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NCI Awardee Skills Development Consortium

What Does it Take to Get FDA Approval?

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NCI UE5 supported “Immuno-Oncology for the Translational Researcher"

Memorial Sloan Kettering
Cancer Center

Financial Relationships

Commercial Interest	Relationship
Merck, AstraZeneca, Roche/Genentech, BMS, Mirati, Syndax, Nektar, Shattuck Labs, Immunai, Natera, Janssen	Consultant, advisory
BMS	Research funding
BMS, AstraZeneca, Lilly	Travel
Shattuck Labs, Immunai, Arcus	Equity options
A patent has been filed by MSK related to the use of tumor mutation burden to predict response to immunotherapy (PCT/US2015/062208), which has received licensing fees from PGDx.	Patent and licensing

Outline

- » Terminology
- » Process
- » Example: FDA approvals of pembrolizumab for metastatic NSCLC
  - › 2nd line, PD-L1 selected (KN001, KN010)
  - › 1st line, PD-L1 selected (KN024)
  - › 1st line, combination with chemotherapy (KN021, KN189)

Terminology

» Fast Track

» Breakthrough Therapy

» Accelerated Approval

» Priority Review

» Full approval

Fast Track

- Goal: get important new drugs to patients faster
- Setting: “drugs to treat serious conditions and fill an unmet medical need”
- Threshold: superior effectiveness, avoid serious side effect
- Benefit:
  - Earlier, more frequent meetings with FDA, more detailed guidance about proposed trial design and data needed to accomplish approval
  - Eligibility for accelerated approval and priority review

Breakthrough Therapy

- Goal: get important new drugs to patients faster … by coordinated effort to efficiently develop evidence needed to support approval
- Setting: “treat serious conditions and preliminary clinical evidence indicates the drug may demonstrate substantial improvement over available therapy”
- Threshold: improvement on a clinically significant endpoint (e.g. clinical surrogate endpoint, pharmacodynamic marker, safety”
  - All Fast Track benefits plus
    - Guidance on efficient development plans
    - Organizational commitment involving senior managers

Accelerated Approval

- Goal: allow drugs to be used for patients faster, based on a surrogate endpoint
- Setting: Drug demonstrates benefit based on surrogate endpoint (e.g. response rate, rather than wait for overall survival outcomes)
- Threshold: “clinically meaningful” benefit, surrogate “reasonably likely” to predict real outcome (e.g. response rate → overall survival)
- Benefit:
  - Earlier approval to be able to get drugs to patients and commercialize
  - Still required to conduct confirmatory study (e.g. show that OS improved), with potential for withdrawal if not met

Priority Review (vs Standard Review)

- Goal: Improve drug review time
- Setting: Drug with relatively clear trial outcome and benefit
- Threshold: If approved, would yield significant improvement in effectiveness or safety
- Benefit:
  - Direct attention and resources to review application more quickly
  - Review time = 6 months (priority) rather than 10 months (standard).

