

Customized Combination Therapy Overcoming the Lazarus Syndrome Challenge

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Treatment of Medulloblastoma with Hedgehog Pathway Inhibitor GDC-0449

N ENGL J MED 361:12 NEJM.ORG SEPTEMBER 17, 2009

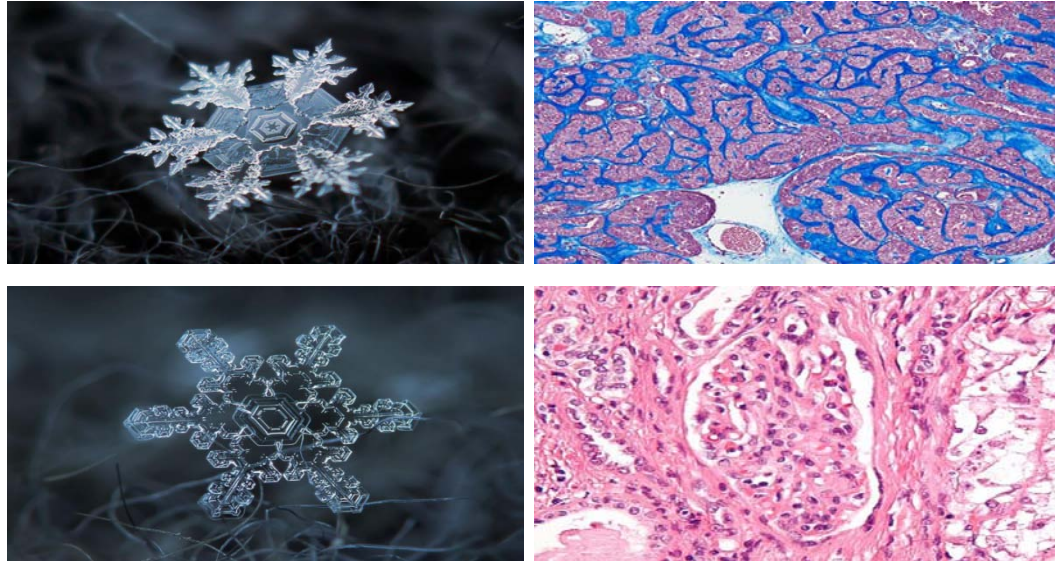


Figure 1. Tumor Response on Positron-Emission Tomographic (PET) Scanning.

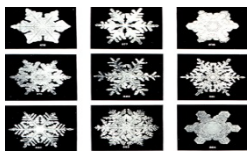
Whole-body projections from ^{18}F -fluorodeoxyglucose (FDG)-PET scans are shown. Panel A shows the pretreatment scan; Panel B, the repeat scan after 2 months of therapy with the hedgehog pathway inhibitor GDC-0449; and Panel C, the repeat scan after 3 months of therapy.

