PERSONALISED COMBINATORIAL APPROACHES TO CLOSING DOWN ALL THE KEY ONCOGENIC DRIVERS

THE AVERA TEAM
OUR TEAM IS ADMINISTERING SEQUENCE-BASED DOUBLE AND TRIPLE THERAPIES NOW
Coexpression of patterns of MYC activation and estrogen independence predicts poor outcome following adjuvant tamoxifen
ER+

- PIK3CA + Loss of function mutations in MAP3K1
- PIK3CA - Loss of function mutations in MAP3K1
- Mutual exclusivity with loss of function MAP2K4 mutations
- GATA 3 ≈ type and duration of endo $R_X$
- Loss of function mutations of RUNX1 (endo resist)
- MLL3 (and lower frequency MLL2) mutations
- 30% Lum B are p53 mutant, and 30% exhibited amplification of the p53 inhibitor, MDM2.
- CDK4 and CDK6 play an important role in estrogen-stimulated proliferation in mid G1 phase.
- MYC
A simplified therapeutic roadmap based on somatic mutations in luminal-type breast cancer

Ellis M J, and Perou C M Cancer Discovery 2013;3:27-34
HER2

• Tumor invasion and metastasis (eg, CXCR4, PLAU, CX3CR1, TGFBR3, and STAT5A)
• Increased PI3K signaling and IGF1R
• Low immune response phenotype/levels observations of lower lymphocytic infiltration
• TCGA; 2 subgroups:
  – High levels of EGFR, Her2 protein phosphorylated and tendency to be ER-
  – Lower level DNA amplification, lower protein-based signaling and tendency to be ER+/luminal.
  – Are these biomarkers of tras and/or lap sensitivity? ESMO data re duration: ER+ vs ER-
• 75% TP53 / 30% PIK3CA / 5% PIK3R1 mutations
• TCGA: 8 somatic Her2 mutations (4 lobular; only 1 amplified) plus 2 others: sensitivity to Neratinib > Lapatinib
BASAL

- Similar to tumors arising from basal layer of epidermis, squamous CA = platinum sensitive diseases/TP53 only gene recurrently deleted in basal-like disease
- Presence of both germline and somatic BRCA1 and BRCA2 → PARP inhibitors (PrE0105)
- plethora of amplification and deletion candidates: EGFR, cKIT, PDGFRA/B, FGFR1-4, FGF ligands, c-MET
- 9% PI3KCA mutation, more frequent deletion, mutation or loss of negative regulators, such as PTEN (35%) and INPP4B (30%)
- MAGI2-AKT3 gene fusion is unique to basal
- Mesenchymal-like TNBC subtypes are sensitive to dasatinib and NVP-BEZ235
- Differential sensitivity of the LAR TNBC subtype to AR and Hsp90 inhibitors
ADENOCARCINOMA OF LUNG

• *EGFR* mutation
• *ALK*
• *ROS1*
• *TRK1*
• *kRAS*
• *HSP90*
• *MET*
• *HER2*
• *BRAF*

• They have moved to In-house Foundation Medicine Assay
SQUAMOUS CARCINOMA OF THE LUNG