Regular (full) approval

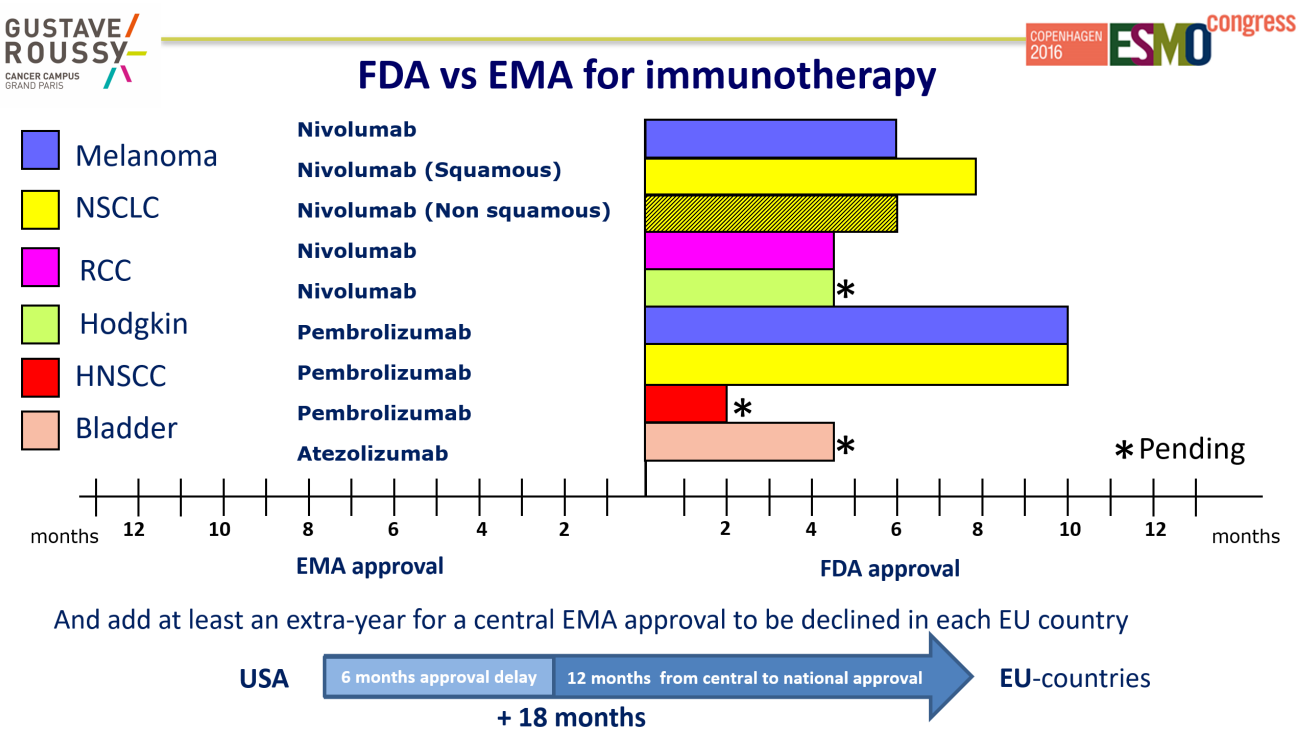
» Often based on Phase 3, randomized study

» Often on basis of improvement of overall survival

Process

1. Preclinical testing
2. Submit investigational new drug application (IND), proposal for human testing
3. Phase 1 → Phase 2 → Phase 3 (often, but always)
4. Pre-new drug application (NDA) period (meeting with FDA)
5. Submit NDA asking FDA for consideration
6. FDA has 60 days to decide if will accept for review
7. If accepted, FDA assigned team to review submission / information for label / inspect manufacturing facilities
8. FDA Approval (or not)

Contextualizing pace of FDA approval process



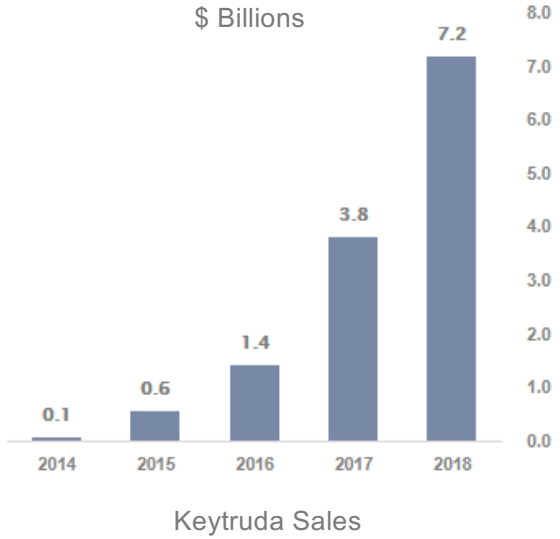
Soria, ESMO plenary discussion 2016

Example: Pembrolizumab in NSCLC

2009:
Program stopped, planned for out-licensing

How'd we get here?