Fundamental Premise

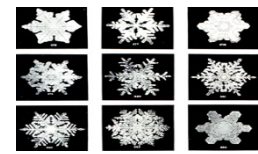
Every tumor is complex and unique



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Malignant Snowflakes

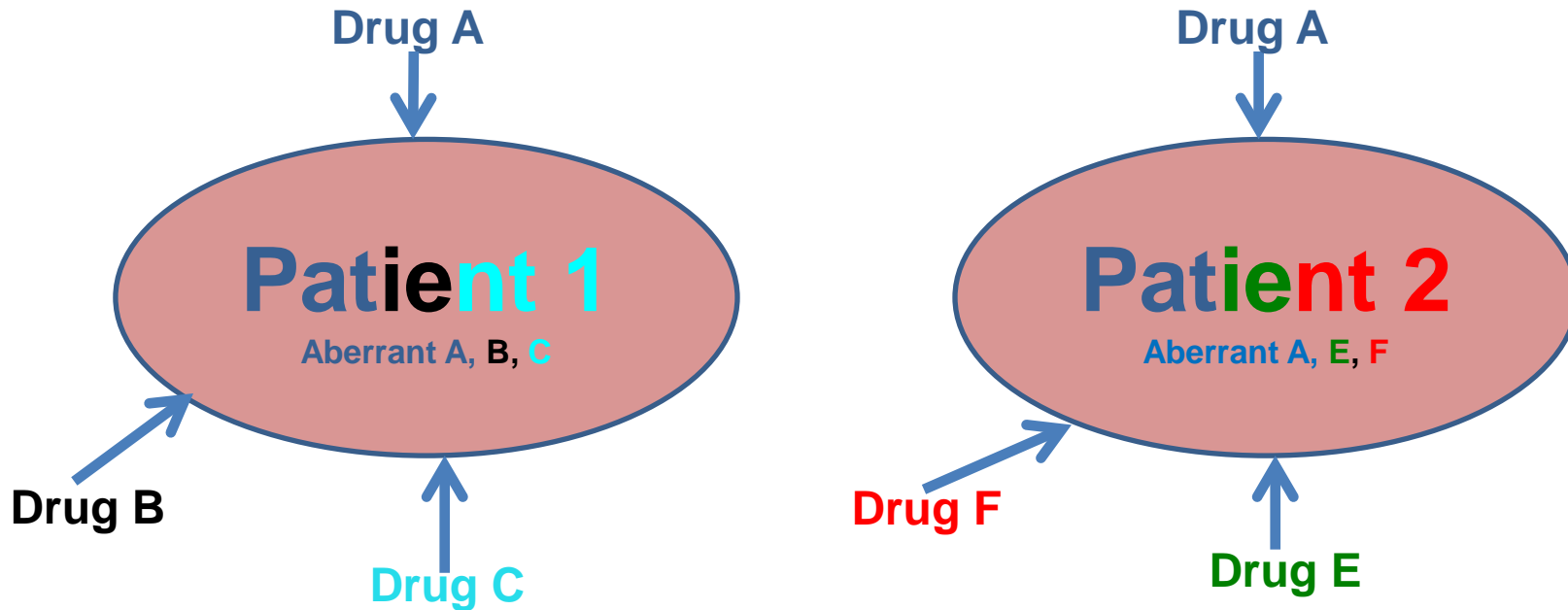


Pt number	Molecular Results (236 genes; NGS)—Breast Cancer
1	PIK3CA amplification, SOX2 amplification, TP53 G302fs*42, FLT3 L260*
2	AKT1 (E17K)
4	EGFR amplification, CCND1 amplification, CDKN2A/B loss, FGFR1 amplification, MYC amplification, TP53 P151A
42	ERBB2 amplification, PIK3CA H1047L, AURKA amplification, TP53 R342P, CREBBP P858S, ZNF217 amplification
25	ERBB2 amplification, MYC amplification, CDK6 amplification, TP53 R213*
7	ESR1 Y537S
13	GATA3 *445fs*2+
16	RET C634R, GATA3 P436fs*11+
18	AKT3 amplification, MYC amplification, MYCL1 amplification, TP53 R248Q
54	NF1 R1276Q

Wheler....Kurzrock. Oncotarget. 2014: Wheler....Kurzrock. Cancer Research, 2014;
Kurzrock Giles. Cell Cycle. 2015

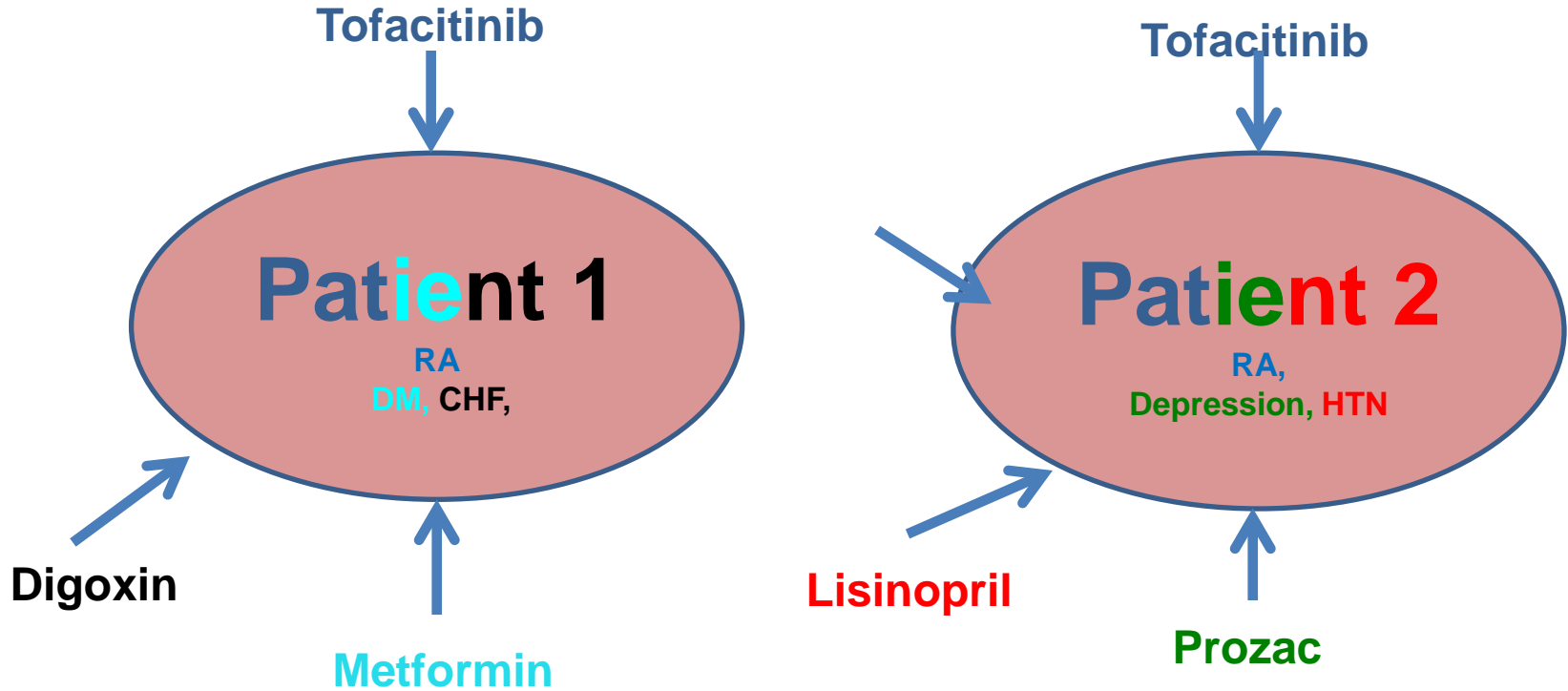
Patient-Centric Trial (New)

Find the drugs for the patients (N of One)



Strategy: Molecular matching for each patient with customized therapy combination

We already customize therapy



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A Fundamental Error

Where is the safety data?

- **TDM1 (ado-trastuzumab emtansine)**
- Alprazolam
- Arformoterol tartrate
- ASA
- CoQ10
- Folate / Vit B6 / Vit B12
- Levothyroxine
- Beclomethasone dipropionate
- Tiotropium bromide
- Bupropion
- Benzonatate
- Saliva substitutes topical
- Dextromethorphan and guaifenesin
- Ipratropium nasal
- Levalbuterol
- Spironolactone
- Fondaparinux

Dosing de novo combinations....
Liu, Nikanjan, Kurzrock,
Oncotarget 2016