Innovative Clinical Trial in the Era of Genomics

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Contents

- Overview of precision medicine
- Genomics-driven clinical trials
- **Oncoseq** in patients with refractory MBC in SMC
- Incorporation of immune-oncology into precision medicine
Genetic Heterogeneity in Human Disease

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Strong evidence suggests that rare mutations of severe effect are responsible for a substantial portion of complex human disease. Evolutionary forces generate vast genetic heterogeneity in human illness by introducing many new variants in each generation. Current sequencing technologies offer the possibility of finding rare disease-causing mutations and the genes that harbor them.

“Happy families are all alike; each unhappy family is unhappy in its own way.”

Leo Tolstoy, Anna Karenina
Enabling Components for Genomics-driven Cancer Medicine

“Tonight, I'm launching a new **Precision Medicine** Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier.”
Declaring War Against Cancer

The signing of the National Cancer Act of 1971 by then U.S. President Richard Nixon is viewed as the beginning of the war on cancer.

President Richard Nixon signs the National Cancer Act, Dec. 23, 1971, launching a $1.6 billion federal crusade to conquer cancer. (AP)
JOIN US WEDNESDAY
FOR REMARKS FROM VICE PRESIDENT
JOE BIDEN

Wednesday, April 20
Plenary Hall F
Doors open at 10:15 AM

AACR Annual Meeting
American Association for Cancer Research
2016 • NEW ORLEANS
The workflow of integrating omics data in cancer research and clinical application

Patient

Technologies

Genomics
WGS, WES

Transcriptomics
RNA-Seq

Epigenomics
Bisulfite-Seq
ChIP-Seq

Data Analysis

point mutation
Small indels
Copy number variation
Structural variation
Differential expression
Gene fusion
Alternative splicing
RNA editing
Methylation
Histone modification
Transcription Factor binding

Integration and interpretation

Functional effect of mutation
Network and pathway analysis
Integrative analysis

Further understanding of cancer and clinical applications
‘Genomic Tsunami’

Analysis of this big data is launching the era of precision medicine—but enormous scientific, engineering and institutional challenges remain.

“You’re shooting yourself in the foot if you’re collecting data you don’t know how to interpret.”

Nature 2009, 458; 719-724

November 2015 / Vol 527 / Issue No 7576
Breast Cancer Treatment in 10 years

Predictions

- The era of HER2 is almost over.
- BRCA testing will become ubiquitous.
- We will continue to target proliferation and survival pathways.
- Cancer genomics will become ubiquitous, but we won’t like what we find.
- We will need to do something different.
In late 2015, the ASCO is expecting to launch CancerLinQ, a platform designed to deliver clinical benefits by analyzing aggregated electronic health records from thousands of oncology practices.

“Much of what we know about treating cancer comes from clinical trials that enroll just 3% of the patients diagnosed with cancer every year,”

“With CancerLinQ, we’re trying to learn from the remaining 97% who don’t participate in these studies.”
1. Vaccines to prevent public health epidemics
2. Genomic directed clinical trials
3. Gene editing using CRISPR
4. Water purification system for prevention of infectious diseases
5. Cell-free fetal DNA testing
6. Cancer screening via protein biomarker analysis
7. Naturally controlled artificial limbs
8. First-ever treatment for HSDD
9. Frictionless remote monitoring
10. Neurovascular stent retriever
Randomized trial designs with integral biomarkers

- Basket design
- Umbrella design
- Enrichment design with biomarker
- Stratified design according to with or without biomarker
- Hybrid design
Clinical trial designs utilizing molecular profiling

**Umbrella trials**
- Multiple drugs targeting multiple mutations
- Variety of tumors carrying a variety of genetic aberrations X, Y, & Z
- Randomized or nonrandomized
- Rules-based treatment assignment or per patient based on review of individual profile data

**Same tumor type**
- Molecular profile
- Drug A
- Drug B
- Drug C

**Variety of tumor types**
- Drug A
- Drug B
- Drug C
- Drug A

**Basket or bucket trials**
- Single drug targeting a single mutation
- Variety of subtypes carrying glioblastoma aberration X

**Exceptional responder trials**
- Any cancer type and drug where a patient had an unusually robust clinical benefit

**Tumour type A** (lung cancer)
- Tumour molecular analysis
- Biomarker 1
- Biomarker 2
- Biomarker 3
- Biomarker 4
- Drug 1
- Drug 2
- Drug 3
- Drug 4