2021:
$11 billion/year in sales



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https://www.forbes.com/sites/greatspeculations/2019/08/29/how-important-is-keytruda-for-merck/?sh=6be9a52f1b4d

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First Pembrolizumab Approval: Second Line, PD-L1 Selected

KEYNOTE-001: Phase 1 Study of Pembrolizumab

- Patients with previously-treated, metastatic NSCLC
- Non-randomized, single arm, Phase 1 study
- Explored various thresholds of PD-L1 expression as predictive biomarker

KEYNOTE-001: Phase 1 Study of Pembrolizumab

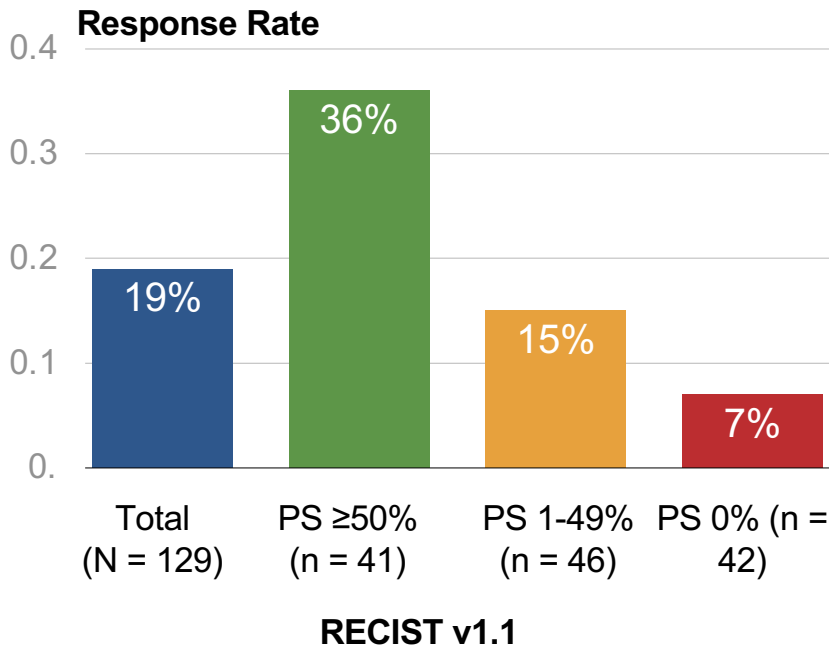
Initial report: response rate ~20%, increased in PD-L1 expressing tumors → apply for "breakthrough therapy" designation

Subgroup	irRC, Investigator Review			RECIST v1.1, Independent Review			
	N	ORR, n (%) [95% CI]	Median PFS, wk (95% CI)	N	ORR,* (%), [95% CI]	Median PFS, wk (95% CI)	Median OS, wk (95% CI)
All	38	9 (24%) [11%, 40%]	9.1 (8.3, 17.4)	33	7 (21%) [9%, 39%]	9.7 (7.6, 17)	51 (14, NR)
Non-squamous	31	7 (23%) [10%, 41%]	9.1 (8.3, 17.0)	26	4 (16%) [4%, 35%]	10.3 (7.6, 17)	35 (14, NR)
Squamous	6	2 (33%) [4%, 78%]	23.5 (2.7, NR)	6	2 (33%) [4%, 78%]	15.2 (1.4, NR)	NR (2.7, NR)
Patients with measurable disease on baseline imaging and an evaluable tumor specimen for PD-L1							
Score ≥ potential cut point	9	6 (67%) [30%, 93%]	—	7	4 (57%) [18%, 90%]	—	—
Score < potential cut point	24	1 (4%) [0%, 21%]	—	22	2 (9%) [1%, 29%]	—	—

