Worldwide innovative networking
in personalized cancer medicine

SUMMER Trial for Adjuvant Treatment of NSCLC

Survival Upgrade for Major Malignancy by Eliminating Relapse

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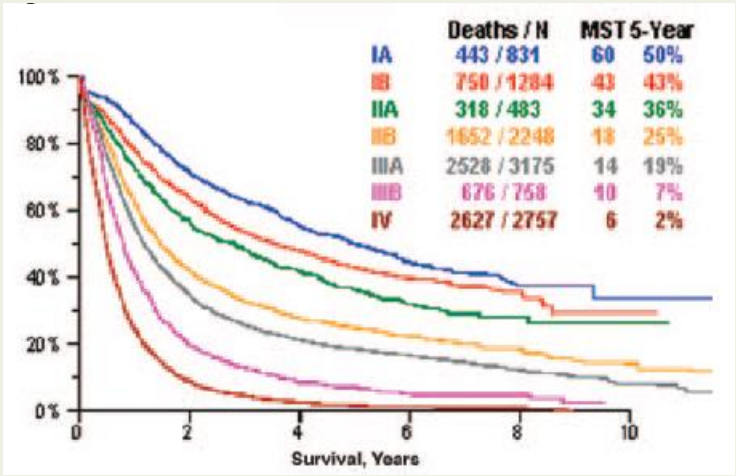
Standard of care and Goal of SUMMER



Detterbeck et al, Chest, 2009

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.

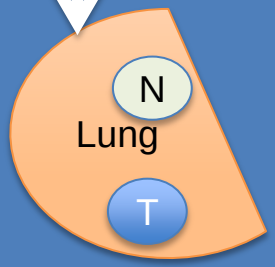
The **overarching goal** is to decrease the number of patients relapsing at 12 months.

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.

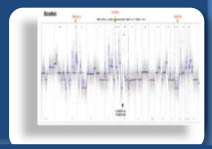
SUMMER overview workflow

Curative Surgery
Tumor and Normal tissues obtained from resection

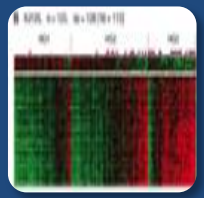


Inclusion: NSCLC stage II A&B, IIIA

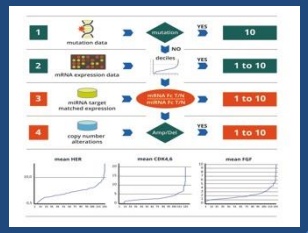
NGS
CNV



Expression mRNA
miRNA
Protein



SIMS integrative algorithm & score



Randomization

Liquid biopsies

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

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

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

(*) 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

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

Central Platforms

- 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.

Nodes	Components of the inteventional points	Examples of drugs acting on interventional points
HER	EGF, TGFA, AREG, EREG, HBEGF, BTC, NRG1, NRG2, NRG4, EGFR, ,ERBB2 , ERBB3, ERBB4	Afatinib Dacomitinib-(Pan-Her inhibitor)
CDK4, 6	CDK4, CDK6, CCND1, CCND2, CCND3, CDKN2A, CDKN2B, CCNE1, CCNE2, CCNE3, RB1	Palbociclib (CDK4,6 inhibitor)
PLK/ AURK	PLK1, AURKA, BORA, ILK, KIF11	Aurora A kin inhib
Angio genes	VEGFA, VEGFB, VEGFC, VEGFD, VEGFR1, VEGFR2, VEGFR3, PDGFA, PDGFB, PDG-FRA, PDGFRB, Kit	Axitinib Motesanib
Angio poietins	THBS1, TGFB1, ANGPT1, ANGPT2, ANGP-TL1, ANGPT4, TIE1, TEK	-
Immune modulator	PD1L, PDCD1LG2, PDCD1, CTLA4, LAG3	Ipilimumab (CTLA4); Tremelimumab (CTLA4), Nivolumab (PD1); AMP514 (PD1), Pidilizumab (PD-1); MED14736 (PD-L1) PF-05082566 (4-1 BB)
PI3K	PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3C2B, PRKCB, PRKCA, PRKCB, PIK3R1, PIK3R2, PIK3R3	PF-384 (PI3K/mTOR-inhibitor) AZD8186 (PI3Kb) PI3Kalpha inhibitor
MET	HGF, MET, AXL, MST1R	Crizotinib, Cabozantinib, Volitinib (cMet)
MEK	MAP2K1, MAP2K2, MAP2K3, MAP2K4, MAP3K1, MAP3K2, MAP3K3, MAP3K4	Trametanib Selumetinib (MEK)
ERK	MAPK3, MAPK1, KSR1, MAPK11	-
Anti-apoptosis	BCL2, BCLXL, BIRC5, XIAP, BAk, TP53	ABT-199 (BCL-2) MK-1775 (Wee-1 inhibitor; p53)
FGF	FGF1 to FGF18, FGFR1, FGFR2, FGFR3, FGFR4	Lenvatinib , Lucitanib AZD4547 (FGFR1, 2, 3)
mTOR	mTor, AKT1, AKT2, PTEN, TSC1, TSC2, STK11, PIM1, PIM2, PIM3	Everolimus, Temsirolimus PF-384 (PI3K/mTOR inhibitor) AZD2014 (TOR kinase) ; AZD5363 (AKT1, 2 ,3) AZD1208 (PIM1, 2) ; TORC1/TORC2 inhibitor
Ras/Raf	KRAS, NRAS, HRAS, RAF1, BRAF, CRAF	Trametinib,Vemurafenib, Dabrafenib Pan-RAF inhibitor
Telomerase	TERT, TERC, TEP1, HSP90AA1, DKC1, PTGES3	-
IGF	IGF1,IGF2,IGF1R,IGF2R,INSR,IRS1,PKM	Cixitumumab Medi-573 (IGF)
Wnt	CDH1, CTNNA1, CTNNB1, WNT 1, FZD1, WNT5A, B, FZD5, WIF1, DKK1	PRI-274
PARP	PARP1, BRCA1, XRCC1, RAD54L, RAD54B, ATM, ATR, CHEK1, CHEK2, WEE1	Olaparib (PARP) AZD1775 (Wee1) AZD6738 (ATR)
HDAC	HDAC1, HDAC2, HDAC3, HDAC4, HDAC5	Vorinostat
JAK-STAT	JAK1, JAK2, STAT1, STAT2, STAT3, SOCS1	Riluxitinib; AZD9150
Hedgehog	SHH, PTCH1, SMO, STK36, PRKACA, SUFU,	Vismodegib
NOTCH	NOTCH1, Adam17, PSEN1, NCSTN, JAG1, SRRT, APH1A	LY3039478
DNA Repair	ERCC1, RAD52, XRCC4, RAD51, BRCA1, NEDD8, NAE1	NEDD8 activating enzyme inhibitor
Others	RET, ALK, ROS1, UB1	Crizotinib, Ceritinib,Sorafenib, Cabozantinib