Neuroscience Trials of the Future:

Lessons from Oncology

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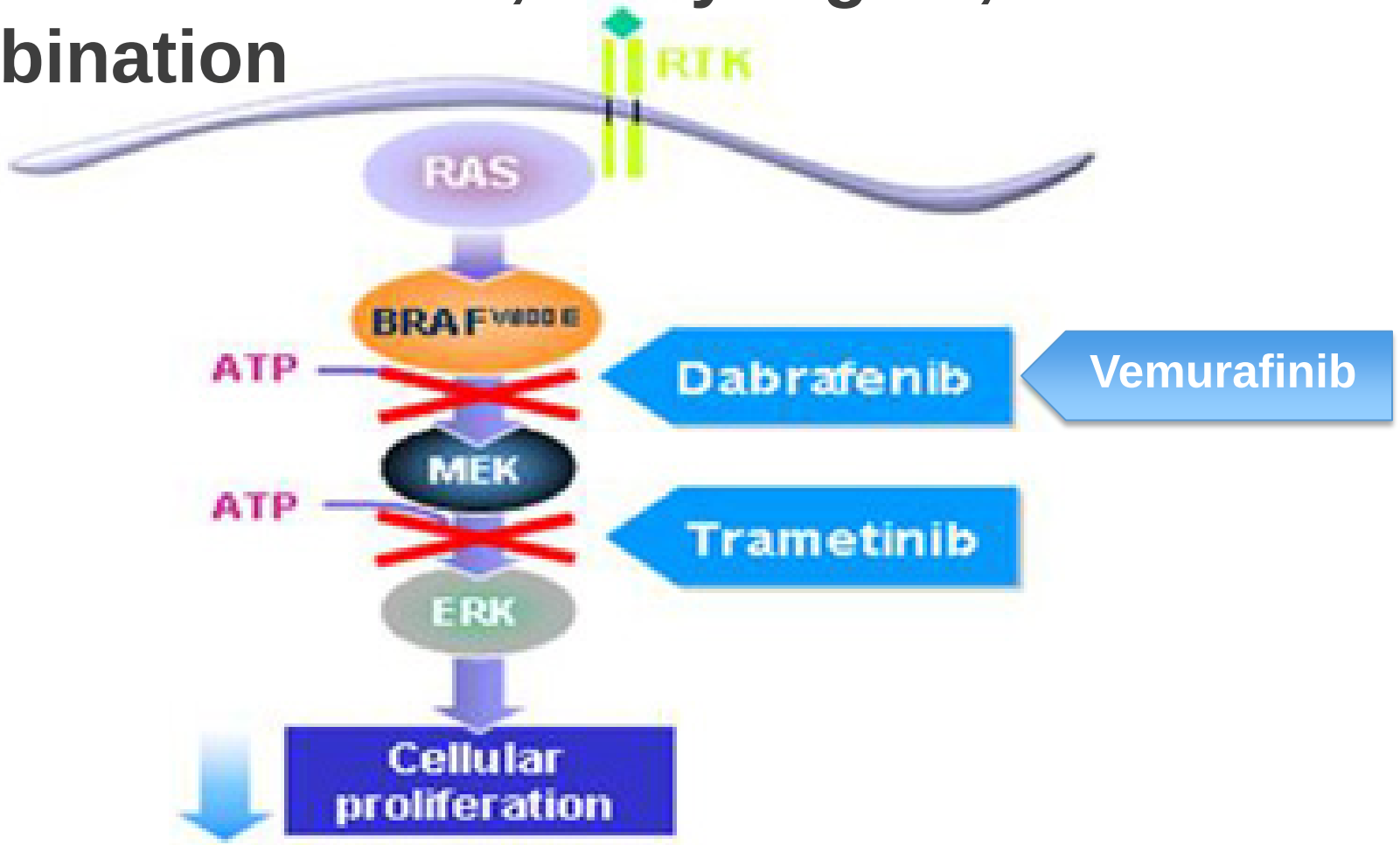
I do not have any current conflicts of interest. Formerly, I was an R & D executive at GlaxoSmithKline.