Garon, WCLC 2013 #2416

KEYNOTE-001: Phase 1 Study of Pembrolizumab

- Emphasis on PD-L1 as a selective biomarker
  - Tumor biopsies obtained within 60 days prior to treatment were stained for PD-L1 using the 22C3 antibody with a prototype assay used to determine study eligibility.
    - ≥1% Tumor PD-L1 expression was considered positive



Gandhi, AACR 2014, Abstract CT105

KEYNOTE-001: Phase 1 Study of Pembrolizumab

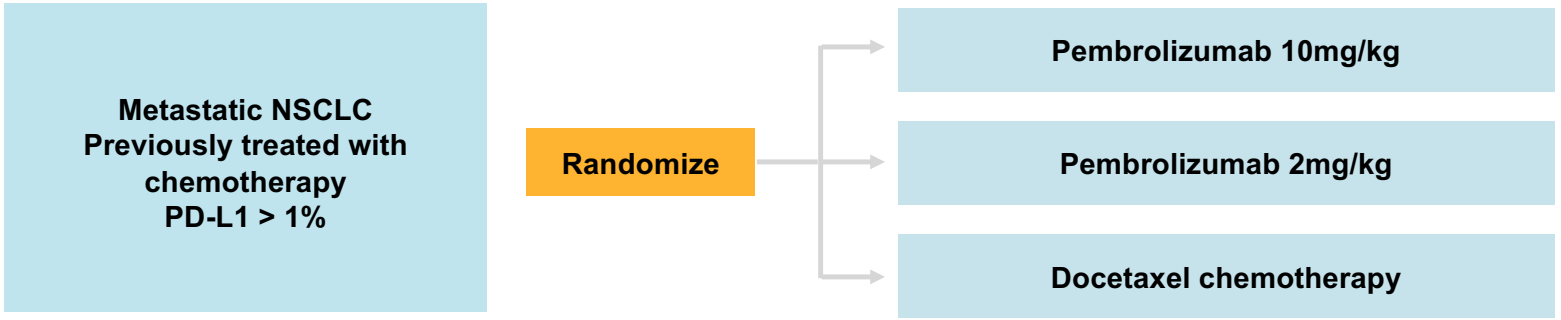
» Ultimately, huge Phase 1 study (n=550) with biomarker focus → **accelerated approval** granted on basis of response rate surrogate

	PDL1 <1%	PDL1 1-24%	PDL1 25-49%	PDL1 50-74%	PDL1 75-100%
ORR	8%	13%	19%	30%	45%

Garon, NEJM 2015

KEYNOTE-010: Phase 3 Study of Pembrolizumab in Second Line

» Full approval predicated on success of Phase 3 study, to demonstrate improvement in overall survival



Herbst, Lancet 2015

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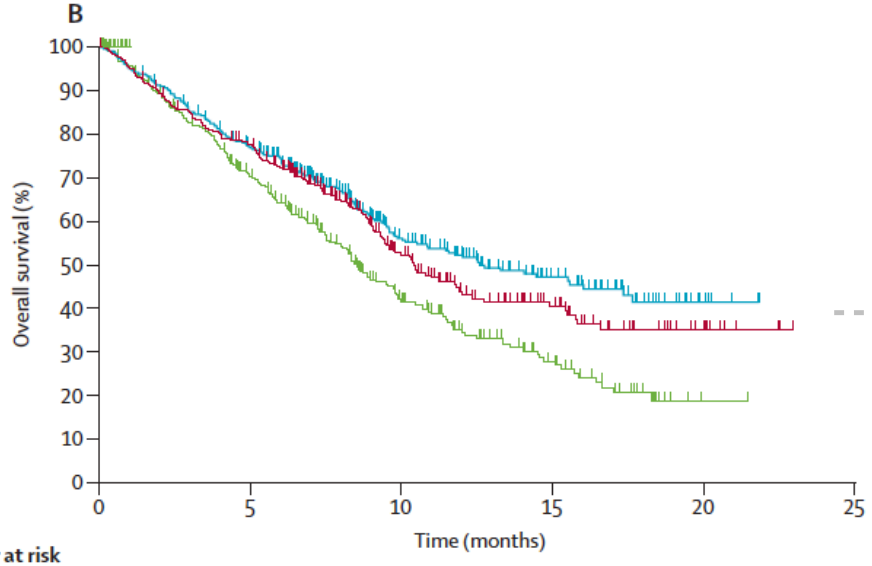

