제68차
한국췌장외과학회
학술대회

- 2021년 12월 11일(토요일)
- Bexco 제2전시장 3층

KPSC Since 2004

한국췌장외과학회
Korean Pancreas Surgery Club

HARMONIC®
HD 1000i
Behind the "WOW"

Unmatched precision

with a unique jaw shape that reduces the need to use a separate dedicated dissecting instrument

Unparalleled strength

with a blade design that delivers more secure seals, even in the most challenging conditions

Optimal efficiency

from increased sealing speed, multi-functionality, and simplified steps for use

*Design Validation Study with surgeons (n=33) operating in simulated procedures in an animate porcine laboratory model. #051950-160425
†In a design validation study with surgeons (n=33) operating in simulated procedures in an animate porcine laboratory model (26/33) #053344-160516
‡In a pre-clinical study, for both iliac dissection and lymph node dissection, the HD 1000i was significantly superior to the predicate devices in dissecting capability ($p<0.001$ in all cases). #051950-160425
*In a pre-clinical study, 100% (56/56) of porcine blood vessels remained hemostatic over a 30-day survival period. #049339-160315
†In a benchtop study with 5-7 mm porcine carotid arteries that compared median burst pressure, HARMONIC® HD 1000i (1878 mmHg) vs. competitor product A (1224 mmHg) ($p<0.0001$). #049305-160315.
‡In a benchtop study with 5-7 mm porcine carotid arteries that compared median burst pressure, HARMONIC® HD 1000i (1878 mmHg) vs. competitor product B (1171 mmHg) ($p<0.0001$). #049315-160315
*In a porcine study comparing sealing times of HARMONIC ACE®+7 and HARMONIC® HD 1000i, HARMONIC® HD 1000i Shears transected vessels faster than HARMONIC ACE®+7 (mean vessel transection time of 9.186 vs 15.291). #051753-160420
†In a design validation study with surgeons (n=33) operating in simulated procedures in an animate porcine laboratory model (26/33) #053344-160515
‡Design Validation Study with surgeons (n=33) operating in simulated procedures in an animate porcine laboratory model (33/33) #053346-160516
§Seal reliability at 240 mmHg of 98.2% vs. 98.4% for HARMONIC ACE®+7 MIN button. Speed based on average time to transect 150 mm of porcine jejunum ($p=0.0000$). #050508-160401
‖Device measurements based on a metrology study (median cut length of 18.87 mm vs. 14.56 mm). #050283-160329
#Based on average device tip grasping force (distal 5 mm of the jaw). #050295-160329

COPY-18008-EN

ETHICON
PART OF THE Johnson & Johnson FAMILY OF COMPANIES
Shaping the future of surgery

ORIGINAL MEROPENEM since 1999[1]

유한메로펜® 주사 500mg

Meropen active ingredient : Meropenem (MEPM)

THE RELIABLE PARTNER YOU CAN TRUST

- Ultra-broad spectrum of activity[2,3,*]
- High stability to ESBLs[4]
- Well tolerated, Low incidence of nausea and vomiting[5,6,†]
- The carbapenem indicated in meningitis[1,7,8]

ESBL: Extended-spectrum β-lactamase

*Meropenem has a very broad spectrum of in vitro activity against Gram-positive and Gram-negative pathogens, including extended-spectrum β-lactamase(ESBL)- and AmpC-producing Enterobacteriaceae.[3]

†In the safety analysis including 46 clinical trials, nausea and vomiting was reported in 1.4% to be related to treatment with meropenem.[5]

References.

1. 식약처 의약품 제조품목 허가증. 2020.4.24 2. J Antimicrob Chemother 1995; 36(Suppl A): 1-17 3. Drugs 2008;68(6):803-838 4. J Antimicrob Chemother 1998; 41(Suppl D):25-41 5. Scand J Infect Dis1999;31(1):3-10 6. J Antimicrob Chemother 1995; 36(Suppl A): 179-189 7. Diagn Micorbiol Infect Dis 1998; 31: 405-410 8. Antimicrob Agents and Chemother 1995; 39(5): 1140-1146

제품요약정보 전문의약품

유한메로펜® 주사 0.5그램 [원료약품 및 분량] 1 바이알 중 유효성분: 메로페넴·건조탄산나트륨(별규) 604mg(메로페넴으로서 500mg(역가)) **[성상]** 백색~담황색의 결정성 분말을 충진한 바이알 **[효능·효과] 1. 유효균종:** 제품 허가사항 참조 **2. 적응증:** 패혈증, 표재성 화농성질환, 림프절염, 항문주위농양. 외과 정형외과 영역 감염증(골수염, 관절염, 창상감염), 호흡기 감염증(폐렴, 편도주위농양, 만성호흡기질환의 2차 감염, 폐화농양, 농흉), 요로감염증(신우신염, 복잡성방광염), 간 담도감염증(담낭염, 담관염, 간농양), 복막염, 산부인과영역 감염증(자궁부속기염, 자궁내감염, 자궁방결합직염), 이비과영역 감염증(중이염, 부비동염), 세균성 수막염(3개월 이상의 소아), 호중구감소증 환자에서의 의심되는 감염, 낭포성 섬유증 **[용법·용량]** • 성인: 메로페넴수화물으로서 1일 0.5 ~ 1g(역가)을 2 ~ 3회 분할하여 30분 이상에 걸쳐 점적정맥주사한다. 병원성 폐렴, 복막염, 호중구감소증 환자에서의 의심되는 감염, 패혈증에는 8시간마다 1g(역가)을 점적정맥주사한다. 낭포성섬유증, 수막염에는 8시간마다 2g(역가)을 점적정맥주사한다. • 소아: 3개월 이상의 소아에 대한 세균성 수막염의 경우 병원균의 감수성과 환자의 상태, 감염의 종류에 따라 8시간마다 체중 kg 당 40mg을 30분 이상에 걸쳐 점적정맥주사한다. 또한 중성에 따라 적절히 증감하지만 중증, 난치성 감염증에는 1일 2g(역가)까지 증량할 수 있다. ※ 신장애 환자 등 기타 자세한 용법·용량은 제품 허가사항 참조 **[사용상의 주의사항] • 다음 환자에는 투여하지 말 것.** 1) 이 약에 대해 쇼크의 병력이 있는 환자 2) 발프로산나트륨을 투여 받고 있는 환자(이 약과의 병용투여에 의해 발프로산의 혈중농도가 저하되어 간질발작이 재발할 수 있다.) 3) 이 약 또는 이 약의 구성성분에 대해 과민반응 또는 그 병력이 있는 환자 4) 다른 카바페넴계 항생물질에 대해 과민반응(예, 심각한 피부 반응)의 병력이 있는 환자 5) 다른 베타락탐계 항생물질(예, 페니실린 또는 세팔로스포린)에 중증의 과민반응(예, 아나필락시스반응, 중증의 피부반응) 환자 **[저장방법]** 밀봉용기, 실온보관 **[개정연월일]** 2019. 5. 14 **[제조 판매자]** ㈜유한양행 본사: 서울 동작구 노량진로 74, 공장: 충청북도 청주시 청원구 오창읍 연구단지로 219 홈페이지: www.yuhan.co.kr 소비자상담실: 080-024-1188 (수신자 요금부담) **※자세한 허가사항은 식약처 의약품통합정보시스템 홈페이지 (http://nedrug.mfds.go.kr/)를 참조하여 주시기 바랍니다. 요약 허가사항에 반영되지 않은 허가 변경이 상기일자 이후에 있을 수도 있습니다.**

유한양행

MRP-A11-094-202006

PN Patient nutrition, evolved.

올리브유 기반의 Olimel은 환자 친화적인 3CB product입니다.

올리브유 기반의 Olimel은,

- ✓ **가장 낮은 삼투압**의 **올리멜**은 **혈관통, 정맥염의 우려를 줄일** 수 있습니다.[1,2]
- ✓ 단백질 함유량이 높아 **충분한 단백질 공급이 가능**합니다.[3]
- ✓ **면역체계를 보존**해 주며, **염증에 중립적**입니다.[4,5]

Baxter

References 1. ESPEN Guideline on Parenteral Nutirtion: Centeral Venous Catheters; 365p
2. TPN Product data **3.** SmPC **4.** Jia et al. 2015 **5.** Clinimix FDA approval lette

OLIMEL®
OPTIMISED NUTRITIONAL BALANCE

TachoSil®

- Quick onset of hemostasis
- Safe tissue sealing
- Easy handling
- Shorter operation time
- Minimize risk of re-bleeding
- Reduce the likelihood of blood transfusion

[원료약품 및 분량]

Tachosil contains per (1㎠)

- Collagen (sponge) ..... 2.1㎎
- Human Fibrinogen ..... 5.5㎎
- Human Thrombin ..... 2.0 IU
- Riboflavin ..... 18.2㎍

[성상]

한면에 황색 약물이 도포된 백색 스폰지

[표능 및 효과]

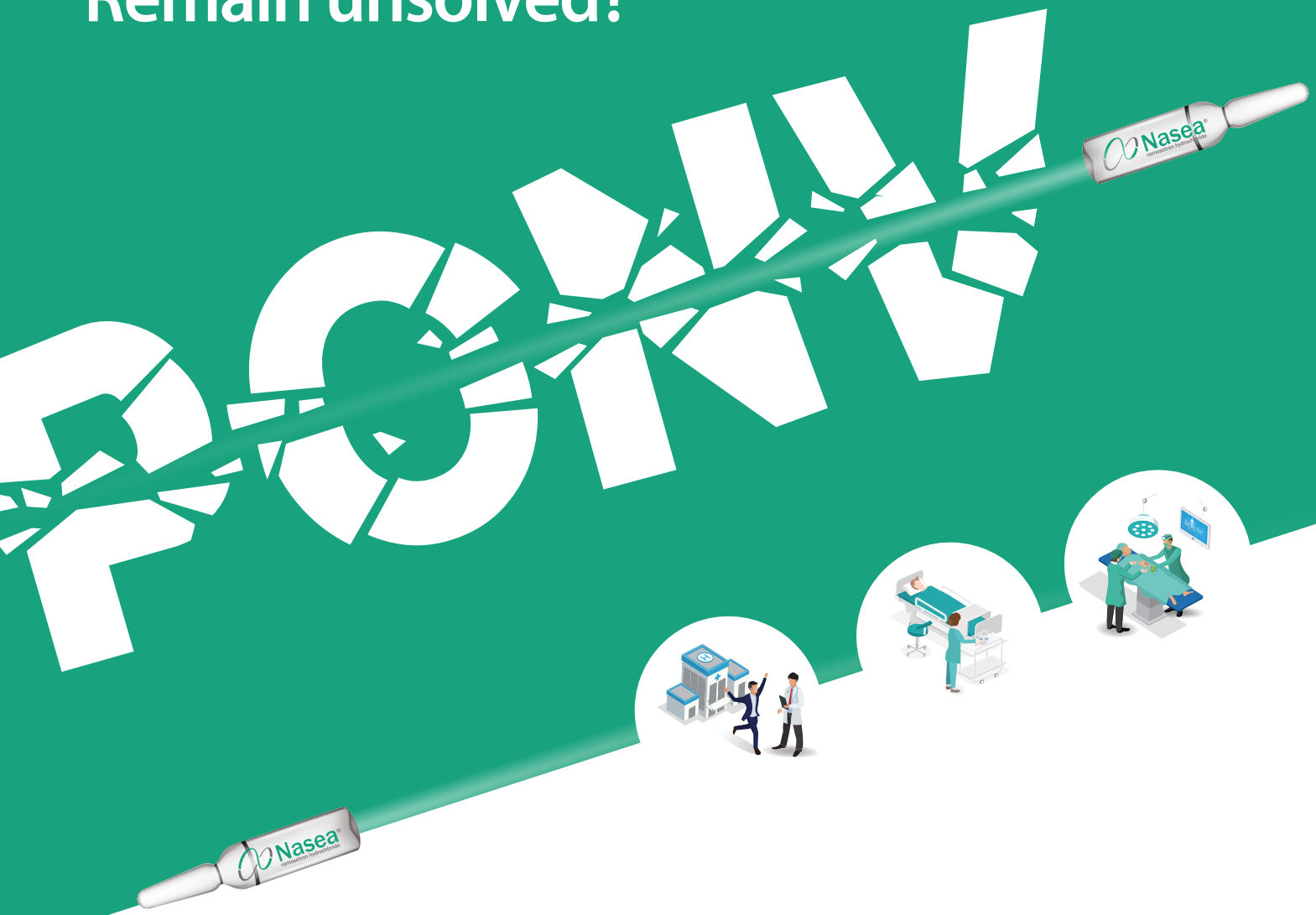
1. 기존 치료법으로 조절할 수없는 경우 또는 기존 치료법으로 불충분하다고 예상되는 경우의 출혈 또는 담즙, 림프, 액, 공기 누출
2. 간, 비장, 췌장, 신장, 폐, 부신, 갑상선, 림프절과 같은 실질적 기관 수술시의 지혈 및 조직접착, 또한 이비인후과, 부인과, 비뇨기과, 혈관계, 뼈(예를 들면 해면골)수술, 외상관련 수술시의 지혈
3. 림프, 담즙, 액의 누공의 예방적 처치
4. 폐수술시 일어나는 공기누출의 봉합

[포장단위]

(9.5X4.8X0.5)㎠ X 1매
(4.8X4.8X0.5)㎠ X 2매
(2.5X3.0X0.5)㎠ X 1매

현대약품(주)
충청남도 천안시 풍세면 남관리 200

Does PONV still Remain unsolved?



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Injection
Nasea®
ramosetron hydrochloride

한국다이이찌산쿄주식회사
Daiichi-Sankyo 서울시 중구 을지로5길 26 미래에셋 센터원빌딩 동관 15층 Tel. 02-3453-3300

나제아®주사액 0.3mg [원료약품 및 분량] 1앰플(2mL) 중 라모세트론 염산염 0.3mg 함유 **[효능·효과]** 1. 항암제(시스플라틴) 투여로 인한 구역 및 구토의 방지 2. 수술 후 구역 및 구토의 방지 **[용법·용량]** 성인 라모세트론 염산염으로서 1일 1회 0.3mg을 정맥투여한다. 효과가 불충분할 경우에는 동일한 용량을 추가 투여할 수 있다. 단 1일량으로 0.6mg을 초과하지 않도록 한다. 증상에 따라 적절히 증감한다. **[사용상 주의사항]** 1. 경고 앰플주사제는 용기 절단시 유리파편이 혼입되어, 부작용을 초래할 수 있으므로 사용시 유리파편 혼입이 최소화 될 수 있도록 신중하게 절단 사용하되, 특히 어린이, 고령자 사용시에는 각별히 주의할 것 **[금기]** 이 약 또는 이 약의 다른 성분에 과민반응을 나타내는 환자 [신중투여] 다른 세로토닌성 약물(선택적 세로토닌 재흡수 억제제(SSRI)와 세로토닌 노르아드레날린 재흡수 억제제(SNRI)를 포함)을 투여 받고 있는 환자 **[이상반응]** 이 약의 개발국인 일본에서 허가시까지의 임상시험에서는 352명 중 18명(5.1%)에서, 시판후 사용성적 조사 및 시판후 임상시험에서는 3,464명 중 260명(7.5%)에서 임상시험 검사치의 이상을 포함한 이상반응이 확인되었다. 1. 중대한 이상반응 쇼크, 아나필락시스 유사증상, 간질유사발작 2. 기타의 이상반응 간기능이상 및 두통, 변비 등 3. 국내에서 재심사를 위하여 6년 동안 3,118명(15세 이하 소아환자 69명 포함)을 대상으로 실시한 시판 후 조사결과 이상반응의 반현율은 1.51%(47례, 60건/3,118례)로 보고되었다. **[상호작용]** 이 약은 주로 간의 약물대사 효소 CYP1A2 및 CYP2D6에 의해 대사되므로 플루복사민과 병용 투여시 CYP1A2 저해 작용에 의해 혈중농도 상승으로 인한 이상반응이 증강될 위험이 있으므로 주의한다. **[개정년월일]** 2017년 11월 1일

본 정보는 요약된 일부의 정보입니다. 따라서 최신 변경된 허가사항이나, 자세한 사항은 당사 홈페이지(www.daiichisankyo.co.kr)나 의약품안전나라(nedrug.mfds.go.kr)의 의약품 정보를 참고해 주십시오.

P19-175-2021.12-V1

selenase

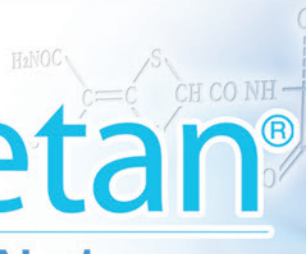
셀레나제100 마이크로그램퍼오랄액 (아셀렌산나트륨오수화물)	2mL X 20Amp.	영양공급으로 보충될 수 없는 셀레늄 결핍 환자에서 셀레늄 보급
셀레나제100 마이크로그램프로주사 (아셀렌산나트륨오수화물)	2mL X 50Amp.	
셀레나제 티프로주사	10mL X 10Vial	

수입원 biosyn 판매원 Huons

Approved by F.D.A.

Yamatetan®은 국제 가이드라인에서 추천하는 수술시 예방 목적에 적합한 2세대 세파 항생제입니다.

- Gram (+),(-)균에서 혐기성균까지 광범위한 spectrum을 나타냅니다.
- Sanford, ASHP Guideline에서 추천하는 수술시 감염예방 항생제입니다.
- β - Lactamase에 매우 안정합니다.
- 유효혈중 농도가 12시간 이상 지속되므로 장시간 수술에 적합합니다.
- 각종감염증에 임상효과가 우수하며, 부작용 발현율이 경미합니다.



Yamatetan®

CEFOTETAN 1g

[성분·함량] 1 vial 중 Cefotetan 1g(역가)
[성　　상] 백색 내지 담황백색 분말이 든 바이알제
[효능·효과] 패혈증, 화상, 수술창등의 표재성 2차 감염, 급·만성 기관지염,
편도염(편도주위염, 편도주위농양), 기관지 확장증(감염시), 만성 호흡기 질환의
2차 감염, 폐렴, 폐화농증, 농흉, 신우신염, 방광염, 담낭염, 담관염, 복막염,
자궁내감염, 골반사강염, 자궁주위염, 바르톨린선염
[보 험 코 드] 645400710
※제품에 대한 자세한 정보를 원하시면 제일약품 마케팅부 02-549-7451로 문의 바랍니다.

제일약품

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OLIMEL

Olive oil for immune function.

Prescribe to preserve

Baxter

보령제약

More convenient

Fish oil based TPN

Only My Precious Nutrition One

오마프원® TPN Total Parenteral Nutrition

Fish oil(ω-3 지방산)을 포함한
최적의 Lipid 조성으로 환자에게
면역기능 강화 및 **항염증 효과**로
빠른 회복력을 **제공**합니다.

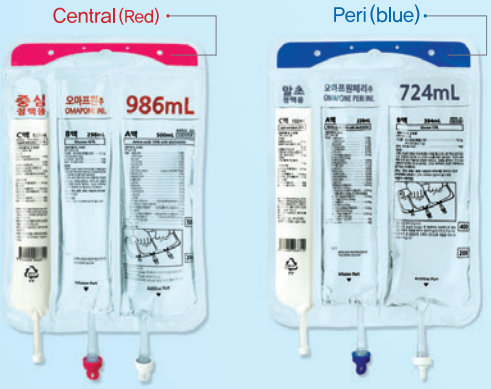
환자의 상태에 따른
다양한 용량 선택이 **가능**합니다.

**차별화된 Device 개발로 보다 안전하고
편리하게 사용하실 수 있습니다.**

Innovation

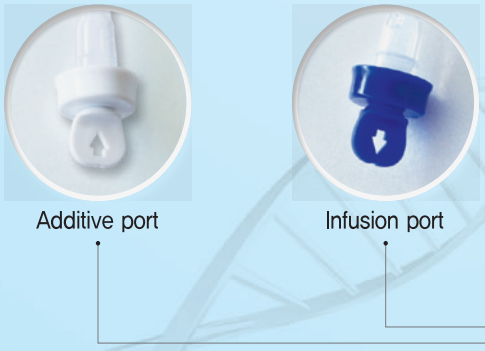
HK inno-N이 자체 개발한 Hanger Bar 색상 구현을 통해

- 말초정맥용과 중심정맥용의 구별이 용이하여 투여 오류를 방지합니다.
- 이동과 수액걸이 사용이 편리하여 사용자 편의성을 제공합니다.
- 지속적으로 Bag의 형태가 유지되며, 잔여량을 쉽게 확인하실 수 있습니다.



Simple

- 양면 오버파우치 디자인 적용으로 투명면을 통해 쉽게 제품 확인 가능
- 각 port의 색상과 탭 화살표 주입 방향은 Infusion Port와 Additive Port 구분 용이



inno.N 서울특별시 중구 을지로 100 파인애비뉴 A동 6층-8층
http://www.inno-n.com 고객상담센터 080-700-8802

제68차
한국췌장외과학회
학술대회

- 2021년 12월 11일(토요일)
- Bexco 제2전시장 3층

한국췌장외과학회
Korean Pancreas Surgery Club

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제68차
한국췌장외과학회 학술대회

일시 | 2021년 12월 11일(토)

장소 | Bexco 제2전시장 3층

PROGRAM

제68차
한국췌장외과학회 학술대회

Scientific Session 1

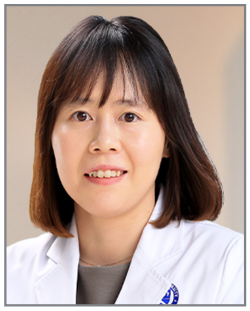
Clinical Issues for Immunotherapy of Pancreato-biliary cancer

허진석(성균관의대), 장진영(서울의대)

KPSC Since 2004
한국췌장외과학회
Korean Pancreas Surgery Club

연/자/소/개

Curriculum Vitae



김 지 형

연세대학교 의과대학 강남세브란스병원 종양내과

학 력 사 항

2007~2011	이화여자대학교 의과대학 의학전문대학원 석사
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경 력 사 항

2011~2012	연세대학교 의과대학 세브란스병원 인턴
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2013~2017	연세대학교 의과대학 세브란스병원 내과 레지던트
2017~2018	연세대학교 의과대학 연세암병원 종양내과 강사
2018~2019	연세암병원 종양내과 진료교수
2019~현재	강남세브란스병원 종양내과 임상조교수

Basic Concept of Immunetherapy

김지형 (연세의대 종양내과)

Severance

COI

- I have nothing to disclose

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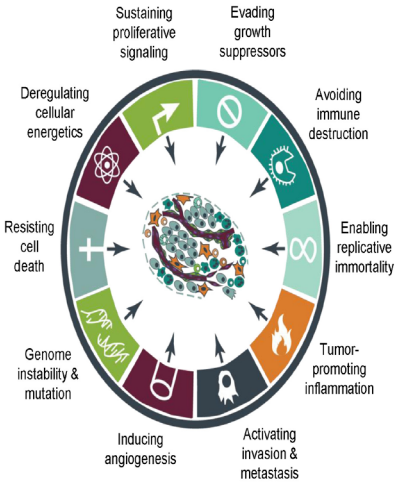
Immune Surveillance and Evasion in Carcinogenesis

- Immune surveillance plays a role in the recognition and destruction of precancerous cells before they can mature into solid tumors.[1]
- Thus, in carcinogenesis, evasion of the immune system is critical to allow cancer to grow and spread.[1]
- PD-1 and its ligands are involved in tumor immune evasion strategies.[2]

Immune Evasion Is a Hallmark of Cancer[1]



PD-1, programmed death receptor 1.

1. Hanahan D, et al. Cell. 2011;144:646-674. 2. Nagai S, et al. In: Azuma M, et al, eds. Co-signal Molecules in T Cell Activation: Immune Regulation in Health and Disease. 1st edn. Springer Nature; 2019:25-51.

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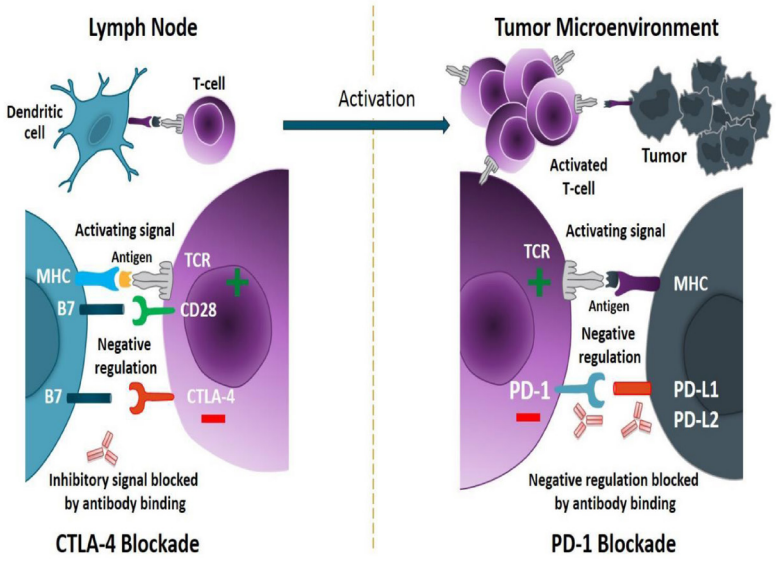
CTLA-4 and PD-1/PD-L1 Checkpoint Blockade for Cancer Treatment



Ribas. NEJM. 2012;366:2517.

