U.S. FOOD & DRUG ADMINISTRATION

Experience in Tissue Agnostic Indication

Statistical Evaluation

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Disclosures

- I have no financial relationships to disclose
- I will not be discussing off label and/or investigational use of named products in my presentation

Tissue Agnostic Indication

- Traditionally: approval for one cancer type
- Recent years: precision medicine leads to biomarker based indications
- New cases: approval based on biomarker status regardless of tumor site
  - "Tissue Agnostic"

Biomarker-Focused, Tissue Agnostic Development

- New approaches evaluating biomarker positive populations in the past 5 years, *regardless of tumor type*
  - Multiple, parallel cohort activity-estimating trials
  - Basket trials, pooling data across all patients
- Pembrolizumab: accelerated approval May 23, 2017
  - Patients with unresectable or metastatic, microsatellite-instability–high (MSI-H) or mismatch-repair–deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options…
  - **regardless of tumor site** or histology

= "Tissue Agnostic"

Tissue Agnostic Regulatory Considerations

- Strength of scientific evidence that biomarker identifies a population with common characteristics (e.g., serves as primary oncogenic driver when present) *regardless of tumor*
- Strength of evidence that drug has the same pharmacologic effects on biomarker across tumor types in nonclinical & clinical studies
- Ability to reliably identify biomarker across tumor types, where biomarker-defined population is a subset of a specific tumor type

Example 1: Pembrolizumab for MSI-H Expressing Solid Tumors

- May 2017, FDA approved pembrolizumab for the treatment of patients with unresectable or metastatic, microsatellite-instability–high (MSI-H) or mismatch-repair–deficient (dMMR) solid tumors, **regardless of tumor site** or histology
- First approval in tissue agnostic indication

Regulatory Strategy

- Breakthrough Therapy Designation (BTD) granted CRC Oct 2015, then non-CRC Oct 2016
- Supplemental biologic licensing application (sBLA): Accelerated approval TA indication
- Post Marketing Requirements (PMR) include more patients and longer duration pf follow up

Source: Pembrolizumab label

Clinical Studies

KN	Design/Eligibility/Pop	N	MSI-H	Dose	Prior therapy
016 JHU	Investigator-initiated, **prospective,** 6 sites, activity finding	28 CRC 30 non CRC	PCR IHC Local	10 mg/kg q2w	**CRC**: received ≥ 2 prior therapy regimens **nonCRC**: ≥1 prior therapy regimen
164	**CRC, prospective**, multi-center	61	PCR IHC local	**200mg q3w**	Prior fluoro+ox, fluoro+irino +/- anti-VEGF/EGFR mAb
012	**Retrospectively identified patients** with PD-L1, gastric, bladder, or triple negative breast cancer	6 of 297	**Retro** PCR central	10 mg/kg q2w	Previously treated; no std therapy
028	**Retrospectively identified patients** with PD-L1positive esophageal, biliary, breast, endometrial, or CRC	5 of 475	**Retro** PCR central	10 mg/kg q2w	Previously treated; no std therapy
158	**Prospective** international multi-center enrollment of patients with MSIH/dMMR non-CRC **Retrospectively identified patients** who were enrolled in specific rare tumor non-CRC cohorts	19 of 713	PCR IHC local	**200mg q3w**	≥1 prior therapy regimen
Total	5 trials	**149**			

60 patients with non-CRC MSI-H tumors

Overall Analysis Plan

- Assumed patients were from the same patient population, i.e. disease based on the biomarker not the histology.
- Sample size not pre-specified
- Analysis Population
  - All Subjects as Treated (ASaT): Subjects who received ≥1 dose
  - Subjects without response assessment counted as non-responders
- Efficacy Endpoints
  - Primary Endpoint: Confirmed ORR by Independent Radiology Review (IRC)

Overall ORR

	n (%)	95% CI
Total	149	
Responders (%)	59 (39.6%)	(31.7%, 47.9%)
CR	11 (7.4%)	
PR	48 (32.2%)	
Response Duration		
Median (range)	NE (1.6+, 22.7+)	
Duration ≥ 6 months (%)	46 (78%)	