Number at risk						
Pembrolizumab 2 mg/kg	344	259	115	49	12	0
Pembrolizumab 10 mg/kg	346	255	124	56	6	0
Docetaxel	343	212	79	33	1	0

FDA regular approval

Herbst, Lancet 2015

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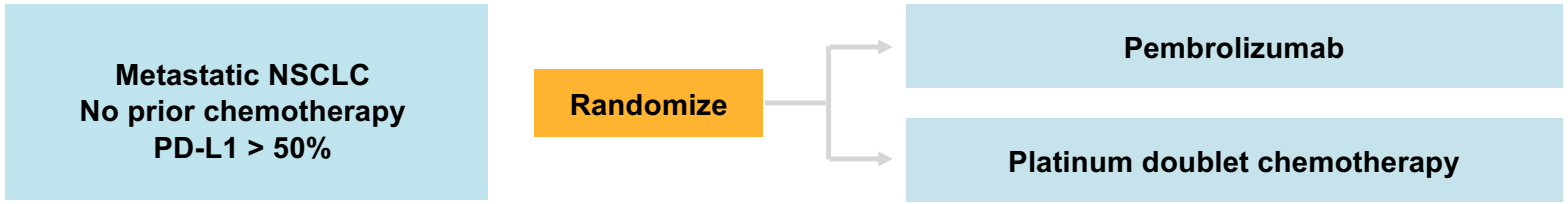
Move into First Line Setting, Higher PD-L1 Threshold

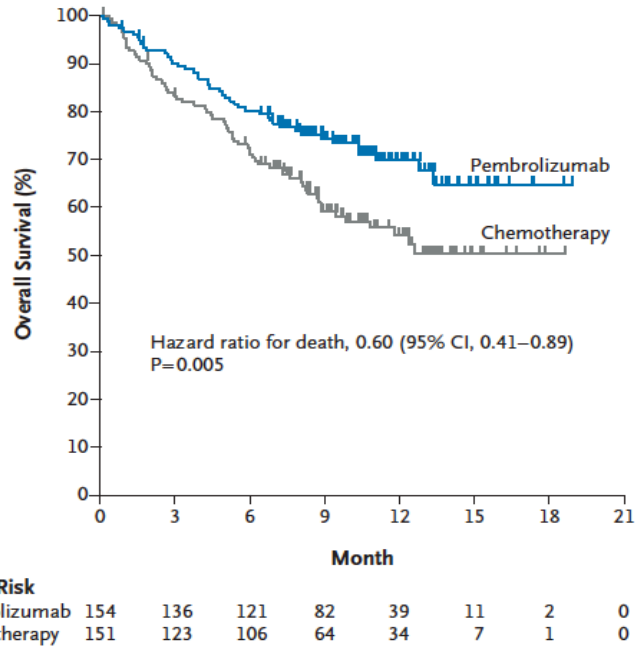
KEYNOTE-024: Phase 3 Study of Pembrolizumab in First Line

» In first line setting, higher threshold for success needed to beat the standard chemotherapy. So higher PD-L1 biomarker threshold pursued



