Protein microarrays
- Rich biobank for correlative studies
Application of SIMS and CMC, with incorporation of proteomic data

• Ben Gurion group will be calculating the SIMS score for use by the Clinical Monitoring Committee (CMC)

• Discussions underway to incorporate proteomic profiling (RPPA) into revised SIMS algorithm

• The incorporation of proteomic data can be especially important in cases where genomic/transcriptomic data is ambivalent about pathway activation

• Propose 1 year duration of treatment with immunotherapy +/- targeted agent.
Potential combination therapies for Arm C or B2

- Likely 5-6 PD-L1/targeted combinations
- Intention to cover majority of patients & activating pathways of interest
- Dependent upon available Phase 1 data and company support.

### Table

<table>
<thead>
<tr>
<th>Nodes</th>
<th>Components of the interventional points</th>
<th>Examples of drugs acting on interventional points</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER</td>
<td>EGF, TGFα, AREG, EREG, HBEGF, BTC, NRG1, NRG2, NRG4, EGFR, ERBB2, ERBB3, ERBB4</td>
<td>Afatinib Dacomitinib (Pan-Her inhibitor)</td>
</tr>
<tr>
<td>CDK4, 6</td>
<td>CDK4, CDK6, CCND1, CCND2, CCND3, CDK2A, CDKN2B, CCNE1, CCNE2, CCNE3, RB1</td>
<td>Palbociclib (CDK4,6 inhibitor)</td>
</tr>
<tr>
<td>PLK/ AURK</td>
<td>PLK1, AURKA, BORA, ILK, KIF11</td>
<td>Aurora A kin inhib</td>
</tr>
<tr>
<td>Angio genes</td>
<td>VEGFA, VEGFB, VEGFC, VEGFD, VEGFR1, VEGFR2, VEGFR3, PDGFA, PDGFB, PDGFR, PDGFRB, Kit</td>
<td>Axitinib</td>
</tr>
<tr>
<td>Angio poietins</td>
<td>THBS1, TGFβ1, ANGPT1, ANGPT2, ANGPTL1, ANGPT4, TIE1, TEK</td>
<td>-</td>
</tr>
<tr>
<td>Immune modulator</td>
<td>PD1L, PDCD1LG2, PDCD1, CTLA4, LAG3</td>
<td>Ipilimumab (CTLA4); Tremelimumab (CTLA4), Nivolumab (PD1); AMP514 (PD1), Pidilizumab (PD-1); MEDI4736 (PD-L1) PF-05082566 (4-1 BB)</td>
</tr>
<tr>
<td>PI3K</td>
<td>PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3C2B, PRKCB, PRKCA, PRKCB, PIK3R1, PIK3R2, PIK3R3</td>
<td>PF-384 (PI3K/mTOR-inhibitor) AZD8186 (PI3Kb) PI3KaP inhibitor</td>
</tr>
<tr>
<td>MET</td>
<td>HGF, MET, AXL, MST1R</td>
<td>Crizotinib, Cabozantinib, Volitinib (cMet)</td>
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<tr>
<td>MEK</td>
<td>MAP2K1, MAP2K2, MAP2K3, MAP2K4, MAP3K1, MAP3K2, MAP3K3, MAP3K4</td>
<td>Trametinib Selumetinib (MEK)</td>
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<tr>
<td>ERK</td>
<td>MAPK3, MAPK1, KSR1, MAPK11</td>
<td>-</td>
</tr>
<tr>
<td>Anti-apoptosis</td>
<td>BCL2, BCLXL, BIRC5, XIAP, BAK, TP53</td>
<td>ABT-199 (BCL-2) MK-1775 (Wee-1 inhibitor; p53)</td>
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<tr>
<td>FGF</td>
<td>FGF1 to FGF18, FGFR1, FGFR2, FGFR3, FGFR4</td>
<td>Lenvatinib, Lucitanib AZD4547 (FGFR1, 2, 3)</td>
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<tr>
<td>mTOR</td>
<td>mTOR, AKT1, AKT2, PTEN, TSC1, TSC2, STK11, PIM1, PIM2, PIM3</td>
<td>Everolimus, Temsirolimus PF-384 (PI3K/mTOR inhibitor) AZD2014 (TOR kinase); AZD5363 (AKT1, 2, 3) AZD1208 (PIM1, 2); TORC1/TORC2 inhibitor</td>
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<tr>
<td>Ras/Raf</td>
<td>KRAS, NRAS, HRAS, RAF1, BRAF, CRAF</td>
<td>Trametinib, Vemurafenib, Dabrafenib Pan-Raf inhibitor</td>
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<tr>
<td>Telomerase</td>
<td>TERT, TERC, TEC1, HSP90A1, DKK1, PTGES3</td>
<td>-</td>
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<tr>
<td>IGF</td>
<td>IGF1, IGF2, IGF1R, IGF2R, INSRI, IRS1, PKM</td>
<td>Cixutumumab Medi-573 (IGF)</td>
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<td>Wnt</td>
<td>CDH1, CTNNBA1, CTNNB1, WNT 1, FZD1, WNT5A, B, FZD5, WIF1, DKK1</td>
<td>PRI-274</td>
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<tr>
<td>PARP</td>
<td>PARP1, BRCA1, XRCC1, RAD54L, RAD54B, ATM, ATR, CHEK1, CHEK2, WEE1</td>
<td>Olaparib (PARP) AZD1775 (Wee1) AZD6738 (ATR)</td>
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<tr>
<td>HDAC</td>
<td>HDAC1, HDAC2, HDAC3, HDAC4, HDAC5</td>
<td>Vorinostat</td>
</tr>
<tr>
<td>JAK-STAT</td>
<td>JAK1, JAK2, STAT1, STAT2, STAT3, SOCS1</td>
<td>Riluzitinib; AZD9150</td>
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<tr>
<td>Hedgehog</td>
<td>SHH, PTCH1, SMO, STK36, PRKCA, SUFU,</td>
<td>Vismodegib</td>
</tr>
<tr>
<td>NOTCH</td>
<td>NOTCH1, Adam17, PSEN1, NCSTN, JAG1, SRRT, APH1A</td>
<td>LY3039478</td>
</tr>
<tr>
<td>DNA Repair</td>
<td>ERCC1, RAD52, XRCC4, RAD51, BRCA1, NEDD8, NAE1</td>
<td>NEDD8 activating enzyme inhibitor</td>
</tr>
<tr>
<td>Others</td>
<td>RET, ALK, ROS1, UB1</td>
<td>Crizotinib, Ceritinib, Sorafenib, Cabozantinib</td>
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