MSI–H Subgroups

	N	Responders	95% CI of ORR	DOR Range (Months)
GI Tumor				
BILIARY CANCER	11	3	(6%, 61%)	(11.6, 19.6)
COLORECTAL CANCER	90	32	(26%, 46%)	(1.6, 22.7)
GASTRIC/GE JUNCTION CANCER	9	5	(21%, 86%)	(5.8, 22.1)
PANCREATIC CANCER	6	5	(36%, 99.6%)	(2.6, 9.2)
SMALL INTESTINAL CANCER	8	3	(9%, 76%)	(1.9, 9.1)
ESOPHAGEAL CANCER	1	PR		18.2, On-going
Non-GI Tumor				
ENDOMETRIAL CANCER	14	5	(13%, 65%)	(4.2, 17.3)
BREAST CANCER	2	PR, PR		7.6, 15.9, ended
PROSTATE CANCER	2	PR, SD		9.8, on-going
BLADDER CANCER	1	Missing		
SARCOMA	1	PD		
THYROID CANCER	1	NE		
RETROPERITONEAL ADENOCARCINOMA	1	PR		7.5, on-going
SMALL CELL LUNG CANCER	1	PR		8.9, on-going
RENAL CELL CANCER	1	PD		

Efficacy Conclusion

- 39.6% ORR in pembrolizumab treated patients.
- Durable response: majority of patients had on-going responses at the time of data cut-off. 46 patients had 6 months or longer DoR.
- Anti-tumor activities observed in multiple types of tumors.

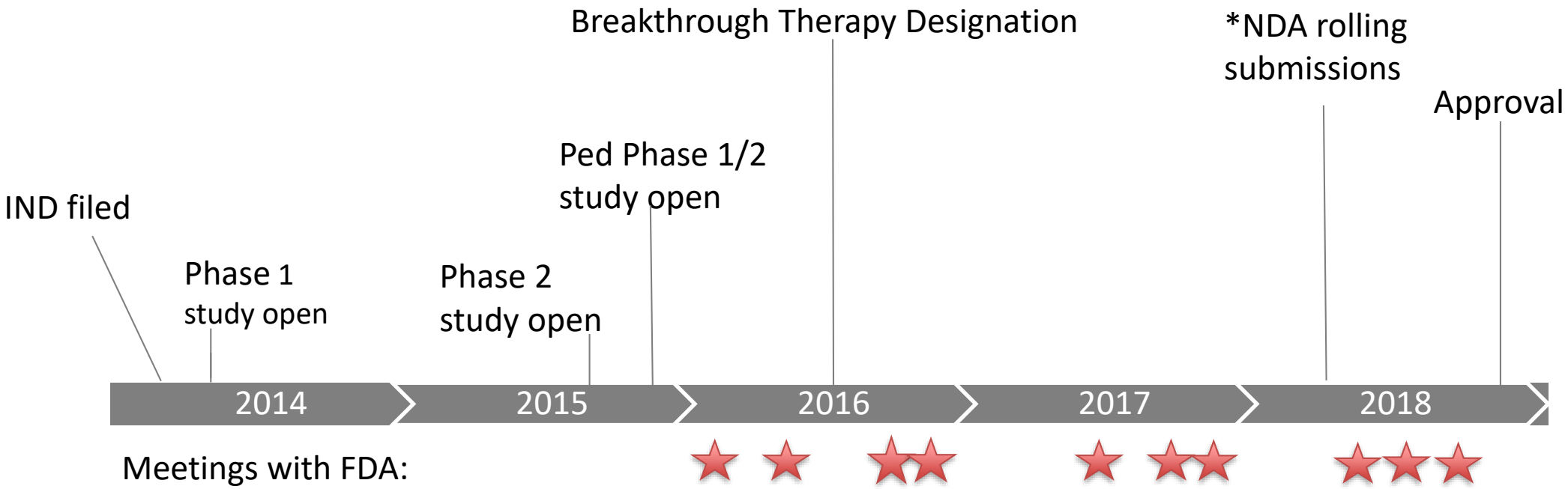
Example 2: Larotrectinib for NTRK Expressing Solid Tumors

- Indicated for the treatment of adult and pediatric patients with solid tumors that:
  - have a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation,
  - are metastatic or where surgical resection is likely to result in severe morbidity, and
  - have no satisfactory alternative treatments or that have progressed following treatment.