**Tumour type B** (gastric cancer)
- Tumour type C (colon cancer)
- Tumour type D (breast cancer)

## Precision-medicine clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Tumour</th>
<th>Phase/design</th>
<th>Location</th>
<th>Arms</th>
<th>Patients†</th>
<th>Clinical trial ID</th>
<th>References</th>
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<td>Bisgrove</td>
<td>All</td>
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<td>18</td>
<td>460</td>
<td>NCT02299999</td>
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<td>Lung MATRIX</td>
<td>NSCLC</td>
<td>Phase II stratified, non-randomized</td>
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<td>21§</td>
<td>2,000</td>
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<td>FOCUS 4</td>
<td>Colorectal cancer</td>
<td>Phase II/III randomized</td>
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<td>4</td>
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<td>Australia</td>
<td>4</td>
<td>90</td>
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</table>

"Master protocol" or "Platform protocol"

*Nature 2015, 526; 361-370*
Screening programmes that feed into precision-medicine trials

<table>
<thead>
<tr>
<th>Programme</th>
<th>Cancer Type</th>
<th>Stage/Type</th>
<th>Country</th>
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<th>Budget</th>
<th>NCT Number</th>
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<td>I-SPY</td>
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<td>Genomic, imaging</td>
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<td>United States</td>
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<td>3,000</td>
<td>NCT02299648</td>
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<td>VIKTORY</td>
<td>Gastric cancer</td>
<td>Screening, route to phase II</td>
<td>Asia</td>
<td>NGS, other#</td>
<td>600</td>
<td>NCT02299648</td>
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<td>LC-SCRUM</td>
<td>NSCLC</td>
<td>Screening, route to phase II/III</td>
<td>Asia</td>
<td>As needed**</td>
<td>Open††</td>
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<td>AURORA</td>
<td>Breast cancer</td>
<td>Screening, route to phase I/II/III</td>
<td>European Union</td>
<td>NGS, other‡‡</td>
<td>1,300</td>
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<td>SPECTAColor</td>
<td>Colorectal cancer</td>
<td>Screening, route to phase I/II/III</td>
<td>European Union</td>
<td>NGS</td>
<td>2,600</td>
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<td>Lung</td>
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<td>NGS</td>
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<td>CGH array, sequencing</td>
<td>1,050</td>
<td>NCT01566019</td>
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<td>SAFIR 01</td>
<td>Breast cancer</td>
<td>Screening, route to phase I/II</td>
<td>France</td>
<td>CGH, sequencing, gene expression array</td>
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<td>NCT01414933</td>
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<td>CRUK SMP1</td>
<td>Selected</td>
<td>Screening, feasibility</td>
<td>United Kingdom</td>
<td>Bespoke panel</td>
<td>9,000</td>
<td>N/A</td>
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</tbody>
</table>
The NCI National Clinical Trials Network (NCTN) structure

- ACOSOG (American College of Surgeons Oncology Group)
- CALGB (Cancer and Leukemia Group B)
- NCCTG (North Central Cancer Treatment Group)
- ECOG (Eastern Cooperative Oncology Group)
- ACRIN (American College of Radiology Imaging Network)
- NSABP (National Surgical Adjuvant Breast and Bowel Project)
- RTOG (Radiation Therapy Oncology Group)
- GOG (Gynecologic Oncology Group)
- SWOG (Southwest Oncology Group)

National Clinical Trial Network (NCTN)

- Alliance for Clinical Trials in Oncology
- ECOG-ACRIN cancer research group
- NRG oncology
- SWOG
Adaptive Bayesian Clinical Trial Design

- To avoid getting the wrong answer!
  - Drawing an incorrect qualitative conclusion
- To avoid taking too long to draw the right conclusion
  - Time, human subjects, and resources
Clinical trials testing **large panel of genes** for treatment decision

<table>
<thead>
<tr>
<th>Trial</th>
<th>Technology</th>
<th>n screened</th>
<th>Matched therapy</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>SAFIR01(^1) (breast)</td>
<td>CGH / sanger seq</td>
<td>423</td>
<td>55 (13%)</td>
<td>30% OR and/or SD &gt; 4 months</td>
</tr>
<tr>
<td>MOSCATO</td>
<td>CGH / NGS</td>
<td>368</td>
<td>85 (23%)</td>
<td>Not available</td>
</tr>
<tr>
<td>MDACC(^3)</td>
<td>11-50 genes</td>
<td>2 000</td>
<td>83 (4%) (P1 trials)</td>
<td>Not available</td>
</tr>
<tr>
<td>Princess Margaret(^4)</td>
<td>48 genes</td>
<td>1595</td>
<td>64 (4%)</td>
<td>22% OR</td>
</tr>
<tr>
<td>T-Gen(^5)</td>
<td>Gene expression</td>
<td>86</td>
<td>66*</td>
<td>27% PFS ratio of ≥ 1.3</td>
</tr>
<tr>
<td>SHIVA(^6)</td>
<td>NGS</td>
<td>741</td>
<td>195(^5)</td>
<td>hazard ratio 0.88, 95% CI 0.65–1.19, p=0.41</td>
</tr>
</tbody>
</table>

No evidence from large clinical trial that sequencing large panel of genes improves outcome!!