Lessons Learned

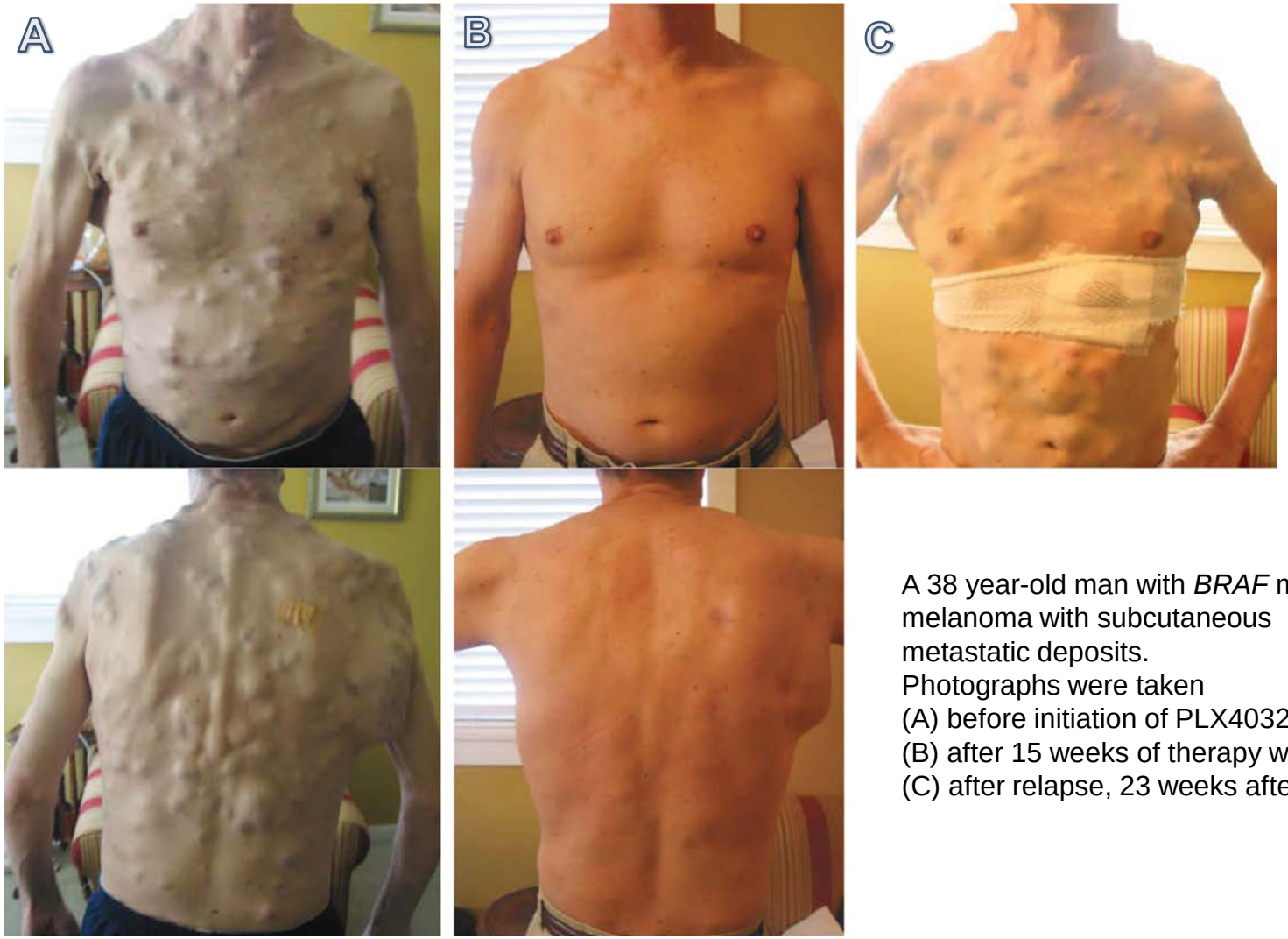
- **By some measures, neuroscience R & D is more efficient than oncology**
  - ~17,000 oncology trials vs ~1500 neuro/psychiatry trials (clintrials.gov)
  - 19 oncology approvals vs 9 neuro/psychiatry approvals 2015
  - But basic neuroscience research and clinical neuro/psychiatry seems less connected than cancer research and clinical oncology
- **Target/pathway validation**
  - genetic association ≠ causality
  - 'phenotypic' screens are of cells
  - mice are not people
  - retain close link to biology
- **Targeted therapy**
- **Precision medicine**
- **Early signals of clinical benefit should not require a statistician**
- **Combinations at the outset**
- **Avoid the herd effect**
- **Creativity in trial design**
- **Clinical trial as standard of care**