Integration of orthogonal datasets: biologically relevant mutated genes in SCLC

R. Thomas & LCGC, Nat Genetics, 2012
Figure 2 Comparison of resected and autopsy samples and identification of candidate driver mutations. (a) Comparison of broad structural genome alterations between surgically resected and autopsy samples. Analysis is based on absolute copy numbers determined using a reconstruction of the allelic state (Supplementary Note). A broad alteration is determined to be present if one-fourth of the chromosome arm is altered accordingly. Differences between resected and autopsy samples of broad SCNAs in 3p, 3q, 5p, 13q and 17p were statistically tested by Fisher’s exact test. (b) Distribution of the mutation frequency observed in SCLC. The average of the mutation frequency in SCLC (red line and text) is compared to various tumor types taken from recent large-scale sequencing studies of melanoma (MEL), SCLC, breast cancer (BC), ovarian cancer (OC), multiple myeloma (MM), ovarian clear cell carcinoma (OCC), prostate cancer (PC), renal cell cancer (RC), and chronic lymphocytic leukemia (CLL). (c) Schematic showing the various steps of our integrated analysis and filtering procedures. All candidate driver genes extracted from sequencing were filtered against gene expression data derived from transcription sequencing. SCNAs were identified from SNP arrays, and candidate SCNA regions that were represented by only a single SCLC sample were subsequently removed. (d) Candidate driver genes identified by significance analysis, presence in the COSMIC (Catalogue of Somatic Mutations in Cancer) database, clustered mutations and genes that are also involved in fusion events. The type of each mutation is shown for every sample, including the gene-specific total number of mutated samples.
80yo woman with AR+
locally advanced TNBC, low ki-67
after 6 mos bicalutamide 100mg QD
FGFR1 amplification occurs in >10% of squamous-cell lung cancers and is a novel target in SCC of the lung.

Cologne patient at 100mg
FORWARD GENOMIC ONCOLOGY

Tumor Biopsy

Sequencing & Analysis

Sequencing Tumor Board

1) Actionable
2) Incidental

Buccal swab

Blood (germline)

Informed Consent & Genetic Counselor

Disclosure of Results

Genetic Counselor
FoundationOne™ Report

Patient and ordering physician information

Summary of results and genomic alterations identified

Targeted therapies and clinical trials that may be relevant based on genomic alterations identified
TheraLink Results on Initial Biopsy
Blue: Downregulated & CNV: Loss
Red: Upregulated & CNV: Gain
A 38-year-old man with BRAF-mutant melanoma and miliary, subcutaneous metastatic deposits, treated with PLX4032 (Vemurafenib).

Baseline | 15 weeks | 23 weeks

Wagle N et al. JCO 2011;29:3085-3096
Recommended Treatment

SEQUENCING PROGRESS NOTE

History of present illness: Wanda is a 71 y/o with history of stage IIIIC ovarian cancer.

Treatment Recommendations:

AKT2 amplification - no approved therapies. Clinical trials of Akt inhibitors for various tumor types. mTOR inhibitors everolimus and temsirolimus are FDA approved for other indications.

PIK3CA – mTOR inhibitors everolimus and temsirolimus are FDA approved for other tumor types. Associated with resistance to Egfr-targeted therapies.

CCNE1 amplification – primary resistance to platinum-based treatment in patients with ovarian carcinoma.

MYC amplification – Preclinical evidence suggests may be more sensitive to 5-fluorouracil (5fu) and paclitaxel.

Our treatment recommendation for this patient would be Taxol +/- 5Fu with Everolimus.

We thank you again for the referral and working with us.

Sincerely,

Dr. Brian Leyland-Jones and team
Avera Medical Group Genomic Medicine
## PATIENT RESULTS

- 7 genomic alterations
- 2 therapies associated with potential clinical benefit
- 0 therapies associated with lack of response
- 8 clinical trials

## TUMOR TYPE: UTERUS ENDOMETRIAL ADENOCARCINOMA PAPILLARY SEROUS

### Genomic Alterations Identified†
- *PIK3CA* C420R
- *PIK3R1* K379fs∗14
- *TP53* Q317∗
- *DNMT3A* splice site 2322+1G>T
- *MYD88* L265P
- *PPP2R1A* R183W
- *PRDM1* truncation exon 1

†For a complete list of the genes assayed and performance specifications, please refer to the Appendix