Is it a new generation of garbage-in/garbage-out???

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Lessons from Genome Profiling Clinical Trials

• **Why these trials failed?**
  – **Drugs** are not bioactive and/or not well matched to alterations.
  – Method for driver identification is *not* optimal: validated and robust tools to interpret biology at the individual level were not available.

• **Rare mutations are....rare.**
  – Uncommon and rare mutations make it very hard to do studies to get drugs approved.
  – *RCT*(randomized clinical trials) vs. *SOC* (standard of care) can be very difficult: Unappealing to pts and their doctors.
Oncoseq Project for Patients with Refractory MBC in SMC

Screening program for ‘N of 1 trial’ experience in SMC for patients with MBC

- Genomic platform for the treatment of the patients with refractory malignancies in SMC based on multi-omics

- 2012-

- WES, WTS, CancerSCAN (targeted sequencing)
Work flow for NGS

1. Informed Consent
2. Surgery
3. Tissue delivery
4. Core biopsy
5. Pathology QC
6. DNA/RNA extraction
7. DNA/RNA QC
8. NGS
Metastatic Breast Cancer between 2012 and 2015 at Samsung Medical Center
(N=129, Sample=170)

Unavailable tissue & Pathology QC failure (N=16)

N=154

low volume tissue & FFPE (N=49)

DNA extraction N=154

DNA QC failure (N=42)

CS or WES (54/92) (N=112)

RNA extraction N=105

RNA QC failure (N=55)

WTS (N=50)

DNA extraction N=154

RNA extraction N=105
MBC WES (WTS paired 34 samples)

- Final mutation data: SNV 3,069 + indel 209 = 3,278
- Most frequent variant: TP53 (n=22 / SNV=14, indel=8)
- 2nd: PIK3CA (n=10, SNV=10)
- TN samples have more SNVs than other groups, especially HER2+.
- ER+/HER2+ samples have fewer indels than other groups.
Case 1.
Medical history (F/36)

# Rt breast ca(pT2(3cm)N(3/8))(ER-/PR-/HER2-)(2007.8)
s/p Rt PM with ALND
s/p AC #4 + paclitaxel #4 + Radiotherapy (2007.10.1-2008.4.28)
- progression on lung (multiple hematogeneous lung metastses) (NED :2Y7M)
s/p palliative PG #20 (2010.03.04-2011.04.18) with CR -> PD
s/p capecitabine #3 (2011.10.24-2012.02.06) -> PD (Pleura)
s/p GP #6 (2012.03.12-2012.07.03) -> SD -> PD
s/p DC #14 (2013.12.16-2014.10.2) -> PR -> PD (Pleura, lung)
s/p eribulin #7 (2015.1.8-2015.6.4) -> SD -> PD
s/p vinorelbine #2 (2015.6.25-2015.7.23)
s/p VATS pleural biopsy and talc pleurodesis, Lt. (2015.8.19)
: metastatic carcinoma, ER/PR/HER2 (+(3)/-/-)ki-67(2+),EGFR(-), AR (-) DDK4/FGFR1 fusion,
FGFR1 amplification (+)
s/p CMF #1 (2015.9.7)
- progression on CNS
s/p WBRT 30Gy/10Fx's (2015.9.16-2015.9.30)
s/p pazopanib (2015.11.20-2016.01.03) with SD
FGFR1
- Fibroblast growth factor receptor 1
- Chr8:38,411,139-38,468,834
- FGFR1 amplification
  - SCLC, SqCC of lung, Breast cancer
- TACC1-FGFR1 (FGFR1-TACC1)
  - Glioblastoma, Prostate cancer, bladder cancer

DKK4
- Dickkopf WNT Signaling Pathway Inhibitor 4
- Chr8:42,229,586-42,236,674
Lead aligned DKK4 is aligned to counter part of FGFR1.
### 1. RT-PCR