Validated Mechanism, Targeted Therapy, Precision Medicine, Early Signal, Combination



BRAF Inhibitor

From Wagle et al, 2011, J Clin Oncol 29:3085



A 38 year-old man with *BRAF* mutant melanoma with subcutaneous metastatic deposits.
Photographs were taken
(A) before initiation of PLX4032
(B) after 15 weeks of therapy with PLX4032
(C) after relapse, 23 weeks after therapy

The combination study of BRAFi + MEKi had multiple parts and answered many questions

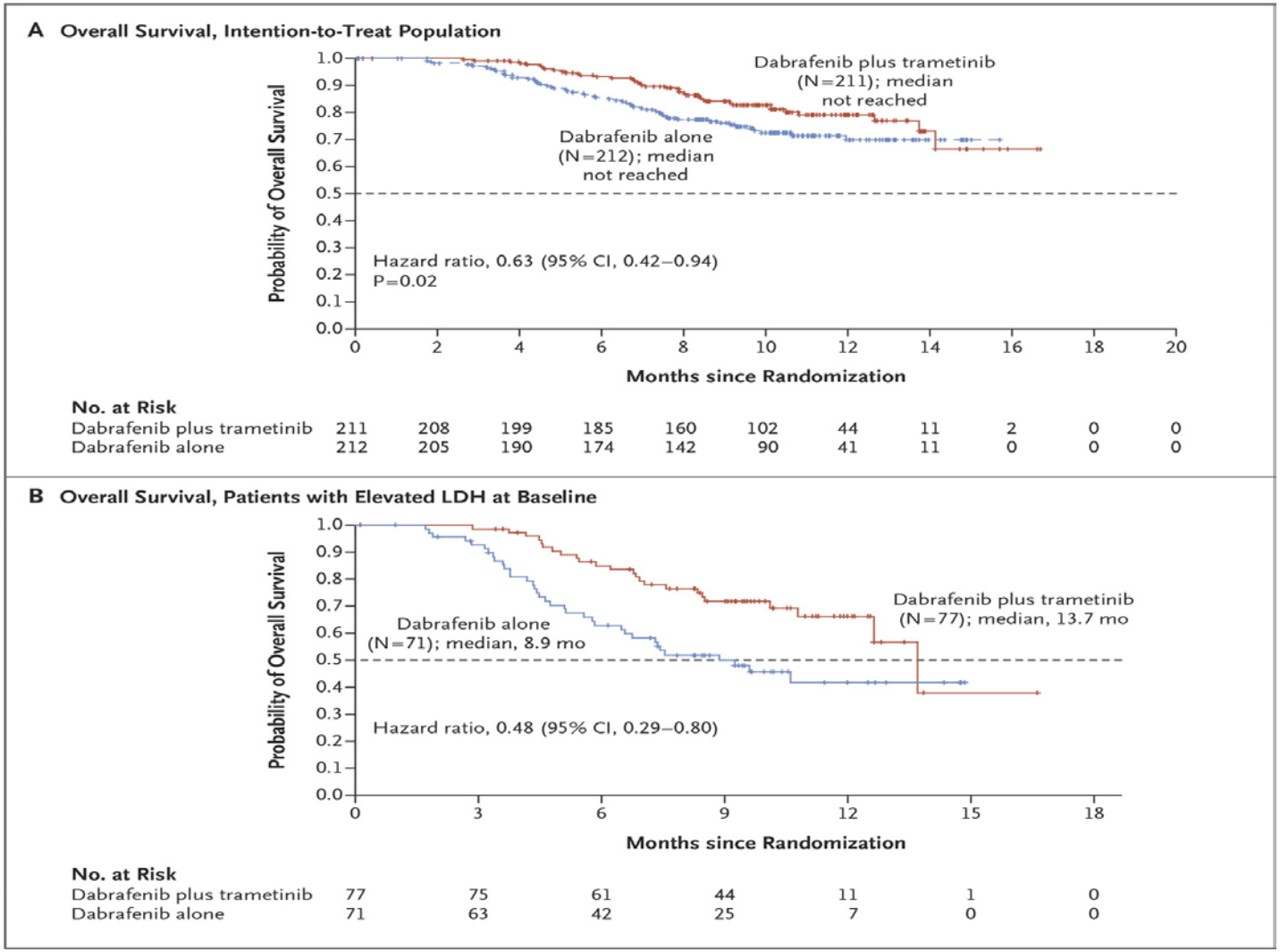
(Flaherty et al 2012 N Engl J Med 367: 1694-1703)