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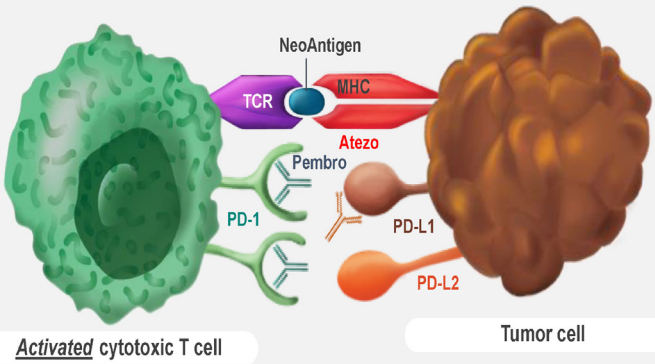
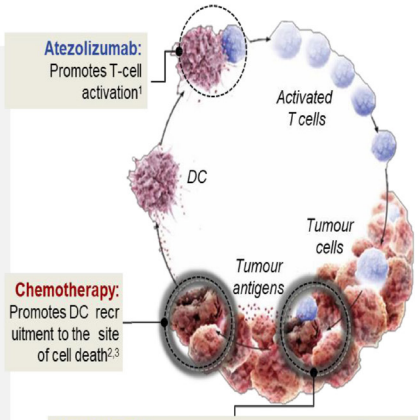
PD-1 inhibitor and PD-L1 inhibitors

- PD-1 inhibitor could interrupt PD-1 and PD-L2 interaction
- Actions between immune cells as well as between Tumor and T cells





Atezolizumab: Restores anti-cancer immunity,[1] with activity further enhanced by chemotherapy-induced antigen exposure

MHC = major histocompatibility complex; PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1; PD-L2 = programmed death ligand 2; TCR = T-cell receptor.

1. Chen *Immunity* 2013. 2. Zitvogel *Immunity* 2013. 3. Emens *CIR* 2015. 4. TECENTRIQ US PI/SmPC 2018. 5. Herbst *Nature* 2014. 6. Emens *JAMA Oncol* 2018. 7. Jotte ASCO 2018. 8. Pohlmann AACR 2018.

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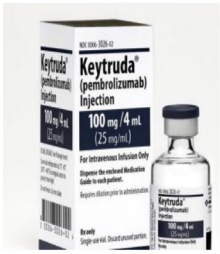
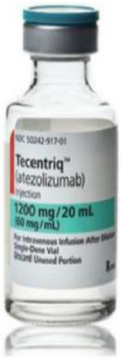
Severance

PD-1/PD-L1 blockades in the market





- CTLA4 inhibitor : Ipilimumab, Tremelimumab
- PD-1 inhibitor : Pembrolizumab, Nivolumab
- PD-L1 inhibitor : Durvalumab, Atezolizumab, Avelumab

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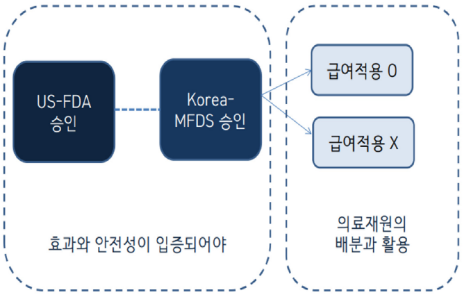
PD-1/PD-L1 blockades in the market

Drug	Commertial name	Owner	Target	First approval date
Pembrolizumab	Keytruda	MDS	PD-1	Sep 2014
Nivolumab	Opdivo	BMS	PD-1	Dec 2014
Atezolizumab	Tecentriq	Roche	PD-L1	May 2016
Avelumab	Bevancio	EMD & Pfizer	PD-L1	March 2017
Durvalumab	Imfinzi	Astrazeneca	PD-L1	May 2017



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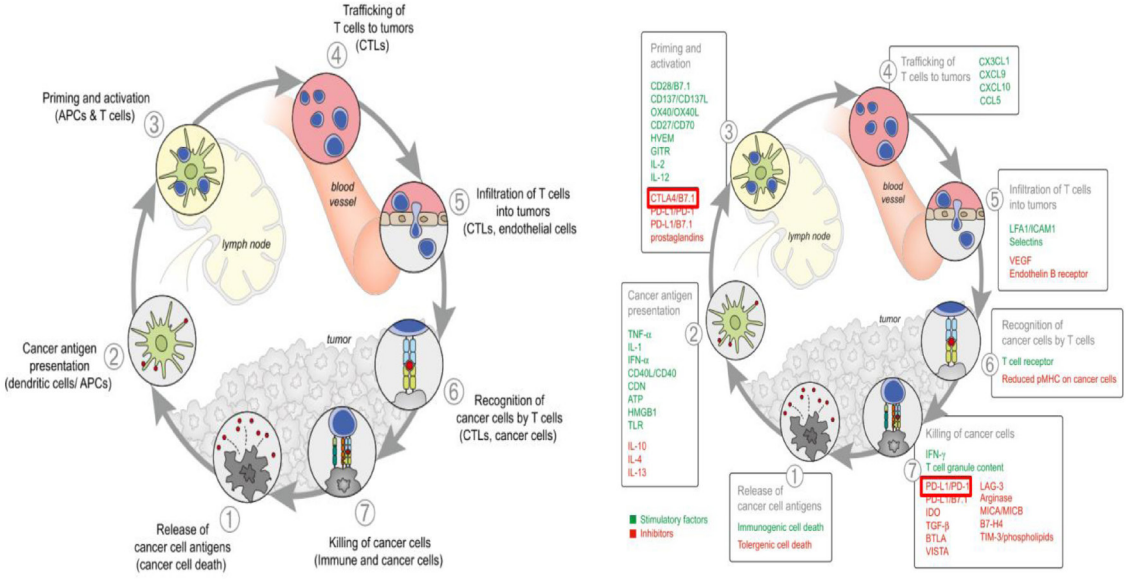
Cancer-Immunity Cycle



Immunity. 2013 Jul 25;39(1):1-10. doi: 10.1016/j.immuni.2013.07.012.

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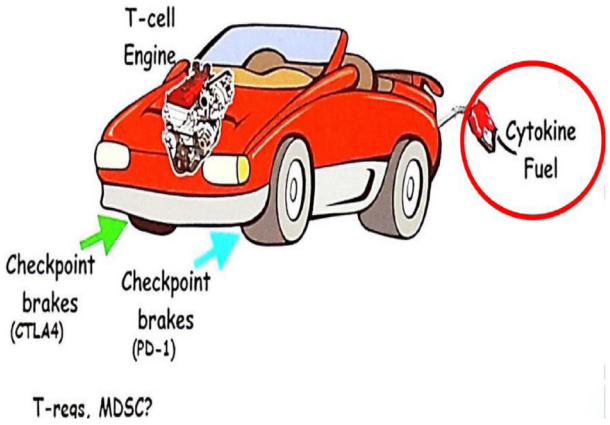
Severance

Accels and Brakes in T-cell



Drew Pardoll (MSKCC), 2015 AACR

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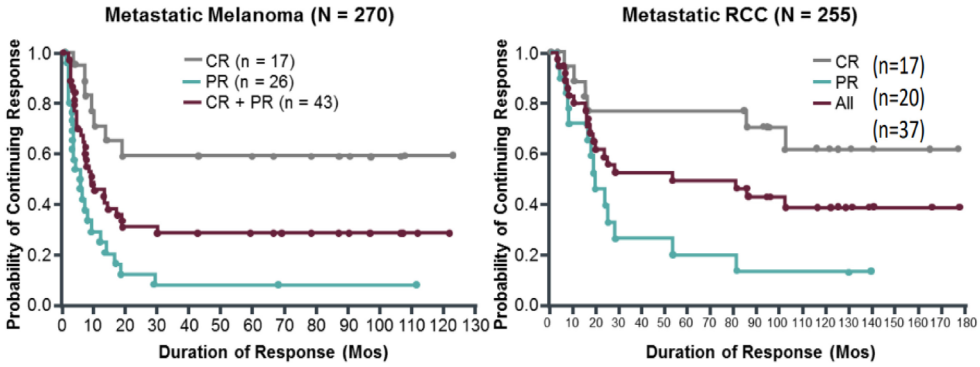
HD IL-2 Therapy : Durable response

- HD IL-2 produces durable response in 6% to 10% of patients with advanced melanoma or RCC, but Toxic and Impractical
- Proof of principle that immunotherapy can produce **durable benefit in certain patients** with cancer



Atkins MB, et al JCO 1999 17: 2105-2116
McDermott DF, et al. Expert Opin Biol Ther. 2004; 4:455-468

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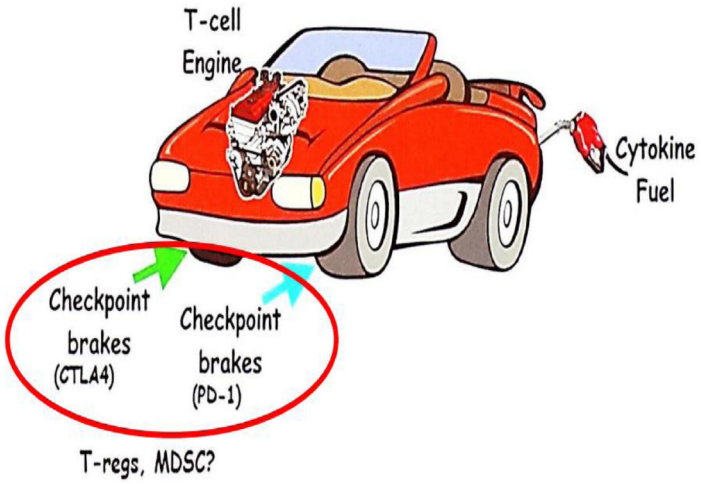
Severance

Accels and Brakes in T-cell



Drew Pardoll (MSKCC), 2015 AACR

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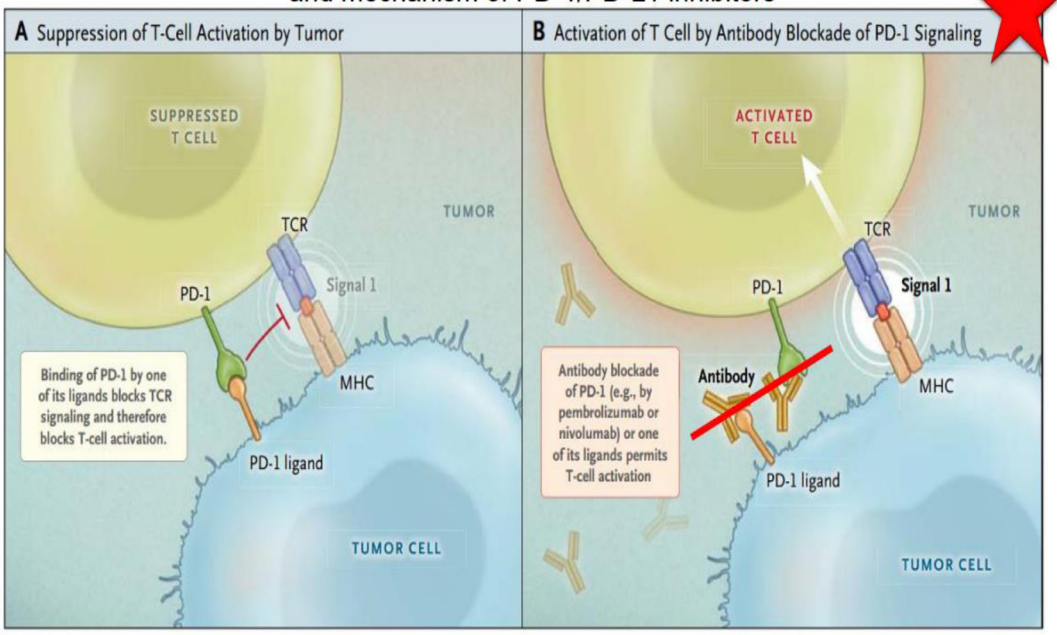
T-cell suppression and reactivation in tumor bed and mechanism of PD-1/PD-L1 inhibitors



N Engl J Med. 2015 Oct 15;373(16):1490-2

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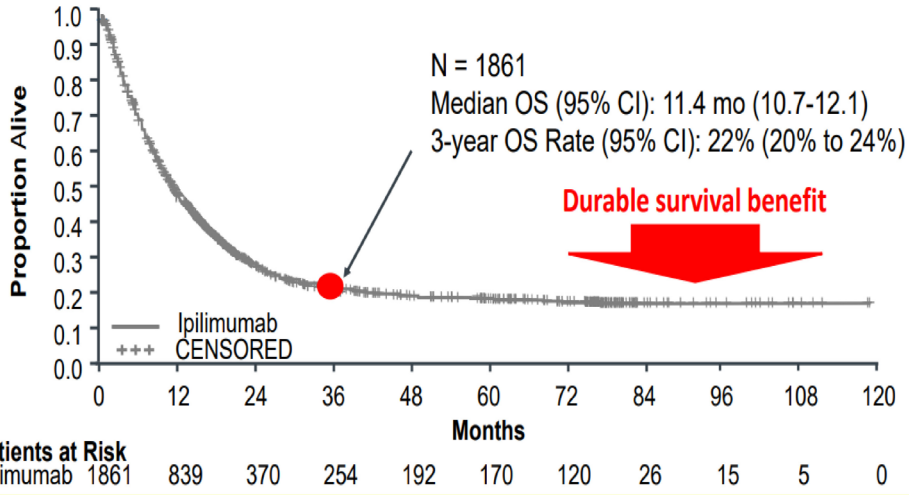
Ipilimumab – CTLA4 inhibitor : Pooled Survival Analysis from Phase II/III Trials in Advanced Melanoma



면역항암제의 가장 큰 장점: 반응율이 세포독성/표적항암제보다 더 높지는 않지만, 면역시스템을 활성화시켜, 내성없이, 장기간 지속되는 효과 → 장기 생존자가 존재한다

Hodi S, et al. 2013 European Cancer Congress. Abstract LBA 24.

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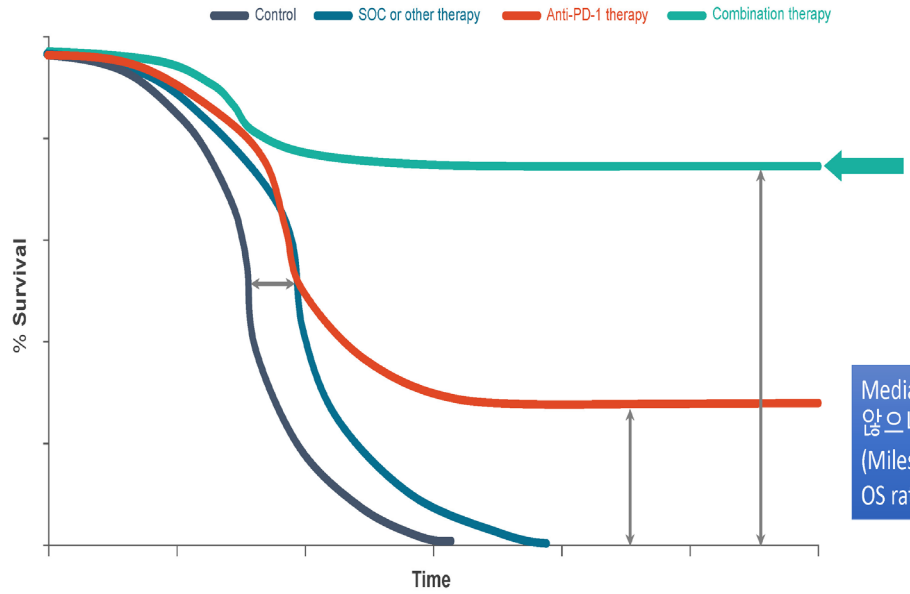
Severance

Raising the tail of the survival curve

• Chemotherapy • Targeted therapy • Radiotherapy • Immunomodulators • Exploratory therapies



Median 값의 변화는 크지 않으나 long tail이 존재한다. (Milestone survival의 증가 1yr OS rate, 2yr OS rate)

Sharma *et al.* J Cell. 2015.

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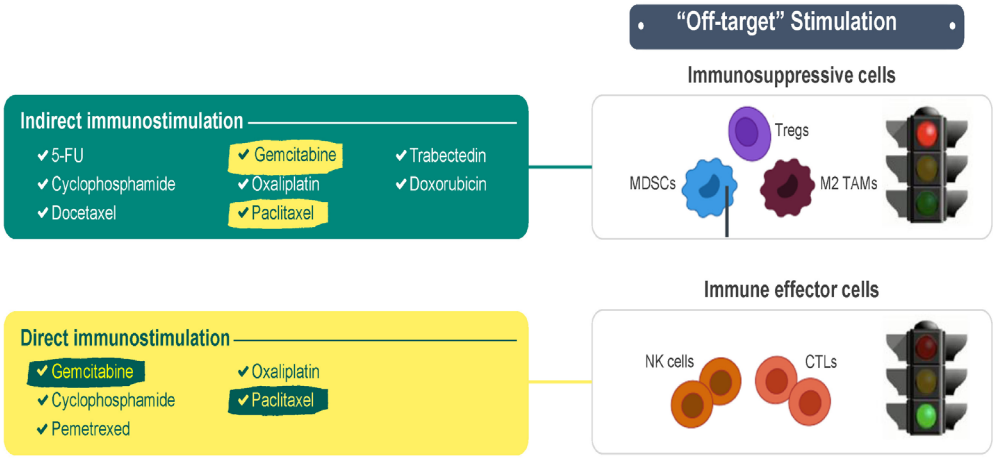
Effects of Chemo + Immunotherapy : Chemotherapy can target immune cell

- **Chemotherapy May Stimulate Immune Responses Directly and Indirectly**
  - Some chemotherapies can target immunosuppressive cells (indirect immunostimulation), and some chemotherapies can target immune effector cells themselves (direct immunostimulation)



1. Galluzzi *et al.* Cancer Immunol Res. 2016;4(11):895-902.

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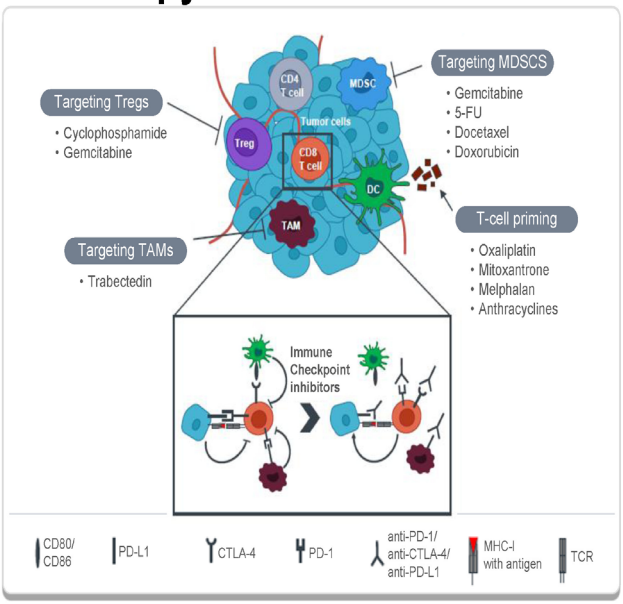
Effects of Chemo + Immunotherapy

- **Immunomodulatory Effects of Chemotherapy May Boost Efficacy of Immunotherapy**
- For patients who do not respond to cancer immunotherapy, rational design of combinatorial cancer immunotherapy strategies may be employed to maximize the success of immunotherapy[1]
- Chemotherapy is a clinically available strategy with demonstrated immunomodulatory properties, and thus may augment antitumor immunity and synergistic activity when combined with immunotherapy[1,2]



1. Kersten K *et al.* Front Immunol. 2015;6(516):1-15. 2. Anraku M *et al.* J Immunol. 2010;185(2):956–966.

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어떤 암종에서 효과가 있나 -> 거의 모든 암종에서!

Melanoma
- for the treatment of patients with unresectable or metastatic melanoma. (1.1)
- for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection. (1.1)

Non-Small Cell Lung Cancer (NSCLC)
- in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations. (1.2)
- in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC. (1.2)
- as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is:
  - stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
  - metastatic. (1.2, 2.1)
- as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA. (1.2, 2.1)

Small Cell Lung Cancer (SCLC)
- for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.[1] (1.3)

Head and Neck Squamous Cell Cancer (HNSCC)
- in combination with platinum and FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC. (1.4)
- as a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test. (1.4, 2.1)
- as a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy. (1.4)

Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer (CRC)
- for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC). (1.9, 2.1)

Gastric Cancer
- for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after 2 or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.[1] (1.10, 2.1)

Esophageal Cancer
- for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:
  - in combination with platinum- and fluoropyrimidine-based chemotherapy, or
  - as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test (1.11, 2.1).

Cervical Cancer
- for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test.[1] (1.12, 2.1)

Hepatocellular Carcinoma (HCC)
- for the treatment of patients with HCC who have been previously treated with sorafenib.[1] (1.13)

Merkel Cell Carcinoma (MCC)
- for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.[1] (1.14)

Renal Cell Carcinoma (RCC)
- in combination with axitinib, for the first-line treatment of patients with advanced RCC. (1.15)

Endometrial Carcinoma
- in combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.[1] (1.16)

Tumor Mutational Burden-High (TMB-H) Cancer
- for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high

Classical Hodgkin Lymphoma (cHL)
- for the treatment of adult patients with relapsed or refractory cHL. (1.5)
- for the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy. (1.5)

Primary Mediastinal Large B-Cell Lymphoma (PMBCL)
- for the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy. (1.6)
- Limitations of Use: KEYTRUDA is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

Urothelial Carcinoma
- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express

2021-03 FDA label - pembrolizumab

Severance

Approvals & Use of anti-PD1/PD-L1 antibodies

- 암의 종류, 치료 차수, 바이오마커 필요 여부(PD-L1 또는 MMRd or MSI-H), PD-L1의 경우 인정되는 PD-L1 검사, 약의 용량 등이 다르다.
- 국내 허가가 되어 있어도 보험 적용 조건은 다를 수 있다.
- 허가되지 않았으나 사전신청으로 사용 가능한 경우도 있다
  - ※사전신청: 약제의 허가범위 초과 사용을 하고자 할 때, 식약처에서 지정하는 요양 기관의 다학제위원회 상의를 거쳐 건강보험심사평가원에 승인 요청을 하면, 암질환 심의위원회 등의 회의를 거쳐 승인 여부를 결정해 줌.
- 계속 변경될 예정

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Contents

I. Basic concept of Immunotherapy

II. **Biomarker of Immunotherapy : PD-L1, MSI status, TIL, TMB**

III. Landmark trials with ICBs in TNBC

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1) Biomarker: PD-L1

- FDA-approved PD-L1 IHC assays related to NSCLC

Drug	Drug Target	Antibody	Developer	FDA status	Reading	Cut-off
Nivolumab	PD-1	28-8	Dako	Complementary	% membranous staining of tumor cells (minimum 100 cells evaluated)	1L : 5% 2L : no cut off
Pembrolizumab	PD-1	22C3	Dako	Companion	% membranous staining of tumor cells (TPS,minimum 100 cells evaluated)	1L: 50% 2L: 1%
Atezolizumab	PD-L1	SP142	Ventana	Complementary	%Tumor and Immune cell PD-L1: TC3/IC3 ≥50% TC2/IC2 5-19% TC1/IC1 1-4% TC0/IC0	1L : TC1/IC1 2L: no cut off
Durvalumab	PD-L1	SP263	Ventana	Complementary	% membranous staining of tumor cells(minimum 100 cells evaluated)	25%
Avelumab	PD-L1	73-10	Dako	Complementary	% membranous staining of tumor cells (minimum 100 cells evaluated)	1%

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Development of companion diagnostic for pembrolizumab in NSCLC

- PD-L1(22C3) development

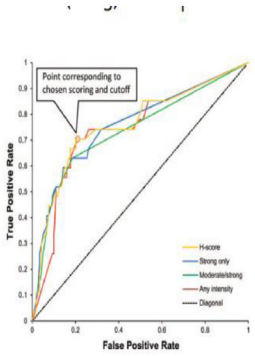
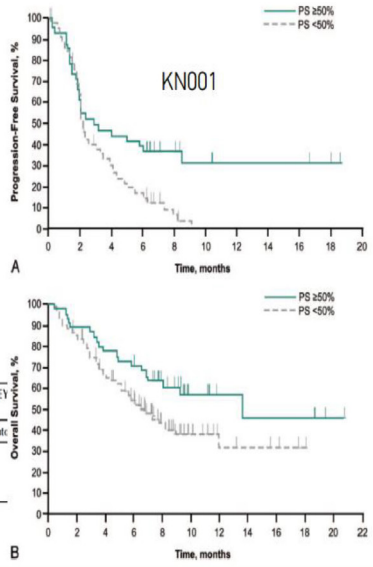


Table 2. Summary Results of the 4 Scoring Methods Used for the KEY ... Similarly

Scoring Method	Area Under the ROC Curve	Youden Index	Cut
PS1	0.743	0.494	
PS2	0.758	0.462	
PS3	0.736	0.445	
HS	0.758	0.502	



Arch Pathol Lab Med. 2016;140:1243–1249

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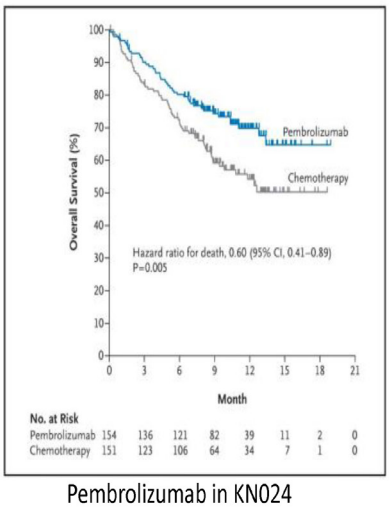
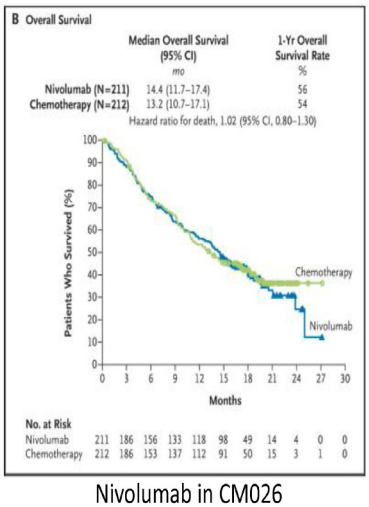
Pembrolizumab/ nivolumab in 1st line NSCLC

- ICI vs. platinum –based chemotherapy, 1st line NSCLC



Pembrolizumab in KN024
PD-L1 ≥ 50%



Nivolumab in CM026
PD-L1 ≥ 5%

N Engl J Med. 2016 Nov 10;375(19):1823-1833.
N Engl J Med. 2017 Jun 22;376(25):2415-2426

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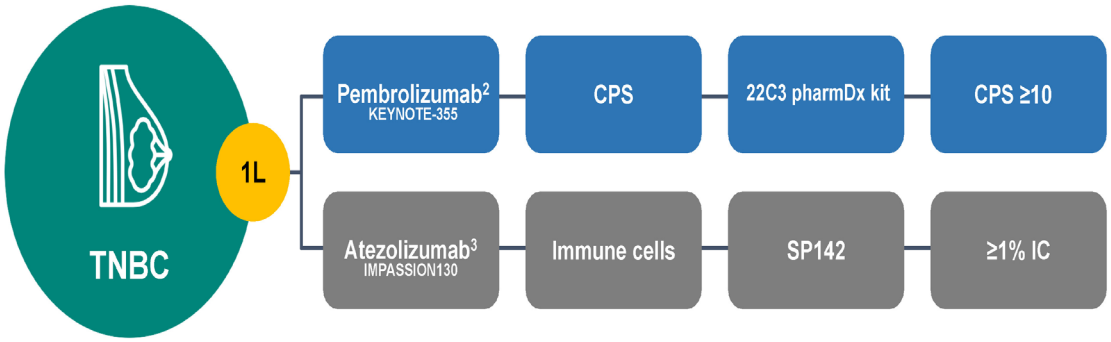
PD-L1 Testing in 1st line mTNBC



CPS = Combined Positive Score, IC = Immune Cells

1. Burtness B et al. Lancet. 2019;394:1915–1928.
2. 키트루다 허가사항, 식품의약품 안전처
3. 티쎈트릭 허가사항, 식품의약품 안전처
4. Cortes J et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trialLancet 2020; 396: 1817–28
5. P. Schmid et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer N Engl J Med 2018;379:2108-21.