Reck, NEJM 2016

KEYNOTE-024: Phase 3 Study of Pembrolizumab in First Line



FDA regular approval

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Reck, NEJM 2016

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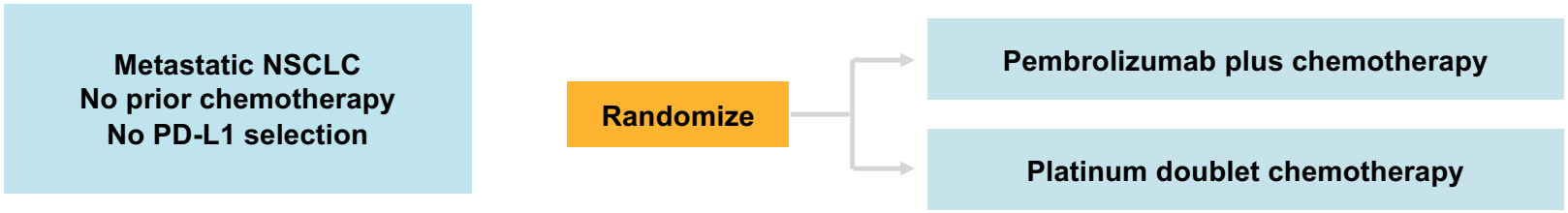
Combination With Chemotherapy

KEYNOTE-021: Phase 2 Study of Pembrolizumab Plus Chemotherapy

If combine pembrolizumab plus chemotherapy, is it better than chemotherapy alone?

Phase 1 study of chemotherapy plus pembrolizumab showed higher than expected response rate, which prompted a randomized Phase 2 study