- Dose escalation
- Drug-drug interactions
- Expansion cohorts
- Randomized phase 2
- Pharmacokinetics
- Dose selection
- Safety/tolerability
- Clinical activity

Combination Therapy

Wagle et al, 2011, J Clin Oncol 29:3085

Increased Efficacy, Decreased Skin Toxicity



Long GV et al. N Engl J Med 2014;371:1877-1888

Table 3. Adverse Events.*

Event	Dabrafenib plus Trametinib (N=209)		Dabrafenib Alone (N=211)	
	Any Grade†	Grade 3	Any Grade†	Grade 3
	number of patients (percent)			
Any adverse event	199 (95)	66 (32)	203 (96)	72 (34)
Pyrexia‡	107 (51)	12 (6)	59 (28)	4 (2)
Fatigue	74 (35)	4 (2)	74 (35)	2 (1)
Headache	63 (30)	1 (<1)	62 (29)	3 (1)
Nausea	63 (30)	0	54 (26)	3 (1)
Chills	62 (30)	0	33 (16)	0
Arthralgia	51 (24)	1 (<1)	58 (27)	0
Diarrhea	51 (24)	2 (1)	30 (14)	2 (1)
Rash	48 (23)	0	46 (22)	2 (1)
Hypertension	46 (22)	8 (4)	29 (14)	10 (5)
Vomiting	42 (20)	2 (1)	29 (14)	1 (<1)
Cough	34 (16)	0	35 (17)	0
Peripheral edema	30 (14)	1 (<1)	10 (5)	1 (<1)
Pain in a limb	30 (14)	3 (1)	33 (16)	1 (<1)
Decreased appetite	23 (11)	1 (<1)	25 (12)	2 (1)
Abdominal pain	22 (11)	2 (1)	14 (7)	3 (1)
Elevated alanine aminotransferase	22 (11)	4 (2)	10 (5)	1 (<1)
Elevated aspartate aminotransferase	22 (11)	6 (3)	7 (3)	1 (<1)
Constipation	22 (11)	1 (<1)	18 (9)	0
Myalgia	22 (11)	1 (<1)	24 (11)	0
Asthenia	20 (10)	1 (<1)	27 (13)	1 (<1)
Dizziness	20 (10)	0	12 (6)	0
Nasopharyngitis	20 (10)	0	15 (7)	0
Back pain	[illegible]	[illegible]	30 (14)	4 (2)
Dry skin	19 (9)	0	[illegible]	0
Pruritus	17 (8)	0	26 (12)	0
Alopecia	15 (7)	0	55 (26)	0
Hand–foot syndrome§	10 (5)	0	58 (27)	1 (<1)
Hyperkeratosis	7 (3)	0	68 (32)	1 (<1)
Skin papilloma	3 (1)	0	45 (21)	0
Adverse event of interest occurring in <10% of patients				
Cutaneous squamous-cell carcinoma including keratoacanthoma	5 (2)	4 (2)	20 (9)	8 (4)
Decreased ejection fraction	9 (4)	1 (<1)	5 (2)	1 (<1)
Chorioretinopathy	1 (<1)	0	1 (<1)	0
Blurred vision	5 (2)	0	4 (2)	0
Dermatitis acneiform	16 (8)	0	7 (3)	0

* Listed are adverse events that occurred in at least 10% of patients who received at least one dose of a study drug in any group, except as indicated.