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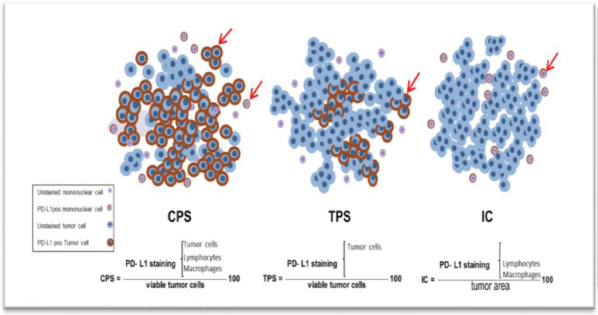
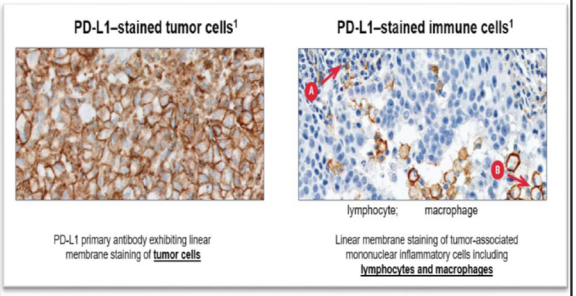
PD-L1 (DAKO 22C3) Scoring: Defining CPS, TPS, and IC

- **CPS(Combined positive score)**
  - Measures the number of PD-L1 staining cells, including tumor cells, lymphocytes and macrophages, divided by the total number of viable tumor cells multiplied by 100. This scoring method is used for **GEJ cancers, Breast cancer(TNBC).**
- **TPS (Tumor positive score)**
  - The percentage of PD-L1 expressing tumor cells(partial or complete membrane staining) relative to total number of tumor cells. This scoring method is used for **NSCLC.**
- **IC (immune cell score)**





1. Agilent Technologies, Inc. PD-L1 IHC 22C3 pharmDx Interpretation Manual—Gastric or Gastroesophageal Junction Adenocarcinoma. 2019

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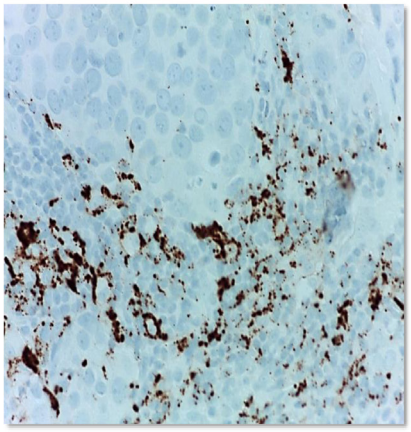
PDL1 (Ventana SP142)

- SP142 uses the proportion of tumour area occupied by PD-L1-positive immune cells to score PD-L1 IC



PD-L1 expression on immune cells was evaluated in IMpassion130[1]

PD-L1 IC scoring criteria	
IC score	% of tumour area
IC0	<1%
IC1	≥1% and <5%
IC2	≥5% and <10%
IC3	≥10%

ICs are scored as the proportion of tumour area that is occupied by PD-L1-stained ICs of any intensity

Any IC staining pattern, irrespective of type of immune cell

1 Schmid P, *et al. N Engl J Med* 2018.

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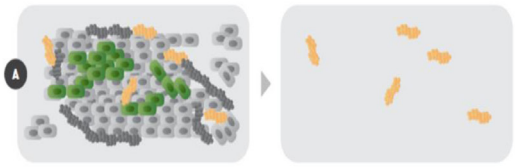
PD-L1 scoring systems - IC vs CPS

Immune Cell Score



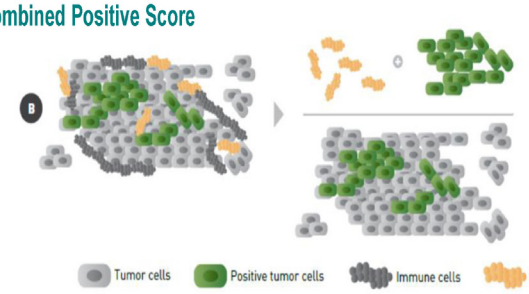
Ventana IC – Score (Drug: Atezolizumab)

IC (%) = % of tumor area covered by positive immune cells (area)

IC

- IC's are scored as the proportion of tumor area occupied by IC showing PD-L1 staining of any intensity.
- Include: lymphocytes, macrophages, dendritic cells and granulocytes
- **Report as percentage**

Combined Positive Score



Combined Positive Score (Drug: Pembrolizumab)

CPS = [(total n of positive TC + total n of IC) / total n of TC] x 100

CPS

- Evaluate the number of PD-L1 staining cells relative to all viable tumor cells.
- Include: TC (membrane partial/complete), lymphocytes, macrophages
- Exclude: granulocytes & plasma cells
- **Report as a number (Max score 100)**

Tumor cells | Positive tumor cells | Immune cells | Positive immune cells

Note: For CPS, the terms IC and mononuclear inflammatory cells (MIC) used interchangeably.
TC = Tumor Cells, IC = Immune Cells

(A) The Ventana SP-142 assay measures PD-L1 expression in tumor-infiltrating immune cells and generates an IC-Score (%). This score is required to assess first-line treatment eligibility with atezolizumab plus nab-paclitaxel for patients with metastatic TNBC; patients are eligible for treatment if the cutoff of 1% is exceeded.
(B) The PD-L1 IHC 22C3 pharmDx assay generates a combined positive score (CPS) by measuring PD-L1 expression in both the tumor cells and tumor-infiltrating immune cells. This score is required to assess first-line treatment eligibility with pembrolizumab and chemotherapy in patients with metastatic TNBC; patients are eligible if they meet or exceed the cutoff of 10.

Republished from Eckstein M, et al. PD-L1 assessment in urothelial carcinoma: a practical approach. *Ann Transl Med*. 2019;7[22]:690, under the terms of a Creative Commons 4.0 License.

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Five Different PD-L1 Diagnostic Tests

- Each anti–PD-1/PD-L1 inhibitor is associated with:
  - **its own specific diagnostic assay and staining platform.**
  - **a specific cutoff point for measurement, which may differ between indications.**
  - **a specific scoring method, involving assessment of tumor cells, immune cells, or both, which may also differ between indications.**

22C3[1] (Dako pharmDx)	SP142[2] (Ventana)	28-8[3] (Dako pharmDx)	SP263[4] (Ventana)	73-10[5] (Dako)
• **Approved as *companion* diagnostic test for pembrolizumab** • Similar TC staining as 28-8 and SP263 • Showed IC staining with greater variability than with tumor cells	• **Approved as *companion* diagnostic test for atezolizumab** • Weaker TC staining than 22C3, 28-8, and SP263 • Showed IC staining with greater variability than with tumor cells	• ***Complementary* test** used in nivolumab studies • Similar TC staining as 22C3 and SP263 • Showed IC staining with greater variability than with tumor cells	• **Approved as *complementary* diagnostic test for durvalumab** • Similar TC staining as 22C3 and 28-8 • Showed IC staining with greater variability than with tumor cells	• ***Complementary* test** used in avelumab studies • Highest sensitivity for TC staining • Showed IC staining with greater variability than with tumor cells

PD-L1, programmed death ligand 1.

1. Agilent IHC 22C3 IM Triple-Negative Breast Cancer. Agilent Technologies, 2020, 2. Roche. Ventana. PD-L1 (SP142) Assay Interpretation Guide for Triple-Negative Breast Carcinoma (TNBC). Last revised June 28, 2019. Accessed September 25, 2020.3. Agilent technologies, Inc. Instructions for use; PD-L1 IHC 28-8 pharmDx. 4. Roche. Ventana. PD-L1 (SP263) Assay interpretation guide. 5.

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Overview of FDA-approved PD-L1 IHC Assays for Use With ICIs in FDA (2021.Nov)

	Agilent PD-L1 IHC 22C3 pharmDx[1]	Agilent PD-L1 IHC 28-8 pharmDx[2]	Ventana PD-L1 IHC (SP142) Assay[3]	Ventana PD-L1 IHC (SP263) Assay[4]
NSCLC	TPS ≥1%	TC ≥1%; TC ≥5%; TC ≥10%	TC ≥50%; IC ≥10%	
Urothelial	CPS ≥10	TC ≥1%	IC ≥5%	TC ≥25%; ICP >1% with IC+ ≥25%; ICP =1% with IC+ =100%
HNSCC	CPS ≥1	TC ≥1%		
Cervical	CPS ≥1			
ESCC	CPS ≥10			
Gastric/GEJ	CPS ≥1			
TNBC	**CPS ≥10**		IC ≥1%	

Expected withdraw | Companion Diagnostic | Complementary Diagnostic

CPS=combined positive score; ESCC=esophageal squamous cell carcinoma; FDA=US Food and Drug Administration; GEJ=gastroesophageal junction; HNSCC=head and neck squamous cell carcinoma; IC=percentage of immune cells with positive staining in total tumor area; IC+=percentage of ICP with positive staining; ICI=immune cell inhibitor; ICP=percentage of tumor area populated by immune cells; IHC=immunohistochemistry; NSCLC=non-small cell lung cancer; PD-L1=programmed death ligand 1; TC=percentage of tumor cells with positive staining in total tumor area; TNBC=triple-negative breast cancer; TPS=tumor proportion score.

1. Agilent Technologies, Inc. Instructions for Use: PD-L1 IHC 22C3 pharmDx. 2. Agilent Technologies, Inc. Instructions for Use: PD-L1 IHC 28-8 pharmDx. 3. Ventana Medical Systems. Instructions for Use: Ventana PD-L1 (SP142) Assay. 4. Ventana Medical Systems. Instructions for Use: Ventana PD-L1 (SP263) Assay. 2018.

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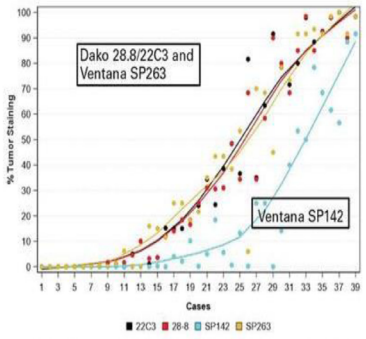
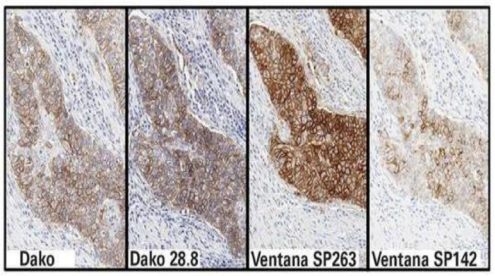
Concordance of PD-L1 assays

- **Blueprint project**
  - Phase I of the Blueprint Project was a feasibility study evaluating 39 tumors stained with four distinct antibodies: Dako 28-8 (for use with nivolumab), Dako 22C3 (for use with pembrolizumab), Ventana SP263 (for use with durvalumab), and Ventana SP142 (for use with atezolizumab).



Each dot represents the mean score of three pathologists



Conclusion: 1: Three assays showed similar staining characteristics for PD-L1 staining on tumor cells, but Ventana SP142 comparatively showed fewer tumor cells stained.

J Thorac Oncol. 2017 Feb;12(2):208-222

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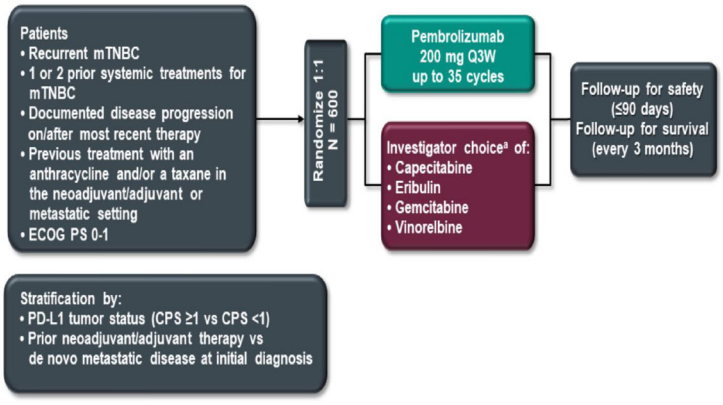
Contribution of Tumor and Immune Cells to PD-L1 as a Predictive Biomarker in mTNBC (2/3L): Analysis From KEYNOTE-119

Cortes KN119 ESMO 2019

KEYNOTE-119 Study Design (NCT02555657)



ECOG PS = Eastern Cooperative Oncology Group performance status; mTNBC = metastatic triple-negative breast cancer; PD-L1 = programmed death ligand 1; Q3W = every 3 weeks.
[a]Maximum enrollment cap of 60% of total enrollment for each chemotherapy drug.

Eric P Winer, KN119, ESMO 2019
Winer. Lancet Oncol. 2021;22:499.

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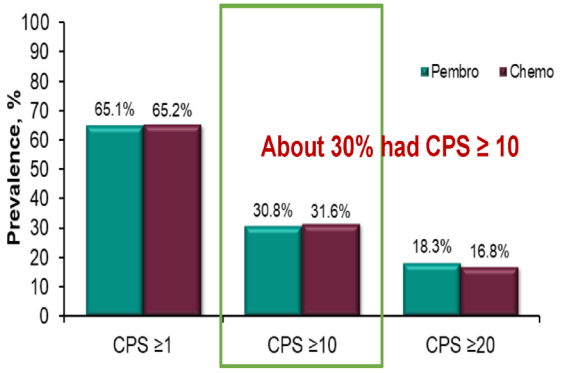
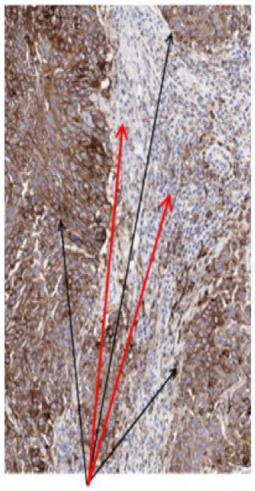
Contribution of Tumor and Immune Cells to PD-L1 as a Predictive Biomarker in mTNBC (2/3L): Analysis From KEYNOTE-119

$$\text{CPS} = \frac{\text{\# PD-L1 staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total \# of viable tumor cells}} \times 100$$

- PD-L1 IHC 22C3 pharmDx (Agilent Technologies)
- Positive PD-L1 expression: CPS ≥10 and CPS ≥1





PD-L1 positive cells
(Tumor Cells, Immune Cells)

Eric P Winer, KN119, ESMO 2019
Winer. Lancet Oncol. 2021;22:499.

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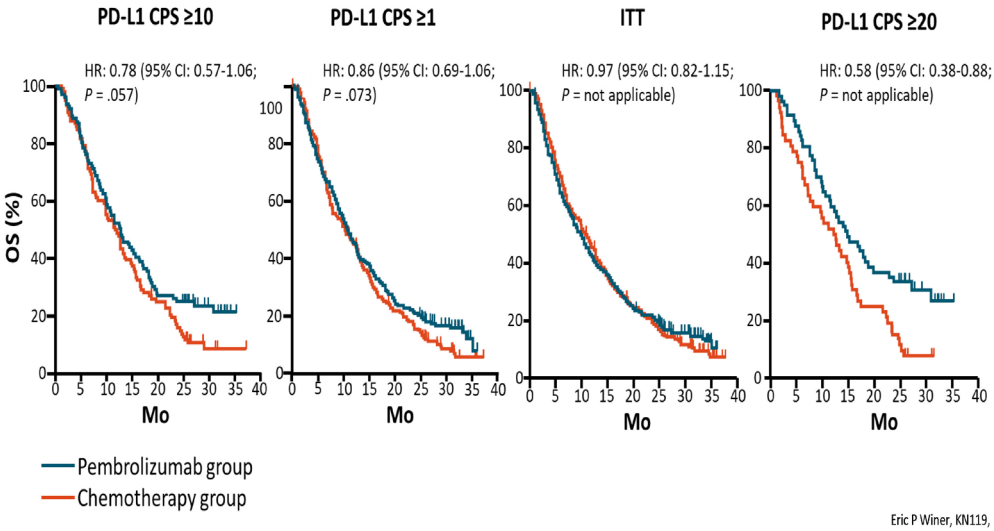
Contribution of Tumor and Immune Cells to PD-L1 as a Predictive Biomarker in mTNBC (2/3L): Analysis From KEYNOTE-119

- Pembrolizumb favored in the group with CPS ≥ 10 or 20
- KEYNOTE-119: Association Between PD-L1 CPS Score and OS With Pembrolizumab in Previously Treated mTNBC



Eric P Winer, KN119, ESMO 2019
Winer. Lancet Oncol. 2021;22:499.

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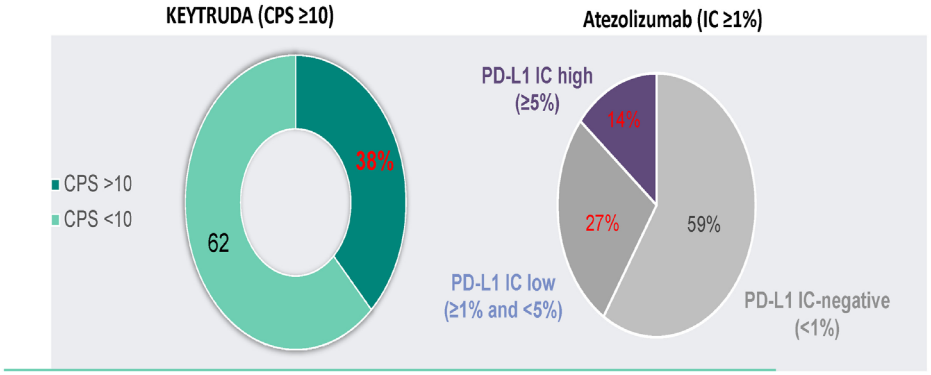
Contribution of Tumor and Immune Cells to PD-L1 as a Predictive Biomarker in mTNBC (1L) : Analysis From KEYNOTE-355 and IMpassion130



	KEYTRUDA (CPS ≥10)	Atezolizumab (IC ≥1%)
Prevalence	38%	41%
PFS	9.7 mo vs 5.6 mo (HR 0.66)	7.5 mo vs 5.3 mo (HR 0.63)
OS	23 mo vs 16.1 mo	25 mo vs 18 mo * Not formally tested per prespecified testing hierarchy.
Ref	KEYNOTE-355[1]	IMpassion130[2]

1. Hope Rugo Presented. KN355 ESMO 2021
2. Emens et al. Ann Oncol. 2020 Sep; 31: S1148..

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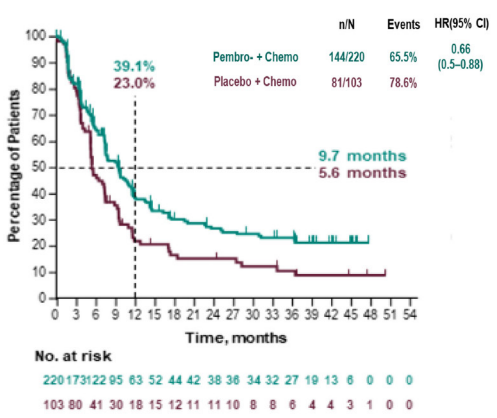
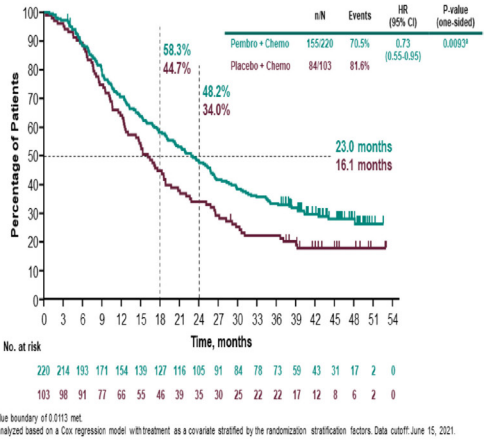
KEYNOTE-355: PFS & OS, PD-L1 CPS ≥10

Progression-Free Survival : PD-L1 CPS ≥10



Overall Survival: PD-L1 CPS ≥10



*Prespecified P value boundary of 0.0113 met.
Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff: June 15, 2021.

Hope Rugo Presented. KN355 ESMO 2021

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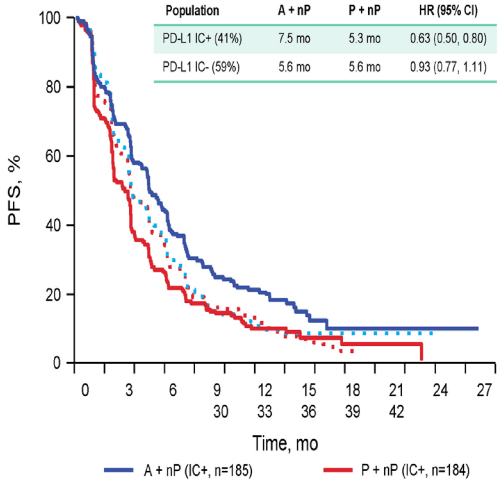
IMpassion130: Updated OS and PFS (ESMO 2019, 2020)

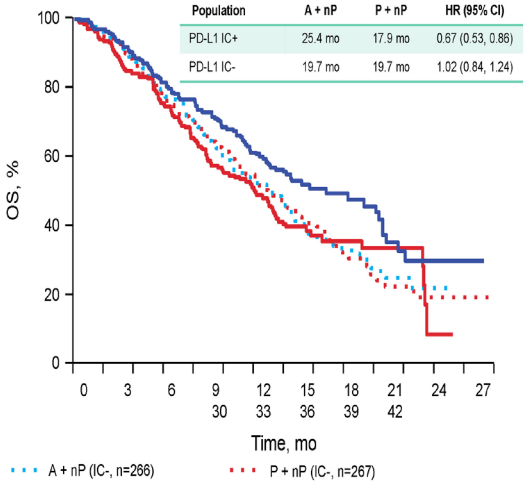
mPFS Analysis

Population	A + nP	P + nP	HR (95% CI)
PD-L1 IC+ (41%)	7.5 mo	5.3 mo	0.63 (0.50, 0.80)
PD-L1 IC- (59%)	5.6 mo	5.6 mo	0.93 (0.77, 1.11)



mOS Analysis

Population	A + nP	P + nP	HR (95% CI)
PD-L1 IC+	25.4 mo	17.9 mo	0.67 (0.53, 0.86)
PD-L1 IC-	19.7 mo	19.7 mo	1.02 (0.84, 1.24)



A + nP = atezolizumab + nab-paclitaxel; P + nP = placebo + nab-paclitaxel.
PD-L1 IC+: PD-L1 in ≥1% of immune cells as percentage of tumor area assessed with the VENTANA SP142 assay. NCT02425891.
Stratification factors: prior taxane use, liver metastases, and PD-L1 immune cell status. Co-primary end points in ITT and PD-L1 IC+: PFS and OS. Clinical cutoff date: January 2, 2019.