‡See Appendix for details

## THERAPEUTIC IMPLICATIONS

<table>
<thead>
<tr>
<th>Genomic Alterations Detected</th>
<th>FDA Approved Therapies (in patient’s tumor type)</th>
<th>FDA Approved Therapies (in another tumor type)</th>
<th>Potential Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>PIK3CA</em> C420R</td>
<td>None</td>
<td>Everolimus Temsirolimus</td>
<td>Yes, see clinical trials section</td>
</tr>
<tr>
<td><em>PIK3R1</em> K379fs∗14</td>
<td>None</td>
<td>Everolimus Temsirolimus</td>
<td>Yes, see clinical trials section</td>
</tr>
<tr>
<td><em>TP53</em> Q317∗</td>
<td>None</td>
<td>None</td>
<td>Yes, see clinical trials section</td>
</tr>
<tr>
<td><em>DNMT3A</em> splice site 2322+1G&gt;T</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><em>MYD88</em> L265P</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><em>PPP2R1A</em> R183W</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><em>PRDM1</em> truncation exon 1</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
1. **Hypermorphic mutation**
   - Activation of PI3K Pathway – Everolimus ok

2. **Hypomorphic mutation**
   - No true activation of PI3K pathway -

3. **Neomorphic mutation**
   - Activation of RAS-MAPK Pathway initiated – Need to use in combo with MEKi
Different EGFR mutations while all activating EGFR machinery/pathway, may respond to distinct therapeutic interventions.

• In general, the exon 19 aberrations such as L747_A750 del that delete the four amino acids LERA, as well as the L858R at exon 21 mutation, are sensitive to reversible EGFR tyrosine kinase inhibitors including erlotinib and gefitinib.

• In contrast, in-frame insertions and/or duplication of 3 to 21 base pairs clustered between codons 761 and 774 in EGFR exon 20 are resistant to both reversible and irreversible tyrosine kinase inhibitors (TKIs);

• T790M in exon 20 mutations are also resistant to some irreversible TKIs, such as afatinib in the clinic but recent studies suggest that dual inhibition of EGFR with cetuximab plus afatinib showed some activity. Interestingly, 3rd generation mutation-specific EGFR inhibitor AZD9291 showed good efficacy in lung cancer patients who have EGFR T790M mutation.

Pradip De
Dabrafenib/Trametinib Extends OS Versus Vemurafenib in Phase III Melanoma Trial

• A phase III study comparing trametinib (Mekinist) plus dabrafenib (Tafinlar) with single-agent vemurafenib (Zelboraf) has been stopped early following a positive interim analysis, according to an announcement from GlaxoSmithKline (GSK), the company developing the combination.

• The randomized trial, labeled COMBI-v, investigated the combination in 704 patients with stage IIIc or IV BRAF V600E/K-mutated melanoma. The decision to stop the trial early followed a recommendation from an independent data monitoring committee that found a significant prolongation in the primary endpoint of overall survival (OS) during an interim analysis.
1. Although RAF inhibitors such as vemurafenib have produced impressive response rates of approximately 60%-80% in patients with BRAF–mutant melanoma but vemurafenib demonstrated disappointing results in patients with BRAF mutants colorectal cancer.

2. Data show that rapid EGFR-mediated reactivation of the MAPK pathway (mainly p-ERK) contributes to the relative insensitive of BRAF-mutants CRC cells to vemurafenib. Laboratory data also show that concomitant inhibition of RAF and EGFR in BRAF-mutant CRC leads to sustained suppression of MAPK signaling and to markedly increased therapeutic efficacy in vitro and in vivo.

3. That means EGFR–mediated reactivation of MAPK signaling in BRAF-mediated CRC leads to incomplete p-ERK suppression to vemurafenib, resulting in reduced sensitivity.
Genomic Oncology Challenges

• Extremely complex in most cases: recent biopsy is critical

• Available assays all have significant weaknesses
  – Quality and tumor content of sample
  – Quality of DNA, RNA, and protein
  – Storage and shipping methods
  – ? Germline
  – Multi-platform
  – Approved drugs only: INSURANCE!!
  – Sensitivity: what is needed for response

• Pharmacology of combination treatments needs to be critically evaluated
• A change in HER2 status was observed in 26% of cases
• 5/31 (16%) cases underwent a negative to positive conversion in HER2
• 3/31 (10%) cases underwent a positive to negative conversion
• All 5 patients that underwent a negative to positive conversion in HER2 had disease that was metastatic to the liver
• Overall, 45% (5/11) of patients with metastatic disease in the liver had a negative to positive conversion in HER2 status
### Patient Results

- 1 genomic alteration
- 0 therapies associated with potential clinical benefit
- 0 therapies associated with lack of response
- 4 clinical trials

### Tumor Type: Ovary Serous Carcinoma

**Genomic Alteration Identified\(^\d\)**

7P53 F134L

\(\d\)For a complete list of the genes assayed and performance specifications, please refer to the Appendix.