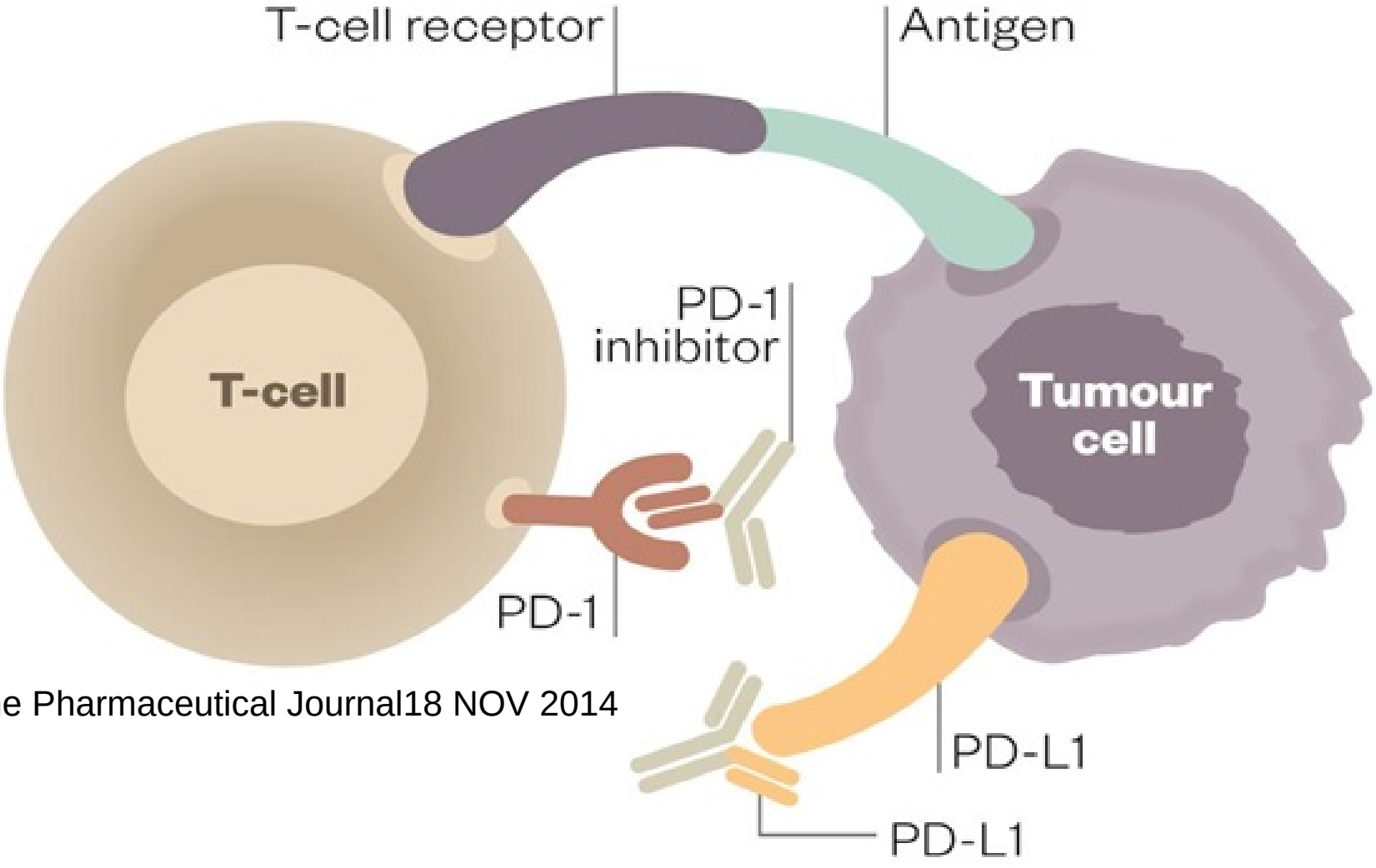
† A total of eight grade 4 events occurred in seven patients (3%) in the dabrafenib–trametinib group (anemia, decreased lymphocyte count, hypoglycemia, pulmonary embolism, brain edema, hepatic hematoma, metastases to central nervous system, and pancytopenia) and in seven patients (3%) in the dabrafenib-only group (dyspnea, thrombocytopenia, hypokalemia, cutaneous squamous-cell carcinoma, brain edema, hypercalcemia, febrile neutropenia, and hypovolemic shock). Grade 5 events were reported in four patients (2%) in the dabrafenib–trametinib group (pneumonia and cerebral hemorrhage [in three patients]).

‡ Pyrexia was defined as a body temperature of 38.5°C or higher.

§ The hand–foot syndrome included the terms palmar–plantar erythrodysesthesia, palmar–plantar hyperkeratosis, and palmoplantar keratoderma.