Rugo H et al. ESMO 2019. Abstract 6571
Emens LA. ESMO 2020 - IMpassion130 Final OS.

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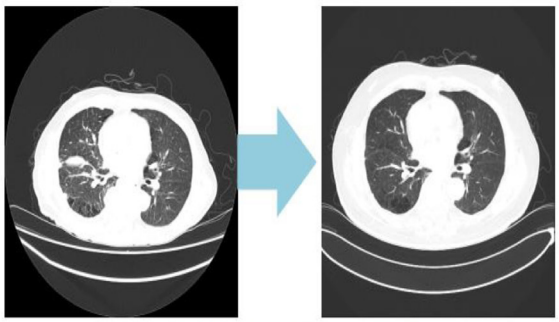
Even low PD-L1 expression, but

- Even no PD-L1 expression, clinical benefit can be exist



On Nivolumab (14months)

- In KN001 (phase 1b),
  - Around 10% of PD-L1 <1% showed response to pembrolizumab.

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PD-L1 검사, 무엇을 고려해야 하나?

- PD-L1 검사가 필요한가?
  - 비소세포폐암 2차 요법 보험여부 (nivolumab, pembrolizumab, atezolizumab)
  - 비소세포폐암 1차 요법 허가내 사용 (pembrolizumab)
  - 방광암 1차 요법 허가내 사용 (cisplatin ineligible, pembrolizumab)
  - 방광암 2차 이상 요법 보험 여부 (atezolizumab)
  - 삼중음성유방암 1차 요법 허가내 사용 (pembrolizumab, atezolizumab)
- 어떤 방법이 필요한가?
  - TPS : 비소세포폐암 (pembrolizumab)
  - CPS : 방광암, 유방암 등 (pembrolizumab)
- 어떤 antibody 로 검사해야 하는가?
  - Pembrolizumab의 경우 22C3를 우선으로
  - Nivolumab의 경우 28-8, SP263 가능
  - Atezolizumab은 SP142 검사로 시행

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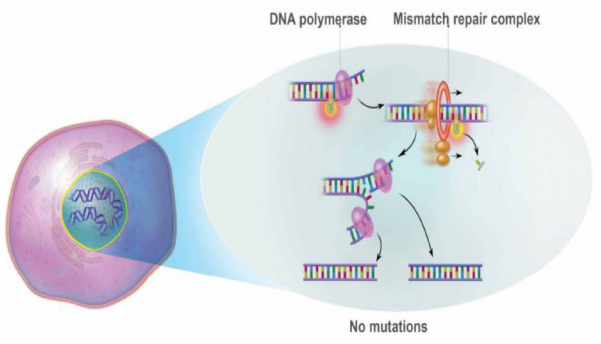
2) Biomarker: Mismatch repair system



Successful repair of mismatched base pair by pMMR system
Adapted from Li et al.

- Microsatellite instability (MSI) is the condition of genetic hypermutability that results from impaired DNA mismatch repair (MMR).

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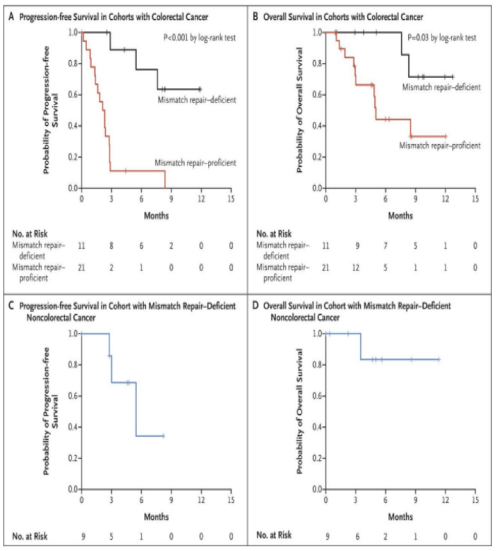
Microsatellite instability

- Pembrolizumab in Mismatch-Repair Deficiency



MMRd -> Beneficial

Durable clinical benefit

N Engl J Med 2015; 372:2509-2520

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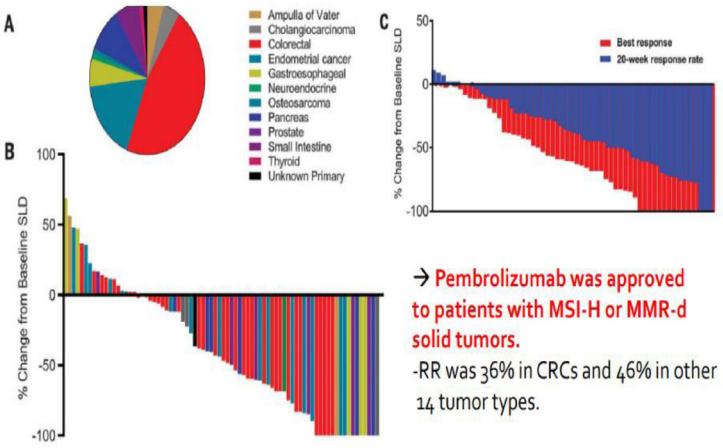
Microsatellite instability

- Pembrolizumab in tumors with Mismatch-repair deficiency : sensitive regardless of origin



→ Pembrolizumab was approved to patients with MSI-H or MMR-d solid tumors.
-RR was 36% in CRCs and 46% in other 14 tumor types.

Science 357, 409–413 (2017)

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Testing for MSI and MMR deficiency

- MSI-H phenotype : **IHC, PCR, NGS**
- Concordance rate over 92%
  - DNA testing (sensitivity 77-89%)
    - 5 microsatellite markers are necessary (2 mononucleotides, BAT25,BAT26, 3 dinucleotide repeats, D2S123, D5S346, D17SD250)
    - MSI-H: if 30% or more of the repeats are unstable
    - MSI-L: if fewer than 30% of repeats are unstable
    - MSS-S: no repeats are unstable
  - IHC (sensitivity:77-83%)
    - loss of one or more of the mismatch repair proteins (MLH1,MSH2,MSH6, PMS2)
    - MSI-H or MMR-d: Loss of MMR protein
    - MSI-L or MSS: intact MMR protein
    - m/c: loss of MLH1 and PMS2 + normal staining of MSH2 and MSH

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MSI-H or MMRd, 무엇을 고려해야 하나?

- 직결장암, 위암에서는 PCR검사가 급여되므로, PCR, IHC검사 모두 가능
- 이외 암에서는 PCR검사가 급여되지 않으므로, IHC 검사를 고려
  - Loss of expression of one of MLH1, MSH2, MSH6, PMS2 (negative staining)

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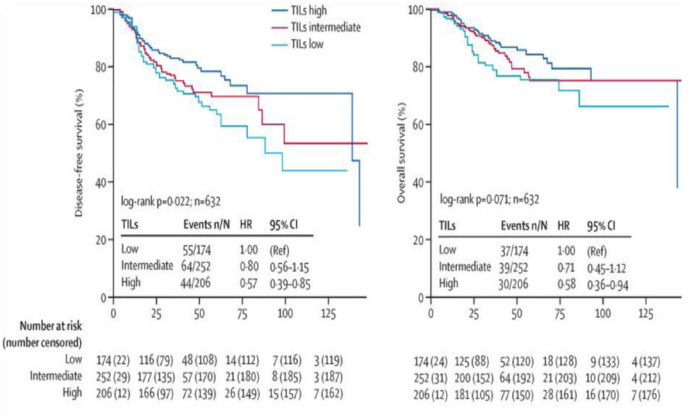
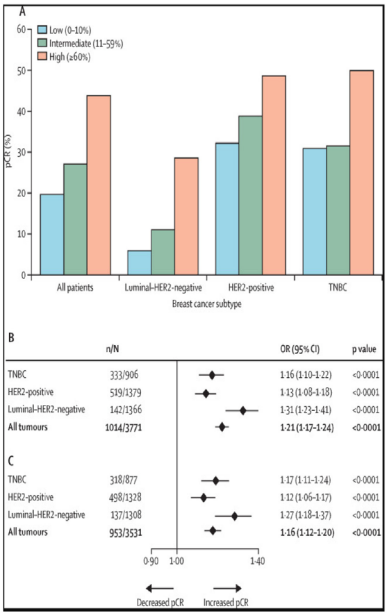
3) Biomarker : TIL (tumor infiltrating lymphocytes)

- **TILs as a Prognostic & Predictive Factor in TNBC**
  - Higher tils strong favorable prognostic marker early stage TNBC treated adjuvant chemotherapy
  - Higher TIL s predictive marker for neoadjuvant pCR and survival advantage in TNBC





The Lancet 2018;19:40-50.

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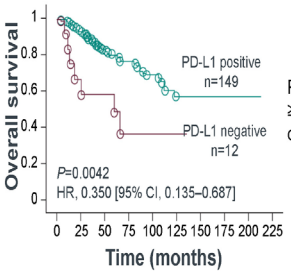
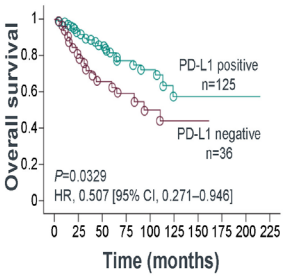
PD-L1 Expression: Correlation with TILs and Survival in TNBC

- TIL density in TNBC carries both predictive and prognostic value.[1]
- PD-L1 expression correlates with TIL level.[2]
- In TNBC, PD-L1 expression in both tumor and immune cells are biologically relevant and may be key factors in clinical decision-making for immune-che ckpoint inhibitor therapy.[3]
- Both tumor and immune cell PD-L1 expression correlate With longer OS in TNBC[3]



PD-L1 expression in ≥1% stromal immune cells



Cytoplasmic PD-L1 expression in ≥1% tumor cells

HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand 1; TIL, tumor-infiltrating lymphocyte; TNBC, triple-negative breast cancer.
1. Dieci MV, et al. *Semin Cancer Biol.* 2018;52:16-25. 2. Loi S. *Ann Oncol.* 2017;28(suppl 5):v605-v649. 3. Beckers RK, et al. *Histopathology.* 2016;69:1-10.

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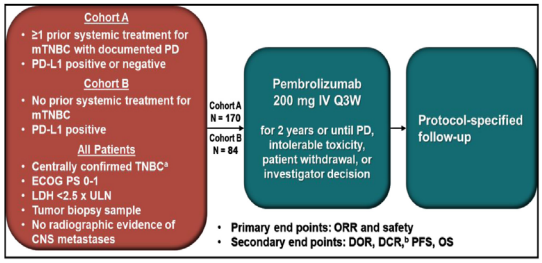
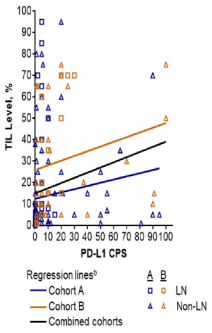
TILs Correlate with PD-L1 Expression Level and Possess Predictive Value for Response to Pembrolizumab in TNBC (KEYNOTE-086)

- PD-L1 positivity was defined as CPS ≥1



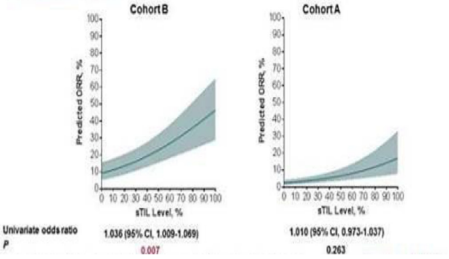
PD-L1 CPS vs sTIL Level



Significant Correlation Between sTIL levels and PD-L1 CPS
- Cohort A: rho = 0.408; *P* < 0.0001[a]
- Cohort B: rho = 0.485; *P* = 0.0003[a]
- Combined cohorts: rho = 0.496; *P* < 0.0001[a]

ORR as a Continuous Function of sTIL Levels

S Lo_ESMO 2017



* KEYNOTE-086 is not an approved indication of pembrolizumab.
* Pembrolizumab is NOT approved in 2L+ and as monotherapy in Korea

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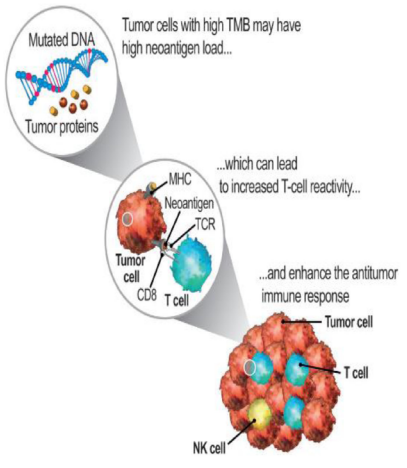
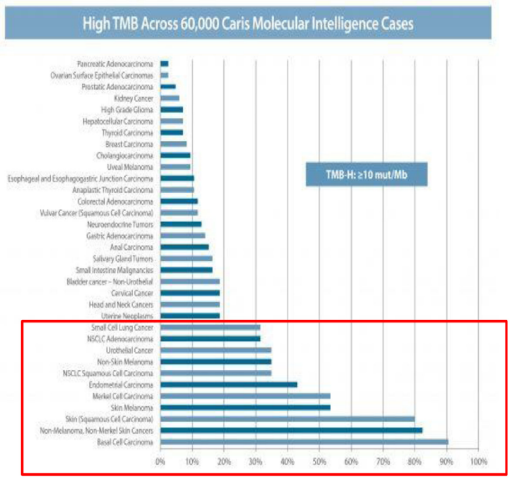
4) Biomarker : TMB (tumor mutational burden)



TMB association with the antitumor response.
Abbreviations: CD8, cluster of differentiation 8; MHC, major histocompatibility complex; NK, natural killer; TCR, T-cell receptor



Genomic profiling with Caris Molecular Intelligence can help you make more informed therapy decisions when considering immune checkpoint inhibitors

1. SAMUEL J. KLEMPNER et al. Tumor Mutational Burden as a Predictive Biomarker for Response to Immune Checkpoint Inhibitors: A Review of Current Evidence The Oncologist 2020;25:e147–e159
2. Stenzinger, A, Allen, JD, Maas, J, et al. Tumor mutational burden standardization initiatives: Recommendations for consistent tumor mutational burden assessment in clinical samples to guide immunotherapy treatment decisions. Genes Chromosomes Cancer. 2019; 58: 578–588. https://doi.org/10.1002/gcc.22733

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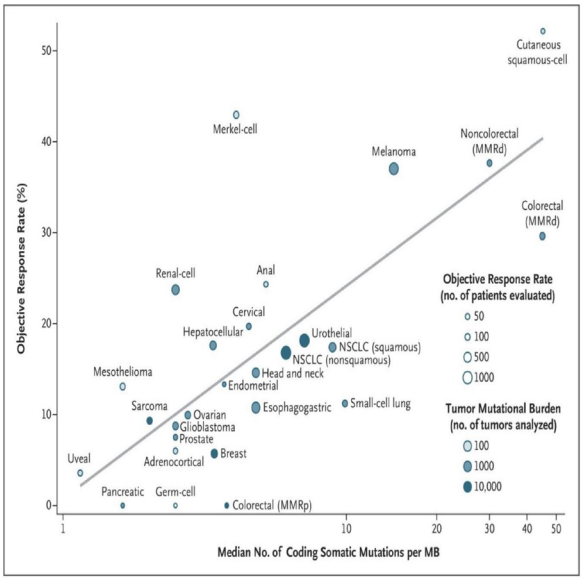
Tumor Mutational Burden and Response Rate to PD-1 Inhibition

- Correlation between Tumor Mutational Burden and Objective Response Rate with Anti–PD-1 or Anti–PD-L1 Therapy in 27 Tumor Types.



Mark Yarchoan et al. Tumor Mutational Burden and Response Rate to PD-1 Inhibition N Engl J Med 2017; 377:2500-2501

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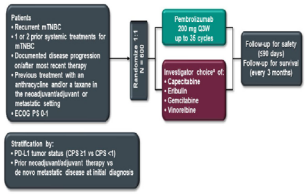
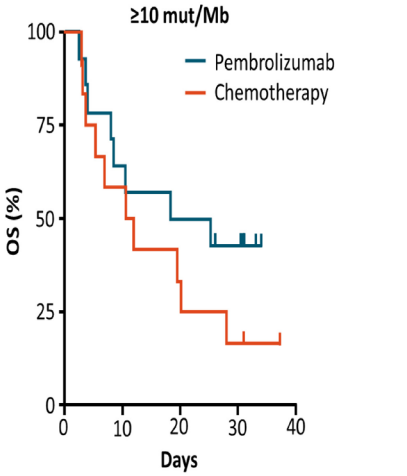
KEYNOTE-119(2/3L mTNBC): Association Between TMB and Clinical Outcomes by Treatment

KEYNOTE-119 Study Design (NCT02555657)



Outcome	TMB ≥10 mut/Mb (n = 26)		TMB <10 mut/Mb (n = 227)	
	Pembro (n = 14)	CT (n = 12)	Pembro (n = 118)	CT (n = 109)
ORR, % (95% CI)	14.3 (4.0-39.9)	8.3 (0.4-35.4)	12.7 (7.9-19.9)	12.8 (7.8-20.4)
PFS, HR (95% CI)	1.14 (0.42-3.07)		1.24 (0.92-1.67)	
OS, HR (95% CI)	0.58 (0.21-1.57)		0.81 (0.61-1.07)	



- Trends toward improvement in ORR and OS in those with TMB ≥10 mut/Mb
- Minority (10.2%) had TMB >10 mut/Mb

Winer. Lancet Oncol. 2021;22:499.

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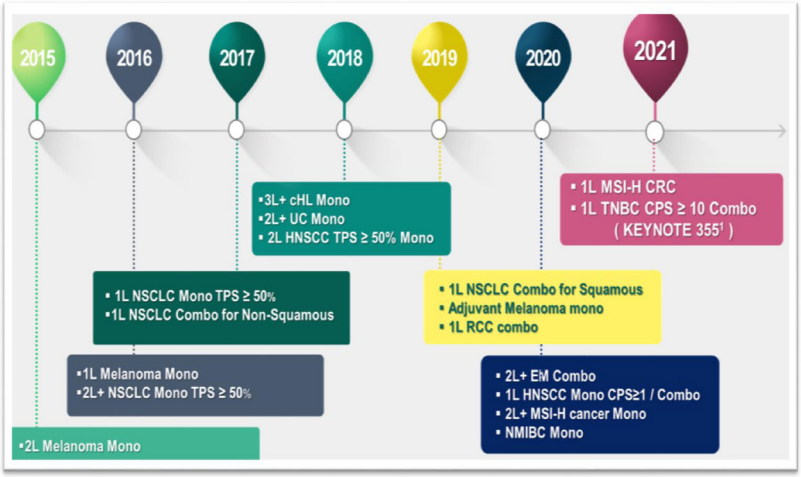
KFDA 허가사항

- Indication Approval Summary for Pembrolizumab in the KOREA



Pembrolizumab (Keytruda®) [full prescribing information].; Jul 2021
1. Cortes et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial . Lancet 2020; 396: 1817–28

HNSCC = Head and Neck Squamous Cell Cancer, NSCLC = Non-Small Cell Lung Cancer, cHL = Classical Hodgkin Lymphoma, UC = Urothelial Carcinoma, MSI-H = Microsatellite Instability-High Cancer, EM = Endometrial Carcinoma, NMIBC = Non-muscle invasive bladder cancer, colorectal cancer = , TNBC = Triple-negative breast cancer

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Pembrolizumab

- 용량: 200mg every 3weeks
- Melanoma 1L, NSCLC 2L, NK-T cell lymphoma, Nasopharynx cancer, Merkel cell carcinoma에서는 2mg/kg every 3weeks

- **비소세포폐암 2차 이상요법에서 보험급여 적용을 받기 위해서는 PD-L1확인이 필요 (22C3또는 SP263 antibody 사용)**
- **자궁경부암에서는 PDL1 양성 또는 CPS >1 (SP263, 22C3) 이상에서 허가 되어있어 확인이 필요 (허가초과요법)**
- **전이성 삼중음성유방암에서 PD-L1 양성 (CPS >10)에서 허가 되어있어 확인이 필요 (허가초과요법)**
- **PD-L1 양성 진행성 담도암, 담낭암 2차이상 요법에서 허가 되어 있어 확인 필요 (허가초과요법)**
- **PD-L1양성 난소암 2차 이상 요법에서 허가초과 요법**
- **Solid tumor (자궁내막암, 위암, 소장암, 난소암,췌장암, 담도암, 직결장암 제외)에서 MMR-d or MSI-H, 2차 이상요법 (허가초과요법)**
- 그 외의 암에서는 PD-L1 확인이 필요 없음

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Cancer type	Cancer Status	Study	Biomarker PD-L1 (22C3 or SP263)	FDA approval	MFDS Approval	Insurance
HNSCC	Metastatic, after platinum CTx	KN012	필요 X	2016.8	O	X
HNSCC	Metastatic, 1st line Monotherapy or combination with FP	KN048	PD-L1 CPS ≥1%	2019.6	X	X
Classical Hodgkin Lymphoma	Refractory, ≥3rd line	KN087	필요 X	2017.3	O	X
Urothelial carcinoma	Metastatic, after progression of platinum CTx or progression within 12months of neoadj or adj tx with platinum based CTx(2nd line)	KN052	필요 X	2017.5.	O	X
Urothelial carcinoma	Metastatic, 1st line		**PD-L1 CPS ≥10%**	2017.5	O	X
Any solid tumors with MSI-H or dMMR	Inoperable, metastatic, ≥2nd line		MSI-H or MMRd(PD-L1 필요없음)	2017.5	X	X(사전신청, ≥2nd line, CRC경우는 ≥3rd line)
Gastric or GEJ cancer	Recurrent, locally advanced or metastatic, ≥2nd line	KN059	PD-L1 CPS ≥1%	2017.9	X	X(사전신청, ≥3rd line) X(Refractory to FP, EBV ISH+,≥2nd line)
Cervical Cancer	Recurrent or metastatic, ≥2nd line	KN158	PD-L1 CPS ≥1%	2018.6.	X	X(사전신청)
Primary mediastinal Large B-Cell lymphoma	Refractory, ≥2nd line	KN170	필요 X	2018.6.	X	X(사전신청)
Hepatocellular carcinoma	After sorafenib	KN224	필요 X	2018.11	X	X
Merkel cell carcinoma	Recurrent locally advanced or metastatic, 1st line	CITN09/KN017	필요 X	2018.12	X	X(사전신청)
RCC (+axitinib)	Metastatic, 1st line	KN426	필요 X	2019.4.	X	X
Small cell lung cancer	Progressed after platinum based and ≥2nd line	KN028	필요 X	2019.6	X	X(사전신청≥3rd line)

Severance

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Nivolumab

- 용량: 3mg/kg every 2weeks

- **비소세포폐암 2차 이상요법에서 보험급여 적용을 받기 위해서는 PD-L1확인이 필요 (28-8 pharmDx assay, TC≥1%)**
- **전이성 재발성 두경부 편평세포암, 2차이상에서 보험적용 받기 위해 PD-L1 확인 필요 (28-8 pharmDx assay, TC ≥1%)**
- **MMR-d or MSI-H 직결장암, 3차이상요법 (허가초과요법)**
- 그 외의 암에서는 PD-L1 확인이 필요 없음
  - **Gemcitabine 기반 요법에 실패한 전이성 담도암, 2차이상 요법 (허가초과요법)**

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Cancer type	Cancer Status	Study	Biomarker	FDA Approval	MFDS Approval	Insurance
Melanoma	Unresectable or metastatic, ≥ 1st line	CM067	Not needed	2014.12	Yes	Yes
Melanoma (+ipilimumab)	Unresectable or metastatic, ≥ 1st line	CM069	Not needed	2015.11	Yes	No
Melanoma	adjuvant	CM238	Not needed	2017.12	Yes	No (사전신청)
NSCLC (sqcc)	Metastatic, after platinum based CTx, ≥ 2nd line	CM017	PD-L1 관계 없음	2015.3	Yes	Yes (Stage IIIB-IV, PDL1≥10%) No (<10%)
NSCLC (non-sqcc)	Metastatic, after platinum based CTx, ≥ 2nd line	CM057	PD-L1 관계 없음	2015.10	Yes (after TKI)	Yes (Stage IIIB-IV, PD-L1 ≥10%) No (<10%)
RCC	Metastatic, ≥ 2nd line	CM025	Not needed	2015.11	Yes	No
RCC(+ipilimumab)	Metastatic, ≥1st line, clear cell carcinoma, IMDC risk (int or high risk)	CM214	Not needed	2018.4	Yes	No
HNSCC	Metastatic, after platinum based CTx, ≥ 2nd line	CM141	Not needed	2016.11	Yes	No
Urothelial carcinoma	Metastatic, after progression of platinum CTx or progression within 12months of neoadj or adj Tx with platinum based CTx	CM275	Not needed	2017.2	Yes	No (공식비급여)
Biliary tract cancer	Metastatic, after progression of gemcitabine based CTx, ≥ 2nd line		Not needed		Yes	No (사전 신청)