\(\d\)See Appendix for details.

### Therapeutic Implications

<table>
<thead>
<tr>
<th>Genomic Alterations Detected</th>
<th>FDA Approved Therapies (in patient's tumor type)</th>
<th>FDA Approved Therapies (in another tumor type)</th>
<th>Potential Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53 F134L</td>
<td>None</td>
<td>None</td>
<td>Yes, see clinical trials section</td>
</tr>
</tbody>
</table>

Patient is known germ-line BRCA2 + and Lynch +
A.K. History
1/28/1980
Colon adenocarcinoma

- July 2013: laparoscopic right hemicolectomy. Path showed invasive moderately differentiated adenocarcinoma with mucinous features. Positive lymphovascular invasion and 5/31 lymph nodes positive.
- August 2013 – January 2014: FOLFOX x 12 cycles. Oxaliplatin stopped after 10 cycles due to neuropathy. Follow up CT c/a/p showed new lesion in liver
- January 2014: biopsy of liver lesion revealed metastatic adenocarcinoma consistent with colonic primary. PET/CT showed uptake in the liver lesion
- February 2014: resection of liver lesion. Path showed tumor to be K-ras wild type. Re-imaging performed prior to initiation of chemo, which showed concerning lymph nodes and other questionable areas in liver.
- April 2014 – May 2014: FOLFIRI + cetuximab. Experienced significant flare of acne rash on face, scalp, upper chest, and back. Switched cetuximab to avastin (has received 3 cycles of chemo – last cycle without cetuximab or avastin)
- May 2014: Having significant chest pain and was admitted to hospital. Progressive disease noted in liver and new substernal soft tissue mass.
A.K. Foundation Medicine

<table>
<thead>
<tr>
<th>Genomic Alterations Detected</th>
<th>FDA Approved Therapies (in patient’s tumor type)</th>
<th>FDA Approved Therapies (in another tumor type)</th>
<th>Potential Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAF V600E</strong></td>
<td>Regorafenib</td>
<td>Dabrafenib, Trametinib, Vemurafenib</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>CDKN2A p16INK4a A57V</strong></td>
<td>None</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>MYC Amplification</strong></td>
<td>None</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>TP53 R175H</strong></td>
<td>None</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>APC S1545fs<em>1, T1556fs</em>3</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>SMAD4 R361C</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
A.K. TheraLink
A.K. Recommendations

• Foundation One testing shows the following alterations:
  – BRAF matched to regorafenib, dabrafenib, trametinib, and vemurafenib
  – Added Oxaliplatin (since targeted + chemo- therapies synergistic and supported by p53)
  – MYC amplification (potential increased sensitivity to fluorouracil and taxanes)

• Based on this information we suggest for therapy to start with dabrafenib, trametinib, and oxaliplatin.
A.K. Outcome

- 8/20/14 tolerating treatment well
- 8/20/14 CT showed impressive response to therapy with interval decreased size of multiple thoracic and abdominal/pelvic lymph nodes and interval decreased size of known hepatic metastatic lesions. No new lesions.
- CT end of January 2015 showed complete resolution of evaluable disease
CH

- 63 yr. old female with stage IIIIC ovarian adenocarcinoma. 4 prior lines of therapy
- Key FM alterations: No actionable targets
- Key Theralink alterations: FGF.ReceptorY653.65(3+); pErk1/2(2+)
- Therapy: Trametinib, Pazopanib, Topotecan
- Outcome: CA-125 decreased from 522 to 287 after 8 weeks of therapy
TK