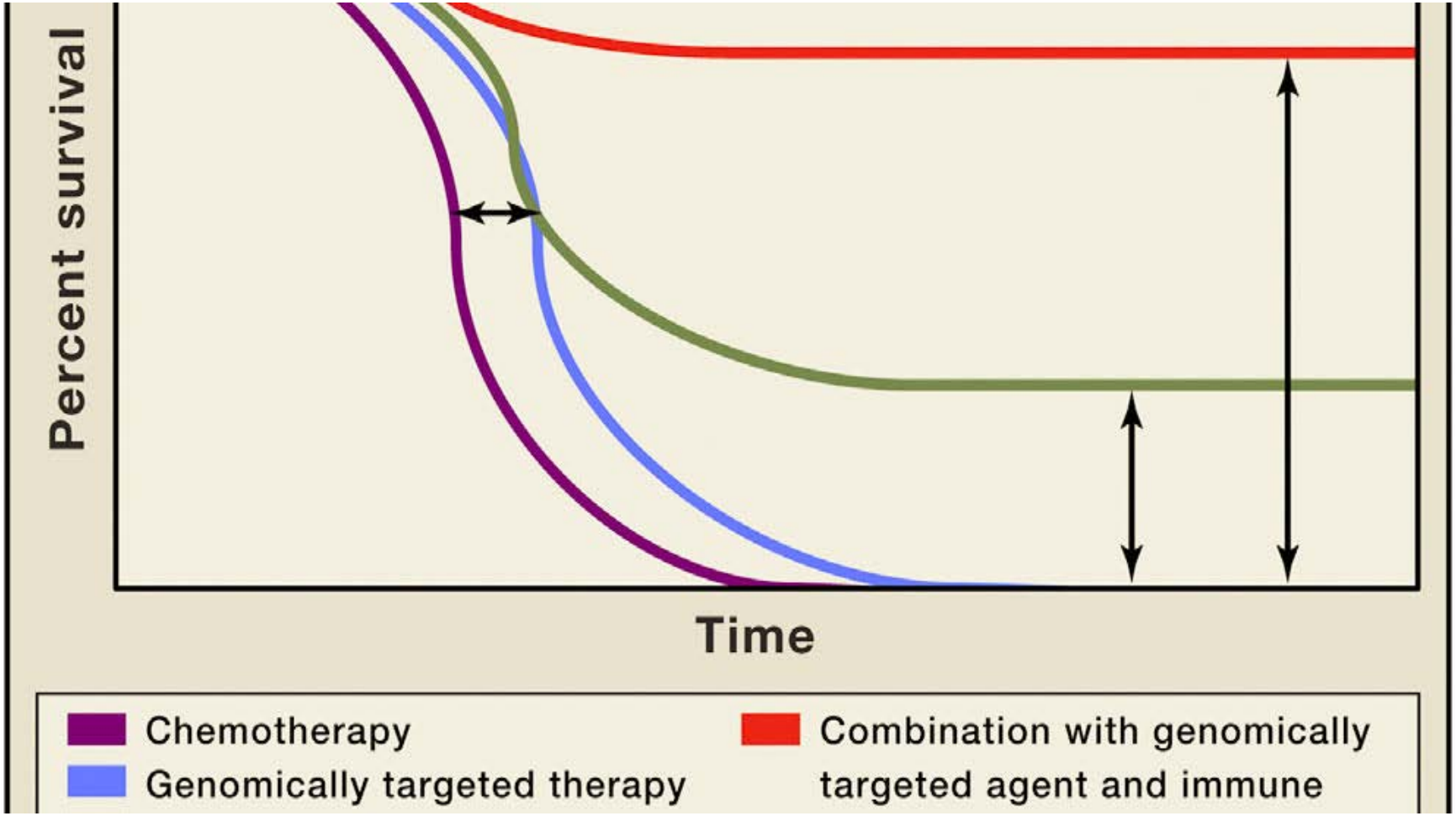
Checkpoint Modulator Immunotherapy

Listen to the patient



The Pharmaceutical Journal18 NOV 2014

Combine Targeted and Immune Therapy



Phase 1 study combining anti-PD-L1 (MEDI4736) with BRAF (dabrafenib) and/or MEK (trametinib) inhibitors in advanced melanoma