<table>
<thead>
<tr>
<th>Class</th>
<th>ChrA</th>
<th>GeneA</th>
<th>DrugA</th>
<th>BreakpointA</th>
<th>Direction</th>
<th>ChrB</th>
<th>GeneB</th>
<th>DrugB</th>
<th>BreakpointB</th>
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</thead>
<tbody>
<tr>
<td>T3</td>
<td>8</td>
<td>DKK4</td>
<td>-</td>
<td>42233274</td>
<td>A&gt;B</td>
<td>8</td>
<td>FGFR1</td>
<td>Fibroblast growth factor receptor1 (DB08577)</td>
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</tbody>
</table>

- **DKK4_FGFR1 Fusion**
  - S03013
  - OB_15_0177_1

- **FGFR1**

- **GAPDH**

S03013 : FGFR1 CN amplification
OB_15_0177_1 : DKK4-FGFR1 fusion

### 2. Q-PCR

**Relative expression levels (FGFR1/GAPDH)**

- S03013
- OB_15_0177_1

### 3. Sequencing

**DKK4 (Exon2)**

**FGFR1 (Intron 2)**

**Breakpoint**
Identification of Targetable FGFR Gene Fusions in Diverse Cancers

Yi-Mi Wu\textsuperscript{1,2}, Fengyun Su\textsuperscript{1,2}, Shanker Kalyana-Sundaram\textsuperscript{1,2}, Nickolay Khazanov\textsuperscript{10}, Bushra Ateeq\textsuperscript{1,2}, Xuhong Cao\textsuperscript{1,7}, Robert J. Lonigro\textsuperscript{1,8}, Pankaj Vats\textsuperscript{1,2}, Rui Wang\textsuperscript{1,2}, Su-Fang Lin\textsuperscript{11}, Ann-Joy Cheng\textsuperscript{12}, Lakshmi P. Kunju\textsuperscript{1,2}, Javed Siddiqui\textsuperscript{1,2}, Scott A. Tomlins\textsuperscript{1,2}, Peter Wyngaa\textsuperscript{d,10}, Seth Sadis\textsuperscript{10}, Sameek Roychowdhury\textsuperscript{1,4}, Maha H. Hussain\textsuperscript{3}, Felix Y. Feng\textsuperscript{1,4,8}, Mark M. Zalupski\textsuperscript{3}.

Case 1: MO\textsubscript{1036}

<table>
<thead>
<tr>
<th>Patient</th>
<th>34-year-old female</th>
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<tbody>
<tr>
<td>Cancer type</td>
<td>Cholangiocarcinoma</td>
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<tr>
<td>SNVs</td>
<td>8 mutations (\textit{ARID1A, PBRM1})</td>
</tr>
<tr>
<td>Gene fusions</td>
<td>8 fusions (FGFR2–BICC1)</td>
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</tbody>
</table>

FGFR2–BICC1 fusion (1663 a.a.)
Aberrant FGFR signalling occurs by diverse mechanisms in many cancer types

**Amplification**

- **FGFR1**: ER+ breast cancer (9-23%), SqNSCLC (10-20%)
- **FGFR2**: Gastroesophageal (9%)

**Fusion**

- **FGFR2**: Cholangiocarcinoma (15%)
- **FGFR3**: Bladder (6%), Glioblastoma (3-7%)

**Mutation**

- **FGFR1**: Endometrial (12%)
- **FGFR3**: Bladder (10%-60%)

Turner N, Grose, R. Nature Reviews Cancer 10, 116–129
Selected overview of clinical trials evaluating FGFR signaling—targeted therapies currently under development.
Case 2
Medical history (F/47)

# breast ca with M/stomach, peritoneum, bone & ovary at 2008 (ER+/PR+/HER2-)
s/p palliative ECX #1 (mis-diagnosed as AGC)
s/p palliative AC #7 (2008.10.08-2009.02.20)
s/p docetaxel #10 (2009.03.17-2009.09.28)
s/p Al + goserelin (2009.12.16-2013.12.30) -> PD (Peritoneal carcinomatosis)
s/p PG #12 (2013.1217-2014.08.18)
s/p tamoxifen (2014.11.10-2015.05.03)
s/p eribulin #11 (2015.5.4-2015.12.28) -> SD -> PD
s/p US guided peritoneum biopsy
: metastatic carcinoma, ER/PR/HER2 +(5)/-/-
HER2 mutation (TKD L755S)
On poziotinib (2016.02.22)
Breast Cancer

• Age <40
• During pregnancy
• Within 1yr after delivery

Young BC clinic
✓ Fast Track Medical Procedure
✓ One Day, One Stop

YBC cohort
✓ Oncoseq2 (YBC)

Surveillance

Localized

Locally advanced

Metastatic Recurrent

CancerScan®, RNASeq, nCounter expression assay

Oncoseq2 (YBC)

Oncoseq2 (YBC)

Oncoseq1,4 (Refractory MBC)