- 32 yr. old female with stage IIIIC ovarian adenocarcinoma. 3 prior lines of therapy
- Key FM alterations: KRAS G12D
- Key Theralink alterations: pmTOR (2+); pMek1/2 (2+); pErk1/2 (3+)
- Therapy: trametinib, dabrafenib, carbo x 8 weeks. Came off dabrafenib due to AEs, continues with trametinib
- Outcome: virtual CR - CT shows peritoneal calcifications after 15 weeks therapy consistent with treated disease. CA-125 almost normalized. (recently added everolimus to trametinib)
BUT ........
J.J.S. History
10/16/1950
ER-PR-HER2-

• January 10th, 2014 biopsy showing breast metaplastic squamous cell carcinoma. Tumor markers were triple negative. Treated neoadjuvantly.

• February 5th, 2014 began standard TC (docetaxel and carboplatin).
<table>
<thead>
<tr>
<th>Genomic Alterations Detected</th>
<th>FDA Approved Therapies (in patient’s tumor type)</th>
<th>FDA Approved Therapies (in another tumor type)</th>
<th>Potential Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HRAS G12D</strong></td>
<td>None</td>
<td>Trametinib</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>CDKN2A/B loss</strong></td>
<td>None</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>MLL2 P1131L</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
Theranostics Report
JS Results

• March 5\textsuperscript{th}, 2014 added cetuximab to regimen based upon TheraLink. Trametinib refused by insurance company.

• Had a pathologic complete response to neoadjuvant therapy

• Received carboplatin and docetaxel + cetuximab
  – Continues to be in CR
• 48 yr. old female with stage III C ovarian adenocarcinoma. 2 prior lines of therapy

• Key FM alterations: PTEN loss

• Key Theralink alterations: pHER2 (2+); HER3 (2+); pHER3 (2+); 4E.BP1S65 (2+)

• Therapy: Cisplatin + everolimus for 4 months. Trastuzumab & pertuzumab then added for 6 months.

• Outcome: NED on imaging and normalized CA-125. CR after 12 weeks. Sustained CR at 1 year
Results: Genomic and proteomic analysis yielded actionable targets in a majority of cases (89%). The most common pathways involved were the following: PI3K/Akt/mTOR (73%), MAPK (46%), ErbB (36%), FGFR (25%), and Jak/STAT (11%). Over 100 unique molecular aberrations were identified in 40 evaluable patients. Current outcomes are summarized in Table 1. The overall response rate was 45%, with another 43% of patients with stable disease. Average number of prior therapies was over 4, with a range of 1-11.

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>NE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ER+/HER2-</strong></td>
<td>3</td>
<td>8</td>
<td>15</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td><strong>ER+/HER2+</strong></td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td><strong>ER-/HER2+</strong></td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Triple Negative</strong></td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total evaluable patients = 40</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overall CR = 13%</strong></td>
<td><strong>Overall PR = 33%</strong></td>
<td><strong>Overall SD = 43%</strong></td>
<td>Overall PD = 13%</td>
<td>Total Not Evaluable = 37 pts (48%)</td>
<td></td>
</tr>
<tr>
<td><strong>Overall Response Rate (ORR) = 45%</strong></td>
<td><strong>CBR = 88%</strong></td>
<td><strong>ORR = 45%</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Gynecologic Cancer

- Enrolled = 34
- Evaluable = 15/34
- Complete Responses (CR) = 20%
- Partial Responses (PR) = 50%
- Stable Disease (SD) = 21.4%
- Progressive Disease (PD) = 14.2%
- Overall Response Rates (ORR) = 70%
- Clinical Benefit Rate = 91.4%
- PFI > 6 mo = 35.7%
- MPFI 16 (0-45) Wk
- MDR = 33 (15 – 45) wks

PFI: Progression free interval, MPFI: median PFI, MDR : median duration of response
Pathology documented, Stage III or IV ovarian, fallopian tube or peritoneal carcinoma, not amenable to optimal debulking surgery at diagnosis.