Larotrectinib Developmental Program

- 2 dose finding studies
  - LOXO-TRK-15002; NAVIGATE (BASKET) TRIAL (NCT02576431)
    - Inclusive eligibility criteria
      - Age 12 and older in adult trials
      - ECOG 0-3
  - Pediatric Trial: LOXO-TRK-15003; SCOUT (NCT02637687)
    - Oral solution formulation
- ORR as common endpoint by blinded independent review committee by RECIST criteria
  - Allowed for pooling patients with multiple diseases and different NTRK fusions partners

Larotrectinib Development Timeline



Source: modified with permission from Loxo, Oncology

* 2 NDAs filed; one for each formulation

Clinical Studies

Study LOXO-TRK	**Study Design/Objectives/ Endpoints**	**Dose/Regimen/ Formulation**	**N**	**60-day safety update**	**Sites**
14001	Open-label, 3+3 dose escalation Adult patients, advanced solid tumors Objectives: safetyand DLT, MTD, ORR	50–600 mg/day capsules solution	8 / 66	70 Pediatric=0	US: 8 sites
15002	Open-label “basket” study 12 years of age or older with NTRK fusion advanced cancer Objectives: ORR	100 mg BID capsules solution	35 / 47	63 Pediatric=3	US, EU, Singapore: 17 sites
15003	Open-label, dose escalation study Pediatric patients with advanced solid or primary CNS tumors Objectives: safetyand DLT, MTD, ORR	Dosing based on adult equivalent of 100 or 150 mg BID, then 100 mg/m2 BID (max of 100 mg BID) solution	12 / 31	43 Pediatric=32	US, EU: 13 sites
Total			55 / 144	176	

Overall Analysis Plan

- Assumed the disease is defined by the NTRK mutation but not the histology
- Efficacy Endpoints
  - Primary Endpoint: Confirmed ORR by Independent Radiology Review (IRC)
- Analysis Population
  - First 55 patients with *NTRK*-fusion solid tumors who were enrolled into the three trials.
  - A sample size of 55 patients could provide 80% power to exclude 30% from the lower bound of a 2-sided 95% exact binomial CI of the estimated ORR assuming that the observed ORR was at least 50%

ORR and DoR

Efficacy Parameter	**VITRAKVI N = 55**
Overall response rate (95% CI)	75% (61%, 85%)
Complete response rate	22%
Partial response rate*	53%
Duration of response**	**N = 41**
Range (months)	1.6+, 33.2+
% with duration ≥ 6 months	73%
% with duration ≥ 9 months***	63%
% with duration ≥ 12 months****	39%

+ Denotes ongoing response.

*Includes one pediatric patient with unresectable infantile fibrosarcoma who underwent resection following partial response and who remained disease-free at data cutoff.

**Median duration of response not reached at time of data cutoff.

***3 patients with an ongoing response were followed < 9 months from onset of response.

****10 patients with an ongoing response were followed < 12 months from onset of response.

ORR by Tumor Types

Tumor Type	Patients (n)	ORR		DOR	
		Responders	95% CI	Range (mo)	≥6 months, n
Soft tissue sarcoma	11	10	(59%, 100%)	3.6+, 33.2+	7
Salivary gland	12	10	(52%, 98%)	7.7, 27.9 +	10
IFS	7	7	(59%, 100%)	1.4+, 10.2+	2
Thyroid	5	5	(48%, 100%)	3.7, 27.0+	4
Lung	4	3	(19%, 99%)	8.2, 20.3+	3
Melanoma	4	2	NA	1.9+, 17.5+	1
Colon	4	1	NA	5.6	1
GIST	3	3	(29%, 100%)	9.5, 17.3	3
Cholangiocarcinoma	2	SD, NE	NA	NA	NA
Appendix	1	SD	NA	NA	NA
Breast	1	PD	NA	NA	NA
Pancreas	1	SD	NA	NA	NA

Efficacy Conclusion

- 75% ORR in treated patients.
- Durable response: 73% of the responders had a duration of response (DOR) of at least 6 months, and 39% had a duration of response of over a year.
- Anti-tumor activities observed across different cancer types.

Discussion

- Both cases are indicated for a rare population with unmet medical need.
- Study results showed a favorable risk-benefit profile
- FDA accepted pooled data from multiple single arm trials due to the extreme rarity of the patient population.
- The approvals were based on the assumptions that the indicated population represents a unique, biomarker-identified disease regardless of histology.
- Small sample size representing multiple cancers.
- PMR required to follow additional patients to confirm clinical benefit.