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Cancer type	Cancer Status	Study	Biomarker	FDA Approval	MFDS Approval	Insurance
Colorectal cancer	Metastatic, after 5-FU, oxaliplatin, irinotecan **MSI-H or dMMR**	CM142	**MSI-H or dMMR (PD-L1 필요 없음)**	2017.8	No	No (사전신청, MMR-d or MSI-H, ≥ 3rd line)
Colorectal cancer (+ipilimumab)	Metastatic, after 5-FU, oxaliplatin, irinotecan **MSI-H or dMMR**	CM142	**MSI-H or dMMR (PD-L1 필요 없음)**	2018.6	No	No
HCC	CP-score 7이하, ≥ 2d line After sorafenib	CM040	필요없음	2017.9	No	No (사전신청)
HCC (+ipilimumab)	CP-class A, and ≥ 2d line					No (사전신청)
Small cell lung cancer	Progressed after platinum based and ≥ 3rd line	CM032	필요없음	2018.8	No	No (사전신청)
AGC or GEJ cancer	≥ 3rd line					No (공식비급여)
Anal cancer (Sqcc)	≥ 2nd line					No (사전신청)
Ovarian cancer	platinum resistance and ≥ 3rd line					No (사전신청)

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Atezolizumab

- 용량:1200mg every 3weeks
- **비소세포폐암 2차 이상요법에서 보험급여 적용을 받기 위해 PD-L1 확인이 필요 (SP142 antibody)**
- **전이성 삼중음성 유방암 1차 요법으로 허가사항 (SP142 IC ≥1%, 허가초과요법)**

Cancer type	Cancer Status	Study	Biomarker(PD-L1 (SP142)	FDA Approval	MFDS Approval	Insurance
NSCLC (+bevacizumab, paclitaxel, carboplatin)	metastatic, 1st line, no EGFR or ALK MT	Impower150	필요X	2018.12	O	X
NSCLC	metastatic, ≥2nd line	OAK	필요X	2016.10	O	O(Stage IIIB↑,PD-L1 ≥TC2/3 or IC2/3)
Urothelial cell carcinoma	Locally advanced or metastatic, ineligible for cisplatin CTx (1st line)	IMvigor210	PD-L1≥5%	2017.4	O	X
Urothelial cell carcinoma	Metastatic, after progression of platinum CTx or progression within 12months of neoadj or adj tx with platinum based CTx(≥2nd line)	IMvigor211	PD-L1 관계없음	2016.5	O	O(PD-L1≥5%)
SCLC(+etoposide, carboplatin)	Extensive-stage, 1st line	IMpower133	필요X	2019.3	X	X
Breast cancer (+nab-paclitaxel)	Metastatic, inoperable TNBC	Impassion130	PD-L1≥1%	2019.3	X	X

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Durvalumab

- 용량:10mg/kg every 2weeks
- PD-L1 필요시 SP263 antibody로 검사

Cancer type	Cancer Status	Study	Biomarker (SP263)	FDA Approval	MFDS Approval	Insurance
NSCLC	Unresectable stage III, after chemoradiation	PACIFIC	필요X	2018.2	O	X
Urothelial carcinoma	Locally advanced or Metastatic, after progression of platinum CTx or progression within 12months of neoadj or adj tx with platinum based CTx(≥2nd line)	DANUBE	PD-L1 +	2017.5	X	X

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Contents

I. Basic concept of Immunotherapy

II. Biomarker of Immunotherapy

III. **Landmark trials with Immunotherapy in TNBC**

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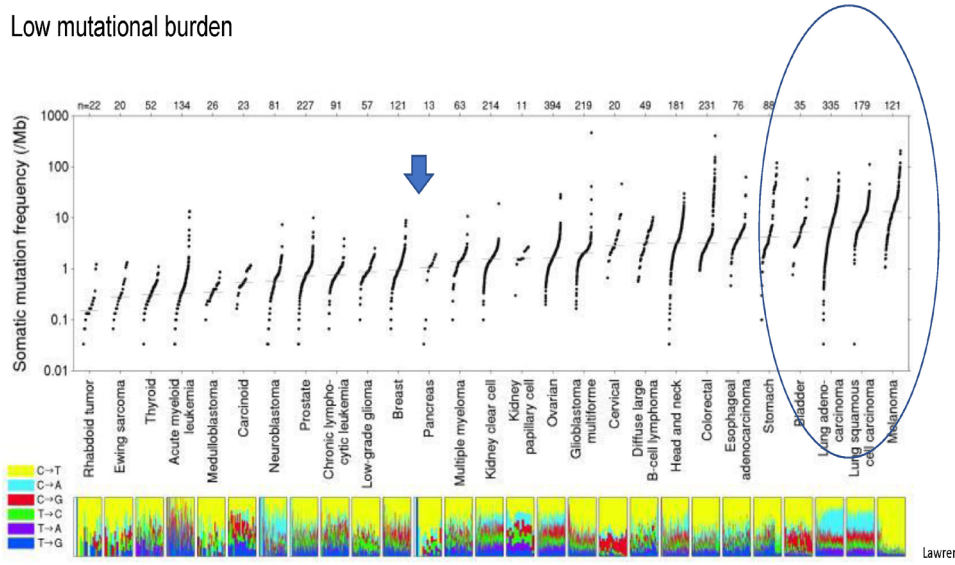
Limitation of immunotherapy

- Classically considered as a less immunogenic tumor
- Low proportion of inflamed tumors
- Low mutational burden



Lawrence et al. Nature 2013

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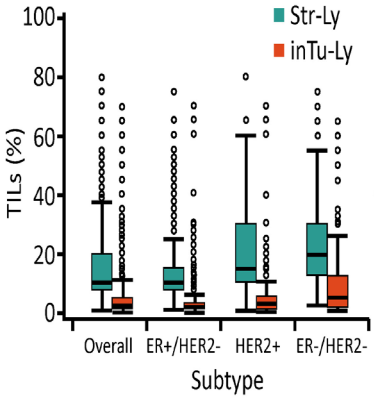
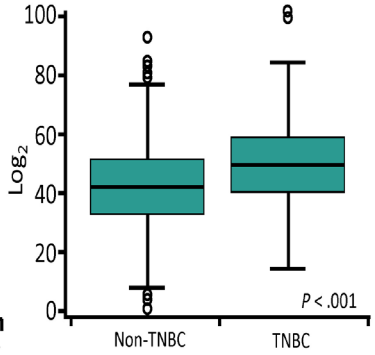
Immunogenicity of TNBC than others

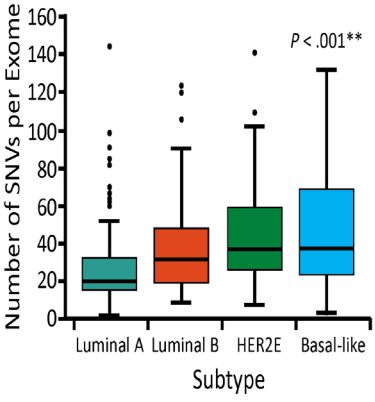
Tumor-Infiltrating Lymphocytes[1]



PD-L1 Expression[2]



Nonsynonymous Mutations[3]



ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; TILs, tumor-infiltrating lymphocytes; TNBC, triple-negative breast cancer.

Loi. JCO. 2013;31:860.
Mittendorf. Cancer Immunol Res. 2014;2:361.
Luen. Breast. 2016;29:241.

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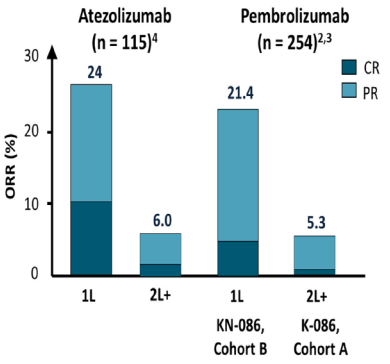
Checkpoint Inhibition in Advanced TNBC: Modest Response Rates With Monotherapy

Agent	N	ORR, %	ORR (PD-L1+), %*
Pembrolizumab			
▪ Single agent (KN-012)[1]	27	18.5	18.5
▪ Single agent (KN-086-A)[2]	170	5.3	5.7
▪ Single agent (KN-086-B)[3]	84	21.4	21.4
Atezolizumab[4]			
▪ Single agent	115	10.0	13.0
Avelumab[5]			
▪ Single agent (JAVELIN)	58	5.2	22.2

*Studies used different antibodies and cutoffs for PD-L1 positivity.



1. Nanda. JCO. 2016;34:2460. 2. Adams. Ann Oncol. 2019;30:397. 3. Adams. Ann Onc. 2019;30:405. 4. Emens. JAMA Onc. 2018;5:74. 5. Dirix. Breast Cancer Res Treat. 2017;167:671.

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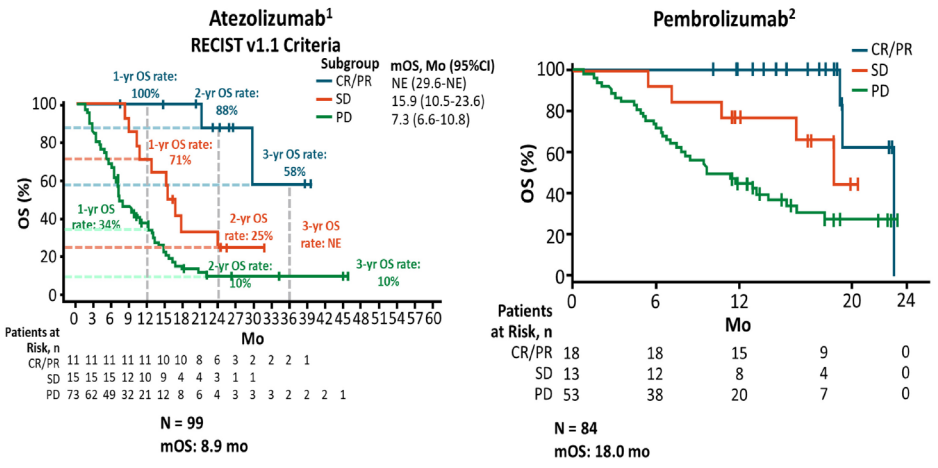
Atezolizumab and Pembrolizumab Monotherapy: Durable Responses

1st & 2nd line atezolizumab

KN086-cohort (1st line pembrolizumab)



1. Emens. JAMA Onc. 2018;5:74. 2. Adams. Ann Onc. 2019;30:405.

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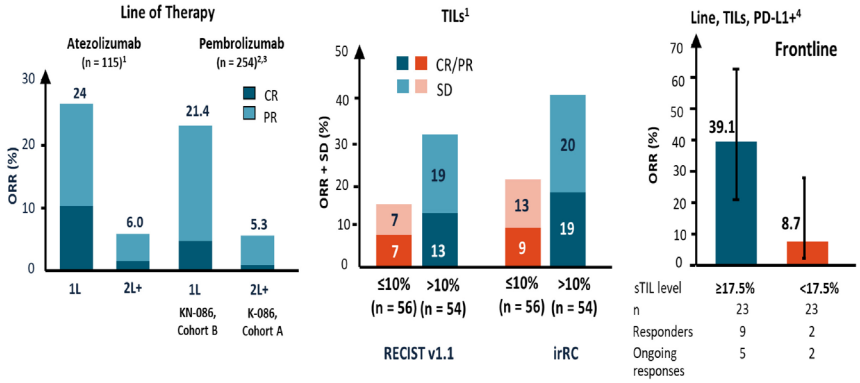
Checkpoint Blockade: Enriching for Monotherapy Responders



- Frontline therapy
- High level of TIL
- PD-L1+
- TMB

1. Emens. JAMA Onc. 2018;5:74. 2. Adams. Ann Onc. 2019;30:397. 3. Adams. Ann Onc. 2019;30:405. 4. Loi. ESMO 2017. Abstr LBA13.

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Overview of Key Immunotherapy Trials in TNBC

Setting	Study Name	Study Treatment		Outcome: ITT	Definition of PD-L1+	% PD-L1+	Outcome PD-L1+
Neoadjuvant	KN-522[2] *	Paclitaxel + carboplatin; AC/EC, or Pembrolizumab/placebo (24 weeks)	Pembro/ placebo (29 weeks)	pCR 64.8% with pembrolizumab vs 51.2%	CPS ≥1[a]	Pembrolizumab: 83.3% Control: 81.6%	68.9% vs 54.9%
	NeoTRIP[a] PDL1[3] *	Nab-paclitaxel + carboplatin, or Atezolizumab/placebo (24 weeks)	AC/EC/FEC (12 weeks)	pCR 43.5% with atezolizumab vs 40.8%	IC 1+, 2+, 3+[b]	Atezolizumab: 57% Control: 54%	51.9% vs 48.0%
1L metastatic	IMpassion130[4]	Nab-paclitaxel +/- atezolizumab		PFS: HR 0.80 *P*=0.0021	≥1% cutoff[b]	Atezolizumab: 50.8% Control: 59.7%	PFS: HR 0.63 *P*<0.001 (PD-L1 IC+)
	KN-355[5]	Pembrolizumab vs nab-paclitaxel/paclitaxel/ carboplatin + gemcitabine		PFS: HR 0.82 (0.69–0.97)	CPS ≥1 or CPS 10[a]	Pembro/control CPS ≥1: 75.1%/75.1% CPS ≥10: 38.9%/36.7%	PFS: HR 0.65 *P*=0.0012 (CPS ≥10)
2L–3L metastatic	KN-119[6] *	Pembrolizumab vs capecitabine/eribulin/gemcitabine/vinorelbine		No significant improvement in OS with pembrolizumab	CPS ≥1 or CPS ≥10[a]	Pembro/control CPS ≥1: 65.1%/65.2% CPS ≥10: 30.8%/31.6%	HR 0.78 *P*=0.057 (CPS ≥10)

*NOTE: Direct comparisons cannot be made due to differences in study population and design

[a]22C3 pharmDx IHC assay. [b]Ventana SP142 IHC assay. *Not yet approved

AC = doxorubicin plus cyclophosphamide; EC = epirubicin plus cyclophosphamide; FEC = epirubicin, 5-FU, and cyclophosphamide.

1. Hamilton K. ASCO 2020. Breast Cancer Highlights Discussion. **2.** Schmid P et al. ESMO 2019. LBA8. **3.** Gianni l et al. SABCS 2019. Poster GS3-04. **4.** Schmid P et al. *Lancet Oncol.* 2020;21:44–59. **5.** Cortes J et al. *J Clin Oncol.* 2020;38: Abstract 1000. **6.** Cortes J et al. *Ann Oncol.* 2019;30(5):v851–v934.

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Severance

Summary

- **Immunotherapy : Low ORR, but durable response in some patients**
  - Predictive biomarker : PD-L1, TMB, TIL, MSI-H..
- **Different PD-L1 scoring methods and assays result in the identification of different populations; this is due to:**
  - Inclusion of different types of cells in the scoring method (IC only vs CPS)
  - Different approaches to PD-L1 scoring (PD-L1- staining coverage area [IC] vs cell counting [CPS])
  - Variability in staining between assays
- **Classically considered as a less immunogenic tumor**
  - Study for enriching biomarker for immunotherapy : *line of therapy, PD-L1, TIL, TMB*

1 Agilent Technologies, Inc. PD-L1 IHC 22C3 pharmDx Interpretation Manual—Triple-Negative Breast Cancer (TNBC). Agilent Technologies, Inc.; November 2020. **2.** Roche. Ventana. PD-L1 (SP142) Assay Interpretation Guide for Triple-Negative Breast Carcinoma (TNBC). Last revised June 28, 2019. Accessed September 25, 2020. https://diagnostics.roche.com/content/dam/diagnostics/us/en/products/v/ventana-pd-l1-sp142-assay/VENTANA-PD-L1-SP142-Assay- TNBC-IG.pdf. **3.** Lee SE et al. *J Breast Cancer.* 2020;23(3):303–313

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연/자/소/개

Curriculum Vitae

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특 이 사 항

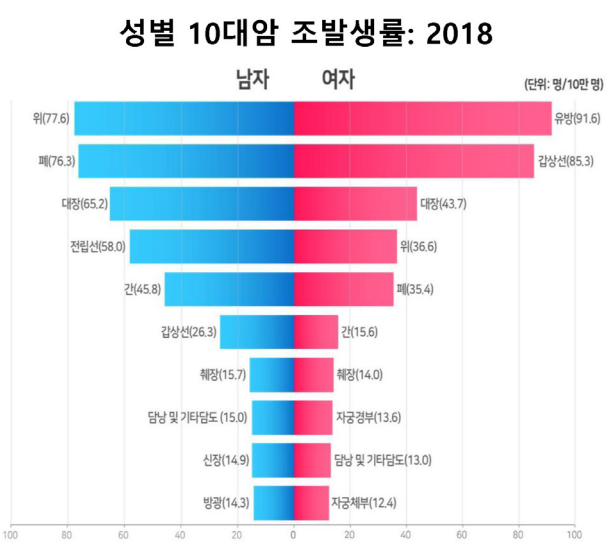
췌담관암의 진단 및 치료

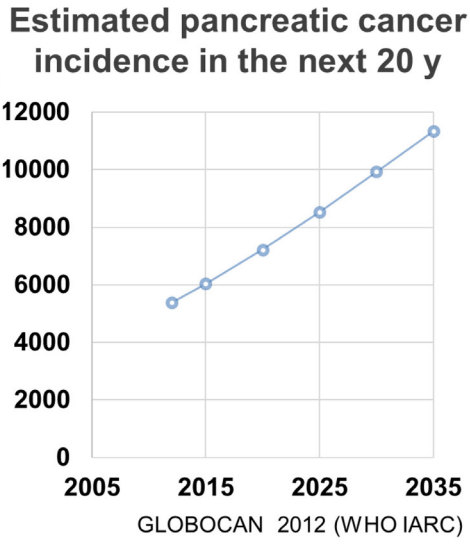
Current Status of Immunotherapy

우상명 (국립암센터 소화기내과)

Unmet needs in pancreatic cancer

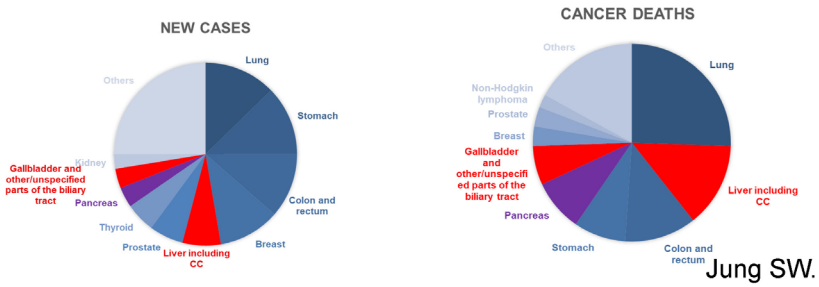
- **Increase in its incidence**





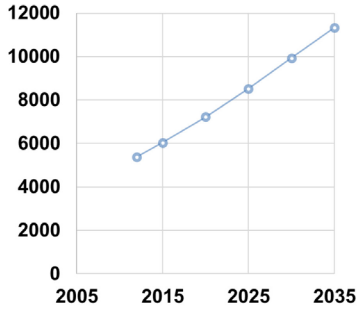
Unmet needs in pancreatic cancer (PC) and biliary tract cancer (BTC)

Estimated new cancer cases and deaths by sex during 2019 in Korea



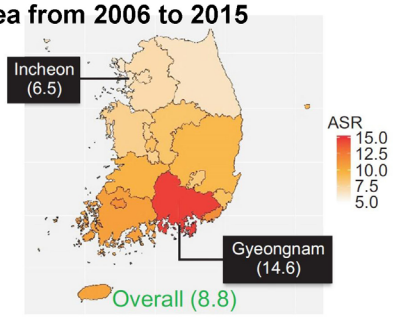
Jung SW. Cancer Res Treat 2019

Estimated pancreatic cancer incidence in the next 20 y



GLOBOCAN 2012 (WHO IARC)

Comparison of sex-, and age-standardized rates (ASR) for IHCCs by region in South Korea from 2006 to 2015



Kim BW. Gut Liver 2019

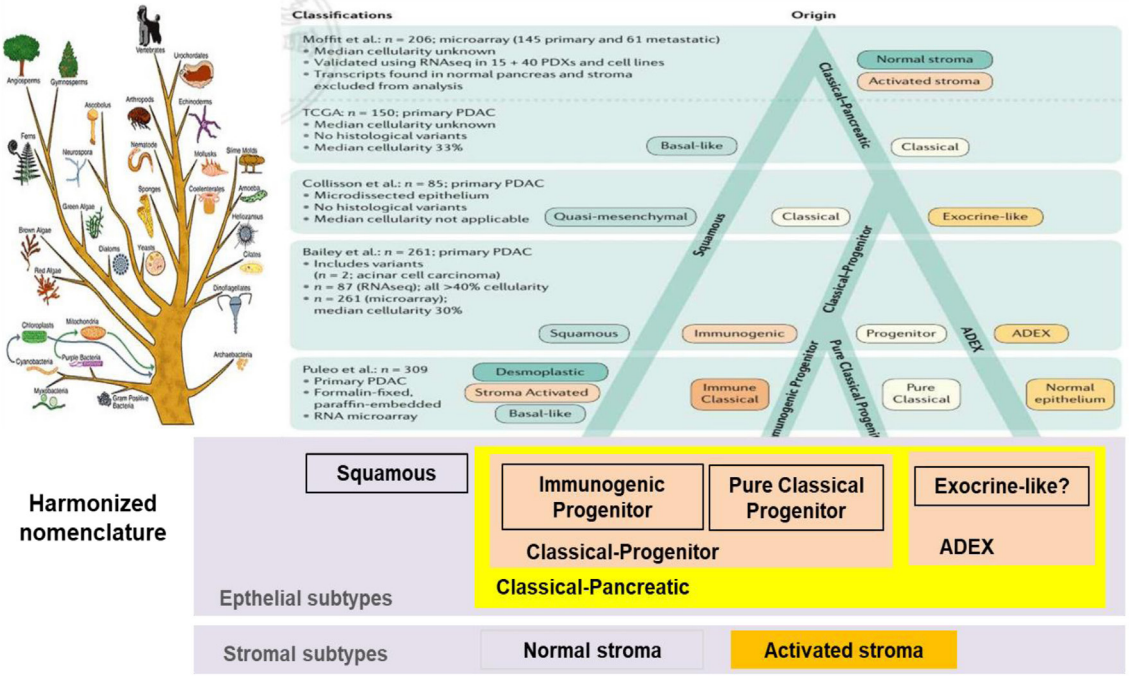
Treatment options in pancreatic cancer

First line / Second line	FOLFIRINOX	Gem + Nab-P
PS 0/1	Gem + erlotinib (approved) Gem + Nab-P (approved) Gem + Capecitabine (not approved)	Nal-IRI + 5-FU (prefered) FOLFIRINOX (approved) Cap + Oxaliplatin (approved) OFF vs FOLFOX? (approved)
PS 2 or less	Gemcitabine (approved) BSC	S-1 (approved) Fluoropyrimidine alone BSC
dMMR or MSI-H*	Pembrolizumab (approved)	

*dMMR, deficiency in mismatch repair; MSI-H, high microsatellite instability

ASCO Clinical Practice Guideline Update. 2018

Phylo-transcriptomic tree of PC

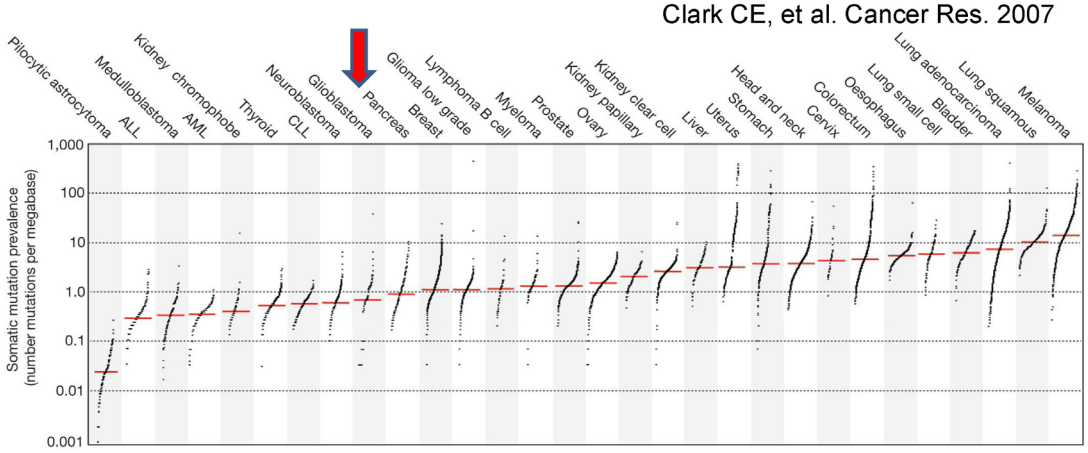


Collison EA. Nat Rev Gastroenterol Hepatol 2019

Pancreatic Cancer : A Nonimmunogenic Tumor?