Randomization 2:1

Genomic & Proteomic assay data directed targeted therapy

3-6 courses of
Carboplatin AUC 4 Q 21 days
Paclitaxel 80 mg/m^2
+ sequence-directed
Targeted Agent(s)

Surgery

3 courses of
Carboplatin AUC 5 Q 21 days
Paclitaxel 80 mg/m^2 weekly

Surgery

3 courses of
Carboplatin AUC 5 Q 21 days
Paclitaxel 80 mg/m^2
+ assay-directed
Targeted Agent(s)
Neoadjuvant Biospecimens Collection

TIMELINE

Neoadjuvant Treatment

Baseline
Start Treatment
3 weeks
Other Cycles
9 weeks
Evaluation (at Clinician’s discretion)
Surgery

SCREENING:
Eg, CT/PET MUGA/ECHO + CONSENT

Tumour Biopsy
Cores: 1-2 FFPE+ 5 FROZEN

Serum, Plasma
Whole blood
MRI
Ki67

Tumour Biopsy
Cores: 1-2 FFPE+ 5 FROZEN

Serum, Plasma
MRI
Ki67

Tumour Biopsy
Cores: 1-2 FFPE+ 5 FROZEN

Serum, Plasma
MRI
RULES (ER+: Grade 1)

FIRST TIMEPOINT:
1. If Ki67<14, start with TAM/AI.
2. If marked decrease in Ki67 and MRI at 3 week timepoint, continue on TAM/AI alone.
3. If Ki67/MRI not improving at 3 weeks, add in CDK4/6 inhibitor. Also look to see which parallel pathways are stimulated at this time, and add in another agent accordingly.
4. At 3 week timepoint, screen for PD1 and PDL-1 as marker for anti-PD1 and anti-PDL-1 therapy.
5. At 9 week timepoint, re-evaluate*. If decreasing, continue on current therapy.
6. At 9 week timepoint, if MRI increasing, rebiopsy, sequence: treat parallel pathways.

* At clinician’s discretion: Phys exam, U/S, MRI…
RULES (ER+: Grade 2 and 3)

FIRST TIMEPOINT:
1. If Ki67>14, start with paclitaxel + whatever is indicated by sequencing.
2. If marked decrease in Ki67 and MRI at 3 week timepoint, continue on this therapy (but also treat parallel pathways based upon 3 week sequencing).
3. If Ki67/MRI not improving at 3 weeks, add in aggressively according to 3 week sequencing data.
4. At 3 week timepoint, also screen for PD1 and PDL-1 as marker for anti-PD1 and anti-PDL-1 therapy.
5. At 9 week timepoint, re-evaluate. If decreasing, continue on current therapy.
6. At 9 week timepoint, if MRI increasing, change to TAM/AI + CDK4/6 inhibitor and rebiopsy, sequence: treat parallel pathways.
RULES (HER2+/ER+)

FIRST TIMEPOINT:
1. If T1/Node -ve, start with taxol, tras +tam/AI.
2. If marked decrease in Ki67 and MRI at 3 week timepoint, continue on taxol, tras, tam/AI.
3. If Ki67/MRI not improving at 3 weeks, add in pert + treat aggressively according to 3 week sequencing data.
4. At 3 week timepoint, also screen for PD1 and PDL-1 as marker for therapy.
5. At 9 week timepoint, re-evaluate. If decreasing, continue on current therapy.
6. If tumour continues not to respond, rebiopsy, sequence: treat parallel pathways.
RULES (HER2+/ER+)

FIRST TIMEPOINT:
1. If T2+ or any Node +ve, start with TCHP +tam/Al.
2. If marked decrease in Ki67 and MRI at 3 week timepoint, continue on TCHP +tam/Al.
3. If Ki67/MRI not improving at 3 weeks, treat aggressively according to 3 week sequencing data.
4. At 3 week timepoint, also screen for PD1 and PDL-1 as marker for anti-PD1 and anti-PDL-1 therapy.
5. At 9 week timepoint, re-evaluate. If decreasing, continue on current therapy.
6. If tumour continues not to respond, rebiopsy, sequence: treat parallel pathways.
RULES (HER2+/ER-)