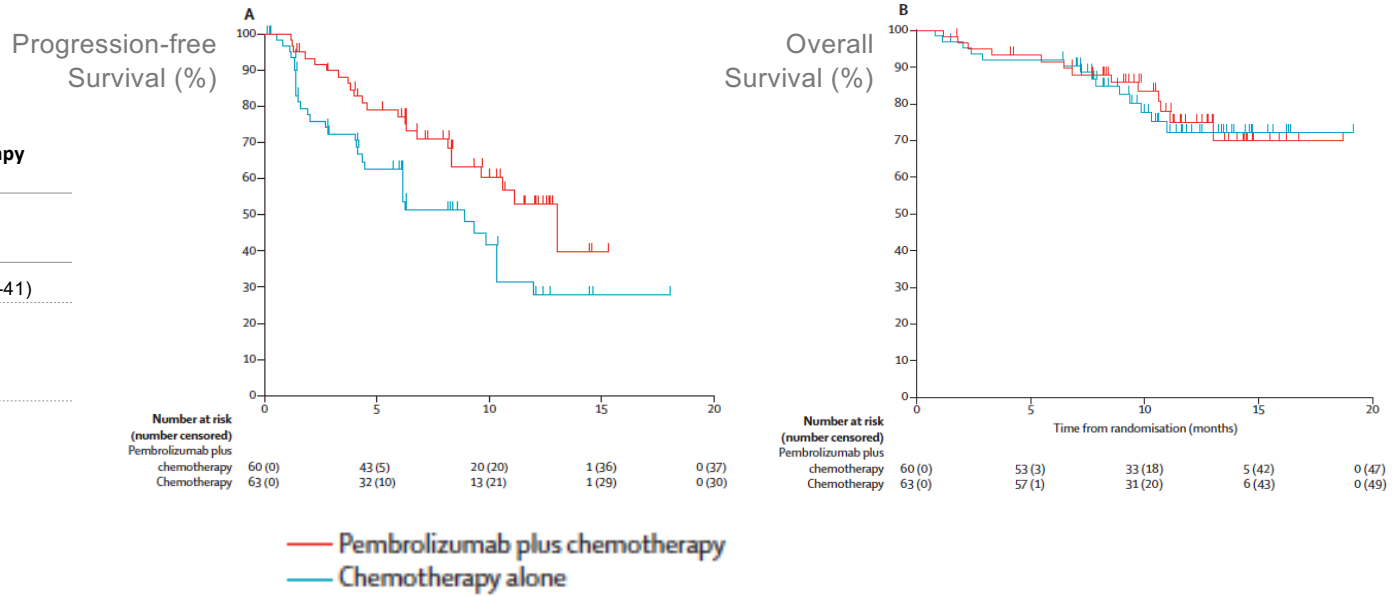


Langer, Lancet Oncology 2016

KEYNOTE-021: Phase 2 Study of Pembrolizumab Plus Chemotherapy

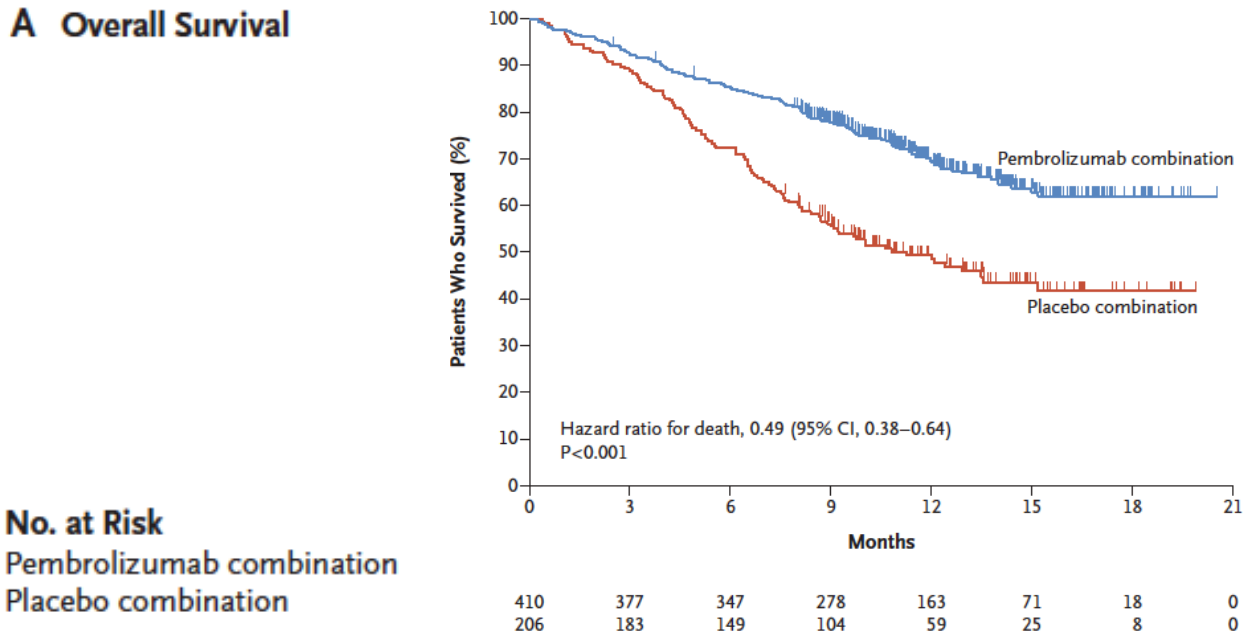
FDA accelerated approval

	Pembrolizumab plus chemotherapy (N=60)	Chemotherapy (N=63)
Objective response		
n (%;95;CI)	33 (55%; 42-68)	18 (29%; 18-41)
Estimated difference, % (95% CI)	26% (9-42)	-
p value	0.0016	-



Langer, Lancet Oncology 2016

KEYNOTE-189: Phase 3 Study of Pembrolizumab in First Line



FDA regular approval

Ghandi, NEJM 2018

Conclusions

- **There are several paths to FDA approval, from single arm Phase 1 studies to randomized Phase 3 studies**
  - There is not always an orderly progression from Phase 1 → Phase 2 → Phase 3
- **Threshold for approval is context-dependent**
  - Biomarkers can facilitate approval
- **Fast-track/breakthrough designations can yield collaborative opportunities with FDA to expedite progress**
- **Accelerated approval can get new therapies to patients faster based on surrogate outcomes**
- **Regular approval generally, but not always, dependent success in improving survival in randomized studies.**