- Striking paucity of activated cytotoxic (effector) CD8+ T-cells and NK cells in GEMMs .

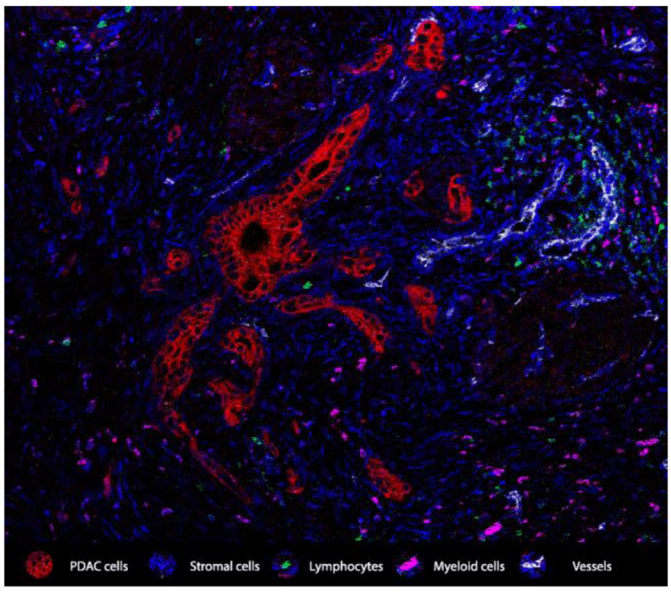
Clark CE, et al. Cancer Res. 2007



- Total mutational load in pancreatic cancer relatively modest vs other solid tumors.

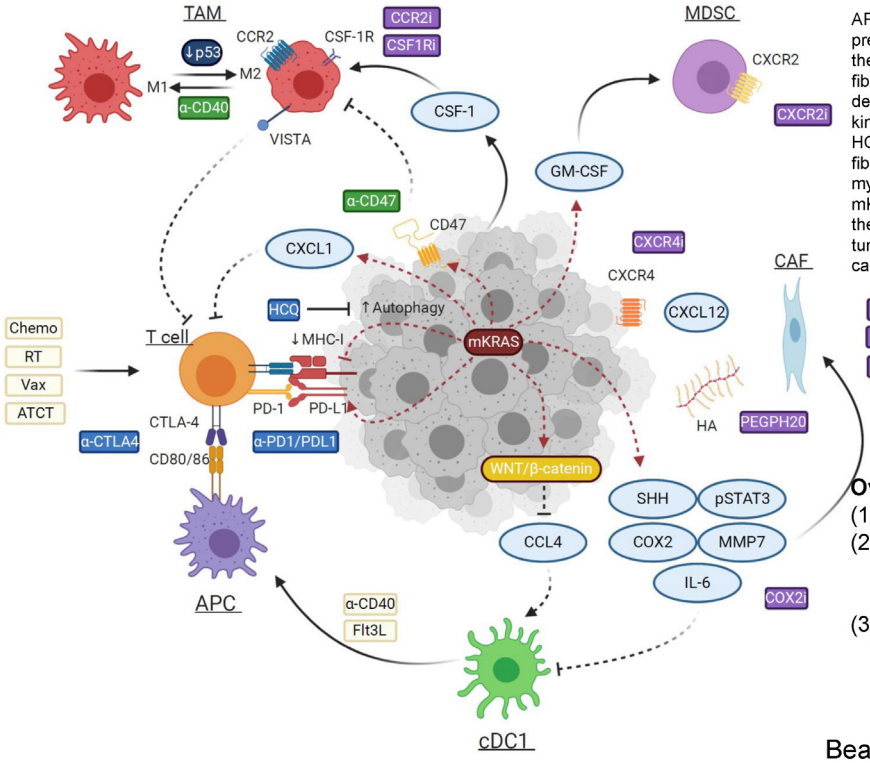
Alexandrov LB. Nature. 2013

PC and its microenvironment.



Brouwer T P. Cell Oncol (Dordr). 2021

Immune resistance and overcoming mechanism



APC,antigen-presentingcell;ATCT,adoptiveTcell therapy; CAF, cancer-associated fibroblast; cDC1, conventional type 1 dendritic cell; FAKi, focal adhesion kinase inhibitor; HA, hyaluronic acid; HCQ, hydroxychloroquine; FAP, fibroblast activation protein; MDSC, myeloid-derived suppressor cell; mKRAS, mutant KRAS; RT, radiation therapy; SHH, Sonic Hedgehog; TAM, tumor-associated macrophage; Vax, cancer vaccine; VitD, vitamin D.

Overcoming mechanism

(1) confer antigen specificity
(2) enhance innate and adaptive immune cell effector function
(3) neutralize immunosuppressive elements within the tumormicroenvironment

Bear AS. Cancer Cell 2020

Immune Checkpoint inhibitors

Intervention	Strategy	Clinical phase/Identifier	Outcomes: Median Overall survival (Months)	Year
Ipilimumab	CTLA-4 inhibitor	Phase II, NCT00112580	No improvement in survival rate, ORR: 0%	2010
Ipilimumab, Gemcitabine	CTLA-4 inhibitor	Phase Ib, NCT01473940	6.9 (95% CI, 2.63-9.57)	2020
Ipilimumab, Nivolumab	CTLA-4 inhibitor, PD-1 inhibitor	Phase I/II, NCT01928394	ongoing	Last update : Nov 2021
Tremelimumab	CTLA-4 inhibitor	Phase II, NCT02527434	4 (95% CI 2.83–5.42)	2015
Tremelimumab, Durvalumab	CTLA-4 inhibitor, PD-1 inhibitor	Phase II, NCT02558894	3.1 (95% CI, 2.2–6.1), combination therapy 3.6 (95% CI, 2.7–6.1), Durvalumab alone	2019
Tremelimumab, Gemcitabine	CTLA-4 inhibitor,	Phase I, NCT00556023	7.4 (95% CI, 5.8–9.4)	2014
Pembrolizumab, Gemcitabine, Nab-paclitaxel	PD-1 inhibitor	Phase Ib/II, NCT02331251	15.0 (95% CI, 6.8–22.6)	2018
Pembrolizumab, Gemcitabine, Nab-paclitaxel	PD-1 inhibitor	Phase I, NCT02309177	9.9 (95% CI, 6.74–12.16)	2020
Pembrolizumab Motixafortide Nanoliposomal Irinotecan, 5-FU, FA	PD-L1 inhibitor, CXCR4/ CXCL12 a	Phase II, (NCT02826486)	5.9 (95% CI, 4.4–9.6)	2021

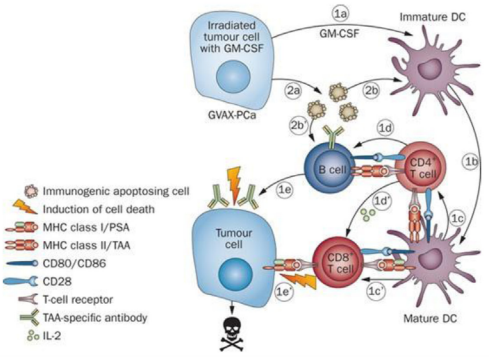
Modified from “Schizas D. Cancer Treat Rev. 2020.”

Vaccine therapy

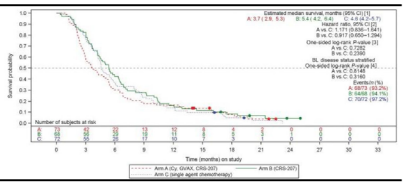
Intervention	Strategy	Cancer stage	Clinical phase, Identifier	Outcomes: Median Overall survival (Months)
GVAX, Chemoradiation	Whole-cell vaccine, Cytotoxic drugs	Stage I, II or III pancreatic cancer	Phase I	Effective anti-tumor immunity
GVAX, 5-FU, Chemoradiation	Whole-cell vaccine, Cytotoxic drugs	Resected stage I or II pancreatic adenocarcinoma	Phase II, NCT00084383	24.8 (95% CI, 21.2–31.6), combination therapy 20.3 (95% CI, 18.0–23.9), 5-FU/chemoradiation
GVAX, Cy, CRS-207	Whole-cell vaccine, Cytotoxic drugs, Listeria vaccine	Metastatic pancreatic adenocarcinoma	Phase 2a, NCT01417000	6.28 (95% CI, 4.47–9.40), combination therapy 4.07 (95% CI, 3.32-5.42), GVAX/Cy
GVAX, Cy, CRS-207	Whole-cell vaccine, Cytotoxic drugs, Listeria vaccine	Previously treated metastatic pancreatic adenocarcinoma	Phase IIb, NCT02004262	3.7 (95% CI, 2.9–5.3), combination therapy 5.4 (95% CI, 4.2–6.4), CRS-207 alone 4.6 (95% CI, 4.2–5.7), chemotherapy
KIF20A-66	Peptide vaccine	Metastatic pancreatic adenocarcinoma	Phase I/II, UMIN000004919	4.7 ± 0.8, KIF20A-66 vaccine 2.7 ± 1.1, Best supportive care
SVN-2B, IFA, IFNa	Peptide vaccine, Immunopotentiator Cytokines	Survivin-positive, unresectable advanced tumor	UMIN000000905	greater than 50% of the patients had positive clinical and immunological responses
KIF20A, VEGFR1, VEGFR2, Gemcitabine	Peptide vaccine, Peptide vaccine, Peptide vaccine, Cytotoxic drugs	Advanced pancreatic cancer	Phase II, UMIN000008082	9.0 months, HLA-matched 10.0 months, HLA-unmatched
Algenpantucel-L	Multi-peptide vaccine	Surgically Resected Pancreatic Cancer	Phase 2, NCT00569387	12-month overall survival was 86%
Algenpantucel-L, Folfrinox, Gemcitabine, 5-FU	Multi-peptide vaccine, Cytotoxic drugs	Unresectable (stage III)	Phase II, NCT02405585	Study terminated No results posted
Algenpantucel-L, Gemcitabine, 5-FU	Multi-peptide vaccine, Cytotoxic drugs	Surgically resected pancreatic cancer	Phase III, NCT01072981	Completed No results posted
Algenpantucel-L Folfrinox, Gemcitabine, Nab-paclitaxel, Capecitabine, 5-FU	Multi-peptide vaccine, Cytotoxic drugs	Resectable (stage II) and Unresectable (stage III)	Phase III, NCT01836432	Study terminated No results posted
MUC1, HLA-A2, ICAM-1, LFA-3, GM-CSF	Vaccinia virus-tumor antigens, Costimulatory molecules	Advanced pancreatic cancer	Phase I	15.3 months, anti CEA/MUC-1 positive 3.9 months, anti CEA/MUC-1 negative
MUC1 pulsed DC-CIK	DC-CIK vaccination	Surgically resected pancreatic cancer	Phase I /II	26 (95% CI, 13–69)
w/ Poly-ICLC plus peptide- pulsed DC-CIK	Immunostimulant DC-CIK vaccination	Metastatic, unresectable pancreatic cancer	Phase I NCT01410968	7.7 months
DC-CIK, Chemotherapy S-1	DC-CIK vaccination, Cytotoxic drugs	Metastatic, unresectable pancreatic cancer	Phase I /II, NCT01781520	7 months; DC-CIK, Chemotherapy S-1 4.2 months; DC-CIK alone 4.7 months; chemotherapy S-1 alone 1.73 months; supportive care only
K-Ras vaccine, GM-CSF	Peptide vaccine, Costimulatory molecule	Surgically resected and advanced disease patients	Phase I/II	25.6 (95% CI, 10–39), resected 10.2 (95% CI, 3–28), unresectable
Ras-peptide, GM-CSF	Peptide vaccine, Costimulatory molecules	KRAS mutant pancreatic cancer		20.3 (95% CI, 11.6–45.3)
GI-4000, Gemcitabine	Multipartite vaccine, Cytotoxic drugs	KRAS mutant pancreatic cancer	Phase II	19.8 months; GI-4000, gemcitabine 14.8 months; Placebo, gemcitabine
GV1001, GM-CSF	Peptide vaccine, Costimulatory molecules	Non-Resectable pancreatic cancer	Phase I/II	7.2 months; Responders 2.9 months; Non responders
GV1001, Gemcitabine, Capecitabine	Peptide vaccine, Cytotoxic drugs	Metastatic pancreatic cancer	Phase III	6,9 (95% CI, 6,4–7,6); treated group 7,9 (95% CI, 7,1–8,8); chemotherapy alone

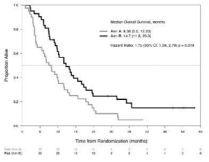
Schizas D. Cancer Treat Rev. 2020

GVAX, a GM-CSF gene vaccine



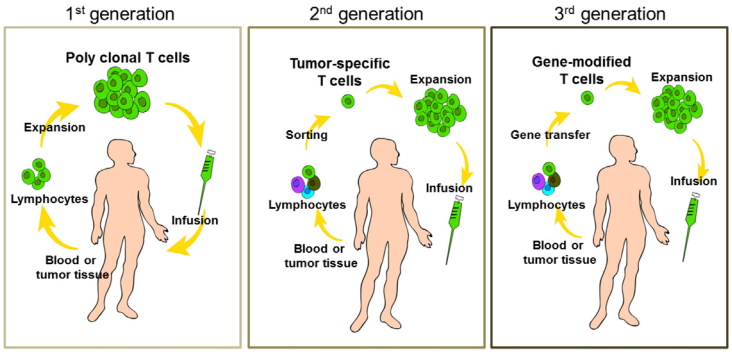
Ref.	Therapeutic protocol	ph	N	Outcomes
Le DT. 2019	Cy/GVAX[1] + CRS-207[2] vs CRS-207 vs Physician's choice among 5 si ngle- agent chemotherapy	IIb	73 vs 68 vs 72	OS: 3.7 mo vs 5.4 mo vs 4.6 mo
Wu AA, 2020	GVAX + Ipilimumab after FOLFIRINOX vs FOLFIRINOX continuation	II	40 vs 42	PFS: 2.4 mo vs 5.55 mo. OS: 9.38 mo vs 14.7 mo





1. two irradiated, allogeneic, GM-CSF–secreting pancreatic adenocarcinoma cell lines (2.5 × 108 cells each; Johns Hopkins University, Baltimore, MD)
2. a live, attenuated *Listeria monocytogenes* (Lm) strain carrying double deletions (LADD) that render it nonvirulent, making it a promising agent for presentation of tumor-associated antigens and activation of immune response.

Adoptive T cell therapy using T cells



- Low tumor specificity
- Low efficacy
- Simple production

- Tumor-specific
- Effective to treat cancers
- Complicate and long production procedure

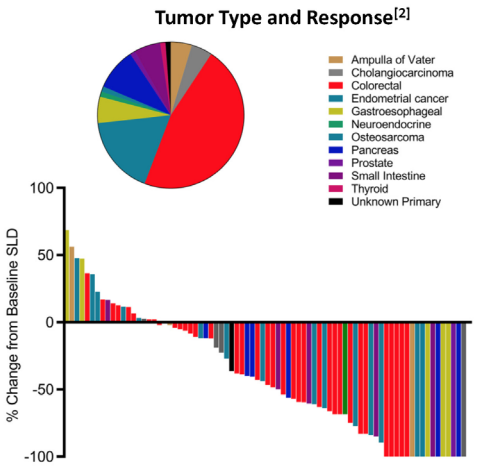
- Tumor-specific
- Effective to treat cancers
- Simple and practical production
- High manufacturing costs

Intervention	Strategy	Clinical phase/Identifier	Outcomes: Median Overall survival (Months)	Year
Mesothelin-specific CAR-T cells	Autologous T cells	Phase I	Disease stabilized in 2/6 patients, with progression-free survival times of 3.8 and 5.4 months.	2018
HER2-specific CAR-T cells	Autologous T cells	Phase I/II, NCT01935843	4.8 (95% CI, 1.5–8.3 months)	2018
DC-CIK, Chemotherapy S-1	DC-CIK vaccination, Cytotoxic drugs	Phase I/II, NCT01781520	7 months; DC-CIK, Chemotherapy S-1 4.2 months; DC-CIK alone 4.7 months; chemotherapy S-1 alone 1.73 months; supportive care only	2017

Modified from "Schizas D. Cancer Treat Rev. 2020."

Response to Pembrolizumab in MSI-H/dMMR Cancers

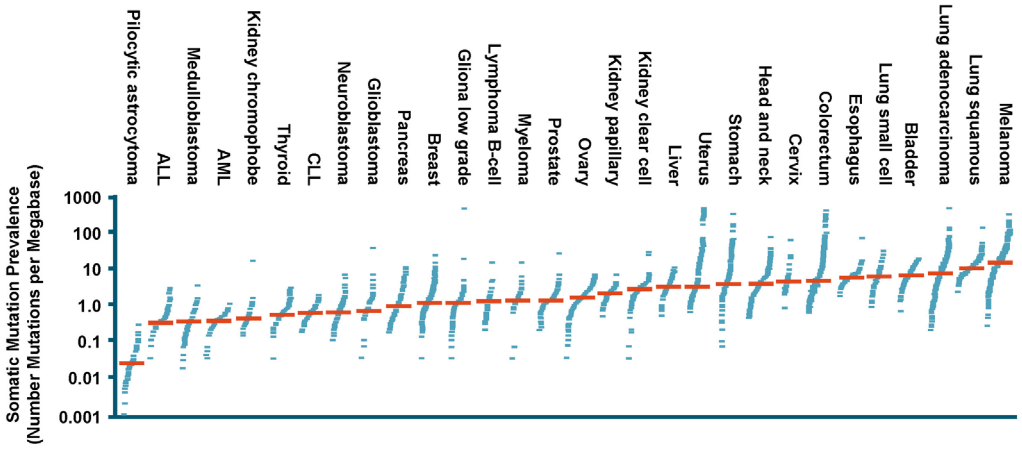
Tumor Type[1]	N	ORR, % (95% CI)
CRC	90	36 (26-46)
Non-CRC	59	46 (33-59)
Endometrial	14	36 (13-65)
Biliary	11	27 (6-61)
Gastric/GEJ	9	56 (21-86)
Pancreatic	6	83 (36-100)
Small Intestine	8	38 (9-76)
Breast	2	PR, PR
Prostate	2	PR, SD
Bladder/esophageal	1/1	NE/PE
Sarcoma	1	PD
Thyroid	1	NE
Retroperitoneal adenocarcinoma	1	PR
SCLC	1	CR
Renal	1	PD



Slide credit: clinicaloptions.com

Le. Science. 2017.

Tumor mutational burden in various tumor types

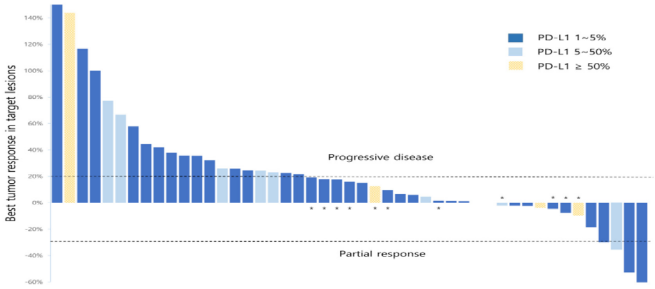


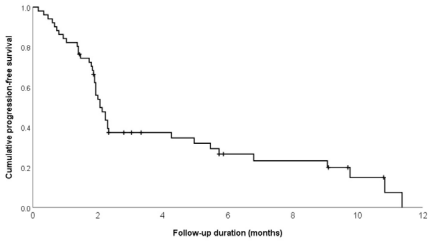
Alexandrov. Nature. 2013;500:415.

Slide credit: clinicaloptions.com

Reported data of pembrolizumab treatment in PDL1 (+) patients with GP-refractory BTC

Reference	Total N	ORR (%)	DCR (n, %)	PFS (months)	OS (months)	All AEs (n, %)	Grade 3/4 AEs (n, %)
Piha-Paul SA[1]	24	13	6 (26%)	1.8	5.7	16 (66.7%)	4 (16.7%)
Kang J[2]	40	10	19 (47.5%)	1.5	4.3	8 (20.5%)	0 (0%)
Lee SH[3]	51	9.8	19 (35.2%)	2.1	6.9	30 (58.8%)	4 (7.8%)

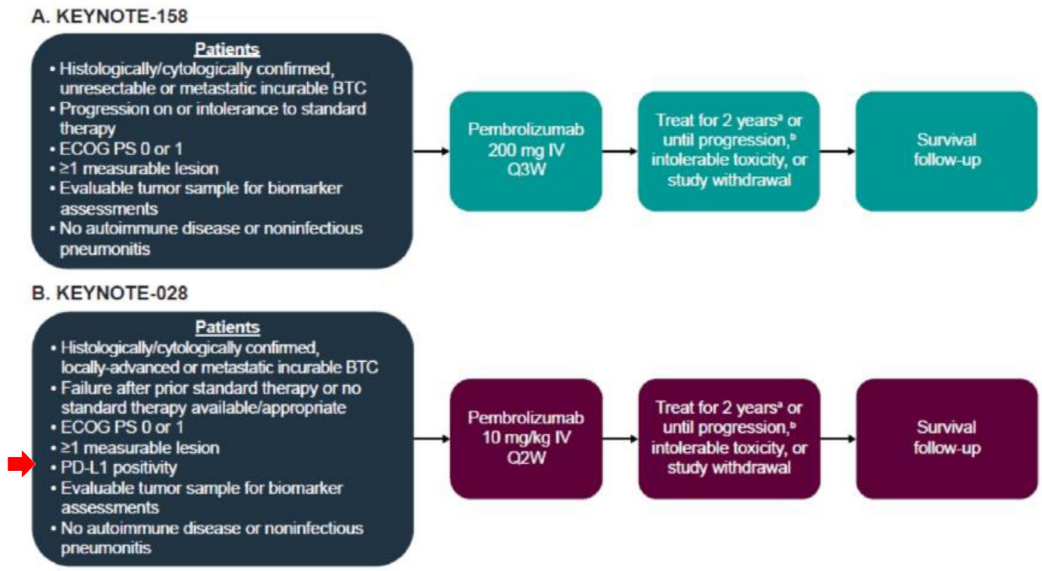




Abbreviations: BTC, biliary tract cancer; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; AE, adverse event.

1.Piha-Paul SA. Int J Cancer 2020
2. Kang J. Cancer Res Treat 2019
3. Lee SH & KSGC J. Clin. Med. 2020

Pembrolizumab for advanced BTC : Keynote-158 and Keynote-028 trials (1)

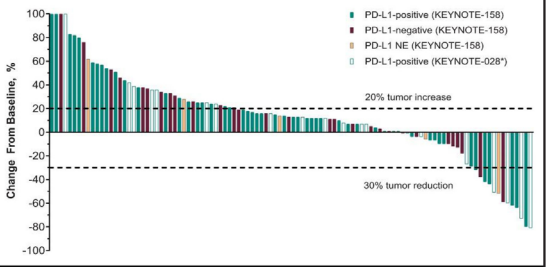


ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; Q2W, every 2 weeks; Q3W, every 3 weeks.
[a]If patients had stable disease or better when pembrolizumab was discontinued and subsequently had progressive disease, they were eligible to resume pembrolizumab for up to 1 year.
[b]If clinically stable, patients remained on pembrolizumab until progressive disease was confirmed in a second assessment performed ≥4 weeks later.