FIRST TIMEPOINT:
1. If T1/Node -ve, start with TCH.
2. If marked decrease in Ki67 and MRI at 3 week timepoint, continue on TCH.
3. If Ki67/MRI not improving at 3 weeks, add in pert + treat aggressively according to 3 week sequencing data.
4. At 3 week timepoint, also screen for PD1 and PDL-1 as marker for anti-PD1 and anti-PDL-1 therapy.
5. At 9 week timepoint, re-evaluate. If decreasing, continue on current therapy.
6. If tumour continues not to respond, rebiopsy, sequence: treat parallel pathways.
RULES (HER2+/ER-)

FIRST TIMEPOINT:
1. If T2+ or any Node +ve, start with TCHP.
2. If marked decrease in Ki67 and MRI at 3 week timepoint, continue on TCHP.
3. If Ki67/MRI not improving at 3 weeks, treat aggressively according to 3 week sequencing data.
4. At 3 week timepoint, also screen for PD1 and PDL-1 as marker for anti-PD1 and anti-PDL-1 therapy.
5. At 9 week timepoint, re-evaluate. If decreasing, continue on current therapy.
6. If tumour continues not to respond, rebiopsy, sequence: treat parallel pathways.
RULES (TN)

FIRST TIMEPOINT:

1. If T1/Node -ve, start with Taxol 90 weekly x12 or Taxotere 75/m2+CTX 600/m2 q 3weekly. If MIP signature positive, start with Taxol 80 weekly x12 + 3-weekly carbo AUC 6.0.

2. If marked decrease in Ki67 and MRI at 3 week timepoint, continue on original chemo regimen.

3. If Ki67/MRI not improving at 3 weeks, treat aggressively according to 3 week sequencing data (and reduce chemo dose to accommodate new targeted therapy).

4. At 3 week timepoint, also screen for PD1 and PDL-1 as marker for anti-PD1 and anti-PDL-1 therapy.

5. At 9 week timepoint, re-evaluate. If decreasing, continue on current therapy.

6. If tumour continues not to respond, rebiopsy, sequence: treat parallel pathways.
RULES (TN)

FIRST TIMEPOINT:
1. If T2+ or any Node +ve, start with Taxol 80 weekly x12 + 3-weekly carbo AUC 6.0.
2. If marked decrease in Ki67 and MRI at 3 week timepoint, continue on original chemo regimen. reduce doses of T(+/-C) sufficiently, in order to add in treatment according to 3 week sequencing data.
3. If Ki67/MRI not improving at 3 weeks, treat aggressively according to 3 week sequencing data (and reduce chemo dose to accommodate new targeted therapy)
4. At 3 week timepoint, also screen for PD1 and PDL-1 as marker for anti-PD1 and anti-PDL-1 therapy.
5. At 9 week timepoint, re-evaluate. If decreasing, continue on current therapy.
6. If tumour continues not to respond, rebiopsy, sequence: treat parallel pathways.
Baseline

3 weeks

9 weeks

Surgery

Start Treatment

Other Cycles

Blood draw

Blood draw

Blood draw

CT SCAN

CT SCAN

CT SCAN (prior to surgery)

Tumour Biopsy
Cores: 2 FFPE+ 5 FROZEN

Tumour Biopsy (only if residual disease)
Cores: 2 FFPE+ 5 FROZEN

Tumour Biopsy
Cores: 2 FFPE+ 5 FROZEN

CT SCAN (prior to surgery)
1. We have run triplet trials (although many are doublet added on to standard therapy) on an N-of-One basis, often without prior Phase 1’s.

2. WE HAVE BEEN VERY CAREFUL RE DOSING.

3. We have had unusual successes, albeit a small “n”, by attempting to close down all the somatic drivers.

4. Potential combination toxicities have been anticipated and extremely well controlled.