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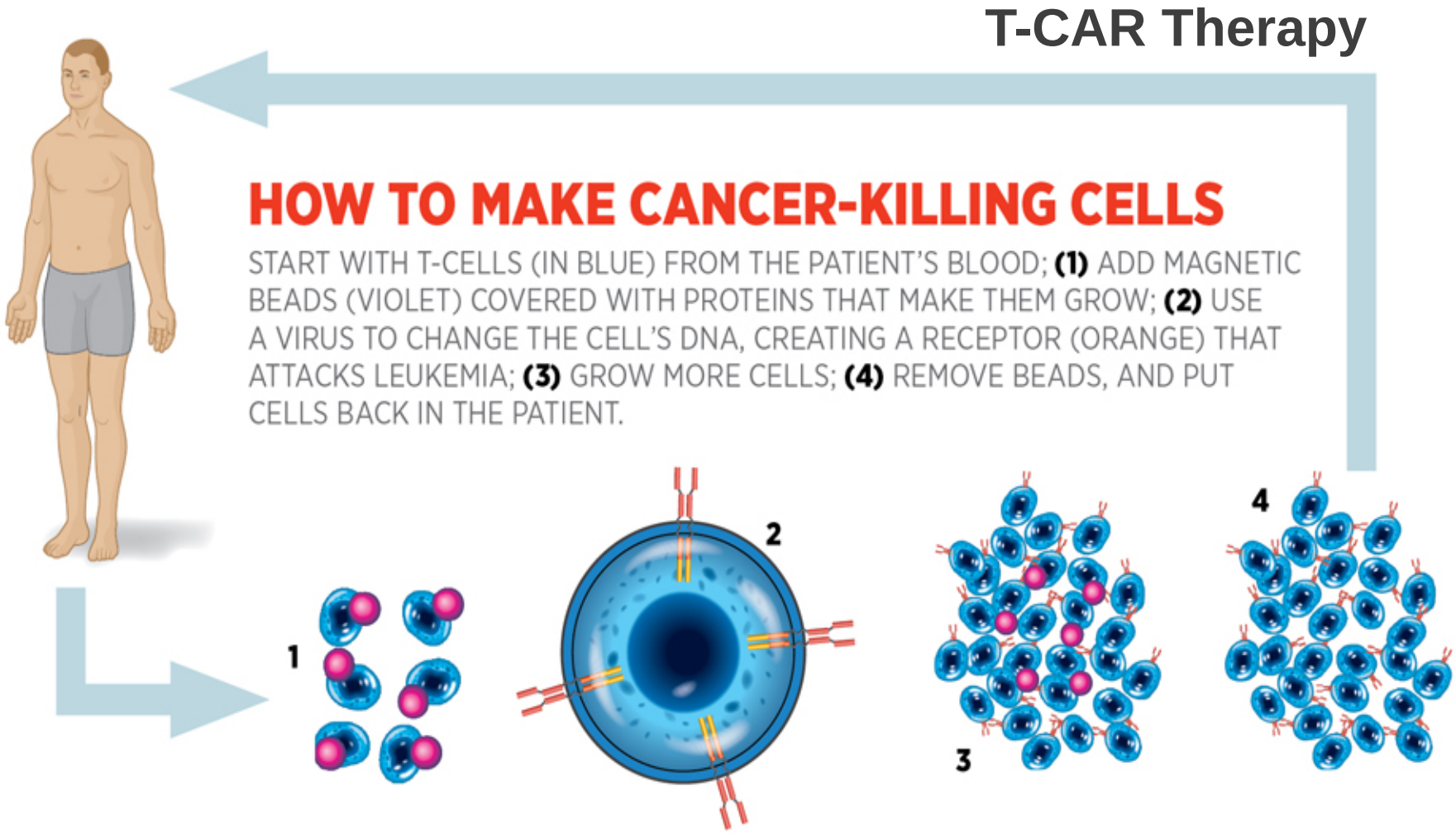
PRESENTED AT: ASCO Annual '15 Meeting

Bespoke intervention for neuro/psychiatry patients?



Moonshot

Perry's Moonshot

Make Clinical Trial Participation at a Comprehensive Cancer Center the Standard of Care for Cancer Patients

- Acute Lymphoblastic Leukemia
  - Pediatrics: 90% cure
  - Adults: 15-40% cure

- >90% of Pediatric Cancer Patients are Treated in Comprehensive Cancer Centers and Enrolled in Clinical Trials

- Most Adult Patients are NOT Treated in Comprehensive Cancer Centers and < 5% Enroll in Clinical Trials

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