Bang et al., ASCO 2019

Efficacy and safety of pembrolizumab for the treatment of advanced biliary cancer: Results from the KEYNOTE-158 and KEYNOTE-028 studies

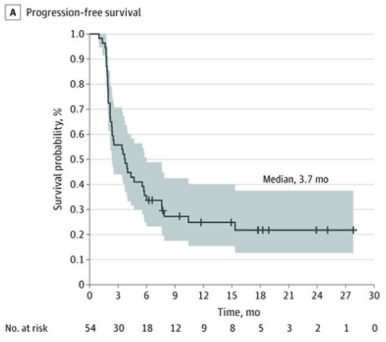
	KEYNOTE-158 n = 104	KEYNOTE-028 n = 24
Age, median (range), years	63 (34-81)	64 (43-70)
≥65, n (%)	44 (42.3)	11 (45.8)
Race, n (%)		
White	67 (64.4)	8 (33.3)
Asian	37 (35.6)	12 (50.0)
PD-L1 expression, n (%)		
Positive	61 (58.7)	24 (100.0)
MSI-H, n (%)	0	1 (4.2)
Number of prior lines of therapy, n (%)		
0	1 (1.0)	0
1	42 (40.4)	3 (12.5)
2	37 (35.6)	9 (37.5)
3	14 (13.5)	10 (41.7)
4	8 (7.7)	2 (8.3)
≥5	2 (1.9)	0



	KEYNOTE -158 n = 104	KEYNOTE -028 n = 24
ORR, % (95% CI)	5.8 (2.1-12.1)	13.0 (2.8-33.6)
Best objective response, n (%)		
CR	0	0
PR	6 (5.8)	3 (13.0)
SD	17 (16.3)	3 (13.0)
PD	65 (62.5)	11 (47.8)
Non evaluable	2 (1.9)	3 (13.0)
No assessment	14 (13.5)	3 (13.0)
Duration of response, median (range), mo	NR (6.2-26.6+)	NR (21.5-53.2+)

Piha-Paul SA. Int J Cancer 2020

A Phase 2 multi-institutional study of Nivolumab for patients with advanced refractory BTC (n=56)



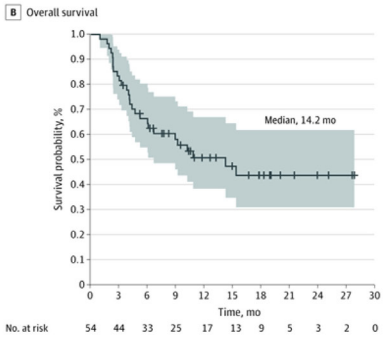
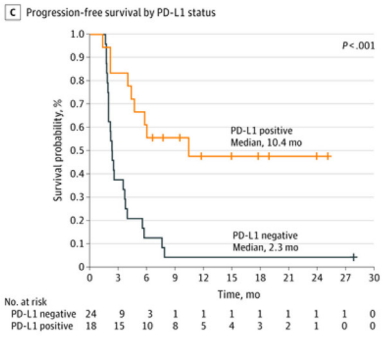
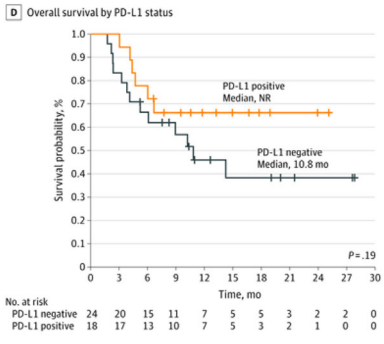
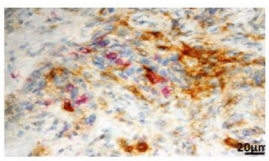


Table 1. Best Overall Response and Disease Control Rate

	No. (%) (n = 46)	
	RECIST, version 1.1	
Best overall response	Investigator review	Central review
CR (iCR)	0	0
PR (iPR)	10 (22)	5 (11)
	1 Unconfirmed	1 Unconfirmed
SD (iSD)	17 (37)	18 (39)
PD (iUPD + iCPD)	19 (41)	23 (50)
Disease control rate	27 (59)	23 (50)





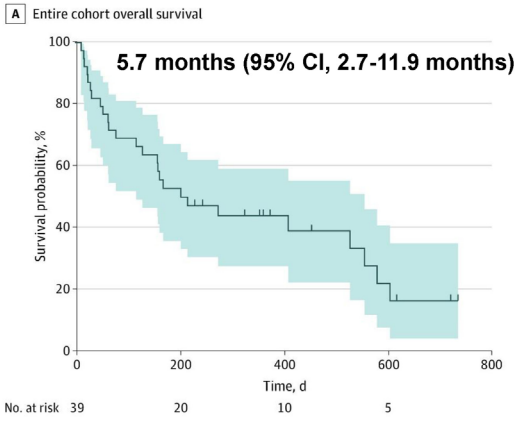


PD-L1: positive (brown)
PD-1: positive (red)

Kim RD. JAMA Oncol 2020

Nivolumab and Ipilimumab -subgroup analysis of a Ph 2 nonrandomized clinical trial-

Best overall response	No. (%)			
	Total cohort (n = 39)	Gallbladder (n = 13)	Cholangiocarcinoma	
			Intrahepatic (n = 16)	Extrahepatic (n = 10)
Objective response rate	9 (23)	4 (31)	5 (31)	0
Disease control rate	17 (44)	9 (70)	7 (44)	1 (10)



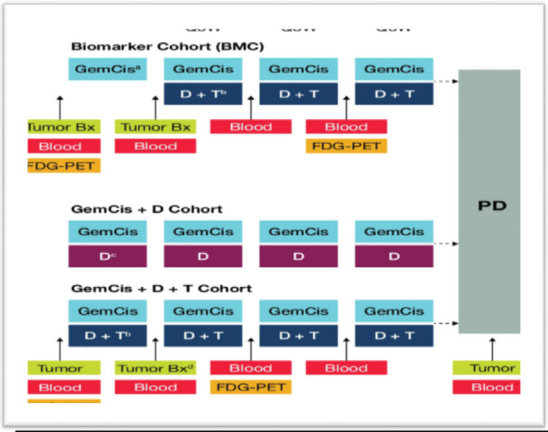
Immune-related toxic events : 49% of patients (n = 19), with 15% (n = 6) - grade 3 or 4 events.

	Grade 1/2	Grade 3/4
Dermatological (Rash, Pruritus)	13 (33%)	0 (0%)
Arthralgia/Arthritis	2 (5%)	0 (0%)
Endocrine		
Thyroiditis/Hypothyroidism	2 (5%)	1 (3%)
Hypophysitis	0 (0%)	2 (5%)
Hepatitis	2 (5%)	1 (3%)
Enterocolitis/Diarrhea	1 (3%)	1 (3%)
Gastritis	0 (0%)	1 (3%)
Pneumonitis	1 (3%)	0 (0%)

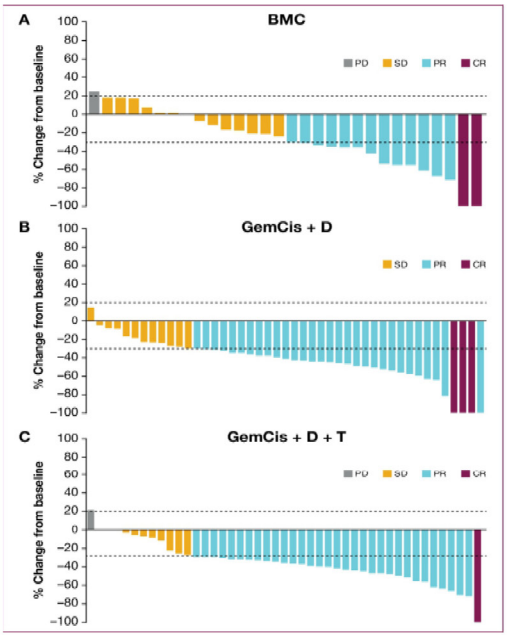
PD-L1 overexpression status was not addressed

Klein O. JAMA Oncol 2020

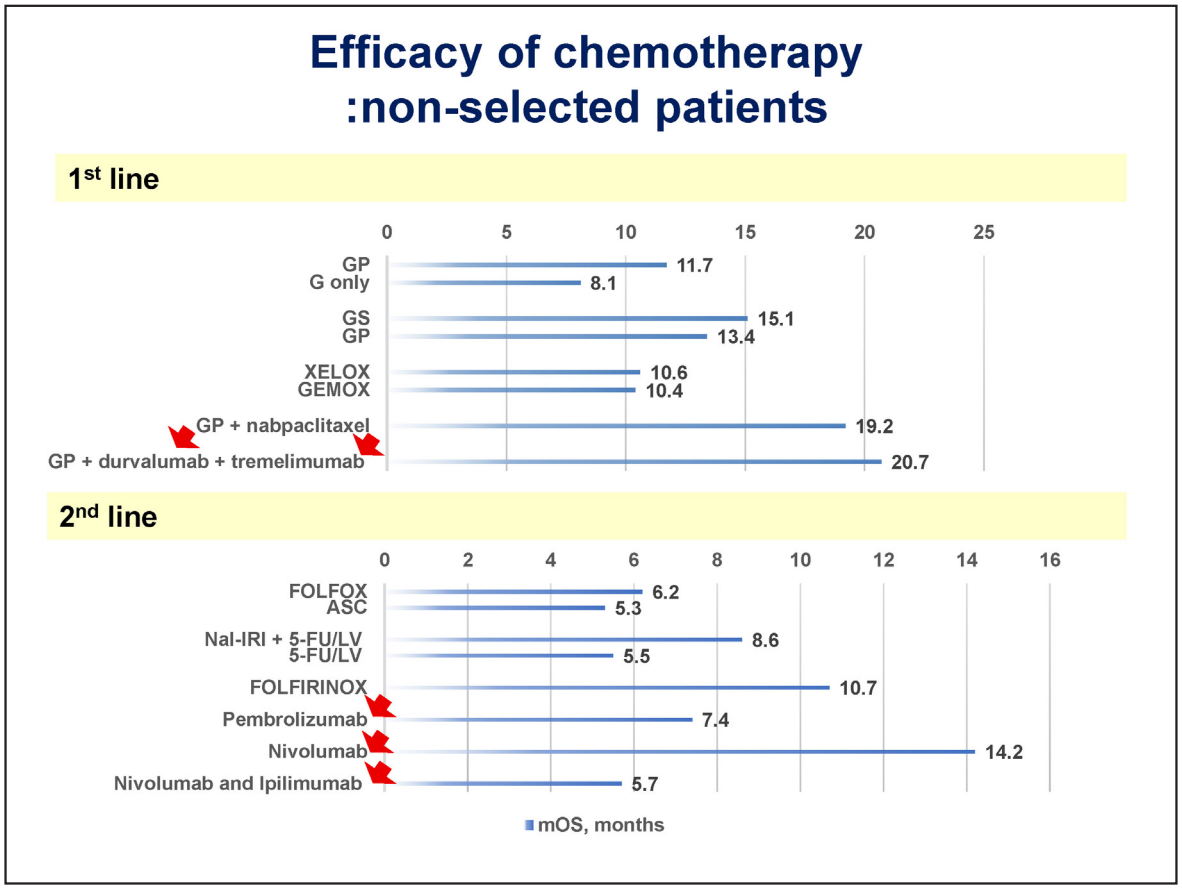
Phase II study assessing tolerability, efficacy, and biomarkers for durvalumab (D) ± tremelimumab (T) and GP in chemo-naïve advanced BTC-1

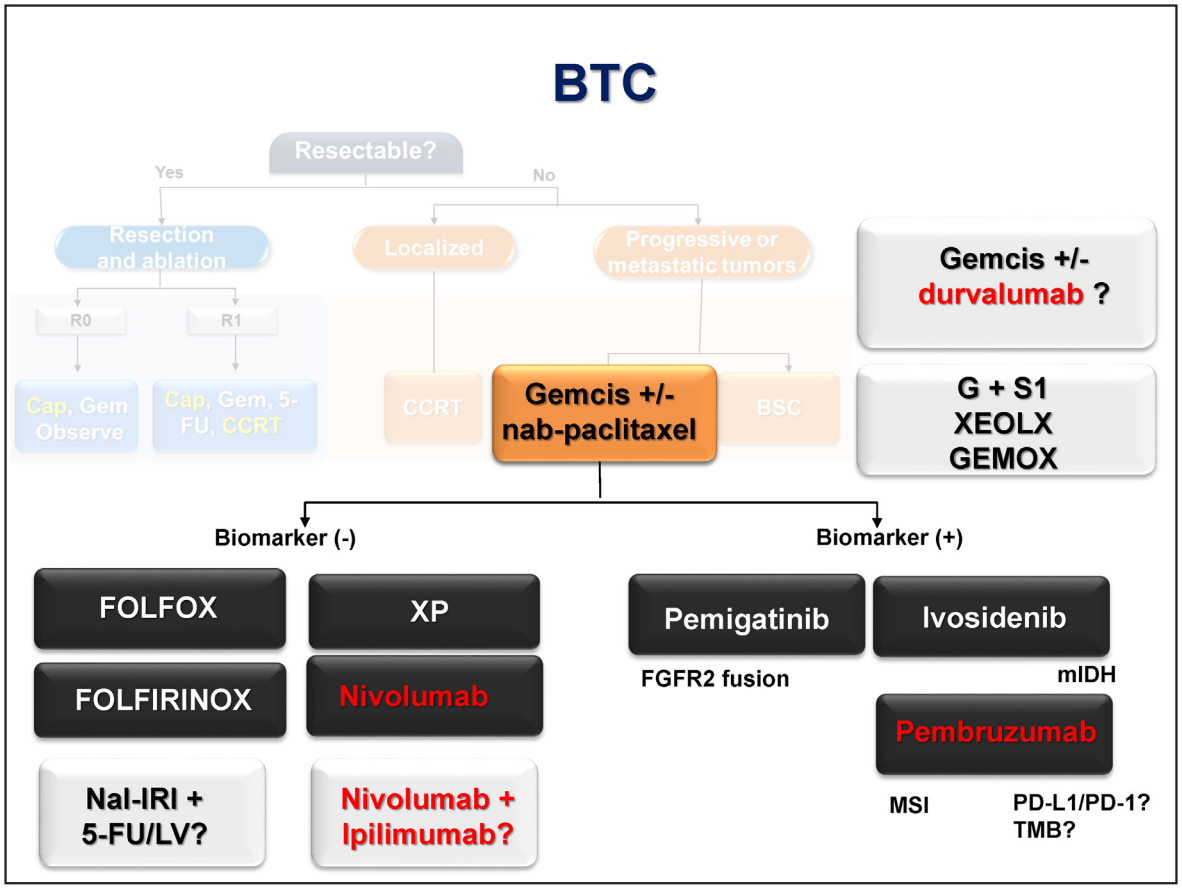


	BMC (n = 30)	3C (n = 45)	4C (n = 46)
ORR (95% CI), %	50.0 (32.1-67.9)	73.4 (60.5-86.3)	73.3 (60.4-86.2)
DCR (95% CI), %	96.7 (90.3-100)	100 (100-100)	97.8 (93.5-100)
mDOR (95% CI), m	11.0 (3.9-11.8)	9.8 (8.1-11.4)	9.1 (4.5-15.0)



Oh DY. JCO.2020 (abstr)


Efficacy of chemotherapy
:non-selected patients
1st line
0
5
10
15
20
25
GP
G only
11.7
8.1
GS
GP
15.1
13.4
XELOX
GEMOX
10.6
10.4
GP + nabpaclitaxel
19.2
GP + durvalumab + tremelimumab
20.7
2nd line
0
2
4
6
8
10
12
14
16
FOLFOX
ASC
6.2
5.3
Nal-IRI + 5-FU/LV
5-FU/LV
8.6
5.5
FOLFIRINOX
10.7
Pembrolizumab
7.4
Nivolumab
14.2
Nivolumab and Ipilimumab
5.7
mOS, months


BTC
Resectable?
Yes
No
Resection and ablation
Localized
Progressive or metastatic tumors
R0
R1
Cap, Gem Observe
Cap, Gem, 5-FU, CCRT
CCRT
Gemcis +/- nab-paclitaxel
BSC
Gemcis +/- durvalumab ?
G + S1
XEOLX
GEMOX
Biomarker (-)
Biomarker (+)
FOLFOX
XP
FOLFIRINOX
Nivolumab
Nal-IRI + 5-FU/LV?
Nivolumab + Ipilimumab?
Pemigatinib
FGFR2 fusion
Ivosidenib
mIDH
Pembruzumab
MSI
PD-L1/PD-1?
TMB?

Conclusions

- Results of immunotherapy have uniformly been disappointing for the majority of these trials in PC.
- A synergistic effect for immunotherapy in combination with cytotoxic drugs in BTC
- Further research needs to focus on how to overcome immunotherapy resistance by targeting multiple immune defects using combinatorial immunotherapy and cytotoxic approaches.

연/자/소/개

Curriculum Vitae

김 형 선

연세대학교 강남세브란스병원 간담췌외과

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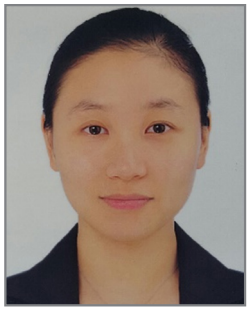
Case 1

김형선 (연세의대)

연/자/소/개

Curriculum Vitae



김 재 리

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Case 2

김재리 (경상의대)

Pembrolizumab is a humanized monoclonal antibody against programmed death 1 (PD-1). PD-1 has antitumor activity and increases activity in tumors that express programmed death ligand 1 (PD-L1). The programmed cell death protein 1 (PD1) is one of the checkpoints that regulates the immune response. Ligation of PD1 with its ligands PDL results in transduction of negative signals to T-cells. PD1 expression is an important mechanism contributing to the exhausted effector T-cell phenotype. The expression of PD1 on effector T-cells and PDL on neoplastic cells enables tumor cells to evade anti-tumor immunity. Blockade of PD1 is an important immunotherapeutic strategy for cancers.

Based on these actions, Pembrolizumab was approved by the FDA for the treatment of advanced melanoma and non-small cell lung cancer. It induced overall response rate of 21-34% in refractory melanoma, and 19-25% in refractory non-small cell lung cancer. Also, pembrolizumab was found to be effective in the treatment of several malignancies: recurrent or metastatic cervical cancer, recurrent locally advanced gastric or gastroesophageal junction adenocarcinoma, recurrent or metastatic head and neck squamous cell carcinoma, primary mediastinal large B-cell lymphoma in adult or pediatric patients with refractory disease, adult and pediatric patients with refractory classical Hodgkin lymphoma, and locally advanced or metastatic urothelial carcinoma.

However, little is known about the therapeutic effects of Pembrolizumab on advanced pancreato-biliary cancer and there are some debates. On today's presentation, I introduce some cases for individual with advanced pancreato-biliary cancer who were treated with various immunotherapeutic agents, as well as Pembrolizumab.

제68차
한국췌장외과학회 학술대회

2021년도 한국췌장외과학회 임상 연구 지원 공모과제 발표

(총 5편 예정)

최인석(건양의대), 이현국(이화의대)

KPSC Since 2004
한국췌장외과학회
Korean Pancreas Surgery Club

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한국췌장외과학회 학술대회

제68차
한국췌장외과학회 학술대회

Scientific Session 2

Technical Issue: Minimally invasive extended cholecystectomy and choledochal cyst excision

나양원(울산의대), 강창무(연세의대)

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연/자/소/개

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2017.03.01~2018.02.28	서울성모병원 임상강사
2018.03.01~2019.02.28	서울성모병원 임상진료조교수
2019.03.01~2020.02.28	인천성모병원 임상진료조교수
2020.03.01~2021.02.28	인천성모병원 조교수
2021.03.01~현재	서울아산병원 촉탁임상조교수

Laparoscopic extended cholecystectomy

곽봉준 (울산의대)

Gallbladder ca.

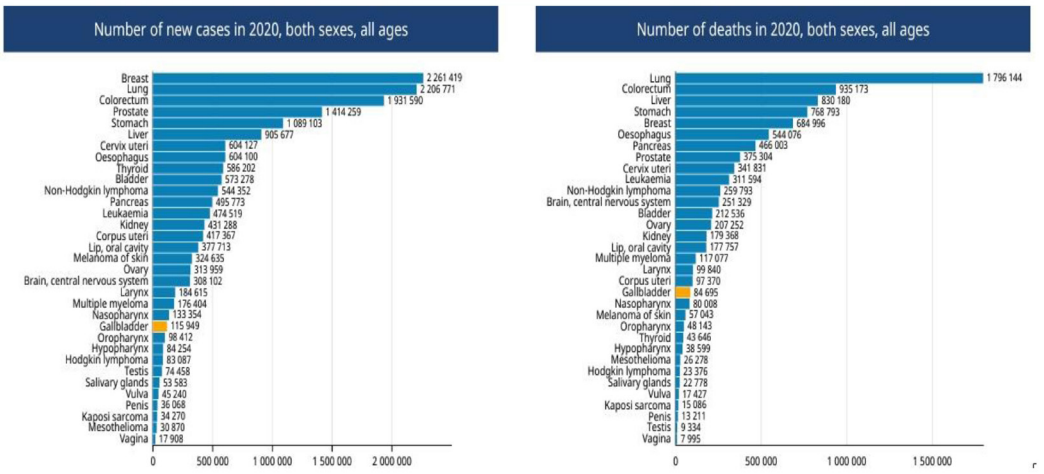
- Rare, most common biliary tract malignancy
- Female >> Male
- Varies significantly by geographic region and racial group
- Poor prognosis
- Complete surgical resection : only potentially curative therapy

Ref. Blumgart's Surgery of the Liver, Biliary Tract and Pancreas 6ed.

Incidence and mortality – World wide

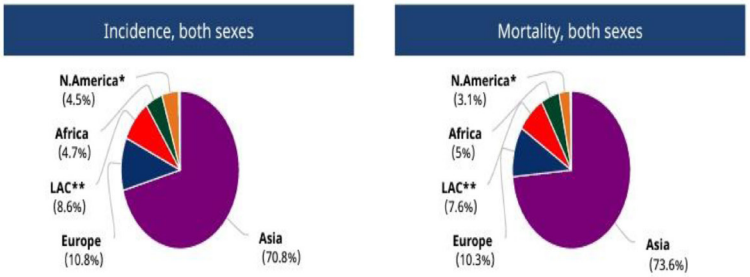
Gallbladder

Source: Globocan 2020



Ref. Globocan 2020

Incidence and mortality – World wide



Population	Number
Asia	82 137
Europe	12 570
**Latin America and the Caribbean	9 990
Africa	5 454
*Northern America	5 259
Oceania	539
Total	115 949

Population	Number
Asia	62 374
Europe	8 717
**Latin America and the Caribbean	6 464
Africa	4 249
*Northern America	2 586
Oceania	305
Total	84 695

Ref. Globocan 2020

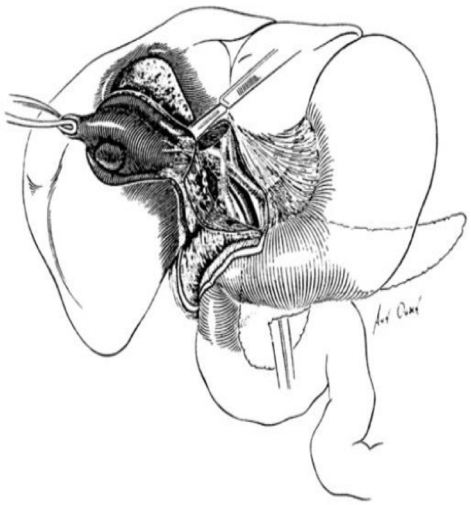
Incidence and mortality – In Korea

▪ 2020년 주요 암종별 사망률 : 남녀전체

암종	국제질병분류(ICD-10)	사망자수	분율(%)
모든 암	C00-C97	82,204	100
폐암	C33-C34	18,673	22.7
간암	C22	10,565	12.9
대장암	C18-C21	8,944	10.9
위암	C16	7,510	9.1
췌장암	C25	6,775	8.2
담낭 및 기타 담도암	C23-C24	5,192	6.3
유방암	C50	2,745	3.3
전립선암	C61	2,194	2.7
비호지킨림프종	C82-C86	2,069	2.5
백혈병	C91-C95	1,825	2.2

Ref. 국가암정보센터

Incidence and mortality – In Korea



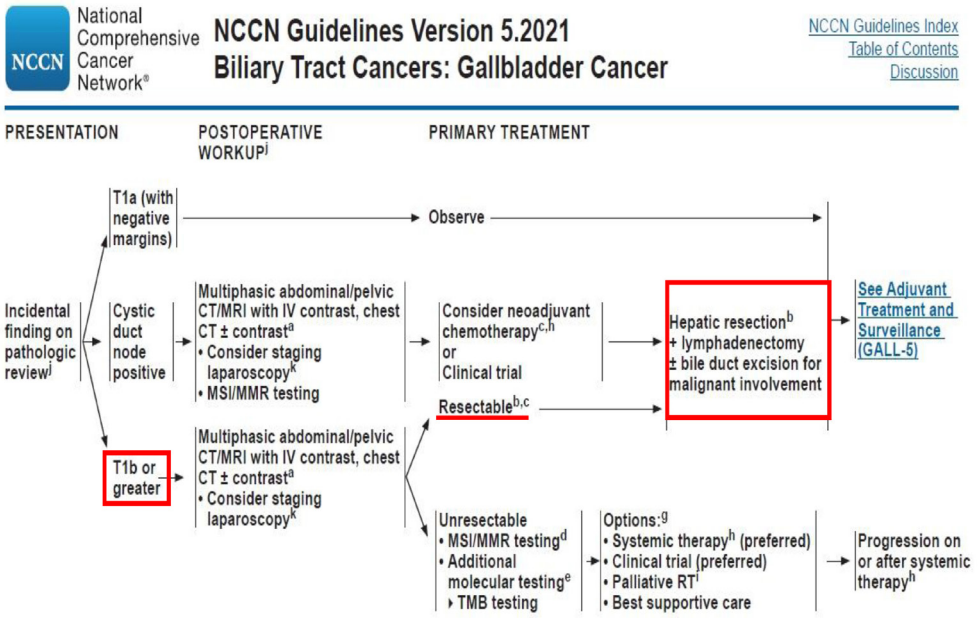
In 1954

Radical cholecystectomy(Glenn operation) for GB ca.