Oncoseq2 (YBC)

Oncoseq3-N (Neoadjuvant)

Oncoseq3-R, M (Recur, Meta)

Oncoseq5 (meta HER2)

PTEN deletion

MARK Inhibitor

EGFR HER2 mutation+, AR pathway

PanHER Inhibitor

Rb pathway

CDK4/6 Inhibitor

Immune pathway

Immune modulator

PIK3CA mutation / pathway

PIK3CA Inhibitor

mTOR/AKT pathway

mTOR/AKT Inhibitor

PanHER Inhibitor

Biomarker Driven Clinical Trial

✓ Biomarker driven personalized medicine
✓ Cancer specific genetic alteration
✓ Drug resistance mechanism for refractory breast cancer

Breast Cancer Precision Medicine Scheme in SMC

Refractory MBC

YBC

Oncoseq 1

WES, WTS

Oncoseq 2

CancerSCAN, WES

Neoadjuvant

Oncoseq 3-N

CancerSCAN, WES, nCounter

Recurrent

Oncoseq 3-R

CancerSCAN, WTS, nCounter

Metastatic 1st line

Oncoseq 3-M

CancerSCAN, WTS, nCounter
Current Limitations of Genomics-driven Clinical Trials Using Multi-Omics

- *Real target?*: oncogenic driver mutation << passenger mutations
- Druggable target??
- Clinical application of Bioinformatics
- Need functional genomics
- Challenging adaptive clinical trial design
- Intra- and/or inter-tumoral Heterogeneity
- *Evolving by-pass tracks* → Resistance to target
- Cancer pathway *Complexity*: multiple targets, cross-talk between pathways
Hope for the Future

- **Treatments to date improve outcomes**
  - in both curative and metastatic settings

- **Clinical trials continue to push the frontier**
  - to better treatments and outcomes

- **Genetic testing of tumor tissue (and now blood!)**
  - helps us understand the driving forces in a cancer
  - Clinical trials testing targeted therapies are ongoing

- **Immunotherapy holds great promise**
  - to better clinical outcomes
  - Clinical trials assessing how to best do this are ongoing
ASCO Plenary 2015

- Insights into immune checkpoint blockade
- CheckMate trial of immunotherapy in melanoma
- Childhood Cancer Survivor Report
- Case for preventive neck lymph node surgery
- Risks of whole-brain radiation therapy
Panacea for Progress or Pandora’s Box?

Room 354, Morial Convention Center
Clinical Trials Design: Part 2

Chairperson: Elizabeth M. Jaffee, Baltimore, MD

10:15 a.m. Successes and challenges in designing combination immunotherapy clinical trials for breast cancer. Leisha A. Emens, Baltimore, MD

10:45 a.m. Issues faced by industry in developing safe and effective combination immunotherapies. Ira Mellman, South San Francisco, CA

11:15 a.m. Statistical challenges in designing combination immunotherapy clinical trials. Katy Simonsen, Princeton, NJ

11:45 a.m. FDA’s point of view on trial designs for accelerating combination immunotherapies across multiple tumor types. Tatiana Prowell, Silver Spring, MD
A likely algorithm for incorporating different therapies into the management of **NSCLC** based on current evidence.
Incorporation of immune-oncology into precision medicine

New Orleans Theater B, Morial Convention Center
Genomics-guided Immunotherapy

Chairperson: Catherine J. Wu, Boston, MA

1:00 p.m. Introduction
1:10 p.m. Tumor-host coevolution: Therapeutic implications. Catherine J. Wu, Boston, MA
1:40 p.m. Immunogenomics and precision cancer medicine. Eliezer Van Allen, Brookline, MA [SY18-02]*
2:10 p.m. RNA based individualized cancer immunotherapy. Ugur Sahin, Mainz, Germany (not eligible for CME credit)

Immunogenomics to search Neo-antigen, ‘inflammed’ types, and proper combination therapeutic strategies
Cocktails for cancer with a measure of immunotherapy

THE PERFECT BLEND

The next frontier in cancer immunotherapy lies in combining it with other treatments. Scientists are trying to get the mix just right.

BY HEIDI LEDFORD

COMBINATORIAL EXPLOSION

Ipilimumab, the first approved checkpoint inhibitor, has been tested in dozens of clinical trials since 2001. And like many other drugs in its class, it is increasingly being tested in combination with other therapies.

Patients generally respond well to targeted therapies (top), which are directed at specific mutations in a cancer but only for a short time. Checkpoint immunotherapies (bottom) do not help as many people, but those they do help tend to live longer. Oncologists are trying to get the best out of both strategies by combining the drugs.

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