En bloc resection of GB, GB bed, LN(portal)

Ref. From Glenn F, Hays DM. The scope of radical surgery in the treatment of malignant tumors of the extrahepatic biliary tract. Surg Gynecol Obstet [now J Am Coll Surg] 1954;99:529–41

Treatment guideline



Ref. NCCN Guidelines Ver 5.2021

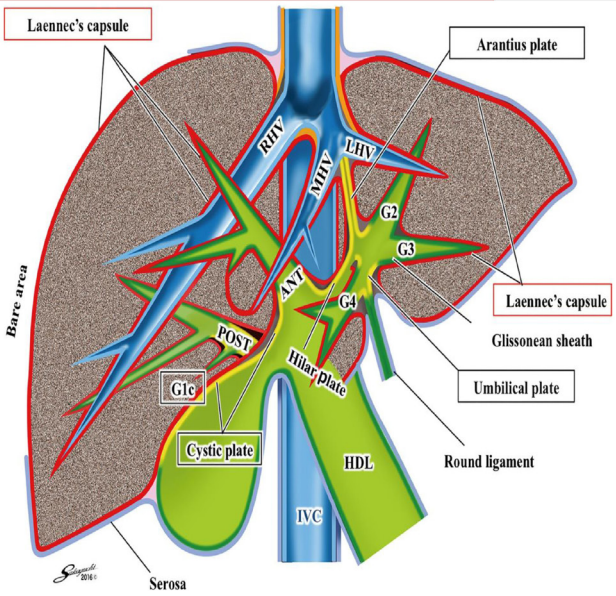
Principle of surgery

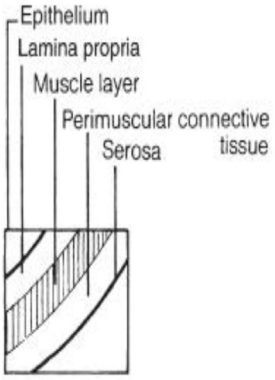
- Radical cholecystectomy(=extended cholecystectomy)
  : Gallbladder + Liver S4b/5 + lymphadenectomy(all LNs in the porta hepatis)
- ➔ T1b에서 liver resection해야되는지는 controversy??
- Obtain negative margin (Liver and cystic duct margin)
- Bile duct resection : not routine
- Port site resection : not recommended
- Preoperative biopsy : not necessary
- Diagnostic laparoscopy : can be considered
  (ex. T3 or higher tumor, poorly differentiated, surgery after margin-positive cholecystectomy)

Ref. NCCN Guidelines Ver 5.2021

Ref. Blumgart's Surgery of the Liver, Biliary Tract and Pancreas 6ed.

Anotomic consideration of Gallbladder





Ref. Journal of Hepato-Biliary-Pancreatic Sciences, Volume: 24, Issue: 1, Pages: 17-23, First published: 03 February 2017

Ref. AJCC 7th ed.

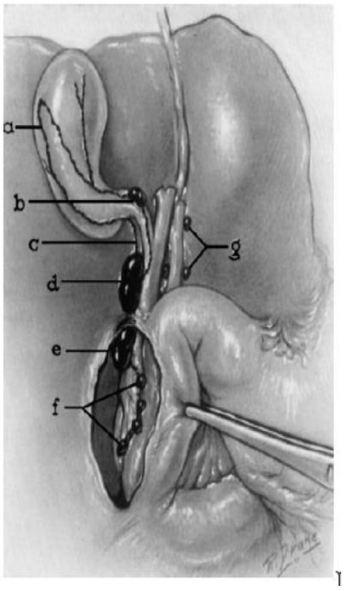
Liver resection

- Goal : ensure a margin of resection of 1~2cm
- Range : 2cm wedge resection of the GB bed ~ extended RH
- More extensive resection over S4b/5 → increased morbidity and mortality
  no survival benefit
  → If necessary, can be performed for R0 resection

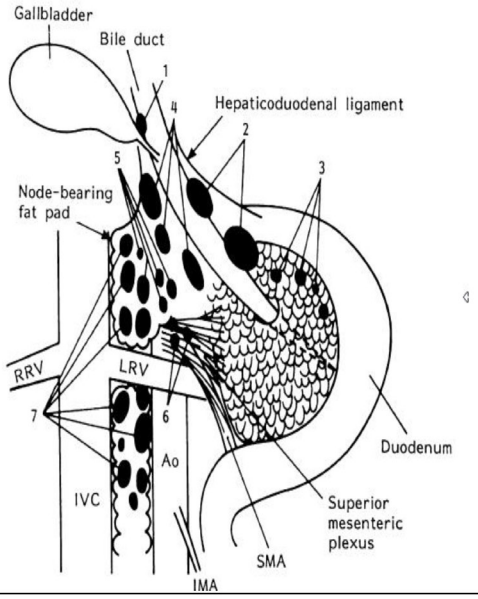
- Caution : <u>bleeding from branches of MHV</u>
  <u>avoid injury of right anterior Glisson and S8 Glisson</u>

Ref. Blumgart's Surgery of the Liver, Biliary Tract and Pancreas 6ed.
Ref. D'Angelica M, et a Ann Surg Oncol. 2009 Apr;16(4):806-16.

Lymphatic drainage around Gallbladder



Ref. Fahim RB, McDonald JR, Richards JC, Ferris DO. Carcinoma of the gallbladder: a study of its modes of spread. Ann Surg 1962;156:114–24



Ref. Shirai Y, Yoshida K, Tsukada K, Ohtani T, Muto T. Identification of the regional lymphatic system of the gallbladder by vital staining. Br J Surg 1992;79:659–62.

Lymphatic drainage around Gallbladder

Definition of Regional Lymph Node (N)

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases to one to three regional lymph nodes
N2	Metastases to four or more regional lymph nodes

AJCC PROGNOSTIC STAGE GROUPS

When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	I
T2a	N0	M0	IIA
T2b	N0	M0	IIB
T3	N0	M0	IIIA
T1–3	N1	M0	IIIB
T4	N0–1	M0	IVA
Any T	N2	M0	IVB
Any T	Any N	M1	IVB

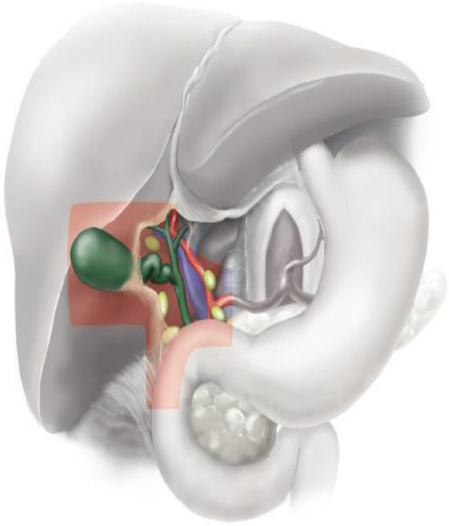
Ref. AJCC 8th ed.

LN dissection

- It is unknown whether lymph node dissection improves outcome
- accurate staging and prognostic information
- Standard extent of LN dissection

Regional Lymph Nodes

The lymph node locations include nodes along the common bile duct, hepatic artery, portal vein, and cystic duct.[2,3]



Ref. AJCC 8th ed.

Ref. Blumgart's Surgery of the Liver, Biliary Tract and Pancreas 6ed.

LN dissection

- Extent of LN dissection

Extent	Portal LND (standard)	Extended Portal LND	Peripancreatic(head only) LND with PD
region	Western style	Japanese style	selective patient, Japanese style
LN station	#8, 12	#8, 12, 13	#8, 12, 13, 17

Ref. Blumgart's Surgery of the Liver, Biliary Tract and Pancreas 6ed.

Ref. Yoshio Shirai Et al, Radical Lymph Node Dissection for Gallbladder Cancer: Indications and Limitations, Surgical Oncology Clinics of North America,Volume 16, Issue 1,2007,Pages 221-232

Video (LN dissection)

Video (Liver resection)

Summary

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경청해주셔서 감사합니다.

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Case presentation

정치영(경상의대), 한성식(국립암센터)

KPSC Since 2004
한국췌장외과학회
Korean Pancreas Surgery Club

GB MANEC (gallbladder mixed adenoneuroendocrine carcinoma)에 대한 수술 증례 1례

조영수 (서울의대)

담낭의 선암 및 신경내분비암의 병발은 매우 드문 질환으로, 전 세계적으로 현재까지 30례 이하만이 보고되었다.

본원에서 담낭암을 진단받고 선행 항암화학요법을 받은 뒤 개복하 확대담낭절제술을 받은 환자 1명에서 해당 증례가 확인되어 보고하고자 한다.

43세 여자로, 2021년 3월 건강검진에서 시행한 초음파 및 전산화단층촬영 상 담낭암 및 간 침윤 의심으로 수술을 권유받고 본원 외과 외래로 내원했다.

영상 상 담낭 종괴는 약 3.5cm, 간 결절은 미상엽에 약 6.3cm으로 확인되었으며, 문맥 주변 림프절 전이가 의심되는 상황이었다.

혈액종양내과에 의뢰하여 입원 후 검사를 진행했고, 내시경 초음파를 통해 확인한 결과 약 4.4cm크기의 종괴 및 근층까지의 침윤은 보이나 장막층까지의 침윤은 보이지 않았고, 췌체부 뒤쪽 8.5cm 크기의 후복막 종괴가 확인되어 조직검사를 시행했다.

조직검사 결과 소세포 신경내분비암으로 진단되었고, 우선 항암화학치료를 먼저 진행하기로 하여 총 6회를 진행 후 담낭 종괴는 2.3cm으로 감소했으며 후복막 종괴의 크기도 줄어들어 수술을 결정했다.

2021년 8월 25일 담낭절제술, 간쐐기절제술 및 림프절곽청술을 받았으며, 수술 후 6일째에 정상적으로 퇴원했다.

조직검사에서 담낭 내 잔존하는 종양은 선암이고, 림프절 전이는 구득된 3개의 림프절 중 2개에서 확인되었는데 모두 신경내분비암으로 진단되었으며, 이는 선행 항암화학요법으로 인해 담낭 종양의 신경내분비암 부위가 소실되었을 가능성이 있음을 나타낸다.

이후 항암화학요법은 본원에서 시행 중이며, 방사선요법은 연고지 관계로 타원에서 시행 중인 상태이다.

Long Term Survivor after Metastasectomy of PDAC

김령고 (동남권원자력의학원)

About half of patients with pancreatic ductal adenocarcinoma(PDAC) are diagnosed at a point when the disease is metastatic and when potentially curative surgery is not an option. Currently, standard treatment for the patients with metastatic PDAC is a palliative chemotherapy or radiation therapy. Recently, a few studies reported that surgery for the patient with metastatic PDAC improved survival compared to non-surgical patients. And there are few reports of long-term survival after liver resection for the patients with hepatic metastasis of PDAC. But to the best of my knowledge there are no reports of long-term survival after hepatic and pulmonary metastasectomy. Here we report a long-term survival case treated with combination of metastasectomy after chemotherapy, showing 5-year recurrence free survival and 9-year survival after first diagnosis. We carefully suggest that metastasectomy can be a curable treatment for highly selective patients with metastatic PDAC. And additional studies are needed to determine the surgical extent, criteria, timing and actual survival outcome.

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Minimally Invasive Pancreatectomy Following mFOLFIRINOX-neoadjuvant Chemotherapy in Resectable Pancreatic Cancer

강창무 (연세의대)

Minimally invasive pancreatectomy is regarded as one of option in treating resectable pancreatic cancer

There is still no RCT comparing open with minimally invasive pancreatectomy (MI-Px) for resectable pancreatic cancer. However, there are accumulating experiences to suggest MI-Px is feasible, safe, and effective, showing comparable long-term survival outcomes in treating pancreatic cancer [1,2]. Recent NCCN guidelines also posted MI-Px can be one of surgical options in treating resectable pancreatic cancer [3]. Moreover, MI-Px following neoadjuvant treatment is now carefully performed in well-selected pancreatic cancer [4,5].

Potential role of neoadjuvnat chemotherapy even in resectable pancreatic cancer?

Although it is known that curative pancreatectomy followed by postoperative adjuvant chemotherapy is standard care for resectable pancreatic cancer, about 60% of patients with radical pancreatectomy could not receive subsequent adjuvant therapy, mostly due to post-operative complications and delayed recovery [6]. Furthermore, pancreatic cancer (pancreatic adenocarcinoma) is regarded as systemic disease at diagnosis because systemic metastases, especially liver, lung, peritoneum, as an early event despite adjuvant chemotherapy following surgical extirpation. Therefore, by applying concept of neoadjuvant chemotherapy even in resectable pancreatic cancer, potential benefit of early treatment of micrometastatic disease, tumor down-staging effect, increasing R0 resection rates, improving systemic delivery of potent chemotherapeutic agents with greater completion rates of standard treatment, and testing tumor biology in advance to

select right patients for curative treatment, could be expected.

However, it is still controversial: loss of potential chance for cure due to tumor progression during neoadjuvant chemotherapy; preoperative tissue confirm is mandatory, patients may not complete treatment schedule due to chemotherapeutic agents-related toxicity, and lack of evidences.

Yonsei experiences: Phase II clinical trials of neoadjuvnat mFOLFIRINOX chemotherapy for resectable pancreatic cancer [ClinicalTrials.gov Identifier: NCT05066802]

In 2030, it is estimated that pancreatic ductal adenocarcinoma (PDAC) will be to the second most common human killing cancer in the world [7]. Currently, margin-negative radical pancreatectomy followed by adjuvant chemotherapy, FOLFIRINOX or gemcitabine plus capecitabine, is now standard of care for resectable pancreatic cancer. However, resectable pancreatic cancer still shows unsatisfactory oncologic outcomes due to early systemic metastasis during the follow up period after surgery. This phase II study is investigating the clinical feasibility and effectiveness of modified FOLFIRINOX as neoadjuvant treatment for resectable pancreatic cancer. Based on NCCN guideline, pathologically confirmed resectable pancreatic cancer is enrolled. After 6 cycles modified FOLFIRINOX chemotherapy (oxaliplatin 85 mg/m2 D1 + leucovorin 400mg/m2 D1 + irinotecan 150 mg/m2 D1 + 5-FU 2,000 mg/m2 42~46h continuous infusion, 12 weeks), surgical resection was attempted. In this presentation, the interim results will be introduced.

Clinical trials on neoadjuvnat chemotherapy in resectable pancreatic cancer

Current treatment recommendations for resectable pancreatic cancer support upfront resection and adjuvant chemotherapy. With emerging potent chemotherapeutic agents, neooadjuvant chemotherapy followed by surgical extirpation is thought to be attractive approach event to resectable pancreatic cancer, However, randomized controlled trials comparing upfront surgery with neoadjuvant approach are lacking. Recent meta-analysis based on 11 studies with 9386 patients with resectable pancreatic cancer showed neoadjvant treatment followed by surgery was related to higher R0 rate and lower incidence of lymph node metastasis. However, there was no significant differences in OS, suggesting more clinical evidences to support its credibility [8]. It was found that only 4 RCTs are noted in this issue (Table 1).

Table 1. Summary of RCT on upfront surgery and neoadjuvant chemotherapy in resectable pancreatic cancer

Study #	Subject (N)	Arms	Comments
PACT-15 [9]	R-PC (62)	PEXG+Surgery+PEXG Surgery+ PEXG	mOS: 38.2 months vs 26.4 months R0: 63.0% vs 37.0% LN-mets: 51.9% vs. 74.1
PREP-02/JSAP-05 [10]	R-PC (364)	Gem+S1+Surgery+S1 Surgery+ S1	mOS : 36.7 months vs 26.6 months LN-mets: 59.6% vs.81.5% R0: similar
PREOPANC-1 [11]	R-PC (133)	Gem-RTx+Surgery+Gem Surgery+ Gem	Mos14.6 months vs 15.6 months R0: 66% vs. 59%
SWOG S1505 [12]	R-PC (102)	.mFOLFIRINOX+ Surgery .Gem/nab-paclitaxel+ Surgery	mOS: 22.4 months vs. 23.6 months 2YOS: 43.1% vs. 46.9% R0: both 85% Both regimens have similar effect as neo-Tx in R-PC.

PEXG, cisplatin + epirubicin + gemcitabine + capecitabine

Ongoing clinical trial investigating role of neoadjuvnat chemotherapy in resectable pancreatic cancer

When reviewing currently available ongoing randomized clinical trial investigating potential role of neoadjuvant chemotherapy in resectable pancreatic cancer, about 5 clinical trials are noted (Table 2). Recently, one of them has completed patients' enrollment and waiting for final results according to the protocol (NCT02172976). Most studies are from Europe and multicenter collaborative works. In near future, it is hoped that our society could contribute to this challenging issue to provide appropriate guideline for optimal use of neoadjuvant chemotherapy in resectable pancreatic cancer.

Conclusions

With the advance of surgical experiences, curative pancreatectomy following mFOLFIRINOX-neoadjuvant chemotherapy is feasible in resectable pancreatic cancer, and even MI-Px could be well performed in some of the patients. However, there are still risk of tumor progression and incomplete treatment due to chemotherapeutic agents-related toxicity during period of neoadjuvant chemotherapy, leading to delayed definitive standard treatment of resectable pancreatic cancer. In addition, short-term oncologic impact of mFOLFIRINOX-neoadjuvant chemotherapy need to be further investigated in resectable pancreatic cancer. Several issues need to be concerned before conducting future RCT, such as selection criteria, chemotherapy regimens, duration (cycles), salvage strategy for patients with progression during clinical trials).

Table 2. Current ongoing RCT about neoadjuvant chemotherapy in resectable pancreatic cancer

Study #	Country	Title	Subject	N	Arm A	Arm B	Arm C	Primary outcomes	Status
NCT02172976	Germany	Randomized Multicenter Phase II/III Study With Adjuvant Gemcitabine Versus Neoadjuvant / Adjuvant FOLFIRINOX for Resectable Pancreas Carcinoma	RPC	40	surgery plus adjuvant gemcitabine, 6 cycles	4-6 cycles FOLFIRINOX neoadjuvant, 4-6 cycles FOLFIRINOX adjuvant	NA	median overall survival	completed
NCT02047513	Germany	Neoadjuvant Plus Adjuvant or Only Adjuvant Nab- Paclitaxel Plus Gemcitabine for Resectable Pancreatic Cancer (NEONAX)	RPC	127	perioperative nab-paclitaxel/gemcitabine	adjuvant nab-paclitaxel/gemcitabine	NA	Time to Disease free survival (DFS)	Active, not recruiting
NCT02959879	French	Neo-adjuvant FOLF(IRIN)OX for Resectable Pancreatic Adenocarcinoma (PANACHE01)	RPC	160	FOLFOX neoadjuvant chemotherapy, 4 cycles, + 8 cycles standard adjuvant chemotherpay	FOLFIRINOX neoadjuvant chemotherapy, 4 cycles + 8 cycles standard adjuvant chemotherpay	adjuvant standard chemotherapy	Number of patients alive Number of patients with complete chemotherapy	Recruiting
NCT02919787	Norway	Nordic Pancreatic Cancer Trial (NorPACT) - 1	RPC	140	adjuvnat FOLFIRINOX	neoadjuvnat FOLFIRINOX +adjuvant FOLFIRINOX	NA	Overall survival	Active, not recruiting
NCT03750669	China	Sequential Use of AG and mFOLFIRINOX as Neoadjuvant Chemotherapy for Resectable Pancreatic Cancer	RPC	416	Neoadjuvant chemotherapy: (nab-paclitaxel plus gemcitabine) and mFOLFIRINOX	Surgical treatment without any neoadjuvant treatments.	NA	Disease-free survival	Recruiting

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Unusual recurrence of pancreatic NET grade 1 after Laparoscopic PPPD

민석기 (이화의대)

41세 남자가 2017년 지속적인 저혈당과 이로 인한 쇼크 반복되어 검사한 결과, 복부 CT상 췌장 두부에 약 2cm의 조영증강 동반한 결절 종양 발견되었으며, Neuroendocrine tumor(NET)의심되어 동년 4월에 Laparoscopic PPPD시행받았음. 당시 조직 검사상 Grade 1의 NET로 크기 약 2cm였음. 환자는 수술 후 약 1주일째 퇴원하고 저혈당 증상 호전되어 일상 생활 유지하면서 지내다가 2021년 초부터 다시 약간씩 저혈당 증상 나타나면서 걱정이 되어 다시 방문하였고, 추가적인 검사로 복부 CT촬영한 결과, 췌장 주변으로 약 5개의 조영 증강 종양 발견되었음. 환자와 상의하에 재수술 결정하였으며, 2021년 7월 개복 수술로 췌장 주변에 위치한 의심되는 5개종양을 모두 찾아서 제거하고 조직 검사하였으며, 모두 Grade 1의 NET로 확인되었음. 환자는 수술 후 다시 저혈당 증상 없이 현재 추적 관찰중임. 최초 종양이 췌장 내부에 국한된 작은 종양이었으며, 당시 검사상 주변에 추가 의심되는 소견없었고 grade 1의 NET라서 추가 치료 없이 추적 관찰 중이었던 분으로, 이후 췌장 내부가 아닌 췌장 절제 주변으로 발생한 다발성 재발 양상을 경험하여 함께 공유하고자 보고합니다.

Laparoscopic Distal Pancreatectomy for Pancreas Body Cancer in Patient with Portal Annular Pancreas

이승재 (건양의대)

Background: Portal annular pancreas (PAP) results from failure in fusion of the ventral and dorsal pancreatic buds around the portal vein. As most of PAP are asymptomatic and recognized incidentally, exact prevalence of PAP is unclear. We present a case report of laparoscopic distal pancreatectomy for pancreatic cancer of PAP.

Case report: A 77 years-old-woman presented to our institute with pancreatic mass in abdomen ultrasonography. Patient's chief complaint was continuing dyspepsia and epigastric pain. Contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) revealed poorly enhancing mass (2.3cm) in pancreas body, and no major vascular invasion. The patient was planned for laparoscopic distal pancreatectomy and splenectomy. Five ports were inserted in the supine position. Inferior and superior margin of pancreas was dissected, and tunneling through inferior border of pancreas was done. We found pancreatic tissue was remaining in posterior side of portal vein, then dissection and tunneling of uncinate process were done. Pancreas and spleen were dissected carefully from the retroperitoneum. Intraoperative finding were suggestive of type 3A PAP, anteportal main pancreatic duct and suprasplenic portal confluence, which is most common type. The operation time was 300 minutes and estimated blood loss was 30ml. Drain was inserted at left sub-phrenic area and was removed on postoperative day 4. The patient was discharged at postoperative day 7 without immediate postoperative complication. The final pathology was revealed adenocarcinoma and pathologic stage was pT2N1, with 1 of 8 peripancreatic lymph nodes confirmed as metastatic adenocarcinoma.

Conclusion: Patient with PAP are known for higher risk of postoperative pancreatic fistula following pancreatic resection. Therefore, it is essential to identify PAP preoperatively and establish proper planning during pancreatic resection.

Recurrence of Extrahepatic Bile Duct Cancer after Long-term Disease-free Survival

김형석 (서울의대)

The 5-year survival rates of extrahepatic bile duct cancer range from 20% to 30%, indicating a high recurrence rate after resection. An aggressive surgical approach will give some survival benefit; however, how long follow-up monitoring should be continued after resection remains unclear. Although NCCN guidelines recommend 5-year surveillance after resection, several studies have reported recurrences of extrahepatic bile duct cancer even after 5 years of resection, and late recurrence is not infrequent. Therefore, long-term follow up is required before declaring cure. Moreover, postoperative surveillance strategies also need to be established.

Case 1: DFS 12Y 1M, A 83-year-old male who had undergone hilar resection 12 years ago due to Klatskin tumor (pT2N0) visited the hospital for the evaluation after cholangitis. MR showed enhancing papillary soft tissue in the remnant distal CBD, suspicious of recurred cancer. Pancreatoduodenectomy was performed, and the pathologic results showed recurrence. He discharged with PCD drainage at POD 9.

Case 2: DFS 12Y 10M, A 80-year-old male who received PPPD for distal CBD cancer (pT2N0) in 2008 was referred for the LFT abnormality. CT and MR showed IHD dilatation with hilar separation, multiple liver mass, and seeding mass at mesocolon. Liver biopsy showed metastasis from extrahepatic bile duct. The patient underwent ileocolostomy due to seeding-induced colon obstruction, and thereafter, died of bacteremia with pneumonia aggravation, brain infarct and GI bleeding.

Case 3: DFS 10Y 2M, A 72-year-old female visited the hospital for imaging abnormality. She had a history of Klatskin tumor (pT2aN1), and hilar resection had been performed in 2011. CT showed soft tissue lesion, abutting to pancreas and celiac axis. She has been on palliative chemotherapy since August 2021.

제68차
한국췌장외과학회 학술대회

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■ **효능 • 효과** 췌장 외분비 기능 장애

■ **용법 • 용량**

성인 및 4세 이상의 소아
투여용량은 췌장(이자) 손상의 중증도(심한 정도)에 따라 항상 다릅니다. 권장용량은 지방 소화력 단위 20,000-40,000 EP 단위/식사 입니다. 소화불량의 정도에 따라, 필요량은 이보다 상당히 높을 수 있습니다.
특히, 낭성섬유증환자에 있어서는 적절한 지방 흡수를 위해 필요한 효소의 용량을 초과하여서는 안되며, 식사의 양과 구성을 고려해야 합니다. 용량은 주의를 기울여 증량(양을 늘림)되어야 하며, 증상(예. 지방변, 위통증)의 개선과 연관되어야 합니다. 1일 체중 kg당 지방소화력단위 15,000-20,000 EP단위의 용량을 초과하지 않습니다.
이 약은 식사 중 충분한 양의 물과 함께 복용합니다. 이 약을 씹거나 캡슐을 개봉할 경우 효능이 감소할 수 있고, 구강내(입안)에서 효소가 용출되어 구강내(입안) 점막을 손상시킬 수 있으므로, 이 약은 통째로 삼키거나, 캡슐을 그대로 삼키기 어려운 경우에는 캡슐을 개봉하여 액체나 부드러운 음식과 함께 섞은 즉시 복용하되, 이 약의 내용물을 씹지 않고 즉시 삼켜야 합니다. 투여기간은 질환의 정도에 따라 다릅니다.

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■ **저장방법** 기밀용기, 25℃ 이하에서 보관

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